Development of Novel Chiral Imidazolinium Salts and Their Application in Asymmetric Catalysis

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Development of Novel Chiral Imidazolinium Salts and Their Application in Asymmetric Catalysis

(Entwicklung neuer chiraler Imidazolinium Salze und deren Anwendung in der Asymmetrischen Katalyse)

DISSERTATION

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Dekan:	Prof. Dr. Albrecht Wolter
Referent:	Prof. Dr. René Wilhelm
Koreferent:	Prof. Dr. Dieter E. Kaufmann

Hiermit erkläre ich an Eides statt, dass ich die vorgelegte Arbeit selbständig, ohne unerlaubte Hilfe verfasst und die benutzten Hilfsmittel vollständig angegeben habe.

Mazhar Amjad Gilani

Hiermit erkläre ich an Eides statt, dass ich noch keine früheren Promotionsversuche unternommen habe.

Mazhar Amjad Gilani

ABSTRACT

Development of Novel Chiral Imidazolinium Salts and Their Application in Asymmetric Catalysis

The thesis deals with the development of enantiopure *N*-heterocyclic carbene precursors incorporating hydroxy groups and their protected analogues. Their application in combination with different metallic salts was evaluated in asymmetric synthesis. Due to the fact that examples of chiral *N*-heterocyclic carbenes are limited in asymmetric synthesis as compared with phosphines, it is desirable to develop novel series of enantiopure carbene precursors and investigated these in different reactions.

The present thesis is divided into three parts, Introduction, Results and Discussion and Experimental.

In the Introduction, different known strategies for the preparation of imidazolium and imidazolinium carbene precursors have been discussed. It also includes the applications of these carbene precursors in some well known reactions that were carried out with the new ligands presented in this thesis.

In the first chapter of Results and Discussion, the preparation of C_2-symmetric diamines is described by two routes: First by direct alkylation of amines and second by ring opening reaction of epoxides. Enantiomerically pure amino alcohols have been synthesized with moderate to high yields. In addition hydroxy groups of the amino alcohols were protected with sterically different silylating reagents. Mono- and bis-hydroxy protected diamines were obtained with moderate yields but in high purity. The synthesis of imidazolinium salts from protected and unprotected amino alcohols by the direct reaction with *ortho*esters in the presence of an acid source is described. The properties of these salts were then modified by using different counter anions. One thiourea precursor has been synthesized from norephedrine based amino alcohol.

The second chapter of Results and Discussion deals with the application of imidazolinium carbene precursors in different catalytic reactions. In part one of this chapter, the diethylzinc addition to aldehydes is described. Optically active secondary alcohols were obtained in high yields with high enantioselectivities. The optimization of this reaction involved screening a number of new ligands with different metallic salts, metal to ligand ratio and several other reaction conditions. The second part of this chapter involves the asymmetric α-arylation. The reaction was optimized by varying a number of reaction conditions. Oxindoles were obtained in excellent yields with good enantioselectivities. In this series of experiments, an important finding is that amino alcohols can also function as ligands for the reaction leading to moderate yield. In the last part of Results and Discussion, the new chiral ligands have been employed in some other reactions like Michael reaction, ring opening reaction, synthesis of propargylic alcohols and others.

Finally, in the Experimental detailed procedures for the preparation of the described compounds and their characterization are given.

Dedicated to

my loving

parents

Acknowledgements

In the first, I really feel unable in having words to thank Almighty Allah Whose blessings are unlimited. My belief in Him developed stronger after knowing even a little about His world of chemistry.

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Finally, I would like to thank the Higher Education Commission, Pakistan for a scholarship.

ABBREVIATIONS

δ	chemical shift
°C	Temperature in degrees Centigrade
Ac	Acetyl
Ad	Adamantyl
aq.	Aqueous
Ar	Aryl
ARCM	Asymmetric ring-closing metathesis
AROM	Asymmetric ring-opening metathesis
BARF	Tetrakis[(3,5-trifluoromethyl)phenyl]borate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
bs	Broad singlet
Bu	Butyl
BuLi	Butyllithium
c	Concentration
$CHCl_3$	Chloroform
CI	Chemical Ionization
cm	Centimeter
Cod	Cyclooctadiene
Cy	Cyclohexyl
d	doublet
DCM	Dichoromethane
dd	doublet doublet
ddd	doublet doublet doublet
de	Diastereomeric excess
DMA	*N*,*N*-dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio

ee	Enantiomeric excess
EI	electron impact
equiv.	Equivalent
ESI	Electron spray ionisation
Et	ethyl
Et_2O	Diethyl ether
EtOH	Ethanol
eV	Electron volt
FCC	Flash column chromatography
g	Gram
h	Hour
HPLC	High pressure liquid chromatograpy
HRMS	High resolution mass spectroscopy
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
hν	Irradiation with light
i	Iso
IL	Ionic liquid
IMe	1,3-Dimethylimidazole-2-ylidene
IMes	1,3-Bis-(2,4,6-trimethylphenyl)-imidazole-2-ylidene
IPA	2-Propanol
IPr	1,3-Bis-(2,6-di*iso*propylphenyl)-imidazole-2-ylidene
^{i}Pr	*Iso*propyl
IR	Infrared
J	Coupling constant
KHMDS	Potassium hexamethyldisilazane
KO^{t}Bu	Potassium *tert*-butoxide
L	Litre
LAH	Lithium aluminium hydride
LDA	Lithium di*iso*propylamide
LiHMDS	Lithium hexamethyldisilazane
M	Molar (mol/L)
m	Multiplet
m/e	Mass to charge ratio
m/z	Mass to charge ratio

Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
min	Minute (Minutes)
mmol	Millimole
mol	Mole
mp	Melting point
MS	Mass spectroscopy
NaHMDS	Sodium hexamethyldisilazane
Naphth	Naphthyl
NMR	Nuclear magnetic reasonance
o	*Ortho*
p	*Para*
Ph	Phenyl
PhMe	Toluene
ppm	Parts per million
Pr	Propyl
q	Quartet
q	Quaternary
R	Alkyl
rt	Room temperature (25°C)
RTIL	Room temperature ionic liquid
TBDMS	*tert*-Butyldimethylsilyl
TIBS	Tri*iso*butylsilyl
TIPS	Tri*iso*propylsilyl
Ts	*para*-Toluene sulfonate

ZUSAMMENFASSUNG

Entwicklung neuer chiraler Imidazolinium Salze und deren Anwendung in der Asymmetrischen Katalyse

Die Doktorarbeit beinhaltet die Entwicklung enantiomerenreiner N-heterocyclischer Carbenvorläufer, welche Hydroxy Gruppen und deren geschützte Analoge beinhalten. Diese Verbindungen wurden in Kombination mit verschiedenen Metallen in der asymmetrischen Synthese untersucht. Aufgrund der Tatsache, dass Beispiele chiraler N-heterocyclischer Carbene in der asymmetrischen Synthese im Vergleich zu Phosphanen immer noch limitiert sind, ist es von großem Interesse neue enantiomerenreine Carbenvorläufer zu entwickeln und in verschiedenen Reaktionen zu untersuchen.

Die vorgestellte Doktorarbeit ist in drei Teile unterteilt, Einleitung, Resultate und Diskussion und dem Experimentellen Teil.

In der Einleitung werden verschiedene bekannte Strategien für die Darstellung von Imidazolium und Imidazolinium Carbenvorstufen diskutiert. Zusätzlich werden auch Anwendungen dieser Carbenvorstufen in einigen gut bekannten Reaktionen präsentiert, welche auch mit den im Rahmen dieser Doktorarbeit neu dargestellten Liganden durchgeführt wurden.

Im ersten Kapitel der Resultate und Diskussionen wird die Darstellung von C_2-symmetrischen Diaminen über zwei verschiedene Synthesewege beschrieben: Zuerst über die direkte Alkylierung von Diaminen und zum zweiten durch die Ringöffnung von Epoxiden. Enantiomerenreine Aminoalkohole konnten in mäßigen bis guten Ausbeuteten synthetisiert werden. Des Weiteren wurden die Hydroxy Gruppen der Aminoalkohole mit unterschiedlich großen Silylgruppen geschützt. Mono- und Bis-Hydroxy geschützte Diamine konnten in angemessenen Ausbeuten und hoher Reinheit isoliert werden. Danach wird die Synthese von Imidazolinium Salzen ausgehend von den geschützten und ungeschützten Aminoalkoholen durch die direkte Umsetzung mit *Ortho*estern in der Gegenward einer Säure beschrieben. Die Eigenschaften dieser Salze wurden durch die Verwendung verschiedener Gegenanionen modifiziert. Es wird auch die Synthese eines Thioharnstoffs Analoga ausgehend von Norephedrin beschrieben.

Das zweite Kapitel der Resultate und Diskussionen beschreibt die Anwendung der Imidazolinium Salze als Carbenvorstufen in verschiedenen katalytischen Reaktionen. Zuerst wird die Diethylzink Addition an Aldehyde besprochen. Optisch aktive sekundäre Alkohole wurden in hohen Ausbeuten und Enantioselektivitäten erhalten. Die Optimierung der Reaktion beinhaltete die Untersuchung einer Reihe von neuen Liganden mit verschiedenen Metallsalzen und der Änderung einer Reihe von Reaktionsbedingungen. Danach wird die asymmetrische α-Arylierung diskutiert. Verschiedene Reaktionsparameter wurden optimiert. Die Oxindole wurden in exzellenten Ausbeuten und guten Enantioselektivitäten erhalten. Des Weiteren wird auch gezeigt, dass die Aminoalkohole selber als Liganden in dieser Reaktion verwendet werden können. Zum Schluss werden die neuen Liganden auch in einigen anderen Reaktionen, wie der Michael Reaktion, der Ringöffnung von Epoxiden und der Synthese von Propargylalkoholen untersucht.

Der experimentalle Teil beschreibt detailliert die Arbeitsvorschriften für die Synthese der neuen Verbindungen und deren Charakterisierung.

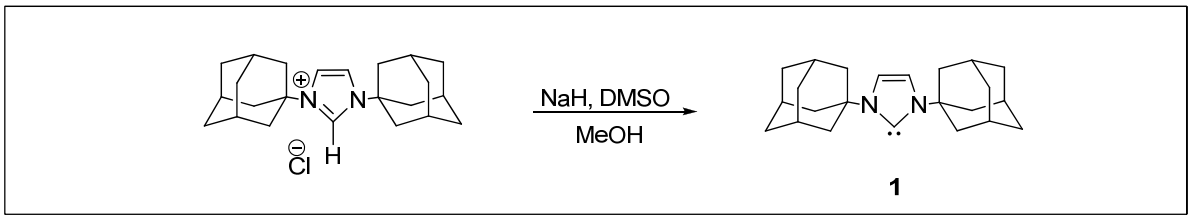
Table of Contents

1. Introduction

Carbenes belong to one of the most investigated reactive species in the area of organic chemistry. As a typical structural feature, all carbenes are neutral and possess a bivalent carbon atom with a sextet of electrons. Traditionally, carbenes were thought to be short lived species and used to introduce a single carbon atom into a molecule. During the last decade, the chemistry of carbenes has gained importance in catalysis because of their use as spectator ligands for transition metals. The spectacular advance in this area is due to the remarkable efforts and strategies developed by chemists to build stable and isolable carbene species.[1] *N*-Heterocyclic carbenes are the best known examples. The field of *N*-heterocyclic carbene (NHC) chemistry has seen a phenomenal growth in recent years with numerous new applications[2] in organometallic chemistry. *N*-Heterocyclic carbenes (NHCs) are widely used as replacements for phosphine ligands.[3] Recently, transition metal NHC complexes have been explored as efficient catalysts for many important transformations including C-C coupling reactions,[4, 5] olefin metathesis,[6] hydrogenation,[7, 8] hydroformylation,[9] hydrosilylation,[10] CO-ethylene copolymerization[11] and hydroboration[12] reactions.

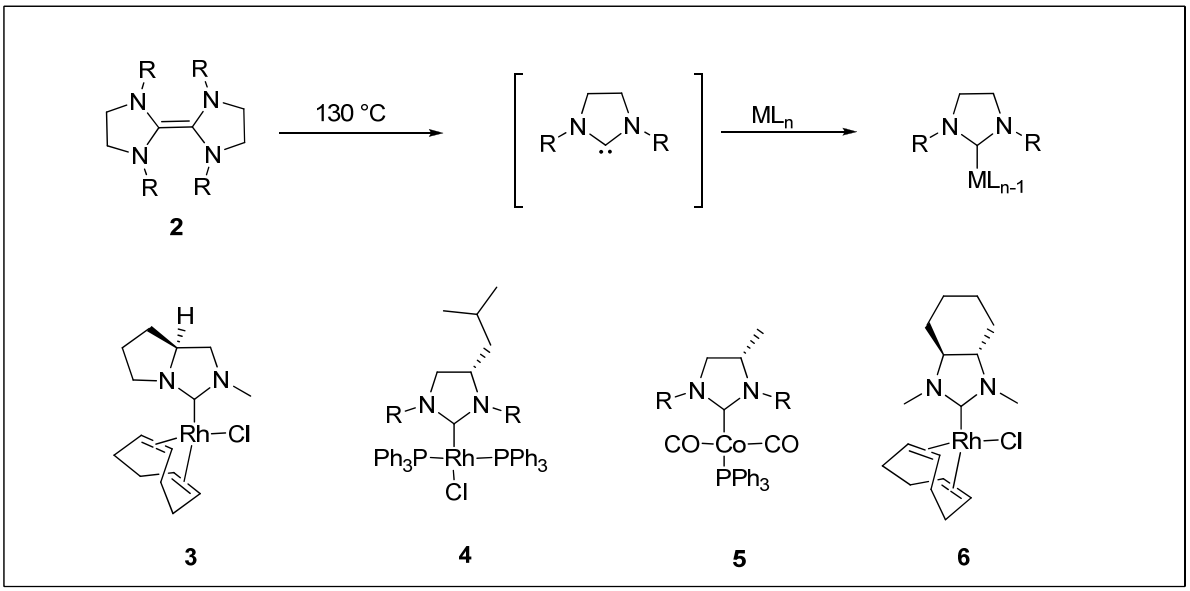
1.1. Historical Background

Investigation of alkaline hydrolysis of chloroform by Hine[13] led to the discovery of a very reactive intermediate which was later on named as carbene by Döring *et al*.[14, 15] who postulated that this carbene could be trapped by an alkene to give a cyclopropane. Till 1960, it was widespread that carbenes are too reactive to be isolated. This was perhaps true for the majority of the carbenes but not for *N*-heterocyclic carbenes. In the early 1960's, Wanzlick was the first who investigated the reactivity and stability of *N*-heterocyclic carbenes.[16] In 1968, Wanzlick *et al.* reported the first application of NHCs as ligands for metal complexes.[17] The field of NHCs remained unattracted by the scientific community for more than twenty years until the discovery of the first stable, isolabe and storable carbene **1** by Arduengo and coworkers in 1991[18] (Scheme 1).



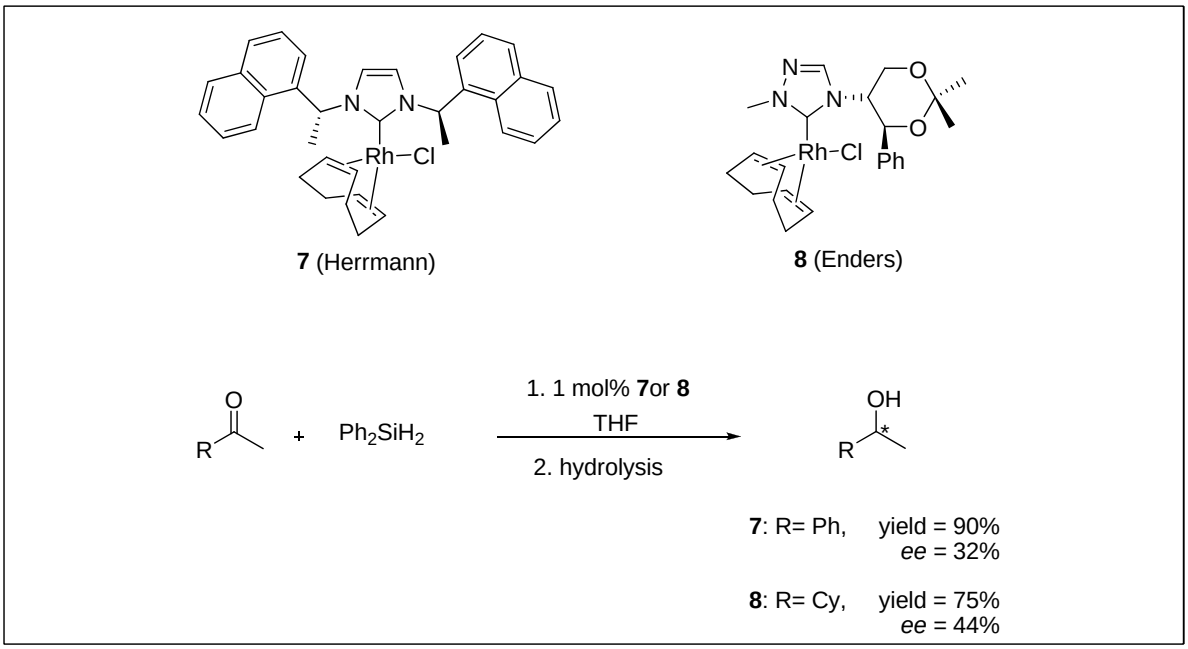
Scheme 1

The next logical extension was obviously the development of a chiral version of these valuable ligands for enantioselective transformations. Although the chiral NHC complexes were reported by Lappert and coworkers[19] in 1983 and employed in stereoselective transformations, yet none of these, fully characterized by NMR and X-ray crystallography. According to the procedure devised by Lappert and coworkers, chiral NHC metal complexes were prepared by first heating an electron rich tetraamine **2** to generate a free NHC which was subsequently *in situ* complexed with the metal ion. Several chiral NHC complexes **3-6** were prepared from chiral tetraaminoethanes, derived from natural amino acids, terpene derivatives or C_2-symmetric diamines by treatment with a variety of rhodium or cobalt complexes (Scheme 2).



Scheme 2

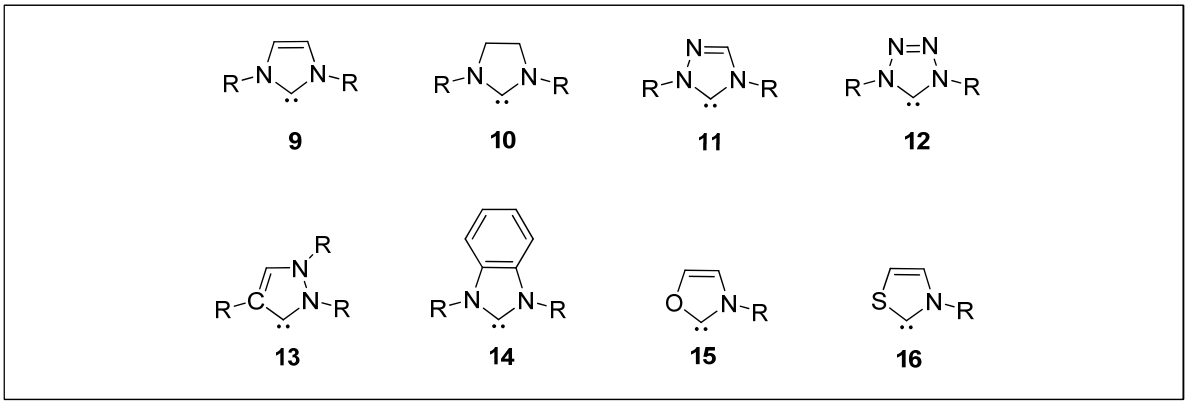
The beginning of asymmetric catalysis was marked by the work of Herrmann[20] and Enders.[21] They prepared chiral NHC complexes and reported the first stereoselective hydrosilylation of acetophenone and cyclohexylmethyl ketone respectively (Scheme 3).



Scheme 3

1.2. Synthesis of Ligand Precursors

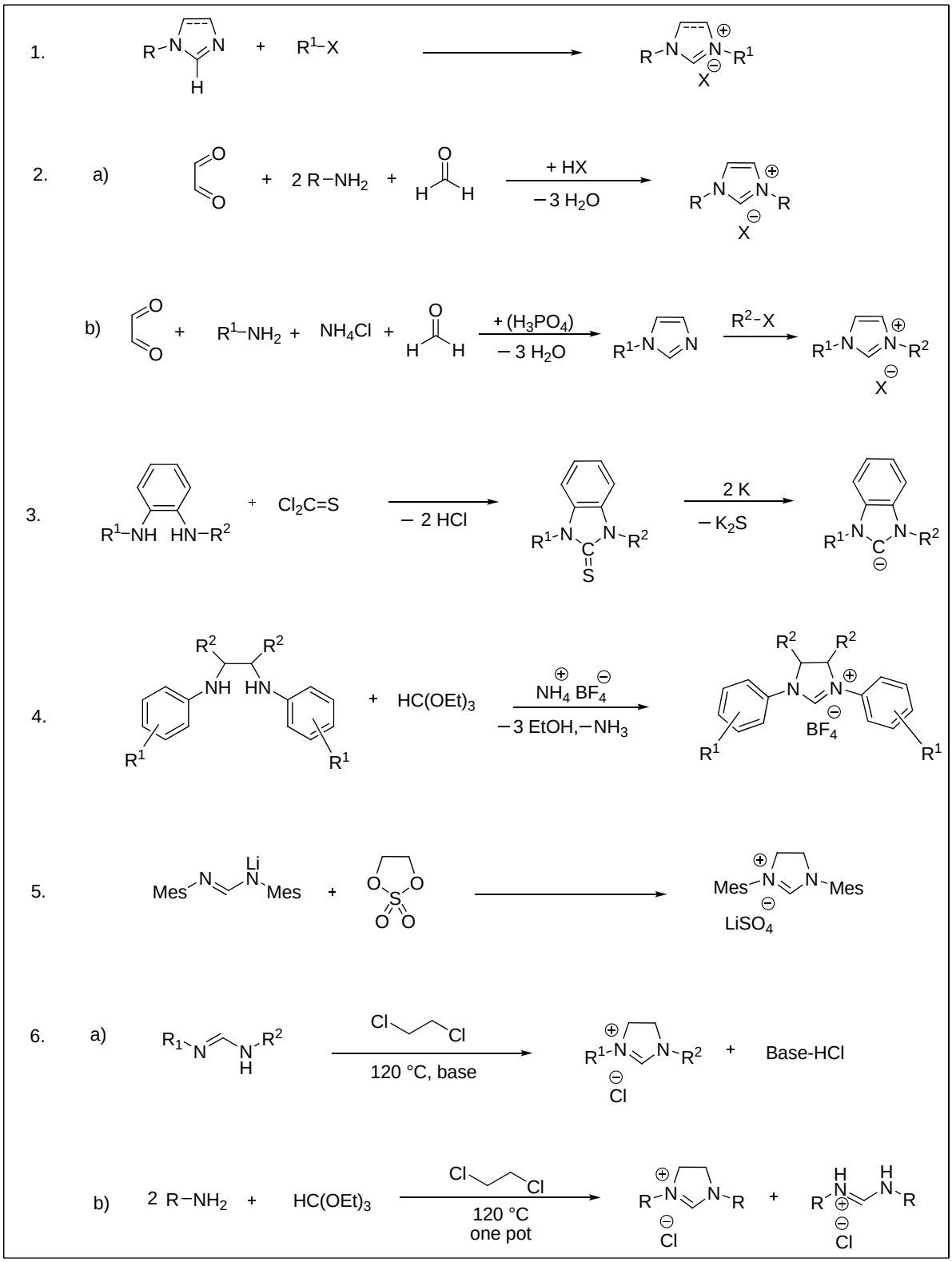
NHCs are often synthesized by deprotonation of the corresponding azolium salts *i.e.* imidazolium, imidazolinium, triazolium, pyrazolium, benzimidazolium, oxazolium and thiazolium salts. The principal classes of NHCs derived from azolium salts are shown in Scheme 4.



Scheme 4

Common routes for the synthesis of azolium salts are described below (Scheme 5):

1. Alkylation of substituted imidazoles/imidazolines with alkyl/aryl halides.


1.
2. a)
b)
3.
4.
5.
6. a)
b)
+ HX
− 3 H2O
+ (H3PO4)
− 3 H2O
R2−X
− 2 HCl
2 K
− K2S
NH4 BF4
−3 EtOH,−NH3
LiSO4
Base-HCl
120 °C, base
120 °C
one pot

Scheme 5

2. One pot condensation of primary amines, glyoxal and paraformaldehyde to prepare symmetrical imidazolium salts. Unsymmetrical imidazolium salts can also be synthesized by condensing one molecule of primary amine with glyoxal and paraformaldehyde and then quaternization of one nitrogen atom by treating with an alkyl halide.

3. By desulfuration of cyclic thiourea derivatives which requires drastic conditions.[22]

4. The *ortho*formate route permits the formation of symmetrical or unsymmetrical imidazolinium salts form *N, N′*-disubstituted 1, 2-diamines under acidic conditions.[23]

5. By the addition of *bis*-electrophiles to lithiated formamidines for the formation of five-, six-, and seven-membered imidazolinium salts.[24]

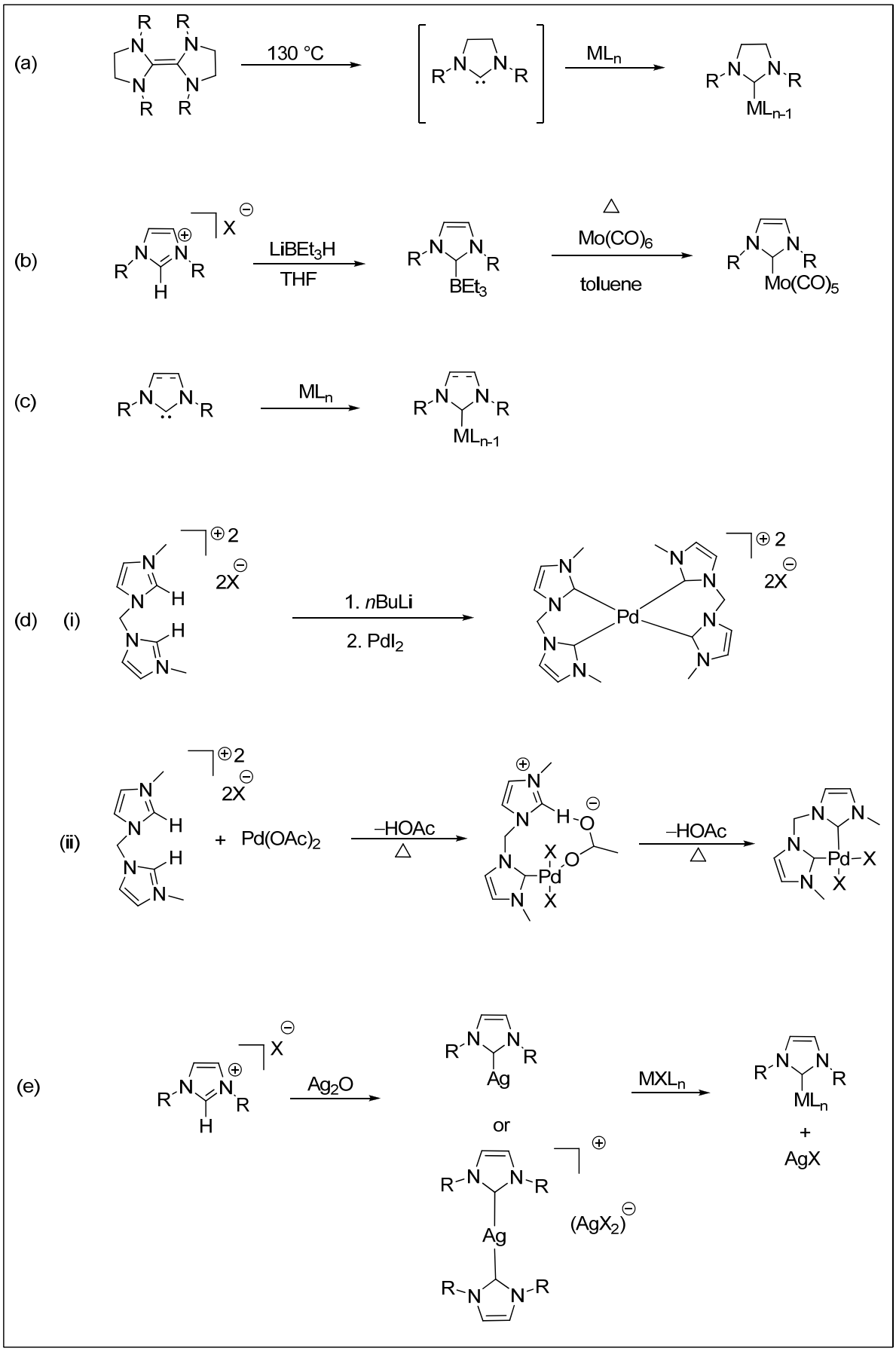
6. Recently, Grubbs and Kuhn developed a new strategy for the synthesis of imidazolinium chlorides by the reaction of formamidines with dichloroethane in the presence of a base. Secondly, this methodology is also applied for the synthesis of symmetric imidazolinium chlorides in a one-step three-component procedure from substituted anilines.[25]

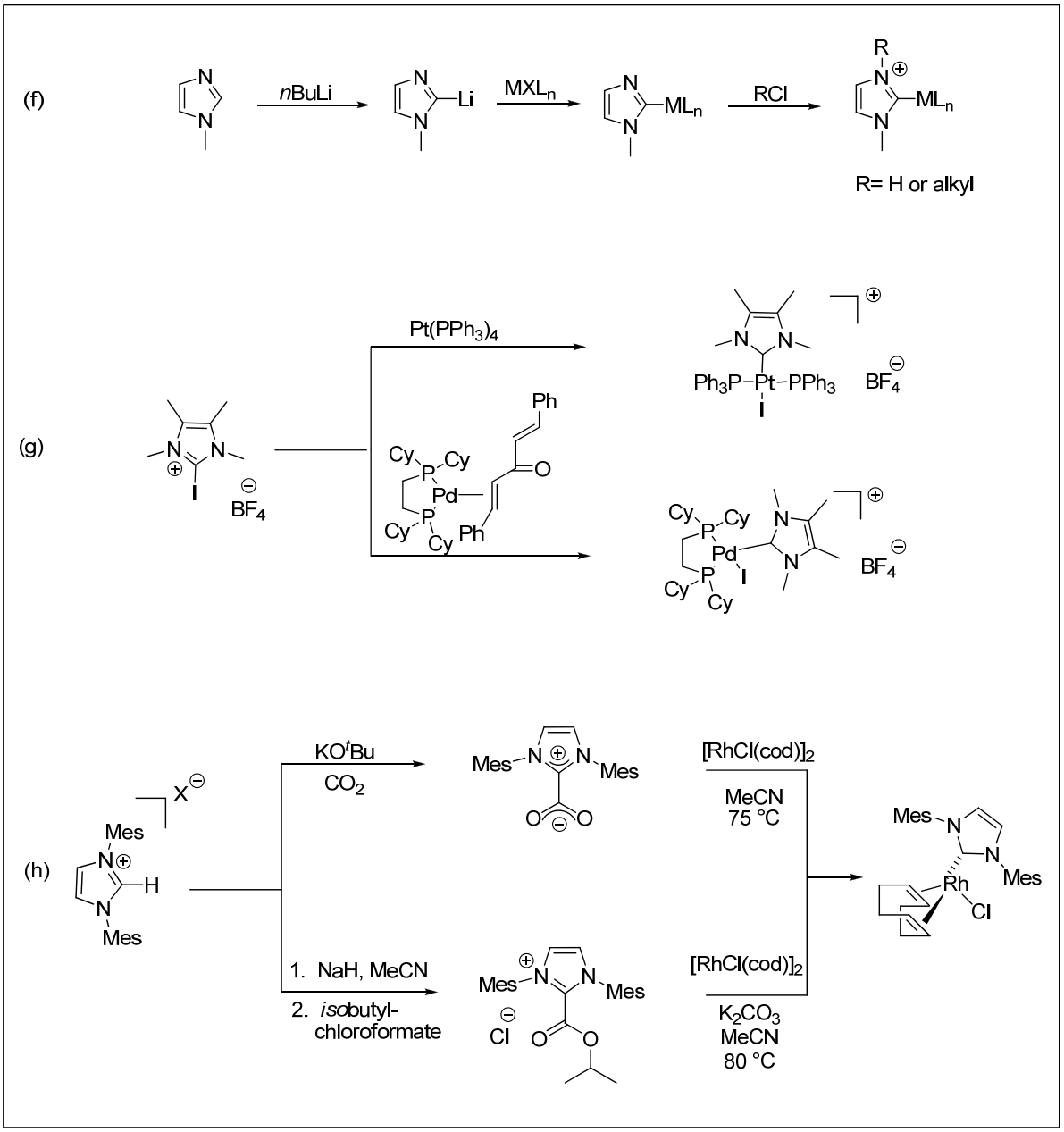
1.3. Synthesis of NHC Complexes

For the complexation of NHCs with different metallic salts, following routes are being employed extensively (Scheme 6):

a. Insertion of metals into electron rich C=C bond of olefins. This method was employed by Lappert and his coworkers.[19] The thermal cleavage is performed with electron rich alkenes and saturated NHCs are obtained in this way.

b. An NHC-borane adduct can be used as a versatile stable synthon for the preparation of NHC complexes.[26]


(a)
130 °C
MLn
MLn-1
(b)
LiBEt3H
THF
BEt3
Mo(CO)6
toluene
Mo(CO)5
(c)
MLn
MLn-1
(d)
(i)
2X
1. nBuLi
2. PdI2
Pd
(ii)
+ Pd(OAc)2
–HOAc
–HOAc
(e)
Ag2O
Ag
or
(AgX2)
MXLn
MLn
+
AgX



Scheme 6

c. Metal complexes are also made from isolated free carbenes since these carbenes are sterically as well as electronically stable. The ability of these carbenes to replace labile ligands is a big advantage in coordination chemistry.

d. *In situ* deprotonation of azolium salt can be carried out by two ways: (i) either with an external base. Mono, bis and tridentate NHC ligands have been prepared in this way or (ii) deprotonation of azolium salt can be carried out by a metal

complex containing basic ligands like acetate, hydride, or acetylacetonate ligands. This method is very convenient for the preparation of NHC complexes.

e. Another convenient method was developed by Lin's group.[27] According to this method, a silver-NHC complex was first synthesized and then transmetallated with several other metals. A weak NHC-Ag bond makes this reagent a good transfer agent. This method is helpful when the deprotonation route is not working due to the presence of other acidic protons in the azolium NHC precursor in addition to azolinium C2-H. This method also avoids complicated workups. Complexes are made with Au, Cu, Ni, Pd, Pt, Rh, Ir or Ru. The driving force for the metal exchange reaction is the lability of the NHC-Ag bond and insolubility of the silver halide.

f. Another less utilized method of complex formation is the transmetallation with lithiated heterocycles.[28]

g. NHC complex formation is also carried out by activation of C2-X bond (X= Me, halogen or H).[29]

h. Another method has been reported by Crabtree and coworkers. in 2005 in which after deprotonation, a C2-carboxylate or ester is formed followed by decarboxylation and coordination with rhodium to form a complex.[30]

1.4. Development and Design of Chiral NHCs

Structure-property relationship to control the enantioselectivity of catalytic transformations is not well established for NHCs, however some general concepts may be employed to explain the enantiocontrol. For example, the presence of a C_2-symmetric axis within the ligand framework can help to reduce the possible competing diastereomeric transition states that play a crucial role in the stereoselective induction.[31] Systematic screening of small ligand libraries to improve the enantioselectivity is also required.[32] As NHC ligands are the logical extension of phosphine ligands, therefore, designing of NHC ligands may be inspired from phosphines. However, Burgess *et al.*[32] noted that design of NHC ligands being topologically different from chiral diphosphines can not be made on

similar lines. For example, aromatic substituents of chiral diarylphosphines have an "edge to face" orientation[33] which is impossible with the molecular architecture of an NHC as it has a planar chelation site. As a result, replacement of a phosphorus unit by NHC in well-defined useful phosphine derivatized ligands is not necessarily fruitful.

1.5. Major Families of NHCs

Depending upon the nature and the relative position of the chiral motif in the carbene framework, NHCs can be categorized into the following major families:

1.5.1. NHCs with *N*-Substituents Containing Centres of Chirality

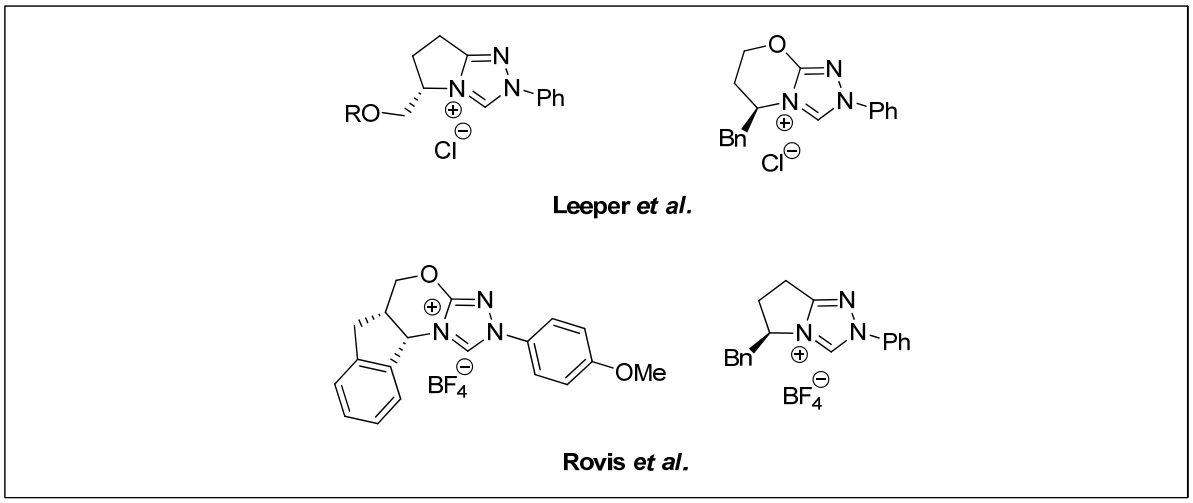
The first strategy which has been chased in the design of chiral NHCs is the introduction of *N*-substituents containing chiral centres. In 1996, Herrmann and Enders developed first chiral NHCs of this type. A symmetric imidazolium salt was synthesized from an enantiopure chiral amine by following a multicomponent condensation reaction.[20] The NHC precursor was coordinated to rhodium (I) and then the complex **7** was tested in the hydrosilylation of acetophenone. The new catalysts showed good activity but low stereoselectivity (see Scheme 3).

Then Enders *et al*.[21] made a nonsymmetrical triazloinylidene ligand containing a single chiral *N*-substituent. Its rhodium complex **8**, consisting of a mixture of diastereomers, furnished low to moderate enantioselectivity, when employed in the hydrosilylation of methyl ketones (see Scheme 3).

The poor enantioselectivity of these types of ligands is due to free rotation of the chiral substituents around the C-N axis and flexibility of the substituents. By surmounting this shortcoming, Leeper's group[34] has developed a new type of ligand *i.e*. triazolinylidene with a bicyclic moiety. Sterically demanding substituents are blocking the internal rotation around the N-C (substituents) axis. These ligands when employed as organocatalysts in benzoin condensations gave an excellent *ee* of 82%. A similar type of ligands developed by Rovis *et al*.[35] afforded very high enantioselectivity in the Stetter reaction (Scheme 7).

Later on, this class of ligands was further elaborated and stereogenic centres have also been introduced in the side chain remote from the carbon joined to the *N*-atoms of the ring.

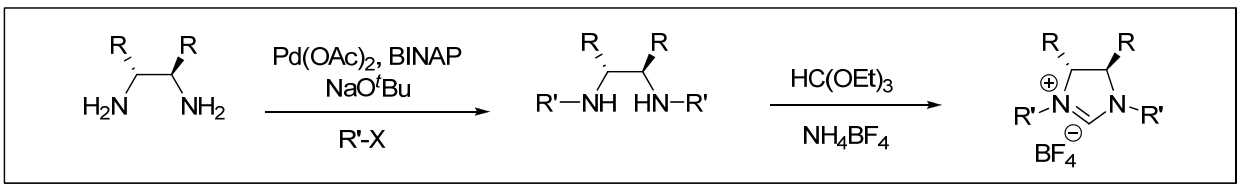
These side chains may contain some additional coordinating groups, thus introducing a new class of functionalized *N*-heterocyclic carbene precursors.[36]



Scheme 7

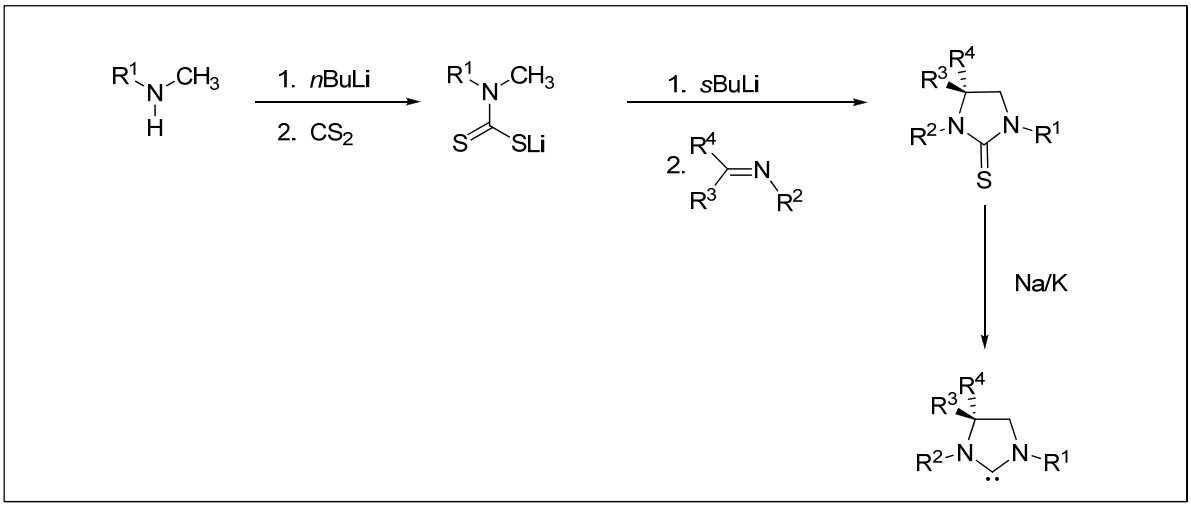
1.5.2. NHCs Containing Chiral Elements within the *N*-Heterocycle

The second strategy for the synthesis of chiral NHCs involves the introduction of chiral centres at the backbone of an imidazolium ring. The chiral information is transferred at the metal centre by means of two *N*-substituents. These imidazolinium carbene precursors are synthesized from C_2-symmetric chiral vicinal diamines as shown in Scheme 8.



Scheme 8

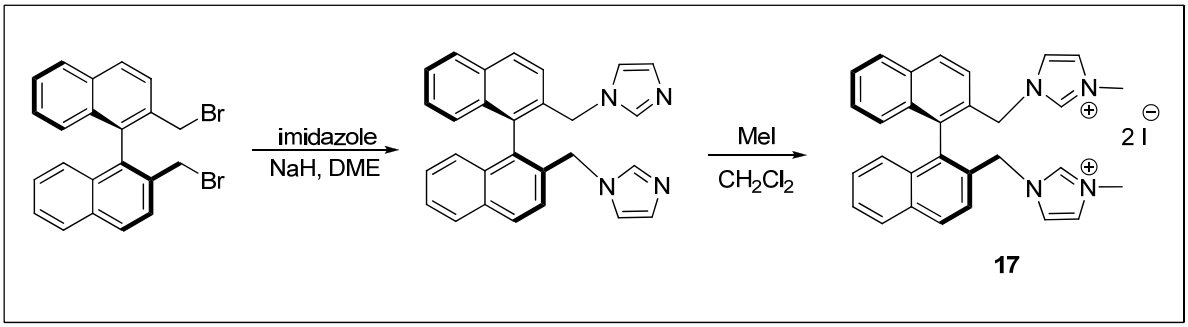
The chiral NHC ligands synthesized by this strategy have been largely investigated in the alkylation of α-enones,[37, 38] stereoselective ring closing metathesis of olefins,[39] Pd(II) catalyzed aerobic oxidation of secondary alcohols to corresponding ketones.[40] In most of the reactions, the ligands gave excellent *ee*s. A recent contribution was made in developing a new strategy for the synthesis of non-symmetrical imidazolylidenes by the reaction sequence shown in Scheme 9.



Scheme 9

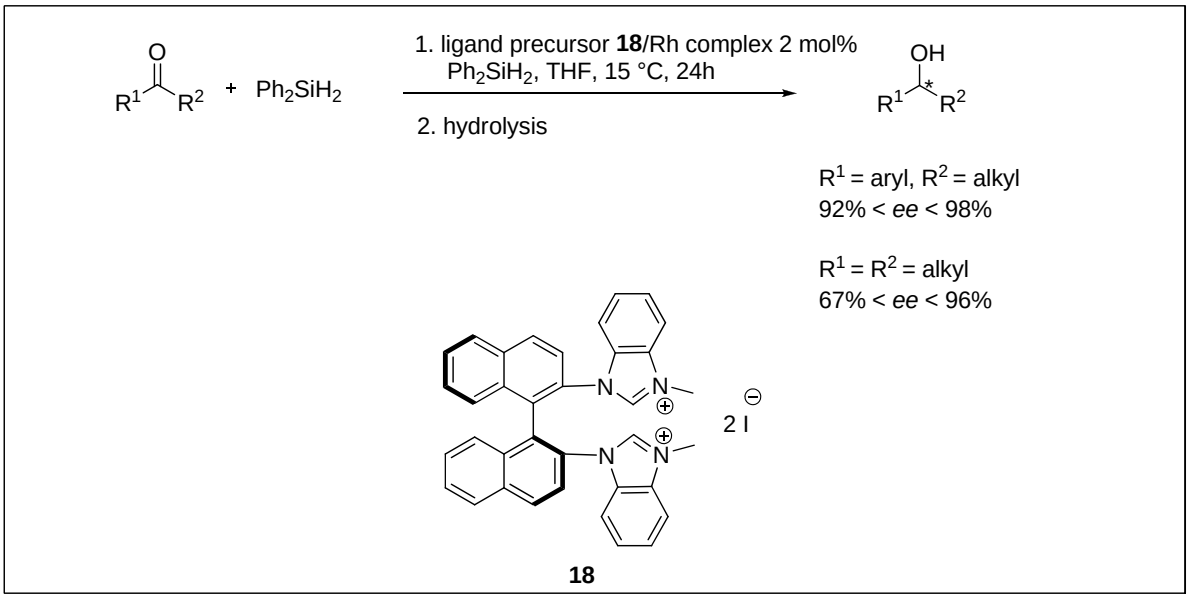
1.5.3. NHCs Ligands Containing an Element of Axial Chirality

The 1,1´-binaphthyl unit is among the most widely used structural moiety for the design of chiral ligands. Asymmetric induction from these types of chiral ligands is due to the configurationally stable atropisomers formed as a result of the blocked rotation around the C-C axis linking the two naphthyl groups.[41] The first chiral NHC containing a 1,1´-binaphthyl unit as chiral entity was synthesized (Scheme 10) in the group of Rajanbabu in 2000.[42] This ligand **17** can be complexed with palladium by refluxing in DMSO. However, due to great flexibility of the ligand, no reports of its stereoselective catalysis have been published.



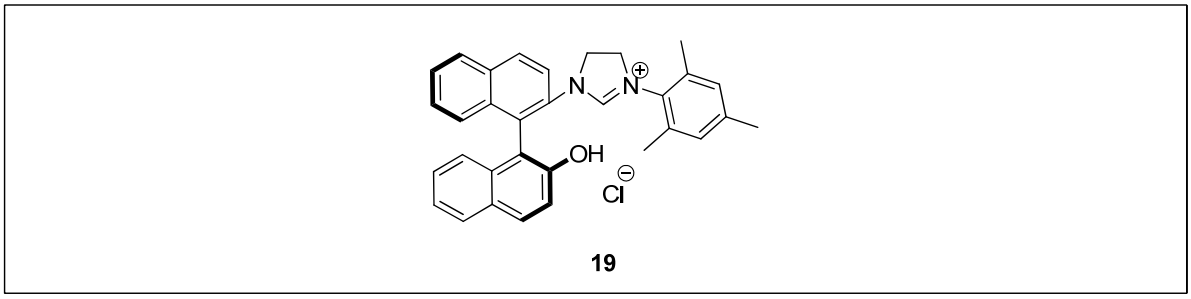
Scheme 10

Min Shi and coworkers have prepared a bis-carbene ligand **18** possessing greater structural rigidity.[43] The rhodium complex of the ligand **18** has been employed in asymmetric hydrosilylation of ketones, displaying good activity and an excellent level of enantioselectivity (Scheme 11).



Scheme 11

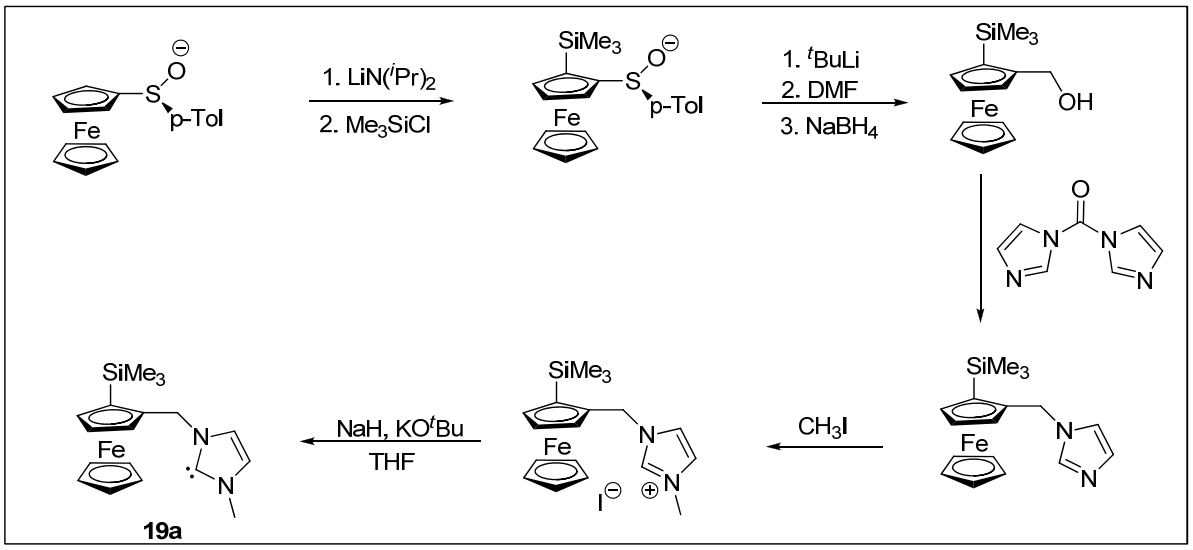
In 2002, Hoveyda *et al.* published the synthesis of chiral anionic bidentate carbene ligand **19** having NHC unit with a phenolate donor and its use in asymmetric olefin metathesis[44] (Scheme 12).



Scheme 12

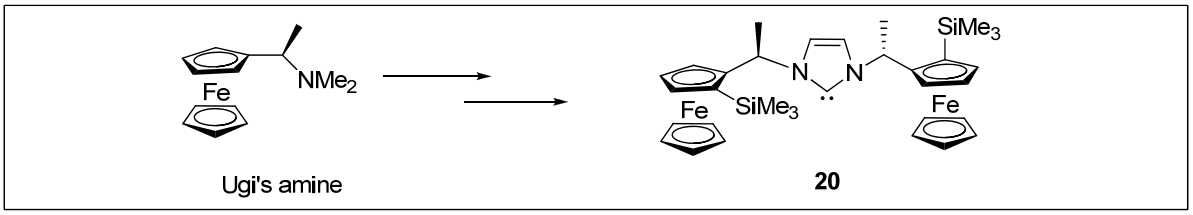
1.5.4. Carbenes Containing an Element of Planar Chirality

Ligands prepared by Togni[45] and Fu[46] containing elements of planar chirality in particular ferrocene derivatives have been used both in organocatalysis and transition metal complexes. The first planar chiral NHC ligand was reported by Bolm *et al.* in 2002.[47] The preparation of this ligand involves the conversion of a chiral sulfoxide to a hydroxymethyl unit. With the aid of *N*-*N*-carbonyl imidazole, an azole ring is introduced and subsequently quaternized with methyl iodide to give the imidazolium ligand precursor (Scheme 13). The ligand **19a** gave no enantioselectivity when employed in the hydrosilylation of ketones.



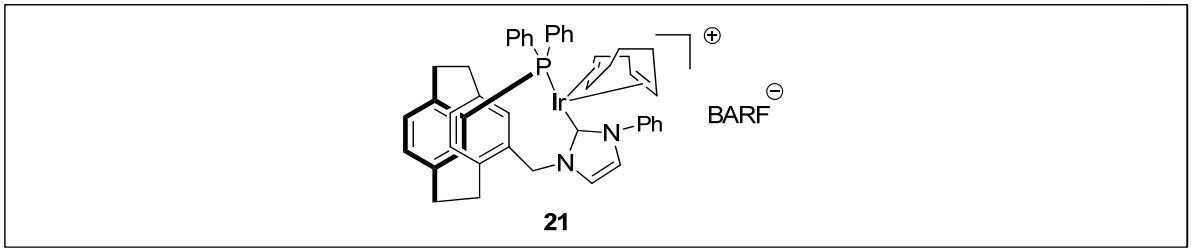
Scheme 13

Later Togni *et al*. reported the synthesis of C_2-symmetric chiral carbene ligand **20**.[48] Two types of chiral elements, planar chirality in the ferrocenyl units and chiral centres at the carbon linking ferrocene with the *N*-heterocycle are present in this ligand (Scheme 14). So far there are no reports of its use in asymmetric catalysis.



Scheme 14

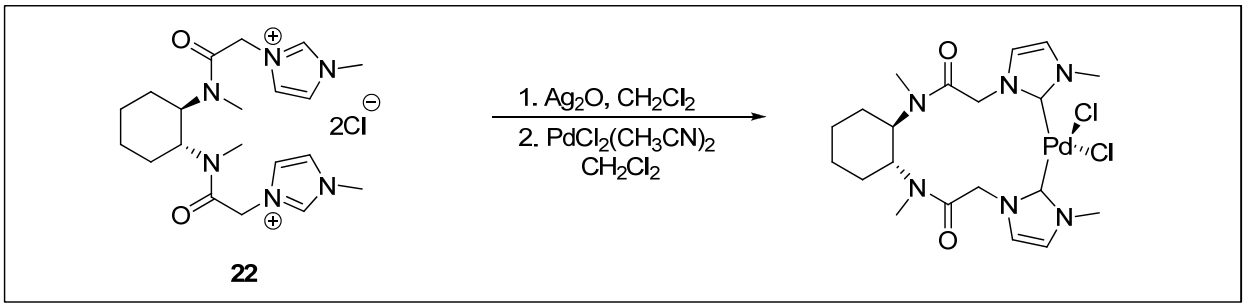
Bolm *et al.* have reported the synthesis of iridium complexes in which a bidentate carbene phosphine ligand contains a chiral pseudo-*ortho*-[2,2]paracyclophane unit (Scheme 15). These complexes were investigated for the asymmetric hydrogenation[49] giving an *ee* of 82%.



Scheme 15

1.5.5. Carbenes Joined by a Chiral *trans*-Cyclohexanediamine Ligand Backbone

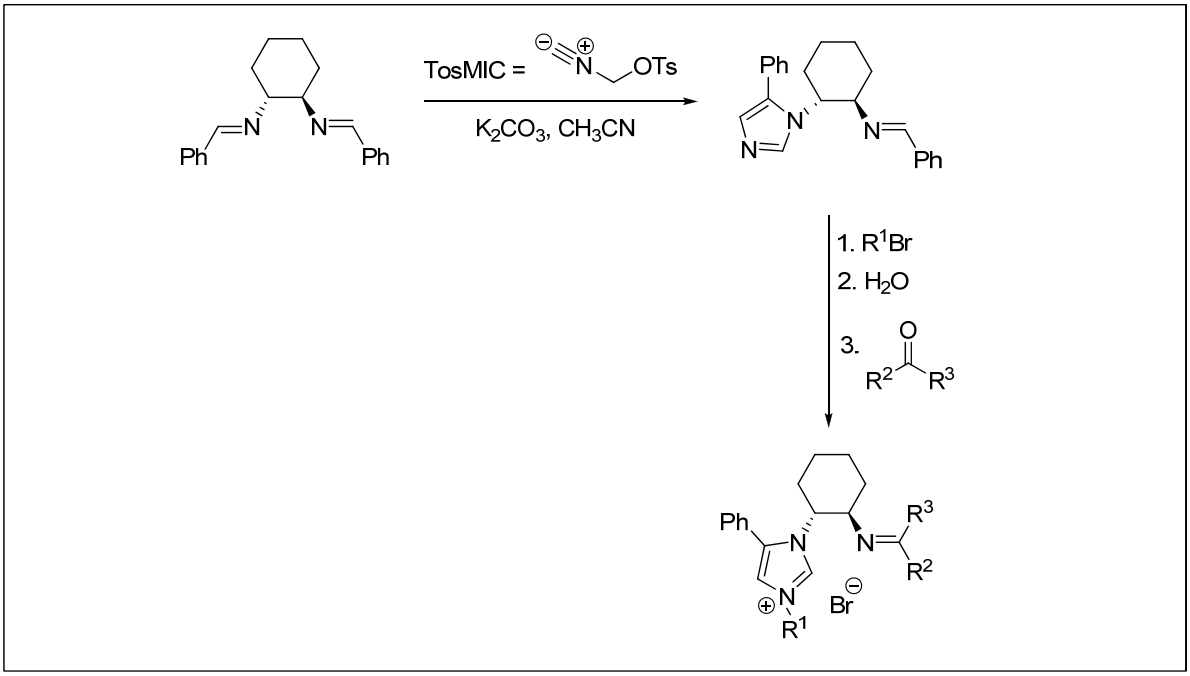
Inspired from previously synthesized chiral salen ligands from enantiopure *trans*-1,2-diaminocyclohexane and its application in Jacobsen's epoxidation catalysis,[50] researchers started the synthesis of NHCs containing a *trans*-cyclohexanediamine backbone. Burgess's group has synthesized the ligand **22** and then made its Pd complex (Scheme 16), but no application has been reported so far.[51]



22

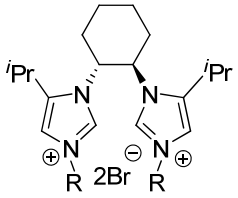
Scheme 16

Later on, Douthwaite *et al.*[52] reported the synthesis of an NHC ligand precursor as shown in Scheme 17 which is attached with an imine with the help of *trans*-cyclohexanediamine



Scheme 17

The carbene derived from this precursor was tested in a palladium catalyzed allylic alkylation giving an *ee* of 92% at 50 °C. The C_2-symmetric bis-imidazolinium salt **23** has been synthesized by the same group[53] and it's palladium complex showed a poor enantioselectivity of 11% in the arylation of amides.

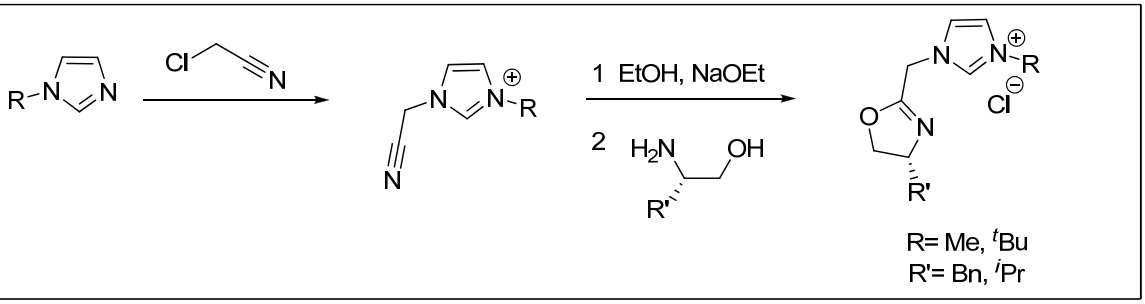


23

Scheme 18

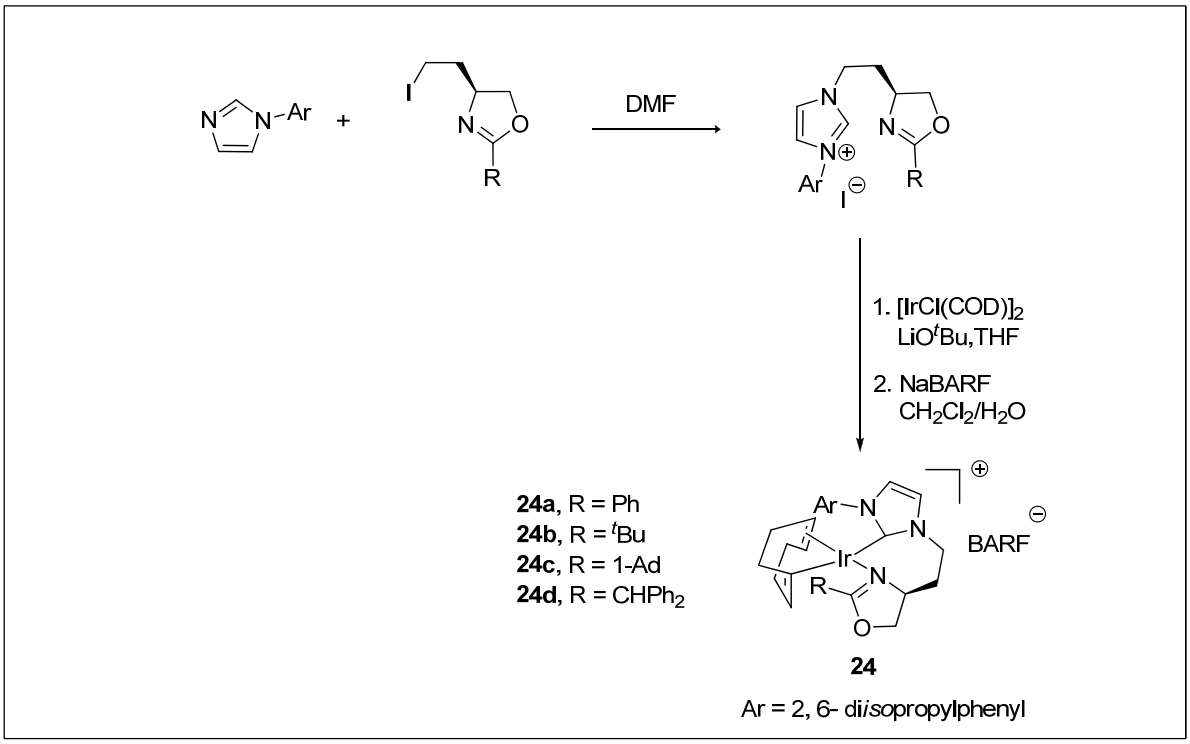
1.5.6. NHCs Incorporating Oxazoline Units

The oxazoline ring has attained the attention due to its rigidity, quasi-planarity, and furthermore its easy accessibility by condensation of an amino alcohol with a carboxylic acid derivative.[54] The first chiral carbene containing an oxazoline unit has been reported by Herrmann *et al.* in 1998.[55] The synthesis involves an acid-catalyzed cyclization of the oxazoline by reaction of an iminoester, formed *in situ* from a nitrile, and an amino alcohol (Scheme 19). A rhodium (I) complex of this NHC ligand was prepared and then employed in the hydrosilylation of ketones giving the secondary alcohols with moderate enantioselectivity (*ee* up to 70%).



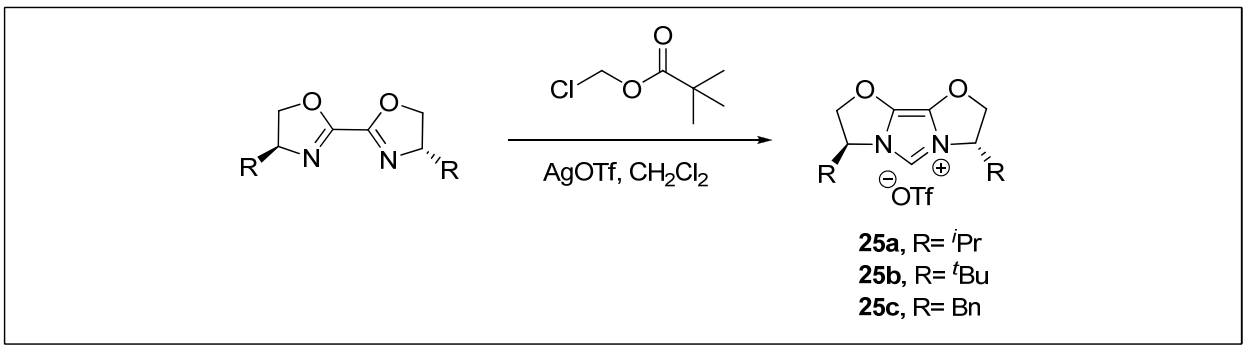
Scheme 19

Burgess *et al.* employed iridium complexes **24a-24d** incorporating differently substituted oxazoline units in the asymmetric hydrogenation of *E*-1,2-diphenylpropene displaying a maximum *ee* of 98% with a yield of 99% (Scheme 20).[56]



Scheme 20

Glorius *et al.* reported the synthesis of imidazolinium salts **25a-25c** by cyclizing bis-oxazolines (Scheme 21).[57]



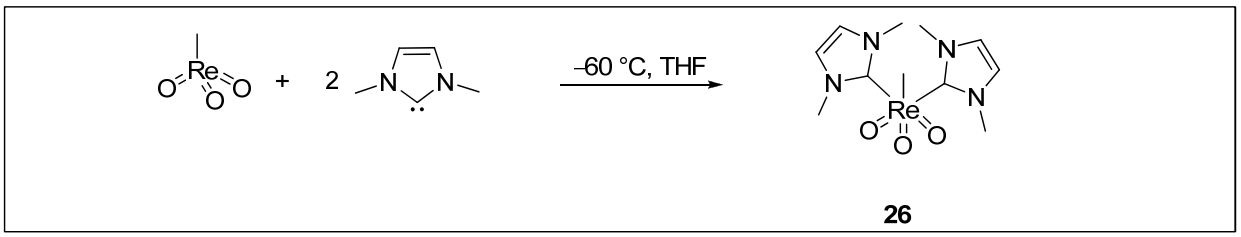
Scheme 21

1.6. Catalysis

NHCs have almost surpassed phosphine based metal catalysis both in activity and scope of applications except asymmetric applications. This is due to the certain features that NHCs display as transition metal ligands such as resistance towards dissociation, easy accessibility and tunability of the molecular architecture.[3] *N*-Heterocyclic carbenes show promising results in oxidation chemistry.

1.6.1. NHCs and High Oxidation State Metals

In 1994, Herrmann *et al*. published results that described the use of NHCs as ligands for stabilizing high oxidation state metals.[58] This was an indication of future applications of NHCs as ligands in organometallic homogenous catalysis. The formation of rhenium complex **26** containing an NHC ligand, which is stable below –20 °C is shown in Scheme 22. The complex **26** is not prone to oxidation whereas to triphenylphospanes eliminate an oxygen ligand from CH_3ReO_3 to yield phosphane oxides with a concomitant reduction of the metal (from Re(VII) to Re(V)).



Scheme 22

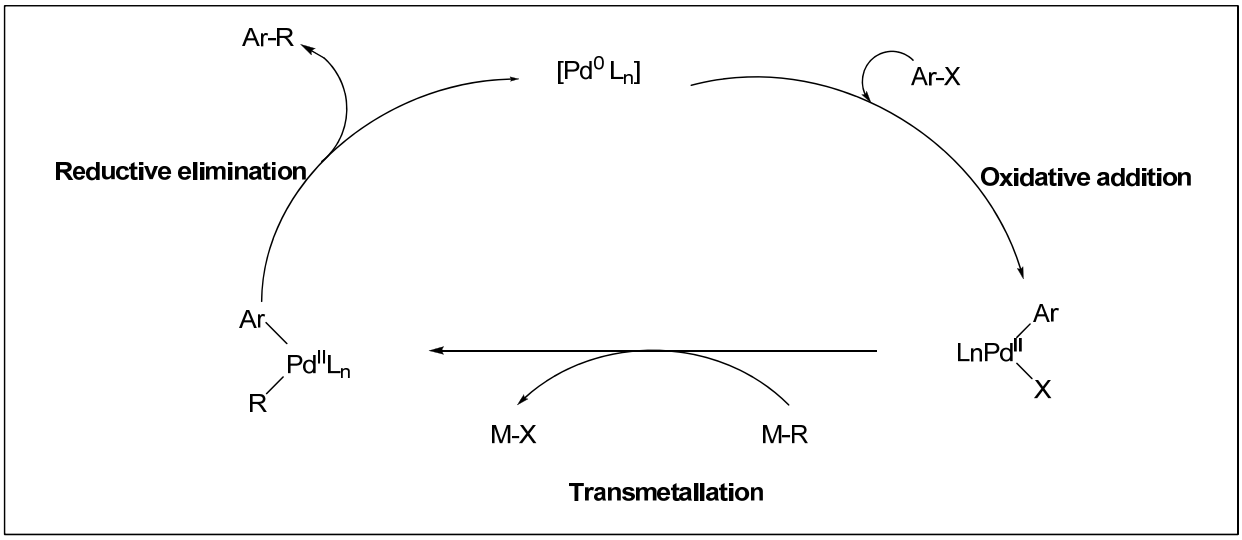
Independent studies carried out by Stahl and Kawashima[59, 60, 61] show that NHCs are playing a role as stabilizing ligands in palladium oxidation reactions. These stable complexes relative to phosphine complexes are quite helpful in further investigation of these fundamental reactions.

1.6.2. Cross Coupling Reactions

Cross coupling reactions are extensively applied to form carbon-carbon and carbon-nitrogen bonds. Palladium complexes incorporating different types of ligands are useful for various transformations. The emergence of *N*-heterocyclic carbenes produces stable metal catalysts especially with palladium.

In general, palladium catalyzed cross coupling reactions proceed *via* a three step cycle (Scheme 23). The first step involves an oxidative addition reaction of an aryl halide with Pd(0). Next follows a transmetallation step in which a nucleophile is attached to the palladium complex. The last step is a reductive elimination in which the product is eliminated and Pd(II) is reduced to Pd(0), thus ready to take part again in the catalytic cycle. The rate determining step depends mainly on the nature of aryl halides. For instance, the

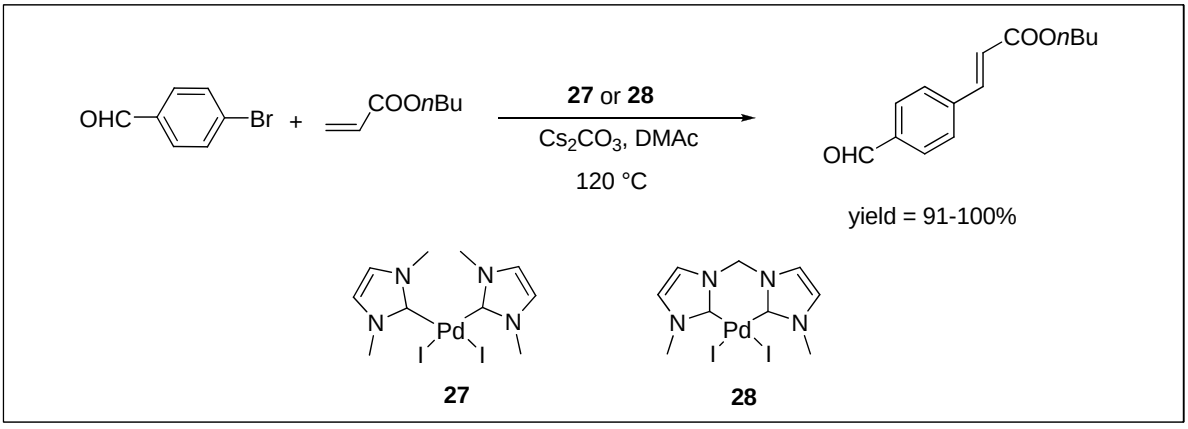
oxidative addition is the rate limiting step in the cases of aryl chlorides and unactivated aryl bromides.



Scheme 23

1.6.3. Heck Reaction

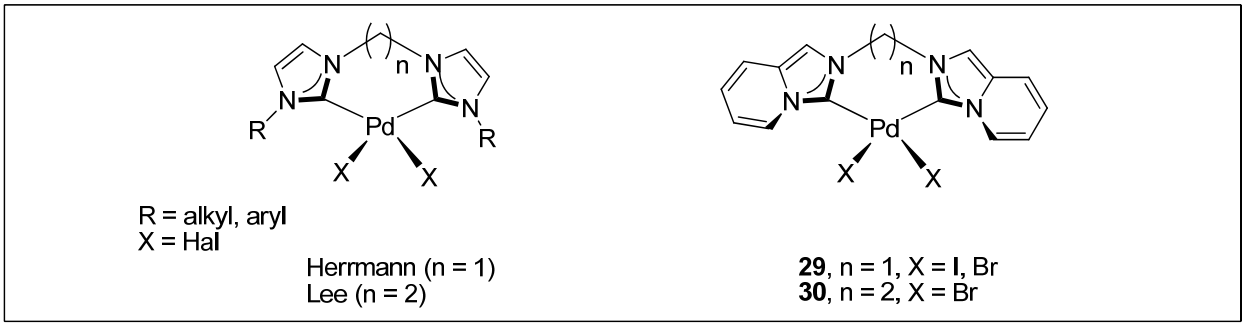
The first catalytic application of Pd-NHC complexes has been reported by Herrmann *et al.* in 1995.[62] This was the beginning of new palladium systems to be discovered later on. The carbene palladium complexes **27** and **28** have been prepared from $Pd(OAc)_2$ and then employed in Heck reactions involving the coupling of aryl halides. The results obtained were quite promising in terms of yield and turnover number of the catalyst (Scheme 24).



Scheme 24

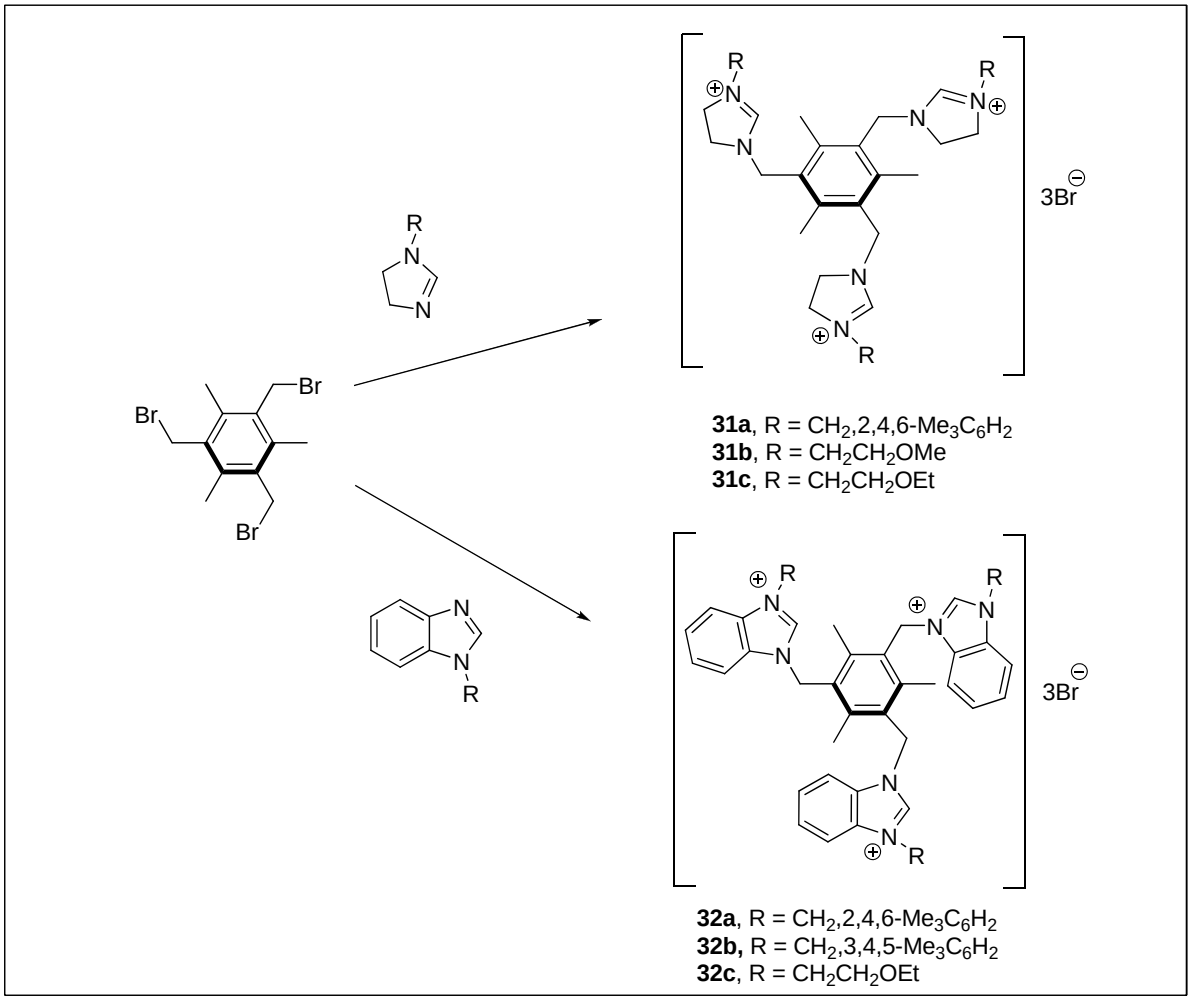
Recently, Kunz *et al.*[63] have synthesized new bidentate imidazopyridine palladium complexes **29** and **30** analogous to the well established bis(imidazolylidenes) ligand system

previously introduced by Öfele and Herrmann *et al.*[64] (Scheme 25). These newly formed palladium complexes were found to be active catalysts in Heck cross-coupling reaction of arylhalides and *n*-butylacrylate.



Scheme 25

Next, tridentate imidazolinium and benzimidazolium carbene precursors **31** and **32** have been synthesized by simple alkylation of imidazoles (Scheme 26).

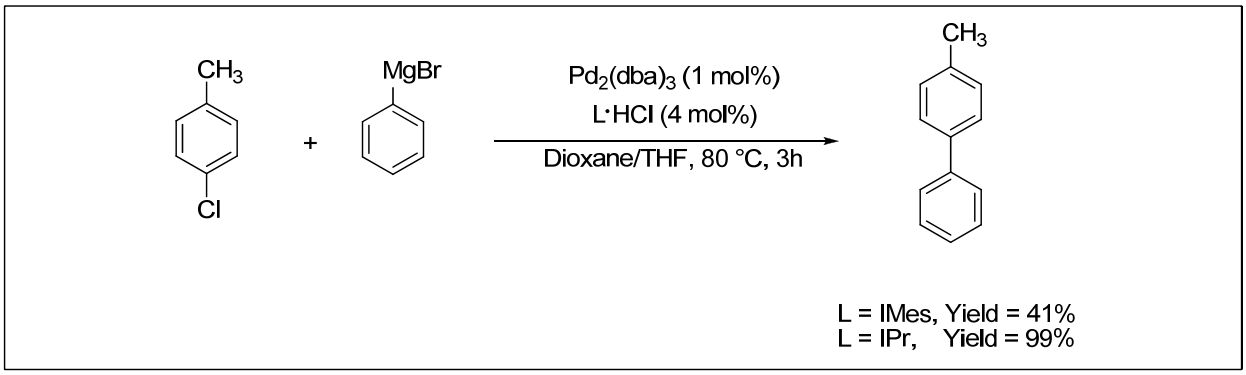


Scheme 26

The *in situ* generated tridentate *N*-heterocyclic carbene ligand/$Pd(OAc)_2$ complex has comparable activity to monodentate imidazolinium/$Pd(OAc)_2$ systems.[65] Another highly efficient catalytic system for the Heck reaction of aryl iodides and bromides with acrylates has been developed combining *N*-heterocyclic carbene ligands IMes·HCl or IPr·HCl *etc.* with $Ni(acac)_2$.[66] With this catalytic system, the reaction parameters such as temperature and duration are crucial for the yield. A high temperature is required for the reaction to be completed in 3h. The reaction works well without any reductant.

1.6.4. Kumada Reaction

The first successful coupling reaction of unactivated aryl chlorides with ArMgBr using an *N*-heterocyclic carbene/palladium catalyst system was reported by Nolan *et al*.[67] The protocol employs Pd(0) or Pd(II) complex and an imidazolium chloride as the ligand precursor. It was shown that the bulky carbene ligand from IPr·HCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) gave the product in 99% yield whereas 41% yield was obtained with IMes·HCl (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene) (Scheme 27).

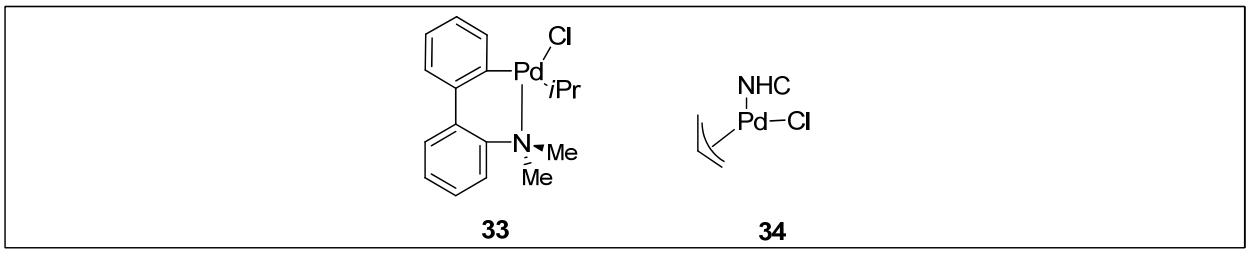


Scheme 27

1.6.5. Suzuki-Miyaura Reaction

This is the coupling of arylboronic acids with aryl halides or triflates. The reaction has been widely used in the synthesis of natural products and pharmaceutical intermediates.[68] Initially, moderate yields were obtained for the coupling of 4-chlorotoluene with phenylboronic acid by employing the catalytic protocol of IMes and $Pd_2(dba)_3$. Then NHC ligands bearing bulky *ortho*-substituted aryl groups on the nitrogen side arm afforded the

highest yields indicating the effectiveness of steric factors on the efficiency of catalytic system.[69] The synthesis of di-and tri-*ortho*-substituted biaryls becomes possible by the usage of (NHC)Pd(palladacycle) **33**.[70] The coupling reaction required a few minutes for completion at room temperature. Another air stable Pd(II) complex **34** containing (IPr) and R-allyl groups shows similar activity as **33**. In this study the catalytic activity was monitored by changing substituents at the allyl moiety of the complex.[71]



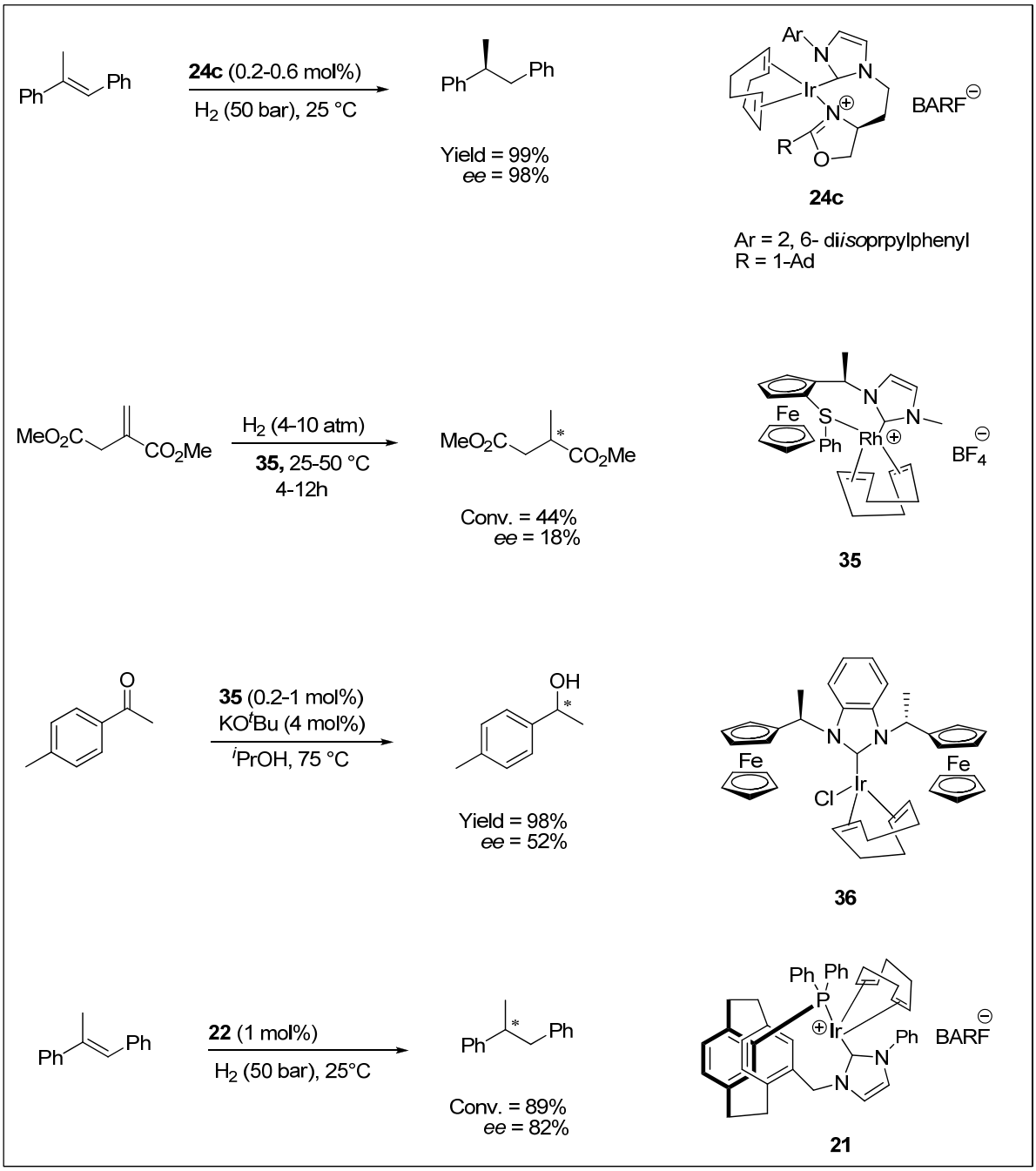
33 **34**

Scheme 28

1.6.6. Asymmetric Hydrogenation

Burgess *et al*. were the first who have applied bidentate oxazoline NHC iridium complexes **24a-d** in asymmetric hydrogenation.[56a] The ligand containing an adamantly oxazoline ring complexed with iridium gave 98% *ee* with a yield of 99% when the hydrogenation of *E*-1,2-diphenylpropene was carried out (Scheme 29). Burgess *et al*. has extended the application of this iridium complex in the hydrogenation of aryl substituted dienes which are relatively difficult to hydrogenate with high enantioselectivity.[56b] This new class of iridium complex enables the hydrogenation at room temperature and ambient pressure of H_2 (Scheme 29).

Chung and coworkers[72] synthesized chiral bidentate ferrocenyl-NHCs having two different elements of chirality, a planar chirality in the ferrocenyl motif possessing a ligating group such as a thioether or a phosphenium and a chiral carbon centre. Prepared from this ligand, the iridium and rhodium complexes were applied in asymmetric hydrogenation. However, the results were not promising as only the rhodium complex **35** gave 18% *ee* of the product. Chung's group also applied the monodentate version of these ferrocenyl based-NHC ligands.[72] The corresponding iridium complex **36** gave a moderate *ee* of 52% when applied in the catalytic transfer hydrogenation of ketones (Scheme 29).



Scheme 29

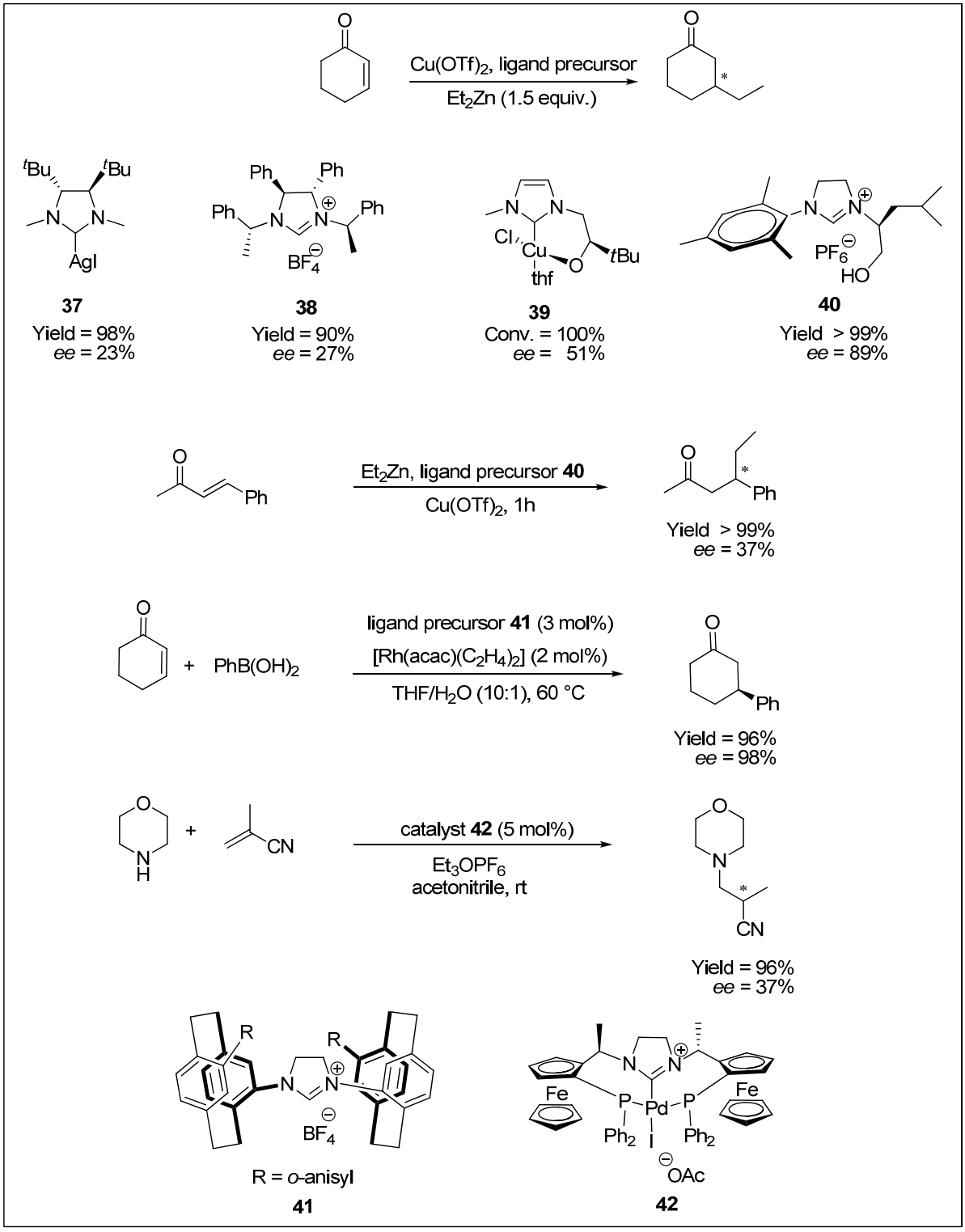
Bolm *et al*.[73] applied iridium complexes, with a planar chiral pseudo-*ortho*-disubstituted paracyclophane skeleton bearing an oxazoline moiety and a imidazolylidene unit, in the hydrogenation of functionalized and simple olefins with low to moderate enantioselectivity. Steric properties of substituents on both chelating units affected the activity of the catalysts. Modification in the structure of the ligand replacing the oxazoline unit with a phosphine substituent resulted in an excellent *ee* of the product (Scheme 29). An efficient catalytic

system with a 1:2 mixture of atropisomers of a rhodium complex containing a bidentate diphenyl-phosphino-imidazolylidene ligand with *ortho*-substituted *N*-aryl substituents in the imidazoline ring has been developed by Helmchen and coworkers.[74] The results are excellent in terms of yield and enantioselectivity of the product.

1.6.7. Asymmetric 1,4-Addition

One of the most powerful method for the formation of C-C bond formation is the 1,4 conjugate addition of nucleophile reagents to unsaturated compounds.[75] The utilization of NHC ligands in a copper catalyzed conjugate addition was first reported by Woodward and coworkers in 2001.[76] Later on, an asymmetric version of this conjugate addition using chiral NHC ligands was reported by Alexakis[37b] and Roland.[37a] Ligand **37** employed by Roland's group contained C_2-symmetry, having chiral centres at the backbone whereas Alexakis's ligand **38** was carrying chiral information at the *N*-substituents as well as at the backbone of the imidazolinium salt. Ligand **37** gave an *ee* of 23% and ligand **38** provided an *ee* of 27% in the 1,4-addition of diethylzinc to cyclohexenone with $Cu(OTf)_2$ as precatalyst. In 2004, first chiral bidentate alkoxy imidazolylidene copper(II) complex **39** was developed and applied in a 1,4-conjugated addition giving an *ee* of 51%.[26] Mauduit made a slight variation of Arnold´s NHC ligand at the stereogenic centre of the side chain. The selectivity of the reaction was improved to 89%. This new class of bidentate alkoxy imidazolylidene ligand **40** was tested for a wide range of enones and dialkylzinc reagents.[77] Unfortunately, the addition to acyclic Michael acceptor did not show promising results (*ee* up to 37%).

Only aliphatic organozinc reagents are added successfully in the copper-catalyzed asymmetric conjugate addition. The introduction of aryl or alkenyl groups is difficult with this copper protocol. Andrus and co-workers applied the chiral monodentate ligand **41** in combination with $[Rh(acac)-(C_2H_4)]$ in the 1,4-asymmetric conjugated addition of phenyl boronic acid to cyclohexenone.[78] The results were excellent in terms of yield and *ee*. The Pd-NHC complex **42,** when tested in the aza-Michael reaction of morpholine onto methylacrylonitrile, gave the amination product in high yield with modest selectivity (37% *ee*).[79]



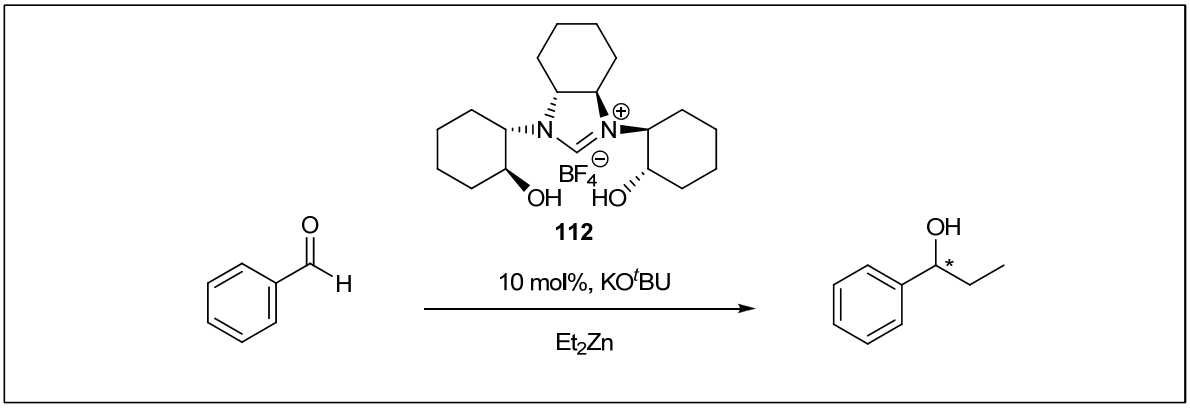
Scheme 30

1.6.8. Asymmetric 1,2-Addition

The asymmetric 1,2-addition to a carbon-oxygen double bond involves a number of reactions like the rhodium catalyzed arylboronic acid addition to aldehydes, rhodium

catalyzed hydrosilylation of ketones and ruthenium catalyzed hydrosilylation of ketones. The diversion from the addition of organolithium and organomagnesium reagents lies in the fact that these reagents are highly sensitive to moisture and thus can not be applied to industrial scale. So far, paracyclophane NHCs,[80] bidentate imidazolium salts,[81] C_2-symmetric imidazoliydene,[20, 82] C_1-symmetric triazoinylidene,[21, 83, 84] biscarbene containing an element of axial chirality and imidazolium salts containing chiral oxazoline groups[85. 86] have been complexed either with rhodium or ruthenium for evaluation in asymmetric 1,2-additions. The results in terms of selectivity are not remarkable indicating potentially still an active area of research.

The diethylzinc addition to aldehydes for the synthesis of optically active secondary alcohols has been extensively studied. Chiral amino alcohols in combination with titanium or zinc are the best entries for this addition. Recently, our group[87] investigated and reported the role of NHCs in diethylzinc addition to aldehydes. Bis-hydroxy imidazolinium carbene precursors have been synthesized from simple amino alcohols. The C_2-symmetric NHC ligand **112** gave 66% *ee* of the product with a yield of 67% (Scheme 31).

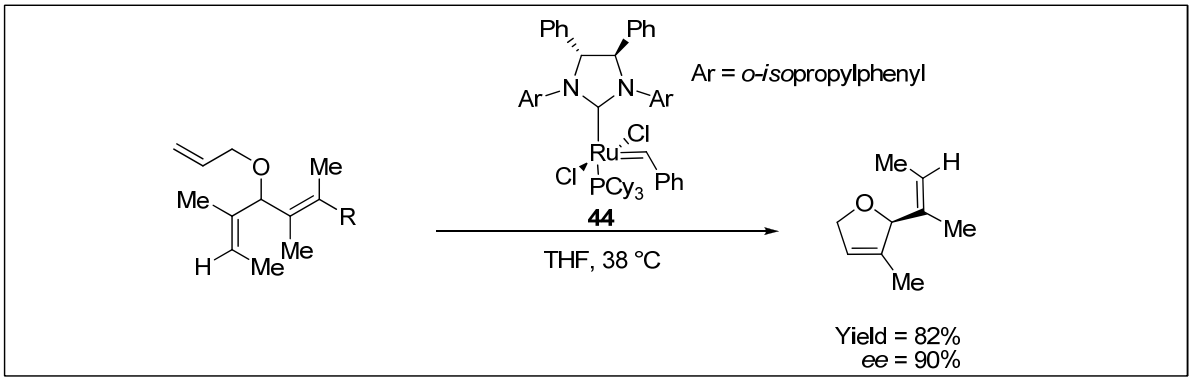


Scheme 31

1.6.9. Asymmetric Olefin Metathesis

The catalytic olefin metathesis permits an easy approach to a wide range of small, medium and large ring carbo- and heterocyclic rings as well as acyclic, unsaturated molecules.[88, 89] The chiral backbone of 1,2-diphenylethylenediamine provides higher enantioselectivities compared with a 1,2-diaminocyclohexane skeleton. Furthermore, replacement of the mesityl group with an *ortho*-monosubstituted *N*-aryl substituents with bulkier iodide improves the enantioselectivity. The first chiral metathesis reaction was

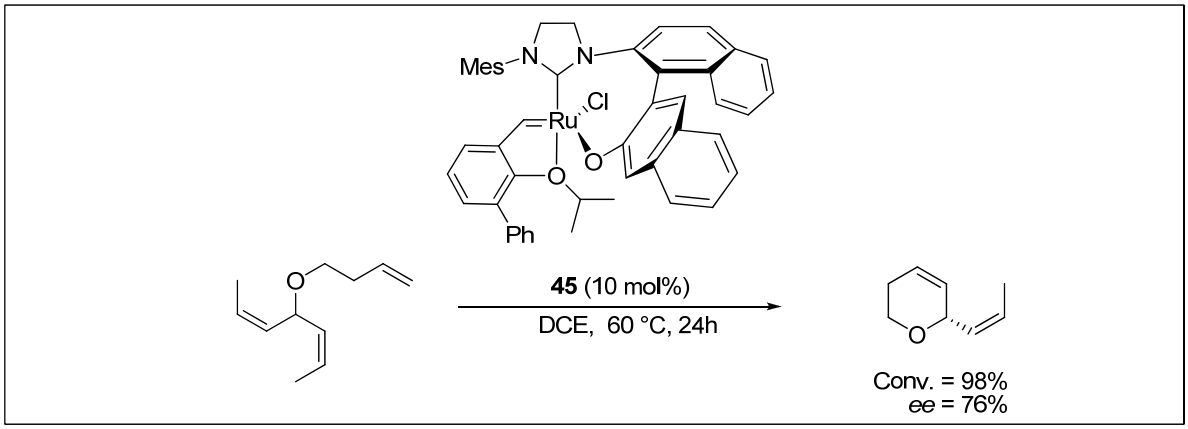
performed by complexes containing molybdenum by Schrock and Hoveyda in 1998.[90] Grubbs and his coworkers have reported the C_2-symmetric chiral NHC-ruthenium complex **44** and its application shown in Scheme 32.[39]



Scheme 32

1.6.10. Asymmetric Ring Closing Metathesis

In the asymmetric ring closing metathesis reaction, catalyst **44** proved to be an excellent and offering an *ee* of 90% (Scheme 32). Hoveyda and coworkers prepared a ruthenium complex **45** containing novel chiral bidentate anionic *N*-heterocyclic carbene ligands containing an element of axial chirality and then applied it in triene desymmetrization reaction.[91, 92] The yield of the product was 98% with 76% *ee* (Scheme 33).

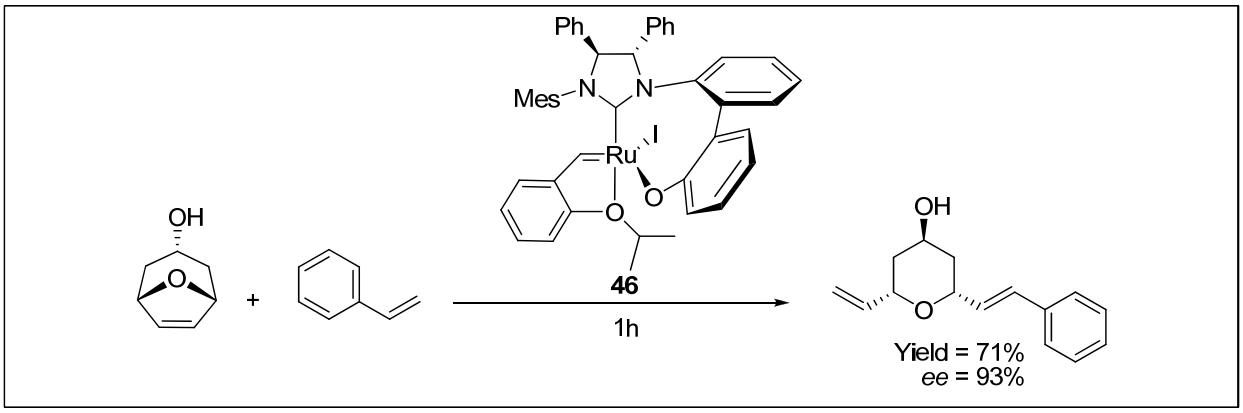


Scheme 33

1.6.11. Asymmetric Ring Opening Metathesis/Cross Metathesis

Chiral NHC-ligands based on an axially chiral binaphthalene skeleton, previously employed in ARCM gave excellent results in asymmetric ring opening metathesis reactions,

comparable to those of chiral Mo-based catalysts. The ruthenium complex having an iodide ion instead of a chloride gave the best results. In 2005, Hoveyda used novel and readily available chiral bidentate NHC ligands using an optically pure 1,2-diphenylethylenediamine skeleton.[93] The Ru catalyst **46** incorporating with a bidentate NHC ligand showed higher *ee* of 93% (Scheme 34). These catalysts used in AROM are air stable and are quite efficient even in undistilled solvents. Moreover, good yields are obtained with compounds which readily polymerize with chiral Mo-catalysts. The recovery of the catalysts by chromatography on silica gel is up to 90%.



Scheme 34

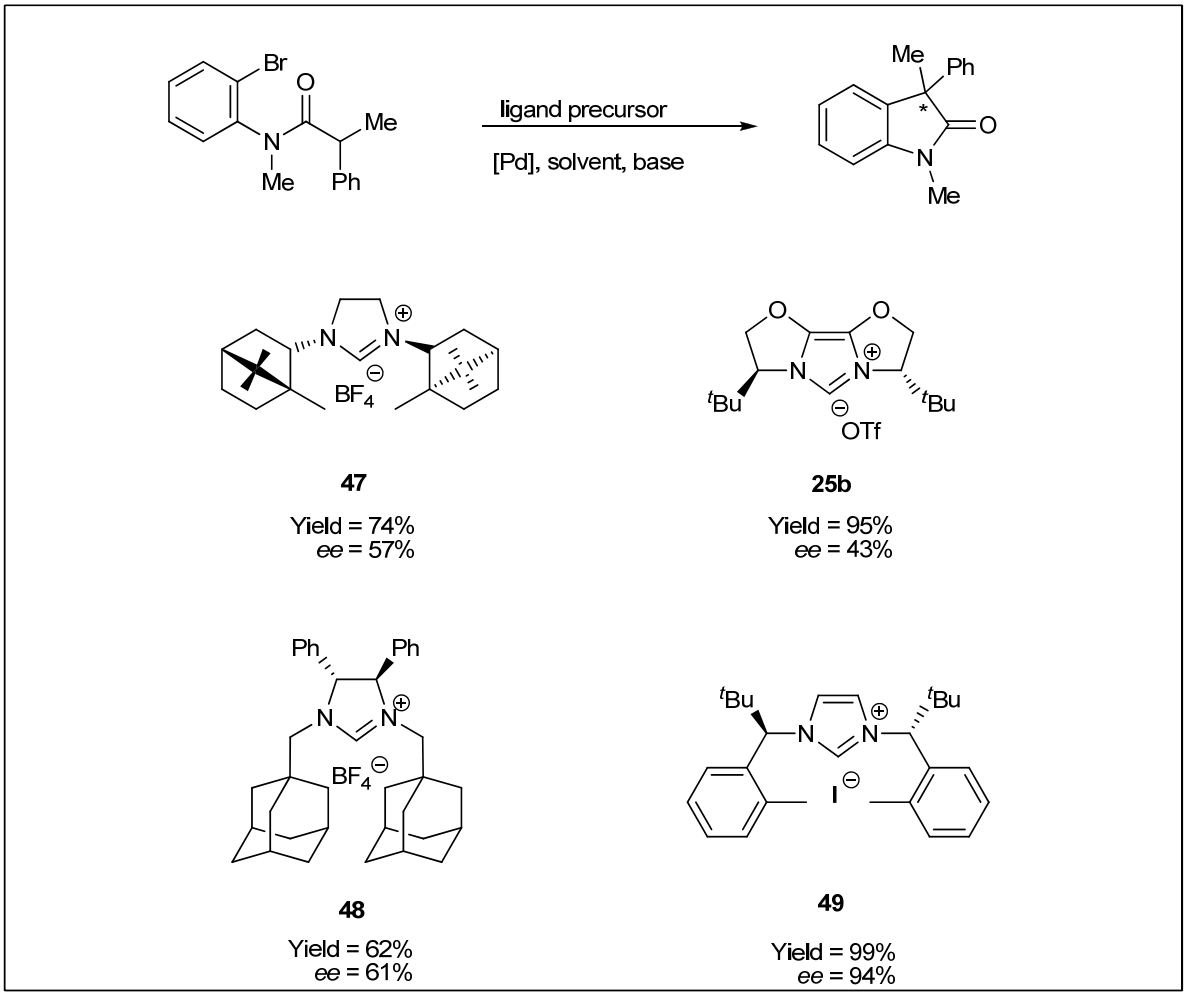
1.6.12. Asymmetric *α*-Arylation

The *α*-arylation of carbonyl compounds is a simple method to construct C-C bonds. In 1997, Hartwig *et al.* [94] and Buchwald[95] have independently reported the coupling of a ketone enolate and an aryl halide in the presence of a transition metal catalyst. Recently, an asymmetric intermolecular α-arylation has been successfully carried out by Hartwig and coworkers[96] by employing ligands such as (*R*)-difluorophos which contains an element of axial chirality. There is no report yet for the intermolecular *α*-arylation reaction being catalyzed by *N*-heterocyclic carbene ligands.

An intramolecular version of an α-arylation was proposed by Murataka and Natsume in 1997.[97] The enantioselective intramolecular α-arylation of amides was carried out for the first time by Hartwig and Lee.[98] In this particular reaction they obtained a yield of 74% with an *ee* of 57% by employing ligand **47**. Glorius *et al.*[57] employed oxazoline based imidazolium salt **25b** and obtained the product in an excellent yield of 95% but with a moderate *ee* of 43%. Later on, *N*-heterocyclic carbene ligand **48** was employed by the group

of Aoyama[99] achieving an *ee* of 61% with 62% yield. Recently, Kündig *et al.*[100] developed the ligand **49** which gave the product in 99% yield with 94% enantioselectivity (Scheme 35).

The scope of the substrates containing different heteroatoms at the stereogenic centre is currently being investigated. Oxindoles containing oxygen and nitrogen atoms at the newly formed stereogenic centre have been synthesized and showing promising results.[101]



Scheme 35

1.7. Conclusion and Outlook

The most striking feature of *N*-heterocyclic carbenes is their resistance towards dissociation thereby making NHCs the most appropriate candidates for asymmetric catalysis. Synthetic strategy for optically pure NHCs involves the utilization of the chiral pool. The structural tunability at different positions helps to understand the structure–selectivity relationship. For example, steric hindrance of aromatic *N*-substituent units of the

diaminocarbene improves selectivity while the orthogonal structural feature between the imidazole or imidazoline ring and the aromatic *N*-substituents can result in the formation of useful chiral atropisomers. Several structural patterns like oxazoline ring, binaphthyl and paracyclophane motifs have been exploited in the design of NHC ligands for asymmetric catalysis. Functionalized *N*-heterocylcic carbenes are emerging as a synthetically important class of ligands. So far, oxygen, sulphur and nitrogen donor atoms have been introduced. These functionalized carbenes show improvement in chelating different metals atoms.

In organometallic chemistry, NHCs are contributing efficiently by providing extra stability to metal complexes, their hemilability for generation of vacant coordination sites around a metal centre. NHCs have proved their affinity successfully with different transition metals, especially with palladium. The formation of 12-electron active (NHC)Pd(0) species by increasing steric hindrance of the co-ligands around the palladium centre allows cross coupling reaction at room temperature in short reaction times.

To obtain enantiopure product is still not an easy task. All known methodologies being employed in asymmetric synthesis are in progress. The area of developing a diversified range of chiral ligands is expanding parallel with a better understanding of chirality induction norms. Although NHCs have surpassed phosphine-based metal catalysis, yet there are still few examples in asymmetric catalysis.

In conclusion, NHC ligands still have to be explored in vast areas in the field of asymmetric synthesis. To design novel chiral NHCs is still amongst the biggest challenges in this research field.

1.8. References

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2. Results and Discussion

2.1. Introduction

The aim of this thesis is to prepare and investigate novel chiral carbene ligands incorporating hydroxy groups and protected analogues. These carbene ligands are derived from imidazolinium salts which in turn can be synthesized from simple, chiral amino alcohols. The newly synthesized ligands will be investigated as tridentate, bidentate and monodentate ligands in combination with different metals in a number of asymmetric transformations such as cross-coupling reactions, metathesis reactions, diethylzinc addition to aromatic aldehydes and hydroamination reactions. Moreover, these imidazolinium salts and their corresponding NHCs would also be evaluated as organocatalysts.

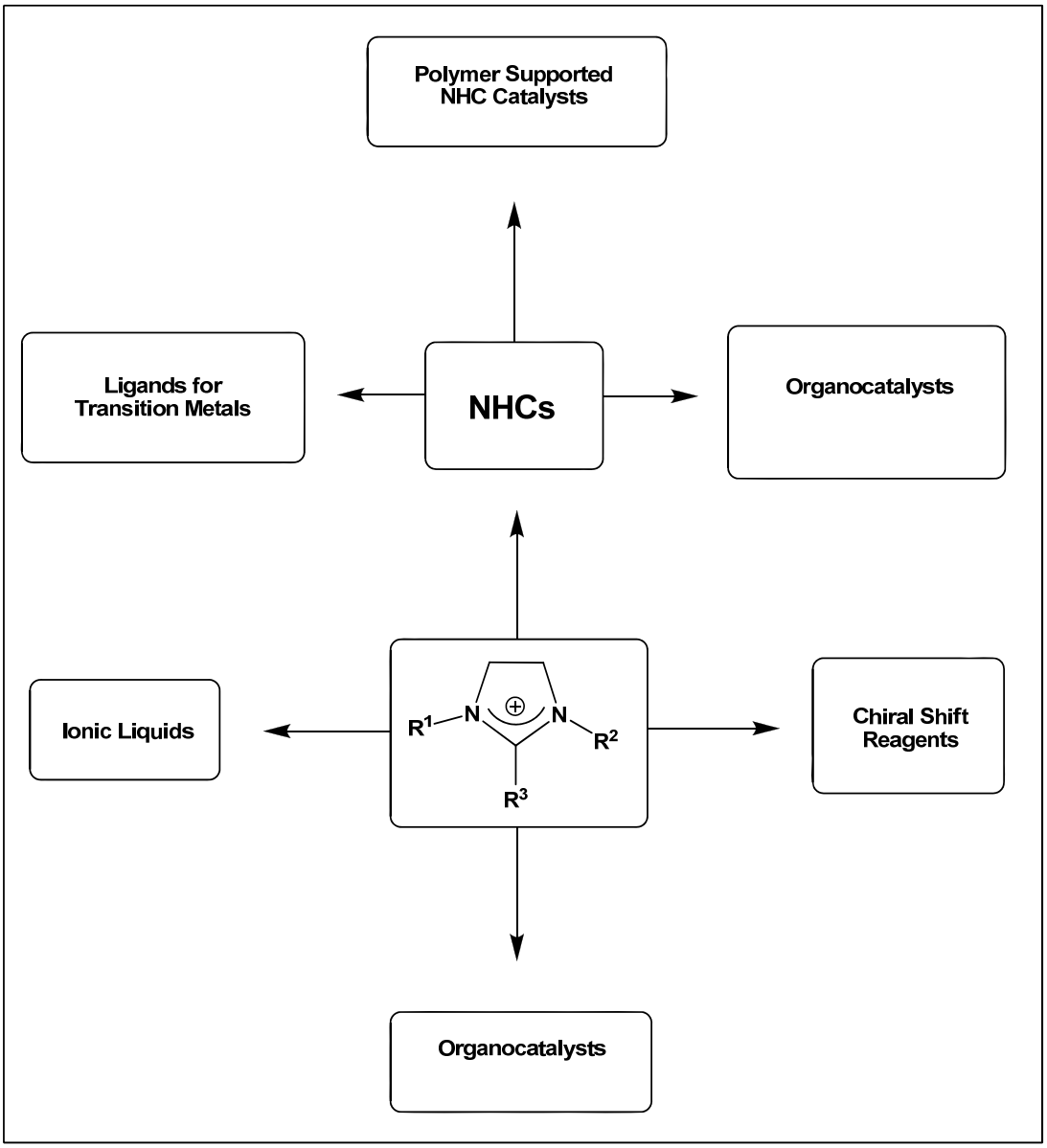
2.2. Synthesis of the Catalysts

We are interested in synthesizing imidazolinium based *N*-heterocyclic carbene precursors due to the following reasons:

1. Imidazolinium salts can be directly used as Lewis acid organocatalyst activators, as some of the imidazolinium salts have proved themselves as efficient catalysts in some chemical transformations.[102, 103]

2. *N*-Heterocyclic carbenes are easily generated by the deprotonation at the C-2 position of the imidazolinium salts. Owing to their nucleophilicity, these *N*-heterocyclic carbenes are acting as ligands for a number of metals. The metal complexes formed in this way are catalyzing many industrially important reactions like hydrogenation of olefins,[7,8] hydrosilylation reaction,[10] and cross-coupling reactions.[4, 5]

3. The importance of *N*-heterocyclic carbenes as ligands derived from corresponding imidazolinium salts is increased by the fact that imidazolinylidene ligands are more electron-donating than the related imidazolylidenes.[104] Thus the catalyst precursor $RuCl_2(CHPh)(PCy_3)(L_1)$ containing the 1,3-bis(mesityl)imidazolinylidene ligand(L_1) gives a more active catalytic species than the corresponding 1,3-bis(mesityl)imidazolylidene carbene complex in several reactions.[105, 106, 107]



Scheme 36

4. Due to the widespread intention of using environment friendly solvents or "Green solvents" by the scientific community, imidazolinium salts were also evaluated as ionic liquids. Some of the imidazolinium salts were meeting the criterion for being ionic liquids and thus serving as reaction media.[108]

5. *N*-Heterocyclic carbenes are nucleophilic in nature and can be directly used as Lewis bases.[109]

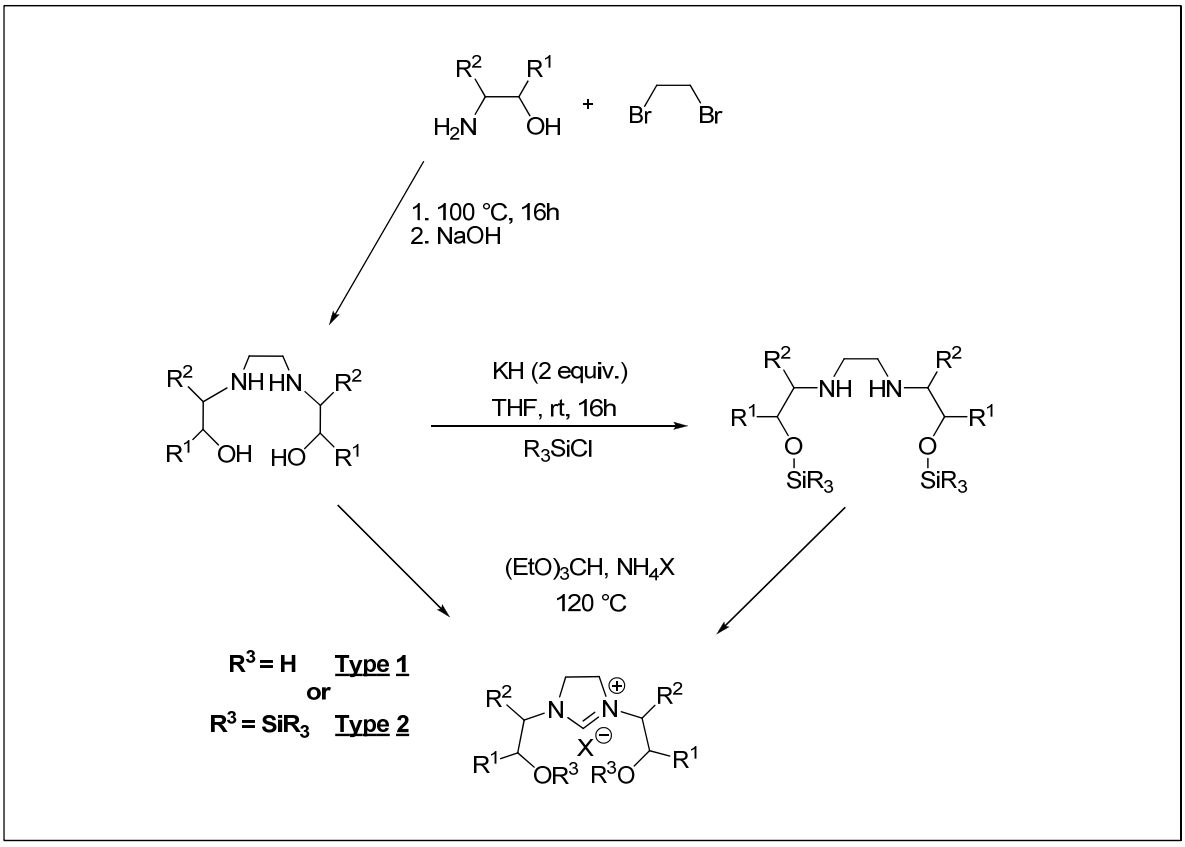
6. Imidazolinium salts are also finding their applications as successful chiral shift reagents.[110]

2.2.1. Synthetic Strategy

The synthetic plan includes the synthesis of four types of ligands as illustrated in Scheme 37a and 37b.

Type 1: Includes the functionalized imidazolinium salts with chiral *N*-substituents incorporating hydroxy groups.

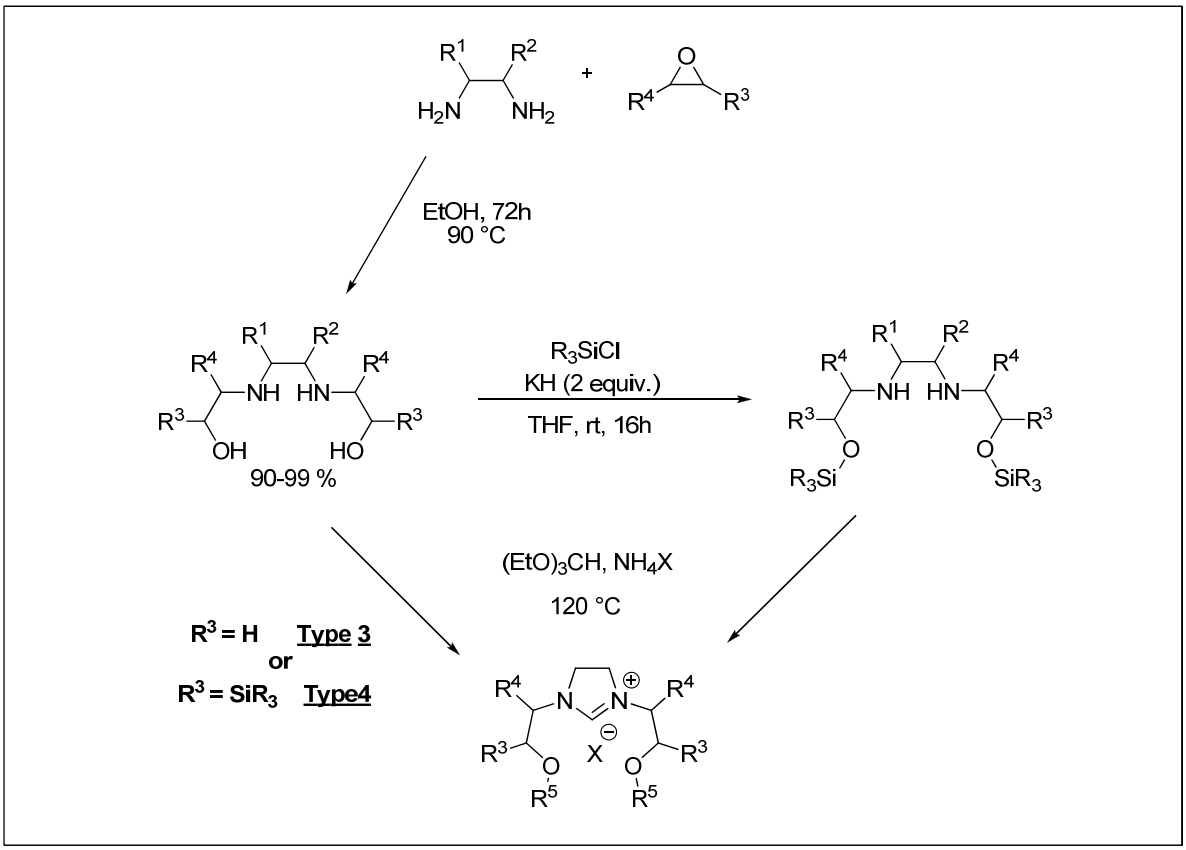
Type 2: Includes the imidazolinium salts with chiral *N*-substituents incorporating protected hydroxy groups.



Scheme 37a

Type 3: Imidazolinium salts with chiral *N*-heterocycle and ligating hydroxy groups in the side chains.

Type 4: Imidazolinium salts with chiral *N*-heterocycle and protected hyroxy groups in the side chains.



Scheme 37b

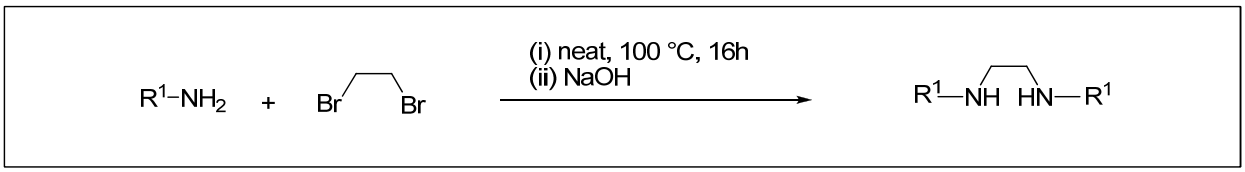
The synthesis starts with the preparation of diamines either by alkylation of amino alcohols or ring opening of symmetrical or regioselective ring opening of non-symmetrical epoxides. These C_2-symmetric amino alcohols are cyclized by direct reaction with *ortho*esters in the presence of an acid and an anion source. Another method is first to protect the hydroxy groups by different silylating reagents followed by the *ortho*ester route in order to obtain imidazolinium salts (Scheme 37a and 37b). Anion metathesis is carried out for introducing various anions. A detailed description of the synthetic route is given in the following section.

2.2.2. Preparation of the Precursors

The synthesis involves the preparation of C_2-symmetric diamines by two routes:

2.2.2.1. By Alkylation:

Diamines bearing hydroxy groups were prepared by simple alkylation of the corresponding chiral amino alcohols with 1, 2-dibromoethane (Scheme 38).



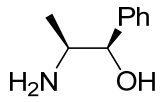
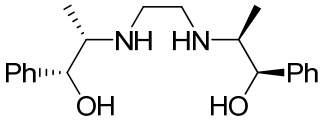
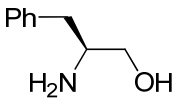
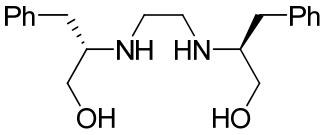
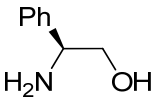
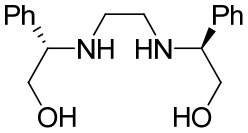
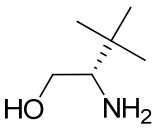
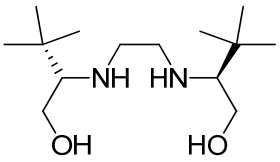
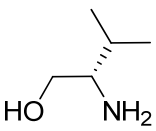
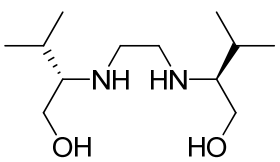
Scheme 38

The reaction was neat giving moderate to excellent yields of the diamines (Table 1). The HBr salt of the corresponding diamine was precipitated as a yellow solid in the reaction mixture which was dissolved in water. After removal of impurities by solvent extraction with chloroform the aqueous phase was basified with 2M NaOH obtaining pure bis-amino alcohols free of acid contents. The amino alcohols could not be purified by flash chromatography because of their affinity with the stationary phases.

Bis-amino alcohol **56** was synthesized from naturally occurring chiral amino alcohol norephedrine **51** with an improved yield of 98%. The yield of bis-amino alcohol **57** was also improved to 93% as compared to previously reported yields in our group.[110a] The reason for this improvement lies in the workup procedure. As mentioned earlier, the HBr salts of corresponding diamines being precipitated as yellow solids were dissolved in water. The complete solubility of salts is ensured by dilution and vigorous stirring of the mixture leaving no salt residues in the water phase. This complete solubility of salts improves the regeneration of the corresponding amino alcohols **56** and **57** in excellent yields (Table 1, entries 1 and 2).

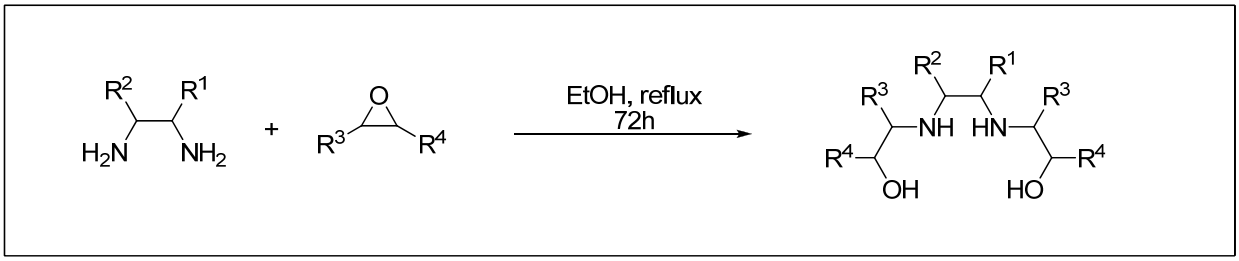
Diamine **58** was earlier synthesized from (–)-phenylgycinol in two steps, first by reacting **53** with glyoxal and then reducing with BH_3-THF to the corresponding product **58**.[111] The presented synthetic procedure employs a one step protocol of chiral phenylglycinol with 1,2-dibromoethane with an excellent yield of 92% (Table 1, entry 3). Amino alcohol **59** was prepared from chiral L-*tert*-leucinol in 91% yield (Table 1, entry 4). Enantiomerically pure L-valinol **55** with 1,2-dibromoethane resulted in bis-amino alcohol **60** in 77% yield (Table 1, entry 5).

TABLE 1: Alkylation of amines

Entry	Amine	Diamine	Yield [%]
1	 **51**	 **56**	9
2	 **52**	 **57**	93
3	 **53**	 **58**	92
4	 **54**	 **59**	91
5	 **55**	 **60**	77

2.2.2.2. By Ring Opening of Epoxides:

C_2-Symmetric amino alcohols were also synthesized by ring opening of epoxides. Here chiral diamines were reacted with chiral and achiral epoxides giving rise to β-amino alcohols (Scheme 39).

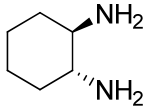
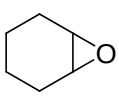
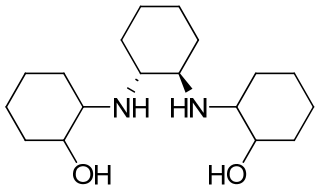


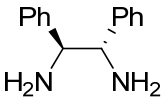
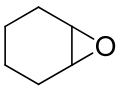
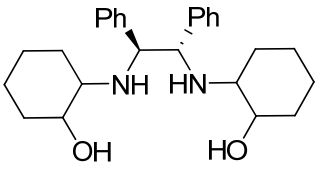
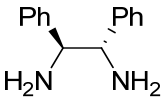
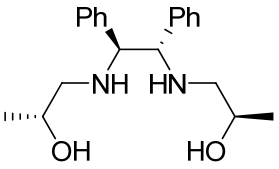
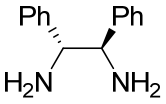
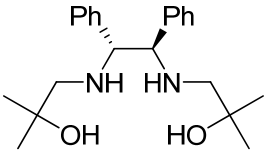
Scheme 39

The mixture was refluxed in EtOH for 72h and acidified to pH 2 with 2M hydrochloric acid. The aqueous layer was washed with chloroform, and basified to pH 11 with 2M NaOH solution. The crude product was obtained by extracting the aqueous layer with chloroform. The amino alcohols **68** and **69** (Table 2, entries 3 and 4) were obtained in excellent yields with high purity and no column chromatography was required.

In the ring opening reaction of non-symmetrical epoxides (Table 2, entries 3 and 4), the nucleophilic attack of the diamines occurred at the least hindered site of unsymmetrical epoxides. This resulted in amino alcohols in which the carbon bearing the hydroxy group is more hindered. This steric crowding around the carbon bearing hydroxy group can influence the outcome of a catalyzed reaction.

Table 2: Ring opening of epoxides

Entry	Diamine	Epoxide	Amino alcohol	Yield [%]
1	 **61**	 **63**	 **66**	85

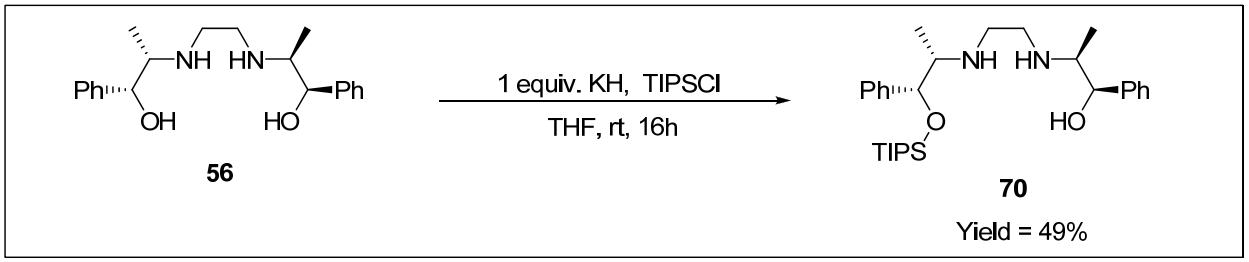
2				43
	62	**63**	**67**	
3				92
	62	**64**	**68**	
4				90
	ent-**62**	**65**	**69**	

2.2.2.3. Synthesis of Hydroxy Protected Diamines with Silyl Reagents:

The hydroxy groups of the previously synthesized amino alcohols are potentially binding sites to electrophilic centers (metal or substrate) when employed as ligands either in the form of amino alcohols or imidazolinium salts. It has been found that if one or both hydroxy groups have been protected with some bulkier group, a marked effect was observed on the stereochemical outcome of catalyzed reactions. Due to this reason we were interested to protect the hydroxy groups with sterically different silyl groups.

2.2.2.4. Synthesis of Monohydroxy Protected Diamine with Tri*iso*propylsilylchloride:

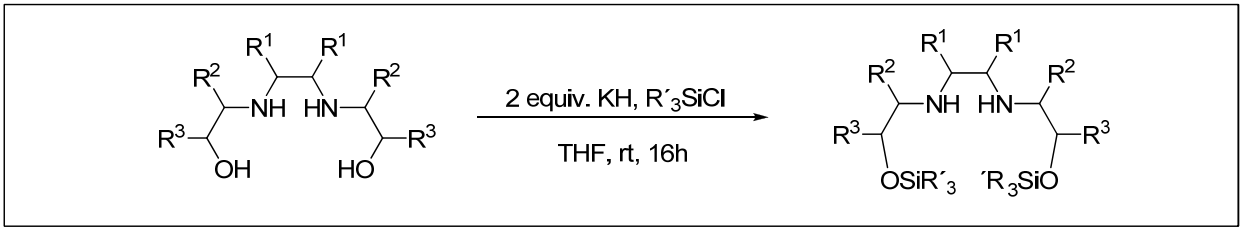
The protection of one hydroxy group is rather selective. It involves the addition of tri*iso*propylsilylchloride in stoichiometric amount. The norephedrine based amino alcohol **56** gave the monohydroxy protected diamine **70** with 49% yield (Scheme 40).



Scheme 40

2.2.2.5. Synthesis of Bis-Hydroxy Protected Diamines:

Different silylating groups have been used to protect both hydroxy groups of amino alcohols (Scheme 41). The silylating reagents have been chosen on the basis of steric crowding around the silyl atom which would be exploited in the stereochemical outcome of catalyzed reactions especially in the asymmetric oxindole formation.

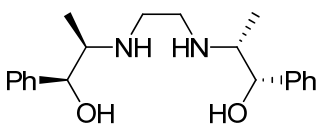
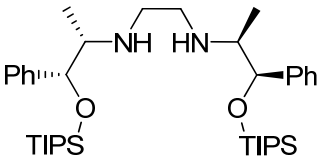


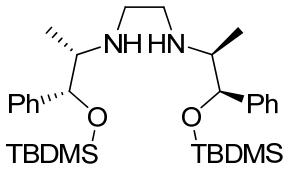
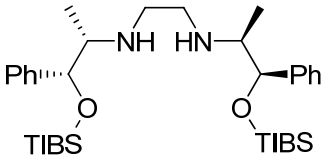
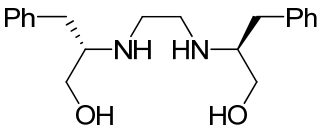
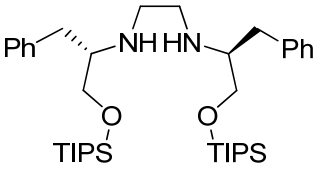
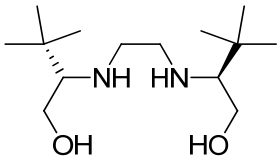
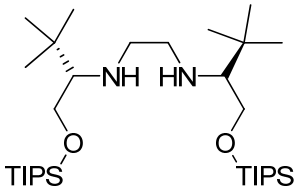
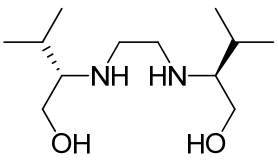
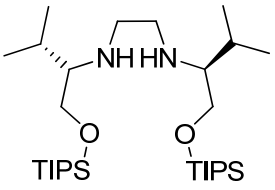
Scheme 41

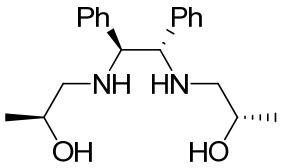
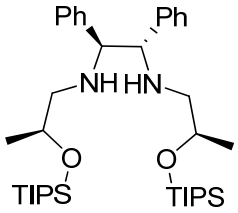
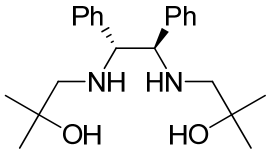
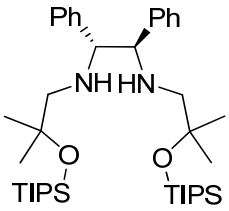
The protection of both hydroxy groups of diamines by different silylating reagents is also required in order to reduce the chelating sites of the diamines and their corresponding imidazolinium salts. This protection is highly desirable in establishing the role of the hydroxy groups and to evaluate where these hydroxy groups participate in the catalyzed reactions.

The results are summarized in Table 3.

Table 3: Synthesis of bis-hydroxy protected diamines

Entry	Diamine	Silylated diamine	Yield [%]
1	 **56**	 **71**	99

2	**56**	 **72**	66
3	**56**	 **73**	57
4	 **57**	 **74**	94
5	 **59**	 **75**	60
6	 **60**	 **76**	88

7	 **68**	 **77**	60
8	 **69**	 **78**	50

The hydroxy groups of diamines were deprotonated by adding potassium hydride. The alkoxides were treated with the silylating reagents. Both hydroxy groups of the diamine **56** were protected with tri*iso*propylsilylchloride giving an excellent yield of 99% whereas the same diamine **56** gave yields of 66% and 57% when protected with *tert*butyldimethylsilylchloride and tri*iso*butylsilylchloride respectively (Table 3, entries 2 and 3). The reason for the low yield with the later silylating group might be due to the sluggishness of the reaction, when introducing bulkier groups around the oxygen atoms.

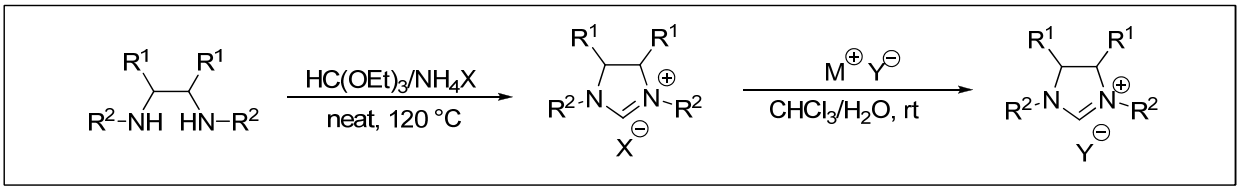
Bis-Hydroxy protected diamine **76** having an *iso*propyl group in the side chain at the carbon atom next to the nitrogen was isolated in 88% yield (Table 3, entry 6). Whereas switching from isopropyl to the more bulky *tert*butyl group influenced the protection step yielding 60% of the product (Table 3, Entry 5). Diamine **57** with benzyl groups at the side chains was protected with tri*iso*propylsilylchloride giving an excellent yield of 94% (Table 3, entry 4). Silylated diamines **77** and **78** were isolated in moderate yields of 60% and 50%, respectively (Table 3, entries 7 and 8).

For the bis-hydroxy protected diamines, column chromatography on silica was necessary to separate the by-products. The protected diamines showed reasonable strong affinity with

the stationary phase (silica), therefore Et_3N was added to the mobile phase in order to elute the protected diamines efficiently.

2.2.3. Synthesis of Imidazolinium Salts

The preparation of imidazolinium salts by the direct reaction of diamines and *ortho*esters in the presence of an anion source represents a convenient method.[23] Ammonium salts are used as a source of protons being provided to the ethoxy group of the *ortho*esters. These salts also act as a source of counter anions for the corresponding imidazolinium salts. Different anions can also be provided by a subsequent counter anion exchange (Scheme 42).



Scheme 42

The salt **80** has been synthesized from amino alcohol **56** with a yield of 74%. A subsequent anion metathesis gave salts **81** (from *ent*-**80**) and **82** with more lipophilic anions in yields of 85% and 56%, respectively (Table 4, entries 2 and 3).

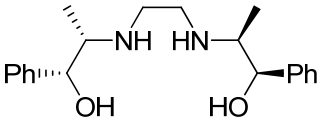
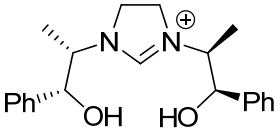
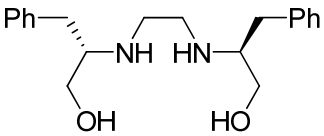
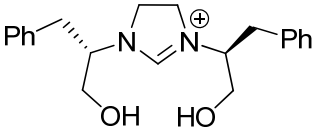
Another way to introduce different anions is, of course, to use different ammonium salts. Iodo, bromo or chloro anion containing salts were synthesized (Table 4, entries 4, 5 and 6). Salts **80**-**87** were not columned for purification as washing with hexane and diethylether and followed by recrystallization from dry ethanol provided the pure salts. Salt **83** was recrystallized in acetone for X-ray crystallography.

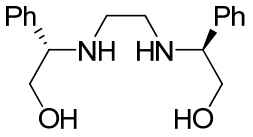
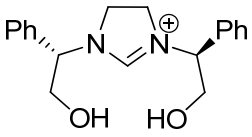
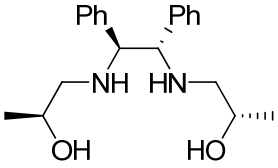
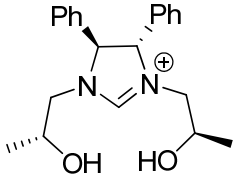
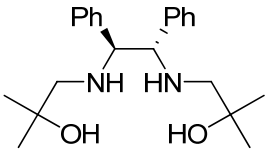
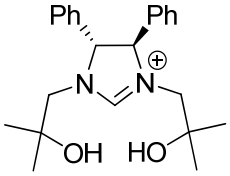
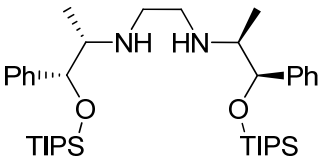
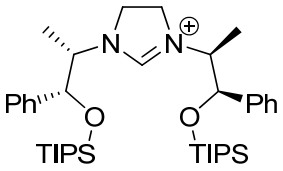
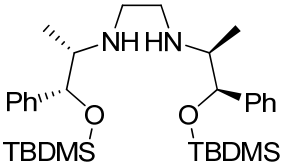
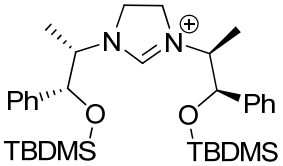
Salt **88** having chiral centres within the *N*-heterocycle and in the side chain was synthesized in high yield of 80%. This salt was purified by column chromatography as washing alone did not suffice pure compound. Another salt **89** having chirality only at the backbone was synthesized in 90% yield (Table 4, entry 10).

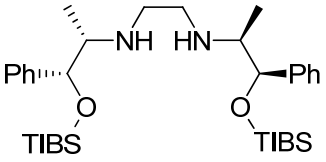
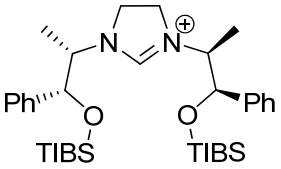
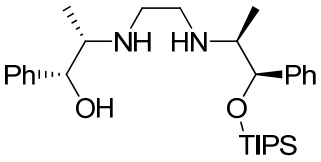
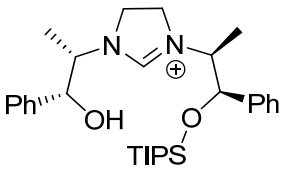
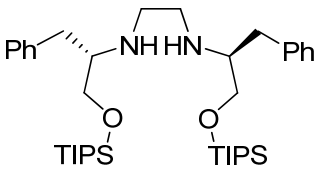
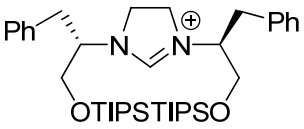
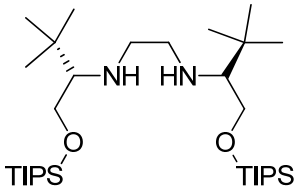
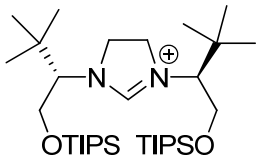
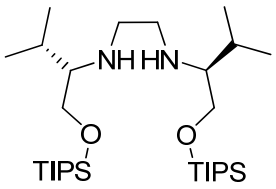
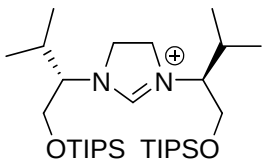
The diamines **71**-**78** were cyclized to their corresponding imidazolinium salts in moderate yields. Salt **91** with a chloride anion was offering advantage over salt **90** as former can be purified by washing with hexane, diethylether and dichloromethane and no column chromatography is required. Dichloromethane washing of salt **91** dissolves the unreacted diamine and other organic impurities. Attempts were made to improve the yield of

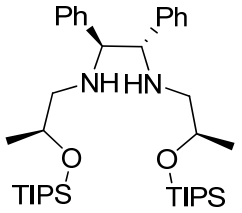
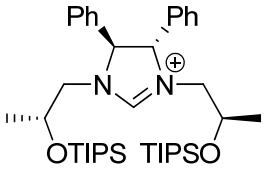
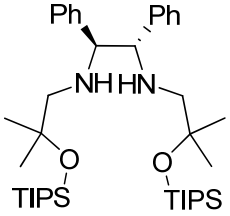
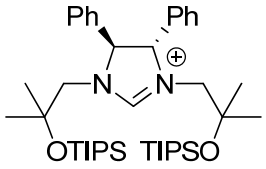
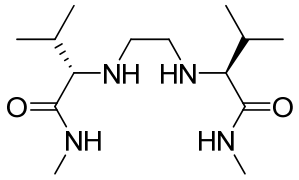
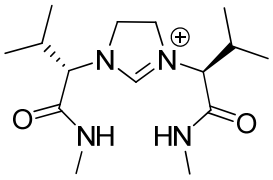
imidazolinium salt **91**. The neat reaction at 120 °C for 16h furnished the product in 62% yield. The reaction was also carried out in toluene at different temperatures. At 80 °C and 100 °C, no reaction occurred. A moderate yield of 49% was obtained in refluxing toluene. Finally, the reaction was carried out at still higher temperature. By refluxing the reaction mixture in excess triethyl*ortho*formate, serving both as reagent and solvent, the yield improved to 68%.

Table 4: Synthesis of chiral imidazolinium salts

Entry	Diamine	Cation	Anion	Salt	Yield [%]
1			BF_4^-	**80**	74
2			BPh_4^-	**81**	85
3	 **56**		B[3,5-$(CF_3)_2C_6H_3]_4^-$	**82**	56
4			I^-	**83**	67
5			Br^-	**84**	66
6			Cl^-	**85**	42
7	 **57**		BF_4^-	**86**	57

8	 **58**		BF_4^-	**87**	66
9	 **68**		BF_4^-	**88**	80
10	 **69**		BF_4^-	**89**	90
11	 **71**		BF_4^-	**90**	65
12			Cl^-	**91**	68
13[a]	 **72**		BF_4^-	**92**	77

14	 **73**		Cl^-	**93**	50
15	 **70**		BF_4^-	**94**	29
16	 **74**		BF_4^-	**95**	75
17			BF_4^-	**96**	72
18	**75**		Cl^-	**97**	59
19			BF_4^-	**98**	75
20	**76**		Cl^-	**99**	55

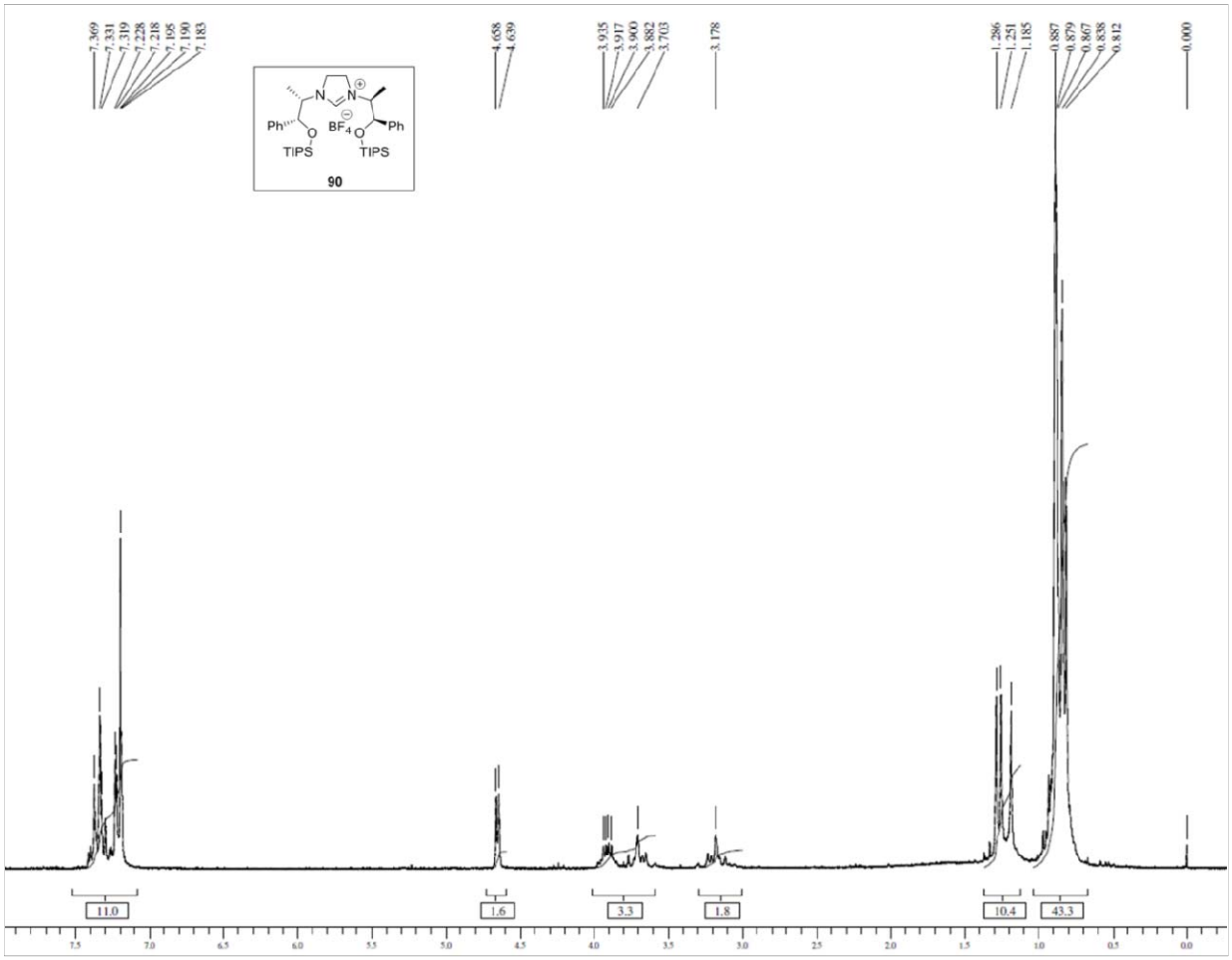
21	 **77**		Cl^-	**100**	73
22	 **78**		Cl^-	**101**	58
23[b]	 **79**		BF_4^-	**102**	25
24			BPh_4^-	**103**	65

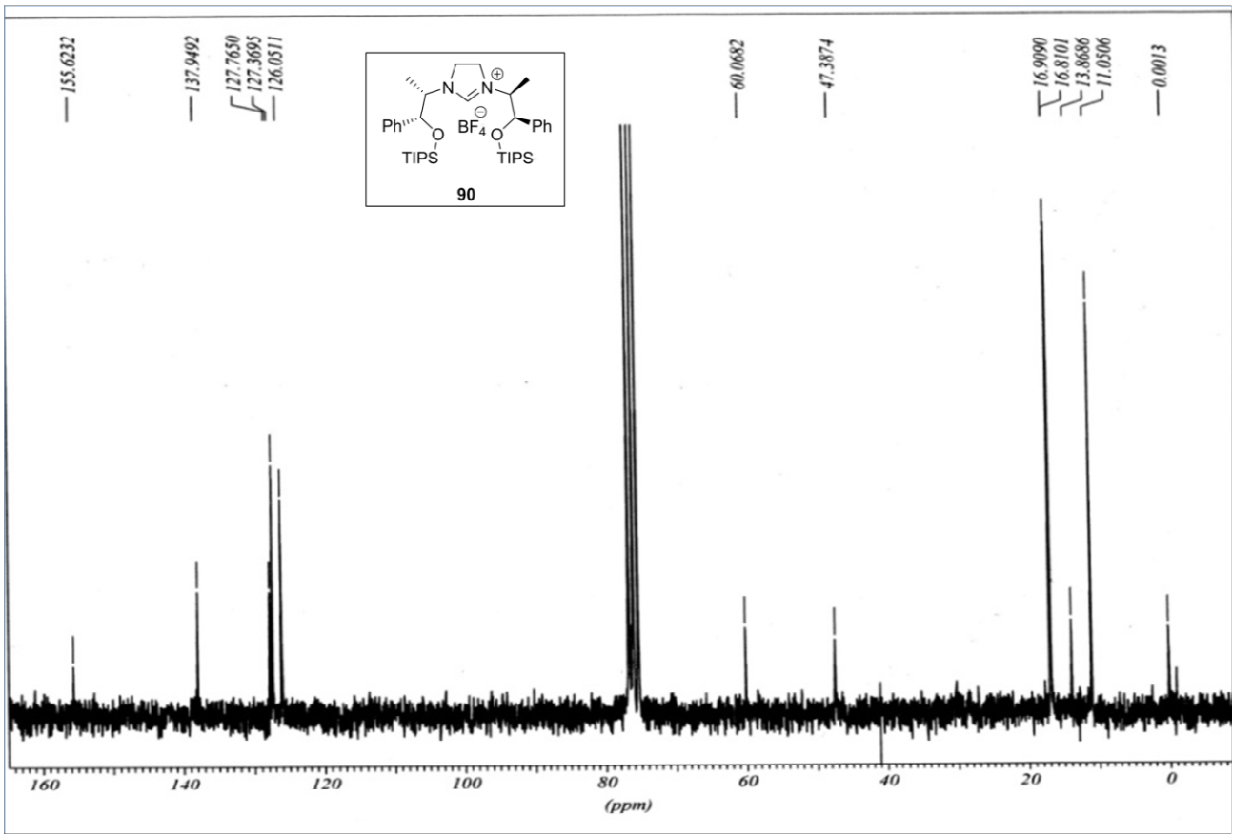
[a] the reaction was performed in refluxing toluene for 16h. [b] diamine **79** was provided by Prof. R. Wilhelm.

It was observed that the steric crowding of protecting groups has an influence over the cyclization process. Salt **92** was obtained in a good yield of 77% as steric crowding around the oxygen atoms is comparatively less due to the TBDMS groups in comparison with the TIPS groups of salt **90** (Table 4, entry 13). As strain in the side chains increases due to the bulkier *iso*butylsilyl groups of diamine **73**, the yield of imidazolinium salt **93** was reduced to 50% (Table 4, Entry 14). Monohydroxy protected salt **94** was obtained in a low yield of 29%. Salts **96** and **98** containing tetrafluoroborate as anion were obtained in higher yields of 72% and 75% as compared with the yields of salts **97** and **99** containing chloride as anion. Bis-hydroxy protected diamine **78** was transformed to the corresponding imidazolinium salt in a low yield of 58% (Table 4, entry 22). Again by comparing the yields of salts **100** and **101** strengthened the assumtion that less strain at the side chains of diamine **77** permits a

high yield as compared with diamine **78** of which carbon atoms bearing protected hydroxy groups are substituted by two methyl groups. C_2-Symmetric diamide **79** was cyclized to the corresponding imidazolinium salt **102** in a very low yield of 25% (Table 4, entry 23). The yield of the salt **103** was 65% when a counter anion exchange of the tetrafluoroborate of salt **102** was carried out with a tetraphenylborate anion (Table 4, entry 24).

Several salts like **90** showed an unusual behaviour in the ^{1}H-NMR. Although in general the C2-H signal of an imidazolinium salt comes around 8.50 with a BF_4 counter anion in deuterated chloroform, for salt **90** the signal was at 7.40 as confirmed by HSQC with the carbon signal at 155.6 (Figure 1). Obviously, the imidazolinium cation is not able to form a hydrogen bond with the BF_4 counter anion. Salt **91** with a chloride counter anion was not soluble in chloroform. In deuterated methanol the C2-H signal was observed at 7.42, while in deuterated acetone the signal was at 8.89.




155.6232
137.9492
127.7650
127.3695
126.0511
60.0682
47.3874
16.9090
16.8101
13.8686
11.0506
0.0013
Ph
BF4
Ph
TIPS
TIPS
90
160
140
120
100
80
60
40
20
0
(ppm)

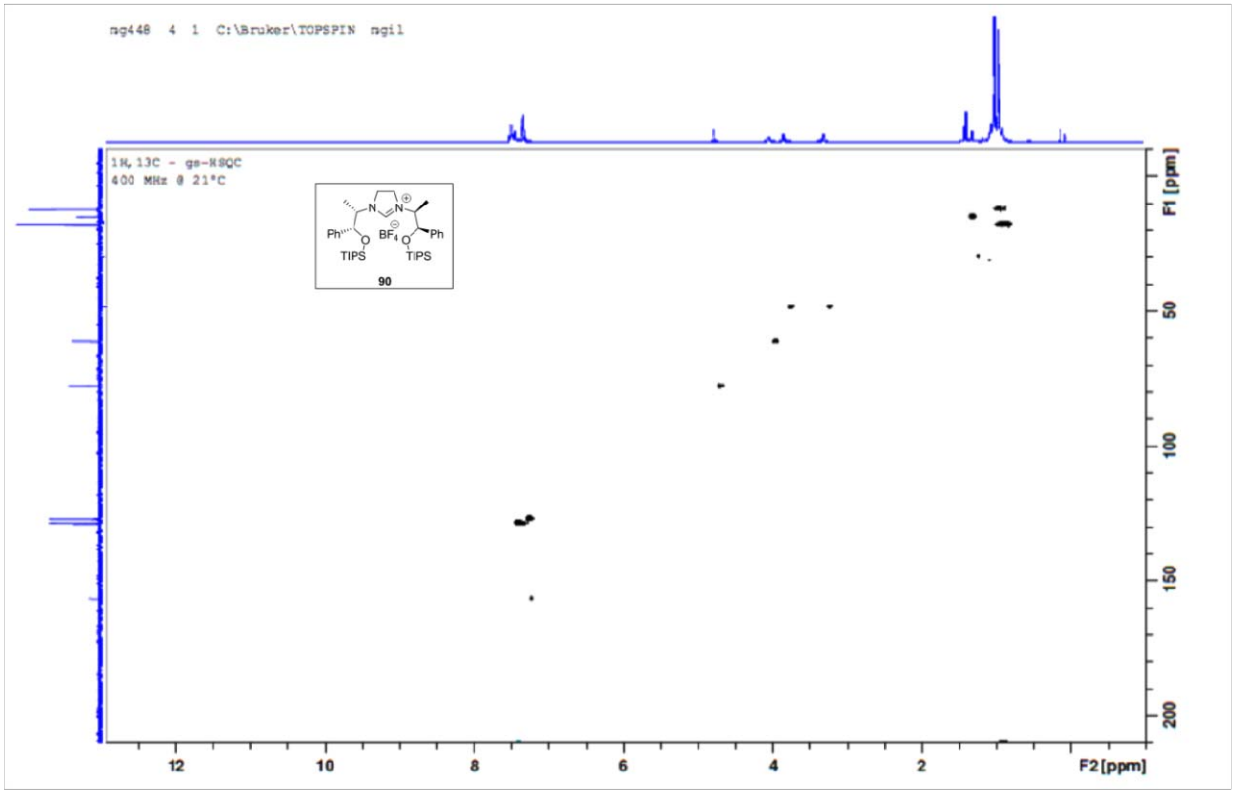

ng448 4 1 C:\Bruker\TOPSPIN ng1l
1H,13C - ge-HSQC
400 MHz @ 21°C
Ph
BF4
Ph
TIPS
TIPS
90
F1 [ppm]
50
100
150
200
12
10
8
6
4
2
F2 [ppm]

Figure 1

2.2.4. Synthesis of Thiourea Precursor

Thiourea compounds are used as hydrogen bond activators for carbonyl[112] and nitro groups.[113, 114, 115] These compounds are also regarded as pseudo Lewis acids. Earlier in our group chiral thiourea compounds were synthesized having thiourea function with an aliphatic chain.[116] Now a cyclic thiourea derivative **104** has been synthesized in 44% yield (Scheme 43) by following the literature procedure[117] in order to evaluate its Lewis base capacity in catalysis.

Scheme 43

2.3. Applications of the Catalysts

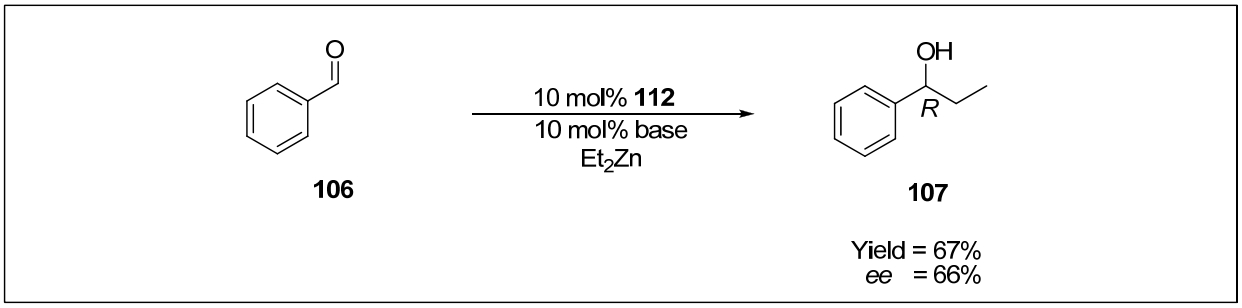
The previously synthesized new imidazolinium salts were applied in different reactions in order to explore their influence in terms of yield and stereoselectivity. The bench mark reactions include the asymmetric diethylzinc addition to aldehydes, the Michael addition, asymmetric ring opening of epoxides and asymmetric *α*-arylation of amides.

2.3.1. Asymmetric Diethylzinc Addition to Aldehydes

The enantioselective Et_2Zn addition to aldehydes is a powerful protocol for the construction of C-C bonds.[118] Optically active secondary alcohols resulting from this enantioselective addition are important intermediates in the synthesis of many natural products. Beginning from the first report by Oguni and Omi,[119] various chiral ligands like *α*-amino alcohols,[120] BINOL,[121] salen,[122] TADDOL,[123] pyridyl alcohols,[124] *β*-amino alcohols[125] and *γ*-amino alcohols[126] have been extensively used in the diorganozinc addition to various aldehydes.

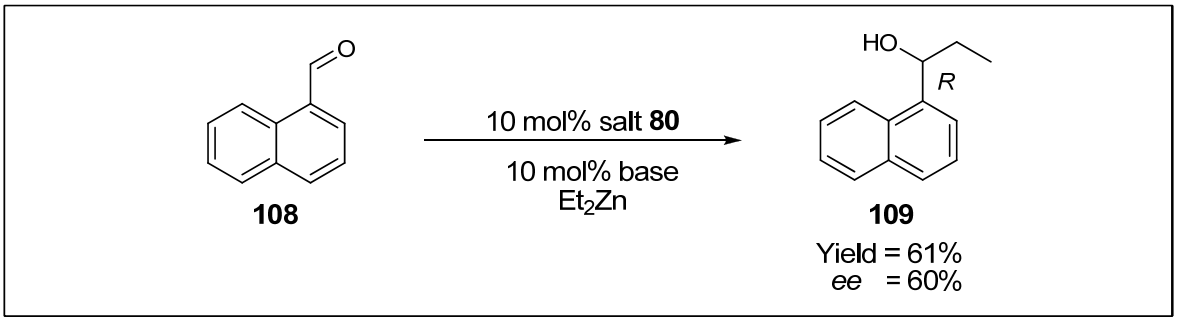
For the first time asymmetric diethylzinc addition to aldehydes was carried out by using *N*-heterocyclic carbenes as ligands in our group.[87] The results were promising as the

diethylzinc addition to benzaldehyde gave up to 66% *ee* and 67% yield of the secondary alcohol **107** without any additional metal salt (Scheme 44).



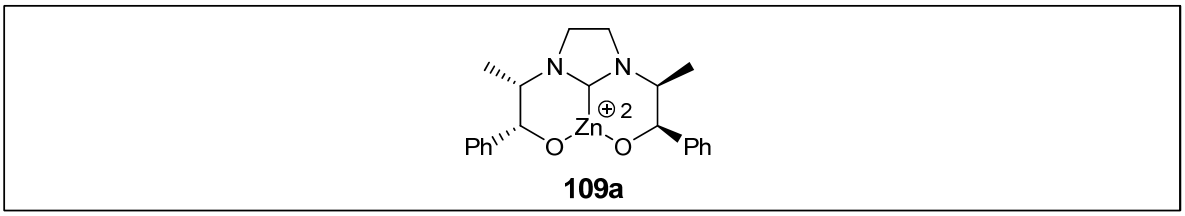
Scheme 44

Furthermore, 1-naphthaldehyde **108** was used as shown in Scheme 45. When the reaction was conducted with catalyst **80** using KO^{t}Bu as a base, the corresponding alcohol **109** was isolated in 61% yield and 60% *ee* (Scheme 45).



Scheme 45

In the diethylzinc addition to aldehydes, the formation of the following catalytic active complex **109a** could be assumed (Scheme 46).



Scheme 46

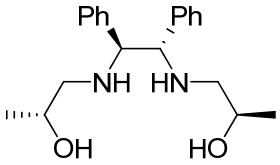
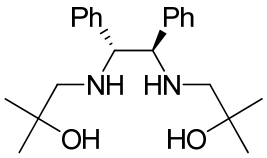
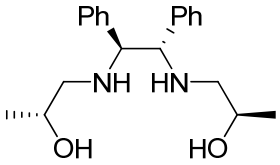
In order to show that the formed carbenes were stable under the optimized conditions, salt **80** was dissolved in toluene. After the addition of KO^{t}Bu, diethylzinc was added and the solution was stirred overnight. After workup with 1N HCl and extraction, salt **80** was recovered and identified by ^{1}H NMR spectroscopy.

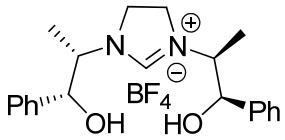
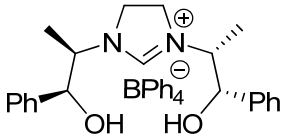
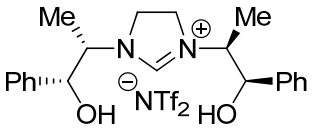
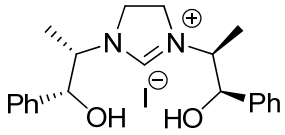
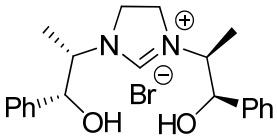
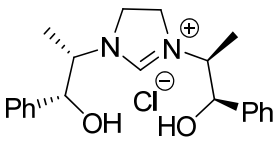
Furthermore, the Et_2Zn addition to 1-naphthaldehyde system (Scheme 45) was used as a benchmark reaction for screening a number of newly synthesized ligands and to optimize the reaction conditions with the best catalytic system.

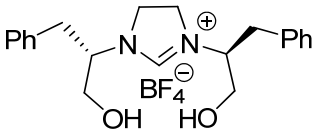
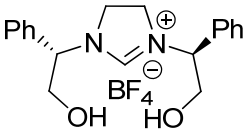
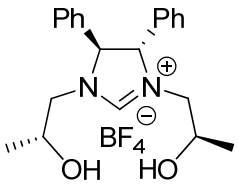
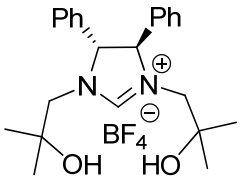
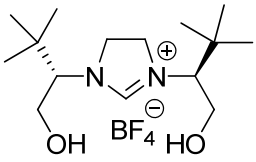
2.3.1.1. Nature of Ligands/Ligand Precursors

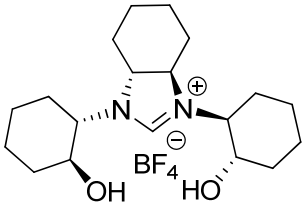
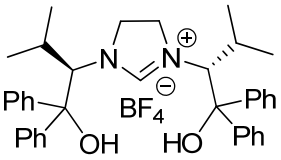
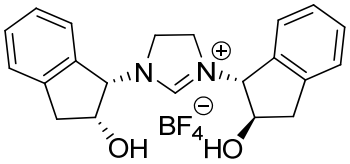
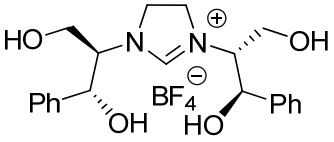
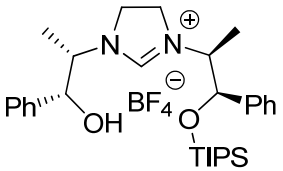
The role of ligand is substantial in the outcome of the reaction. A number of amino alcohols as ligands have been applied for the asymmetric diethylzinc addition to aldehydes. The reported results are excellent both in terms of yield and enantioselectivity.[117, 122, 123] Since there was no report on the application of *N*-heterocyclic carbene ligands in this particular addition reaction, we focused to expand the scope of this class of ligands. The ligands with various structural modifications have been applied in order to evaluate their efficiency. The carbene ligands were employed along with copper(II)triflate This screening of ligands also helped us to establish a structure-activity relationship of the reaction. The results are summarized in Table 5.

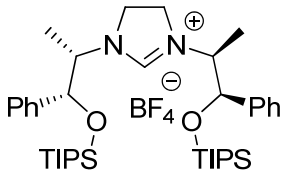
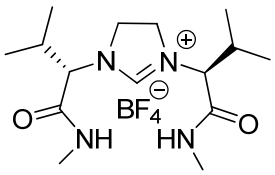
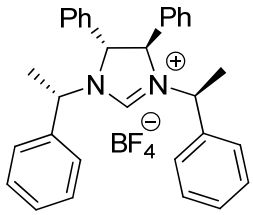
Table 5: Effect of nature of ligand/ligand precursor[a]

Entry	Ligand/Precursor	Yield [%]	*ee* [%]	Config.
1[b]	 **68**	77	53	*S*
2[b]	 **69**	90	43	*R*
3[b]	 **68**	16	0	–

4	 **80**	42	84	*R*
5	 **81**	35	88	*S*
6	 **110**	20	60	*R*
7[c]	 **83**	31	22	*R*
8	 **84**	43	42	*R*
9[c]	 **85**	37	44	*R*

10	 **86**	16	0	–
11	 **87**	13	0	–
12	 **88**	62	15	*S*
13	 **89**	55	34	*R*
14[d]	 **111**	30	16	*R*

15[f]		34	0	–
	112			
16[g]		58	0	–
	113			
17[e,h]		7	25	*S*
	114			
18[f]		12	6	–
	115			
19		27	35	*R*
	94			

20[d]	 **90**	21	0	–
21[d]	 **102**	35	0	–
22[h]	 **116**	traces	–	–

[a] 2.5 mol% $Cu(OTf)_2$, 5 mol% salt, 15 mol% KO^{t}Bu, 46h, rt, toluene. [b] without metal salt; [c] 5 mol% $Cu(OTf)_2$, 10 mol% salt, 30 mol% KO^{t}Bu [d] M:L 1:1; [e] CuI was used. [f] salts were provided by Dr.V. Jurcik. [g] salt was provided by Prof. R. Wilhelm. [h] salts were provided by O. Sereda.

The carbene ligand precursors were employed along with copper(II) triflates. Salt **80** derived from enantiomerically pure norephedrine afforded the secondary alcohol in 42% yield with an excellent *ee* of 84% (Table 5, entry 4). Whereas the salts **81**, **83**-**85,** and **110** having the same cation but with different anions exhibited a marked impact on the yield and enantioselectivity of the product. For example, carbene precursor **110** with a more lipophilic bis-(trifluoromethylsulfonyl)-imide anion gave 20% yield and 60% *ee* of the product **109** (Table 5, entry 6). Imidazolinium salts **83**-**85** were employed in the reaction resulting in low yields of the secondary alcohol. The moderate *ee*s of 42% and 44% have been achieved with salts **84** and **85** containing bromide and chloride anions respectively (Table 5, entries 8 and 9). On the other hand imidazolinium salt **83** with a larger iodide anion provided a low *ee* of 22% (Table 5, entry 7). The large influence of the counter anion on the *ee* can be attributed

to the fact that BF_4 is the least coordinating anion in comparison to Cl, Br and I. The halide anions could coordinate the metal center and therefore altering the catalytic species.

Other carbene ligand precursors with various structural modifications incorporating two hydroxy groups were also applied in the reaction. Among the salts having chiral centres in the side chains, **114** gave an *ee* of 25% but with a very poor yield of 7% (Table 5, entry 17). Salts having chirality at the carbons next to the nitrogen atoms of the ring, carrying substituents of varying size like phenyl, benzyl and isopropyl groups, remained inactive in the catalytic cycle (Table 5, entries 10, 11 and 14). The NHC precursor **113** containing two phenyl groups at the carbon bearing hydroxy groups gave an improved yield of 58% but 0% *ee*. These two phenyl groups might be stabilizing the catalytic metal complex thus preventing it from decomposition. An *ee* of 34% was obtained when salt **89** bearing two methyl substituents in the side chains was tested in the reaction.

A series of experiments was performed in order to get an insight into the coordination number of the copper ion. The salt **115** with four hydroxy groups gave a yield of 12% of the resultant alcohol with 6% *ee* (Table 5, entry 18). One of the two hydroxy groups of the salt **80** was protected with a tri*iso*propylsilyl group and this bidentate salt **94** was applied in the reaction. The yield dropped from 42% to 27% and a marked drop in *ee* from 84% to 35% was observed. Monodentate salt **90** with both hydroxy protected groups gave low yield without any enantioselectivity (Table 5, entry 20). It can be concluded that imidazolinium salt **80** with three coordinating sites is the most appropriate ligand in the asymmetric diethylzinc addition to 1-naphthaldehyde.

Amino alcohols **68** and **69** were also applied in the diethylzinc addition to 1-naphthaldehyde. Amino alcohol **68** gave a good yield of 68% with a moderate *ee* of 53%. Amino alcohol **69** having two methyl groups at the carbon atoms bearing hydroxy groups gave an excellent yield of 90%, but no improvement in *ee* was observed (Table 5, entries 1 and 2). By comparing the results obtained from these two amino alcohols **68** and **69**, it seems that structural modification in ligands can influence the outcome of the reaction as amino alcohol **69** is more crowded than **68**. Moreover, reaction of **68** without any metal salt resulted in a decreased yield of 16% with 0% *ee* (Table 5, entry 3) indicating a need for the addition of metal salt.

As imidazolinium salt **80** gave the best results, therefore further optimization was carried out with this salt.

2.3.1.2. Effect of Different Metals

Because different metal cations can influence the reaction due to their size, co-ordination sphere and charge density, several metal salts were investigated in the reaction. The results are summarized in Table 6. $Cu(OTf)_2$ was found to give the highest enantiomeric excess of 84%, but with a moderate yield of 42%. Cupric ions with different counter anions like chloride gave 80% *ee.* However, the yield decreased to 32% indicating this time the influence of metallic halide counter anion, which coordinates the metal in the catalytic species.

Table 6: Investigation of salt 80 with different metals: (metal salt:salt 80:KO^{t}Bu) (1:1:3), 46h, rt, toluene

Entry	Metal Salt	Salt 80 [mol%]	Yield [%]	*ee* [%]
1	CuI	5	53	80
2	$CuCl_2$	3	32	80
3	$Cu(OTf)_2$	5	42	84
4	$Cu(acac)_2$	10	15	28
5	$FeCl_2$	2	53	63
6	$FeCl_3$	2	32	49
7	$Ti(^iPrO)_4$	3	41	51
8	$TiCl_4$	3	34	15
9	$CaCl_2$	5	60	43

10	$MgBr_2$	5	52	25
11	$Sc(OTf)_3$	5	8	57
12	$Ni(acac)_2$	10	52	18
13	Ag_2O	10	14	10
14	$Zn(OTf)_2$	5	70	63
15	$CrCl_3$	5	45	86

Titanium(IV)chloride gave an *ee* of 15% but titanium(IV)tetraisopropoxide resulted in 51% *ee*. This marked difference can be attributed to the fact that these anions also take part in the transition state formed, depending on their binding strength to the metal cation. Calcium chloride proved to be a better Lewis acid as compared to $MgBr_2$ as can be seen from entries 9 and 10 of Table 6. The results obtained with calcium are remarkable as this metal has not often been used in such a type of catalysis as well as it is an environment friendly cation.

Scandium triflate gave a poor yield of 8% with an *ee* of 57%. $Ni(acac)_2$ and silver oxide led to an *ee* of 18% and 10% respectively. The best yield was 70%, obtained by using zinc triflate with an *ee* of 63%. Fe^{+2} proved to be superior to Fe^{+3} as former gave 53% yield with an *ee* of 63% while later provided 32% yield and 49% *ee*. The best *ee* of 86% was obtained with $CrCl_3$. It can be seen that the ligand based on salt **80** is having a wide range of interaction with several metallic cations.

In these experiments, three parts of KO^{t}Bu were added to one part of imidazolinium salt in toluene. As shown in Table 8 this was important in order to deprotonate the C2 position and both hydroxyl groups. After 30 min metallic salt was added and the mixture was stirred for 1h. Then 1-naphthaldehyde **108** was added, followed by the addition of Et_2Zn (1.5 equiv.). The reaction was stirred for 46h at rt and then quenched with 1M HCl. Considering the fact that the ligand contains two hard oxygen ligator atoms and one soft carbene moiety,

could explain why those metals, being in the middle of the hard-soft scale, gave the best results. As catalytic active species a tridentate ligand can be assumed, as it has been reported for tris-oxazoline ligands,[127] which were able to coordinate to a copper centre to give a hexacoordinated stereo-discriminating complex containing the tridentate ligand and one water molecule leaving two co-ordination sides for the substrate.

2.3.1.3. Effect of Catalyst Loadings

The concentration of the catalyst in the diethyl zinc addition to 1-naphthaldehyde could play a pivotal role on the yield and enantiomeric excess of the product.

Table 7. Investigation of salt 80 with different concentrations: (metal salt:salt 80:KO^{t}Bu) (1:1:3), 46h, rt, toluene

Entry	Metal Salt	Salt 80 [mol%]	Yield [%]	*ee* [%]
1	CuI	20	21	80
2		10	22	77
3		5	53	80
4		3	55	83
5		1	51	60
6	$Cu(OTf)_2$	10	3	–
7		5	42	84
8		3	44	77
9		1	24	6

In order to evaluate the effect of concentration of catalyst, CuI and $Cu(OTf)_2$ were employed as these metal entries were proving as the best candidates for further investigation as shown in Table 7. Metal salt to ligand precursor ratio was 1:1. CuI with 20 mol% of NHC precursor **80** gave 21% yield with 80% *ee*. 10 mol% of ligand precursor gave 22% yield and 77% *ee*, 5 mol% of salt gave 53% yield and 80% *ee*. A yield of 55% and 83% *ee* was found when 3 mol% of the imidazolinium salt was used. With $Cu(OTf)_2$, 5 mol% of ligand precursor was found to be the best concentration as it gave 42% yield and 84% *ee*. It is rare but not unknown in the literature, that lower catalyst loading gives better yield and higher *ee*.[128] In the present case the drop of *ee* at lower catalyst loading and therefore lower concentration can be explained by a competitive ligand free background reaction. On the other hand, at a higher catalyst loading and hence concentration, it may be possible that an inactive dimer with two copper atoms and two ligands could be formed.

2.3.1.4. Effect of Nature and Concentration of Bases

In addition, the influence of the bases KHMDS and KO^{t}Bu to generate the carbenes were investigated. The latter was found to give the best results. KHMDS resulted in 28% *ee* when 3 equiv. was used giving a yield of 44% (Table 8, entry 4) while 31% yield was obtained with a low *ee* of 5%, when 2 equiv. of base were applied. KO^{t}Bu was proved to be the best choice. It can be concluded from entries 1-3 of Table 8 that 3 equiv. of KO^{t}Bu is necessary in order to achieve a yield of 42% and an *ee* of 84%. For all these reactions, $Cu(OTf)_2$ was used and ligand to salt ratio was 1:1. The need for 3 equiv. of KO^{t}Bu supports strongly that a tridentate ligand is present in the active catalyst. In addition the enhanced *ee* resulting with KO^{t}Bu can be attributed to the fact that the released ^{t}BuOH is also participating in the formation of the catalytic active species and could coordinate the metal center. That the alcohol plays a role is also shown later, when sterically less hindered ethanol was added, which increased the *ee*.

Table 8. Investigation of base: (metal salt:salt 80) (1:1), 46h, rt, toluene

Entry	Base	Base Conc.	Yield [%]	*ee* [%]
1	KO^{t}Bu	0.3 equiv.	42	84
2		0.2 equiv.	26	36
3		0.1 equiv.	traces	–
4	KHMDS	0.3 equiv.	10	28
5		0.2 equiv.	31	5
6		0.1 equiv.	traces	–

2.3.1.5 Effect of Temperature

In order to further optimize the diethylzinc addition to 1-naphthaldehyde, the reaction was carried out at different temperatures. It was found that by lowering the temperature to 0 °C, the yield decreased markedly to 8% and also a slight lower *ee* of 73% was observed (Table 9, entry 5). Further decrease in temperature also decreased the *ee* to 9% (Table 9, entry 4). For this experiment, *n*BuLi was used as base instead of KO^{t}Bu, showing again the importance of the presence of ^{t}BuOH for the enantioselective reaction. When the reaction was carried out at 40 °C, the results were almost similar as obtained, when the reaction was performed at rt (Table 9, entries 1 and 2). An increase of the temperature to 60 °C led to a decrease in yield and *ee* of the product, respectively (Table 9, entry 3). The decrease of the *ee* at higher temperature is obvious since an enantioselective catalyzed reaction is kinetic controlled. The decrease of the yield and more important the *ee* at lower temperatures could be explained by the formation of different catalytic copper species and clusters. Similar

unusual relationships have been observed by Hoveyda[129] and Leighton[130] in the copper catalyzed enantioselective conjugated addition with chiral phosphine ligands.

Table 9. Investigation of temperature: (metal salt:salt 80) (1:1), 46h, rt, toluene

Entry	Salt	t [°C]	Yield [%]	*ee* [%]
1	Cu I	rt	53	80
2		40	43	83
3		60	29	56
4[a]	$Cu(OTf)_2$	–50	47	9
5		0	8	73

[a] *n*BuLi was used as a base.

2.3.1.6. Effect of Salt to Ligand Precursor Ratio

It is known that salt to ligand precursor ratio can play a crucial role in controlling the outcome of a reaction particularly in terms of yield. In case of $Cu(OTf)_2$ the yield of the product was increased to 76% from 42% as salt to ligand ratio was changed from 1:1 to 1:2. The enantiomeric excess experienced a slight drop from 84% to 73% (Table 10, entries 1 and 2). The reversal of this optimized M:L ratio gave 35% yield and 11% *ee* (Table 10, entry 3). This can be explained by a ligand free background reaction. In case of $Ti(^{i}PrO)_{4,}$ when metal salt to ligand precursor ratio was changed from 1:1 to 1:2, yield improved from 41% to 54% and the *ee* from 51% to 75%.

Table 10. Effect of salt to ligand precursor ratio

Entry	Salt	Salt:Ligand precursor	Yield [%]	*ee* [%]
1	$Cu(OTf)_2$	1:1	42	84
2		1:2	76	73
3		2:1	35	11
4		1:4	60	70
5	$Ti(^{i}PrO)_4$	1:1	41	51
6		1:2	54	75

2.3.1.7. Role of Additive

Addition of additives in certain chemical reactions has a huge impact upon the yield and enantioselectivity of the products.[131] therefore, the influence of ethanol, as an additive was explored. It was found that addition of ethanol as an additive in the diethylzinc addition to 1-naphthaldehyde showed a marked increase in *ee* of the product i.e. 85% as compared to 73%, which was obtained without addition of any additive. However, the yield decreased slightly from 76 to 65%. The role of ^{t}BuOH has already been explained in the section

Table 11: Role of additive

Entry	Additive	Yield [%]	*ee* [%]
1	–	76	73

2	EtOH	65	85

2.3.1.8. Effect of Solvent

Different solvents have been screened in the reaction. Hexane gave poor results of 48% yield and 7% *ee* of the product. As compared with the results obtained in toluene (Table 12, entry 2), the results with other solvents are not satisfactory. In 1,4-dioxane the formed product was racemic. Dichloromethane and acetonitrile were not obviously expected to give good results as these solvents may also react upon addition of base required for the generation of the carbene ligand.

Table 12: Effect of Solvent

Entry	Solvent	Yield [%]	*ee* [%]
1	Hexane	48	7
2	Toulene	76	73
3	1,4-Dioxane	24	0
4	Dichloromethane	8	10
5	Acetonitrile	12	–

2.3.1.9. Scope of Substrates

Finally, different aldehydes were used under the optimized conditions as shown in Table 13. Benzaldehyde was converted to the corresponding secondary alcohol in 59% yield with 75% *ee*. The electronic effect on benzaldehyde was then explored. The results suggest that electron withdrawing groups at the *para* position of the benzaldehyde activates the aldehyde

group leading to better results. 2-Naphthaldehyde gave lower *ee* and yield as compared to 1-naphthaldehyde.

Table 13: Enantioselective diethylzinc addition to aldehydes[a]

Entry	Aldehyde	Yield [%]	*ee* [%]	Config.
1	2-Naphthaldehyde	57	50	*R*
2	Benzaldehyde	59	75	*R*
3	*p*-Chlorobenzaldehyde	60	78	*R*
4	*p*-Methylbenzaldehyde	50	71	*R*

[a] $Cu(OTf)_2$:**80**:KO^{t}Bu/1:2:3, 46h, rt, toluene.

2.3.1.10. Linear vs. Non-Linear Effect

Furthermore the catalytic system was examined if a non-linear effect is present, since the best results were obtained with a metal:ligand ratio of 1:2. Both enantiomers of norephedrine based on imidazolinium salt **80** were mixed with different ratios. The graph obtained shows a slight deviation from the linearity as can be seen from the following graph below (Figure 2). However, taking the error range into consideration no non-linear effect is present and the benefit of using a larger amount of ligand is in order to suppress a ligand free catalyzed background reaction. It can be assumed that one ligand is coordinating one metal centre and no metallic dimers are formed.

Linear vs. non-linear effect:

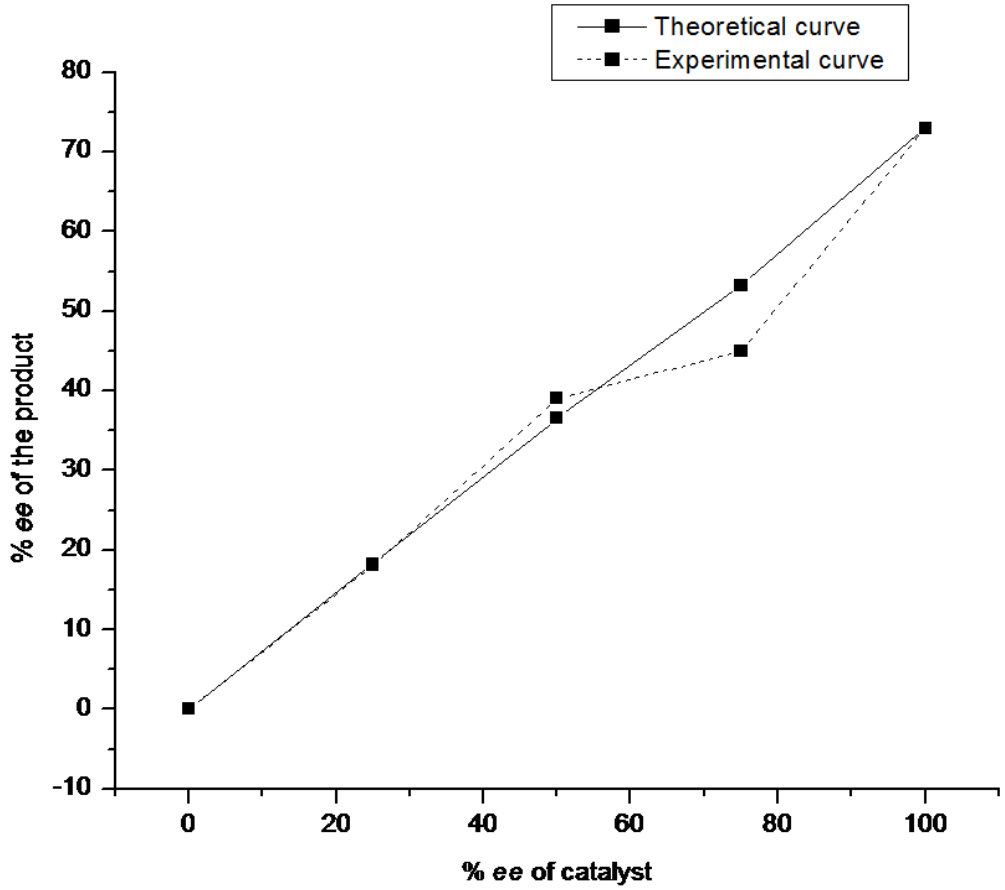
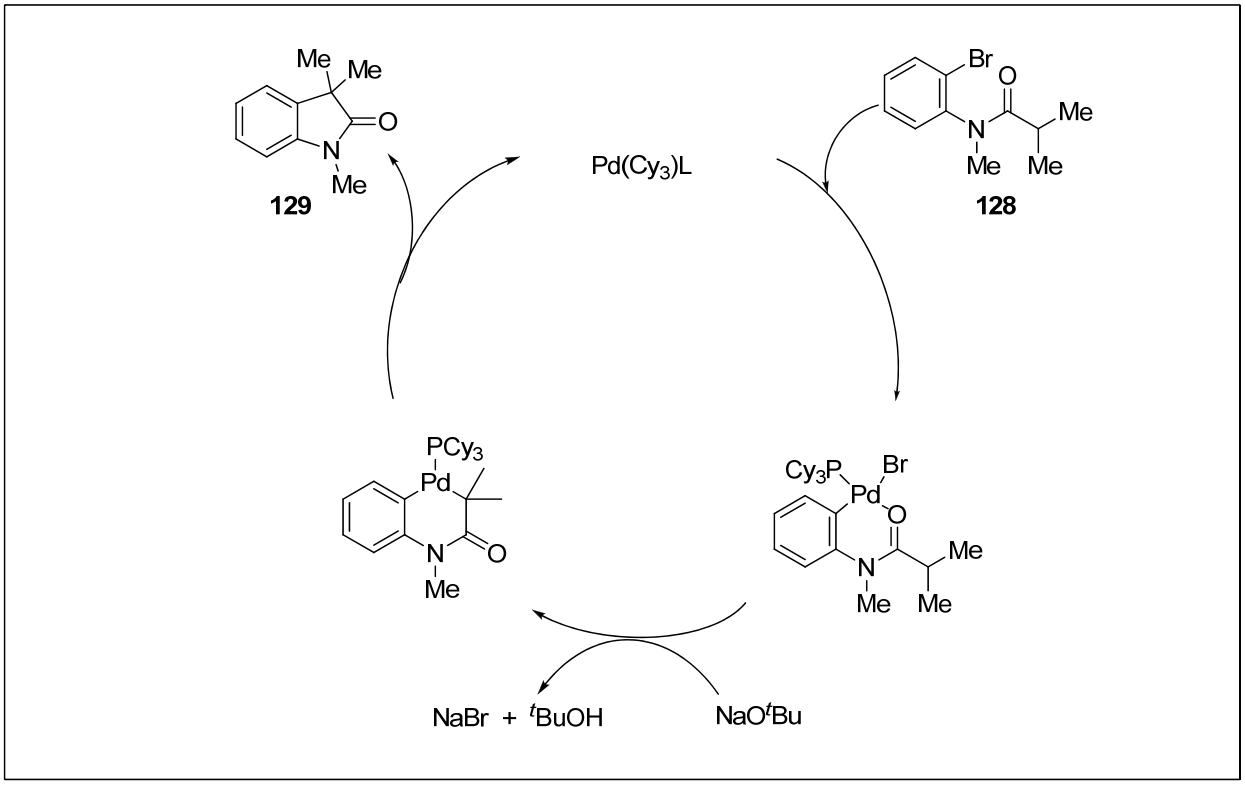


Figure 2. Absence of a non-linear effect

2.3.2. Asymmetric Intramolecular *α*-Arylation of Amides

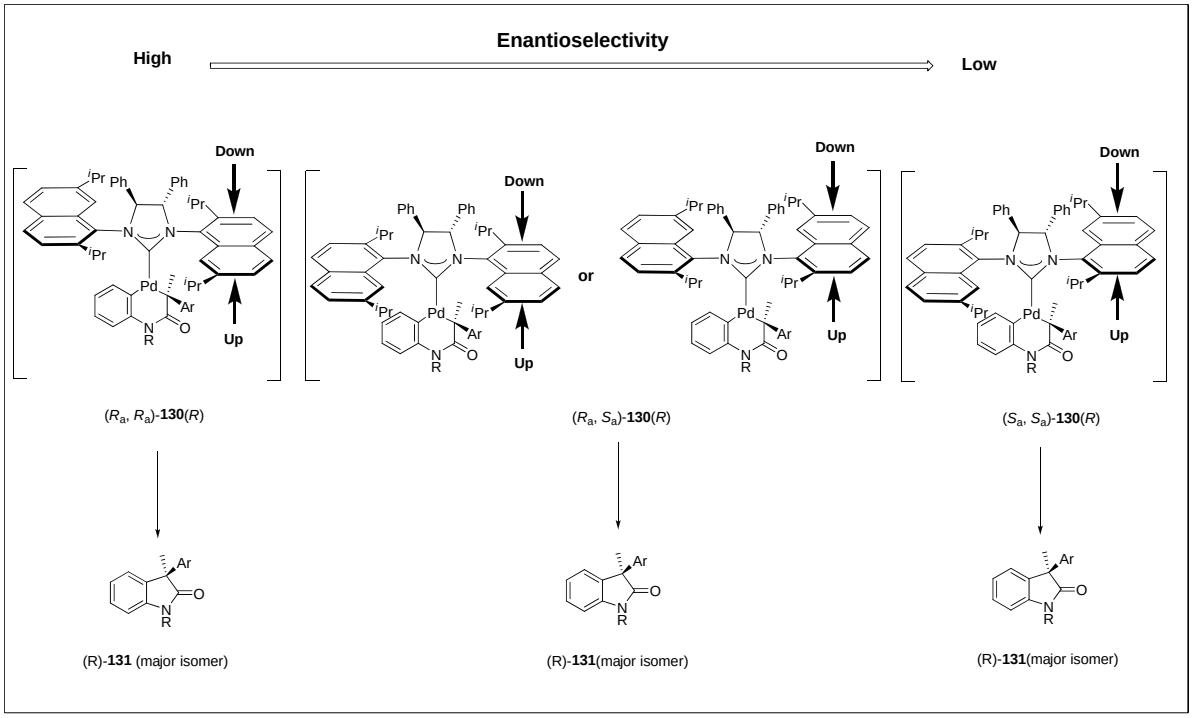
α-Arylation of amides is synthetically an important method for C-C bond formation. The palladium catalyzed *α*-arylation of carbonyl compounds is a simple transformation as compared to traditional methods. Due to the importance of oxindoles in many biologically active molecules,[132, 133] it is highly desirable to design strategies providing high yields and enantioselectivity of oxindoles. The asymmetric intramolecular *α*-arylation was first carried out by Hartwig *et al*.[98] The mechanistic study of the reaction was carried out by the same group. Scheme 47 sketches the proposed mechanism for cyclization to form oxindoles.



Scheme 47

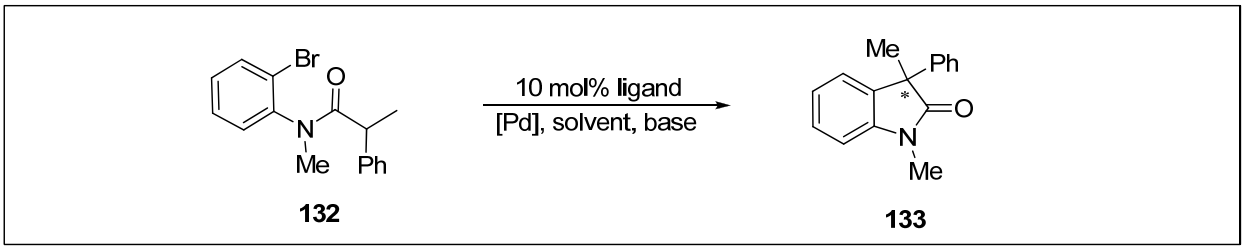
The first step involves the oxidative addition of the substrate resulting in a monomer complex coordinated with the oxygen of carbonyl group. Then deprotonation of the complex formed occurs by treating with NaO^{t}Bu. This deprotonation step is fast as proved by the immediate disappearance of the ^{31}P NMR resonance of the starting complex. The reductive elimination step results in the formation of oxindole product.

A recent study[134] explains the high enantioselectivity of the product **131** achieved when newly synthesized monodentate ligands were employed. Each ligand bearing 2-substituted naphthyl side chains existed in three diastereomeric forms. These diastereomers were isolated when complexed with palladium. The palladium complex of each diastereomers gave different enantioselectivities when tested in the reaction. A model was proposed accounting for the differences in selectivity between the three diastereomeric palladium complexes. Due to the transmission of steric pressure of the NHC-phenyl groups onto the enantiodiscriminating side of the substrate through naphthyl side chains, intermediates **130** were formed predominantly. The reason for getting high enantioselectivity with (*Ra*,*Ra*)-**130**(*R*) diastereomeric intermediate was due to the favored orientation of methyl with respect to aromatic group of the substrate. On the other hand, in (*Sa*,*Sa*)-**130**(*R*) diastereomeric intermediate the orientation of the methyl group is not favored leading to low enantiomeric excess of the product.



Scheme 48

As the reaction was less investigated in terms of factors affecting the yield and enantioselectivity of the product, we were keen to explore the different parameters of the reaction shown in Scheme 49.



Scheme 49

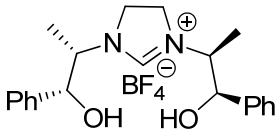
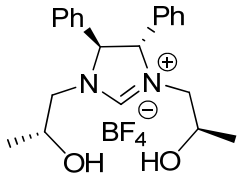
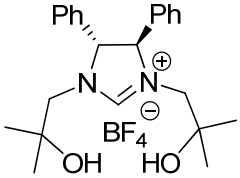
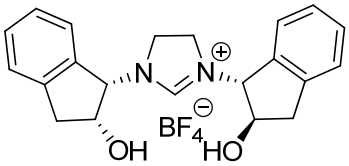
2.3.2.1. Nature of Ligand Precursors

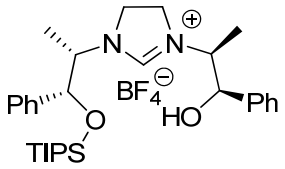
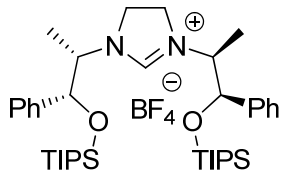
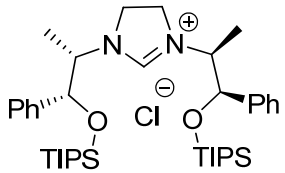
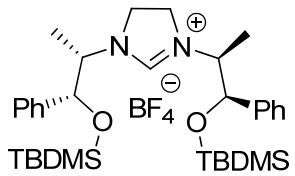
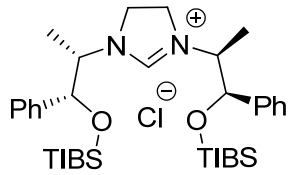
As intrigued from our previous results employing imidazolinylidene ligands incorporating hydroxy groups in the asymmetric diethyl zinc addition to aldehydes,[107] we first thought to use these ligand precursors in combination with palladium in the asymmetric α-arylation reaction (Scheme 49).

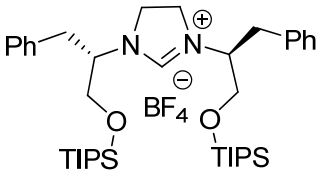
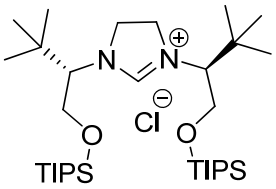
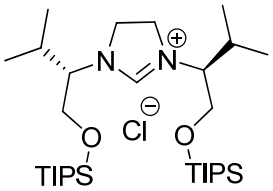
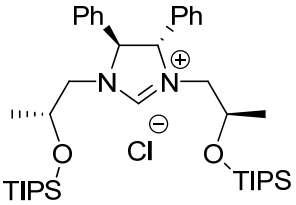
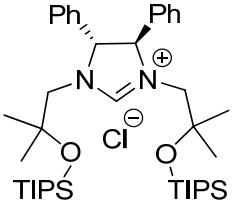
Norephedrine based ligand precursor **80** was initially tested for the reaction. The product **133** was obtained in 17% yield with 7% *ee*. Salts **88** and **89** too gave lower yields and *ee*s. In general, it was noted that the imidazolinium salts incorporating hydroxy groups gave poor yield with no appreciable *ee* (Table 14, entries 2, 3, 4, and 5). Recovery of starting material

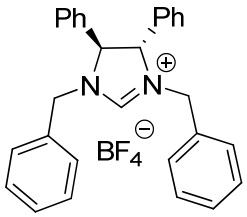
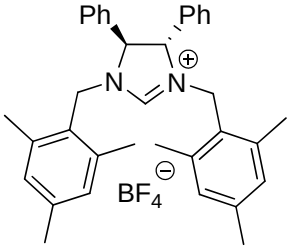
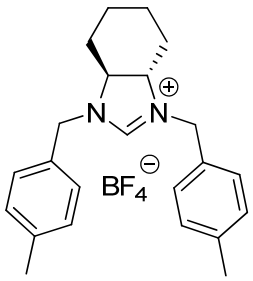
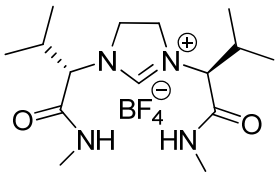
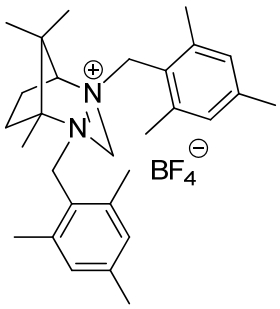
in all these experiments indicated that the hydroxy groups of satls **80, 88, 89** and **114** were not showing compatibility with palladium metal or the rate of decomposition of the *in situ* generated complex was faster than the rate of conversion of the starting material. This postulate was further confirmed when bidentate imidazolinium salt **94**, of which one hydroxyl group was protected with tri*iso*propylsilyl was employed under the same conditions and moderate yield of 43% with an *ee* of 10% was achieved (Table 14, entry 6). The results were improved with monodentate ligands having both hydroxy groups protected with different silylating agents.

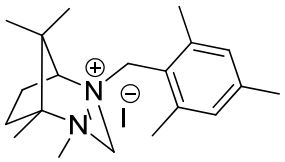
Table 14: Ligand precursors screening in the asymmetric *α*-arylation

Entry	Salt	Yield [%]	*ee* [%]	Config.
1	–	traces	–	–
2	 **80**	17	7	*S*
3	 **88**	20	5	*S*
4	 **89**	27	5	*R*
5[e]	 **114**	traces	–	–

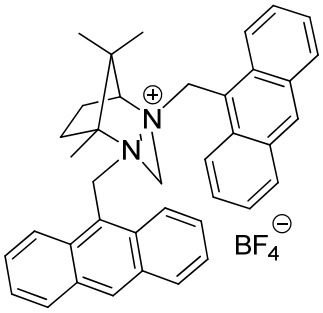
6	 **94**	43	10	*S*
7	 **90**	40	30	*S*
8	 **91**	64	45	*S*
9	 **92**	26	10	*S*
10	 **93**	30	3	*S*

11	 **95**	27	0	–
12[b,c]	 **97**	31	27	*R*
13	 **99**	77	27	*R*
14[c]	 **100**	85	20	*S*
15[d]	 **101**	66	40	*R*

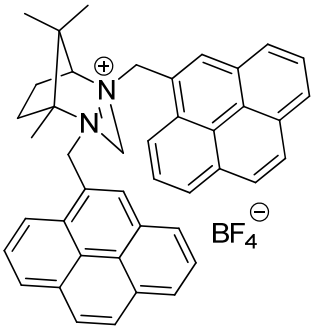
16[e]	 **117**	20	0	–
17[e]	 **118**	20	0	–
18[e]	 **119**	25	0	–
19	 **102**	21	0	–
20[f]	 **120**	88	3	*R*

21[f]		32	3	*R*

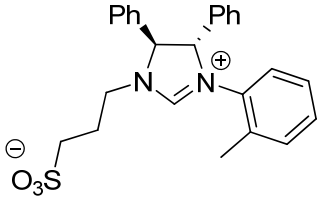
121

22[f]		43	9	*R*

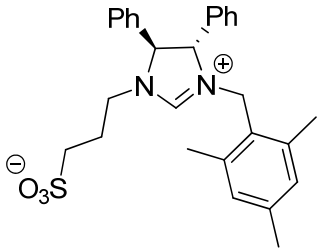
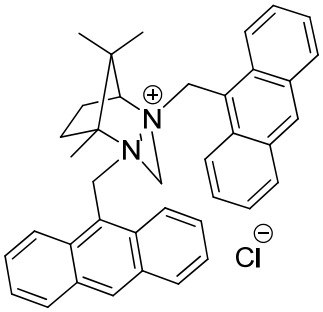
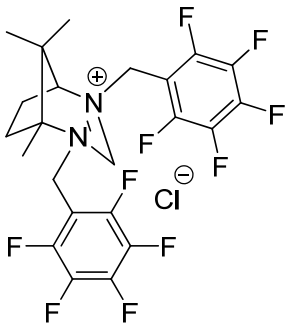
122

23[f]		72	9	*R*

123

24[g]		43	0	–

124

25[g]	 **125**	78	10	*S*
26[h]	 **126**	35	5	*R*
27[h]	 **127**	22	3	*R*

[a] Reaction conditions: Pd:L 1:1 for experiments 1-5 and 1:2 for 6-9 in 1,4-dioxane, 10 mol% $Pd(OAc)_2$, 60 °C, 3 equiv. LiO^tBu, 24h; [b] 1.5 equiv. NaO^tBu as base; [c] Reaction was carried out at 80 °C for 64h since no conversion was observed at 60 °C; [d] M:L 1:2. [e] salts were provided by O. Sereda. [f] salts were provided by Dr. Reddy. [g] ligand precursors were provided by S. Tabassum. [h] salts were provided by Prof. R. Wilhelm,

The introduction of chloride as counter anion in salt **91** instead of the tetrafluoroborate anion of salt **90** provided the ligand in white crystalline form and gave a better yield of 64% and an *ee* of 45% when applied in this arylation reaction (Table 14, entry 8). Attempts were made to improve results by varying crowding around the oxygen atoms with various silylating protective groups. Less bulky TBDMS in comparison with TIPS provided lower yield of 26% with an *ee* of 10%. More bulky TIBS group showed no improvement at all.

The next effort was to observe the change in the outcome of the reaction by varying substituents of different sizes at the chiral centres. The imidazolinium salts having chiral centres in the side chains joined directly with the nitrogen atoms of the ring bearing benzyl, *tert*butyl and *iso*propyl gave no satisfactory results (Table 14, entries 11-13). Then two more imidazolinium salts **100** and **101** were tested which were having two phenyl groups at the backbone. Salt **100** gave an excellent yield of 85% but with a low *ee* of 20% (Table 13, entry 14). Imidazolinium salt **101** with two methyl groups at the carbon next to the oxy-tri*iso*propylsilyl group gave a yield of 66% and moderate enantioselectivity of 40% (Table 14, entry 15).

The previously reported salt **48**[99] possessing chirality in the backbone and sterically crowded adamantly methylene groups as *N*-substituents at the imidazoline ring showed asymmetric induction in the reaction. We have also tested such type of ligand precursors developed in our group. Ligand precursor **117** having benzyl substituents at the nitrogen atoms of the ring gave 20% yield of the product without any *ee* (Table 14, entry 16). Changing the substituent size from benzyl to mesityl did not improve the results.

To date, only a few carbene precursors based on camphor have been reported,[135,136] therefore a series of this type of ligands was developed in our group. The striking feature of these ligands is the NCN unit being embedded in a rigid bicyclic system, so becoming a part of six and seven membered ring. Hence, their carbenes are more basic than carbenes derived from imidazolium and imidazolinium salts.[137] Additionally, by limiting the free rotation of a substituent next to the C-10 methyl group of the camphor skeleton could improve the asymmetric induction in the catalytic reaction. Due to these structural features we screened these new ligands in the asymmetric α-arylation reaction. Salt **120** that contained mesityl-methylene groups as *N*-substituents of the ring was successful in providing an excellent yield of 88% of the oxindole **133** but with poor enantioselectivity. One of the two mesityl-methylene substituents of salt **120** was replaced by a methyl group and this salt **121** with an iodide anion was applied in the reaction. There was no improvement in *ee* and yield also dropped from 88% to 32%. This indicated bulky *N*-substituents on both nitrogen atoms were needed. A yield of 43% with 9% *ee* was observed when camphor based salt **122**, having *N*-anthracene methylene substituents, was applied (Table 14, entry 22). The change of the BF_4 anion of this salt with Cl showed no improvement in the reaction outcome (Table 14, entry 26). The yield was 72% when phenanthrene units were the *N*-substituents of salt **123**. Salt

127 with hexasubstituted fluorobenzyl *N*-substituents gave a yield of 22% with 3% *ee* (Table 14, entry 27).

Also the imidazolinium zwitterions **124** and **125** bearing alkylsulfonate substituents were tested in the *α*-arylation reaction. The yield and *ee* obtained with salt **125** were improved due to the bulky mesityl group (Table 14, entries 24 and 25).

2.3.2.2. Effect of Nature of Base

Different bases were screened in the reaction. NaOTMS and KO^{t}Bu did not result in any product. Whereas NaHMDS gave a poor yield of 33% without any *ee*. LiO^{t}Bu gave a yield of 90% with 65% *ee* of the product and NaO^{t}Bu gave 85% yield with 71% *ee*. The results are summarized in Table 15. In each case 3 equiv. of the base was added and the reaction was performed in 1,4-dioxane. Our findings about the role of KO^{t}Bu being an inefficient base and LiO^{t}Bu providing promising results are in agreement with an earlier report.[99] Bases like NaOTMS and NaHMDS are thought to interact with the catalytic metal complex due to the silyl moiety rendering the catalyst inertness.

Table 15: Effect of nature of base[a]

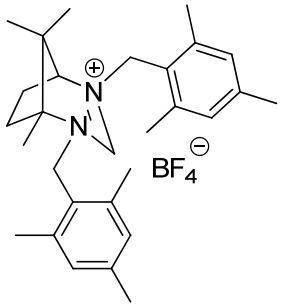
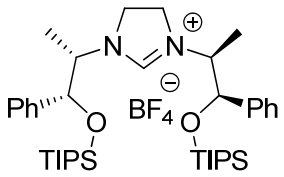
Entry	Base	Yield [%]	*ee* [%]
1	LiO^{t}Bu	90	65
2	NaO^{t}Bu	85	71
3	NaHMDS	33	–
4	NaOTMS	–	–
5	KO^{t}Bu	–	–

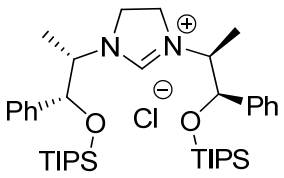
[a] Reaction conditions: 10 mol% salt **91**, 24h, 3 equiv. base, 60 °C, $Pd_2(dba)_3$, M:L 1:2,.1,4-dioxane.

2.3.2.3. Effect of Solvent

In order to evaluate the effect of solvents, the ligands giving the best results were chosen. Salt **120** gave a low yield of 35% with an *ee* of 5% in toluene as compared with 88% yield with an *ee* of 3% when the reaction was carried out in 1,4-dioxane. Hexane showed a marked influence on the reactivity of salt **90** by a drop in yield from 60% to 15% and decrease in *ee* from 40% to 5% as compared with the results obtained with 1,4 dioxane (Table 16, entries 3 and 4). The 1,4-dioxane again proved to be the best solvent when the reaction was carried out with imidazolinium salt **91**. Toluene gave a comparatively low yield of the product. 1,4-Dioxane provided the best results with all ligands tested. The plausible reason could be the coordinating ability of this solvent for LiO^{t}Bu.

Table 16: Effect of solvent[a]

Entry	Ligand Precursor	Solvent	Yield [%]	*ee* [%]
1		1,4-Dioxane	88	3
2	**120**	Toluene	35	5
3		1,4-Dioxane	40	30
4	**90**	Hexane	15	5

5		1,4-Dioxane	90	65
6		Toluene	67	61
7	**91**	DME	–	–

[a] Reaction conditions: 10 mol% ligand precursor, 24h, 3 equiv. LiO^tBu, 60 °C, for experiments 5-6 $Pd_2(dba)_3$ while rest was with $Pd(OAc)_2$, M:L 1:2 for experiments 1-4, while 1:1 for experiments 5-7.

2.3.2.4. Effect of Concentration of Base

The choice of a base is very crucial in this arylation reaction. After screening several bases, LiO^tBu and NaO^tBu were found the best ones for the catalytic system. Effect of concentration of base was evaluated. It was noticed that 1.5 equiv. of LiO^tBu gave the oxindole in 45% yield with an *ee* of 30%. A yield of 40% was observed with same *ee* when 3 equiv. of base was used (Table 17, entry 2). The *ee* dropped from 71% to 60% by using 3 equiv. of NaO^tBu with a slight improvement in yield from 78% to 82%.

Table 17: Effect of concentration of base[a]

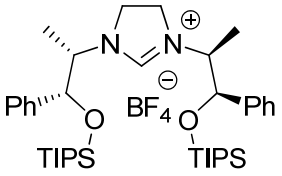
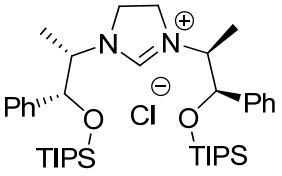
Entry	Base	Conc. Of Base	Yield [%]	*ee* [%]
1	LiO^tBu	1.5 equiv.	45	30
2		3 equiv.	40	30
3	NaO^tBu	1.5 equiv.	78	71
4		3 equiv.	82	60

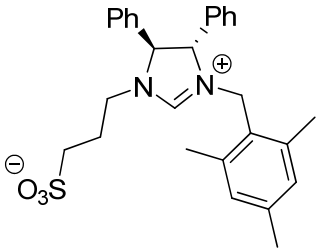
[a] Reaction conditions: 10 mol% ligand precursor, 24 h, 1,4-dioxane, 60 °C, for experiments 1-2 $Pd(OAc)_2$ and M:L 1:1, for experiments 3-4 $Pd_2(dba)_3$ and M:L 1:2.

2.3.2.5. Effect of Salt to Ligand Precursor Ratio

Initially, optimization of reaction conditions was carried out with ligand precursor **90**. By changing M:L ratio from 1:1 to 1:2, the yield improved from 40% to 60% and the *ee* from 30% to 43% (Table 18, entries 1 and 2). Further optimization with salt **91** gave the best results. By using M:L ratio of 1:2, the yield was improved to an excellent level of 95% but with a moderate *ee* of 45% (Table 18, entry 4). This demand of high concentration of ligand as compared to palladium could be explained by a ligand free metal catalyzed background reaction. The results achieved by employing ligand precursor **125** were different as obtained from salts **90** and **91**. With this imidazolinium salt **125**, 1:1 M:L ratio provided a yield of 78%. The yield dropped to 40% when M:L ratio was switched from 1:1 to 1:2. As this imidazolinium zwitterion ligand precursor **125** bears an additional coordinating alkylsulfonate group and therefore assumed to catalyze the reaction by following a reaction route different from monodentate ligand precursors **90** and **91**.

Table 18: Effect of salt to ligand precursor ratio[a]

Entry	Ligand	Salt:Ligand precursor	Yield [%]	*ee* [%]
1		1:1	40	30
2	**90**	1:2	60	43
3		1:1	64	45
4	**91**	1:2	95	45

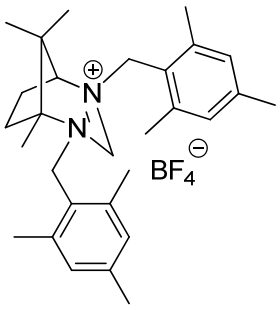
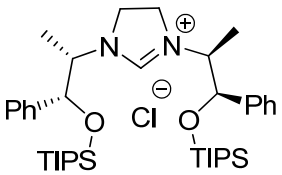
5		1:1	78	10
6		1:2	40	10
	125			

[a] 10 mol% ligand precursor, 3 equiv. LiO^{t}Bu, 1,4-dioxane, 60 °C, 24h

2.3.2.6. Effect of Temperature

For observing the influence of temperature, salt **120** has been selected because it gave an excellent yield of 88% but only 3% *ee* at 60 °C. No improvement in *ee* was observed by lowering the temperature. At 40 °C only traces of the product were formed while no reaction occurred at room temperature. Ligand precursor **91** was screened at different temperatures of the reaction mixture. Again no product was formed at room temperature.

Table 19: Effect of temperature[a]

Entry	Salt	t [°C]	Yield [%]	*ee* [%]
1		rt	–	–
2		40	traces	–
3		60	88	3
	120			
4		30	–	–
5		45	traces	–
6	**91**	60	50	43

[a] Reaction conditions: 10 mol% salt, 24h, 1,4-dioxane, $Pd(OAc)_2$, M:L 1:1 for experiments 1-3 and M:L 1:2 for entries 4-6.

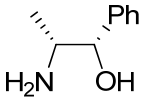
In all these experiments, starting material was recovered after the workup. Thus high temperature requirement for our catalytic complex was indicated. At low temperature no catalytic active complex is formed. Some experiments were also carried out at temperature higher than 60 °C by applying ligand precursor **91** but no improvement was observed.

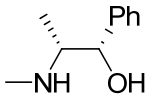
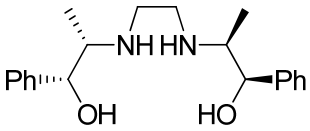
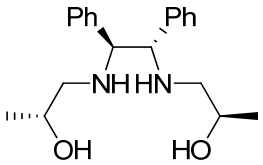
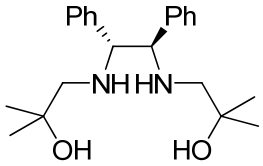
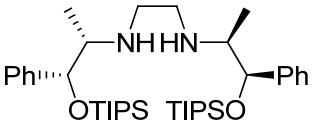
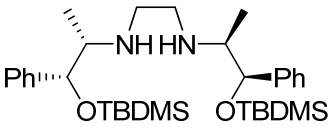
2.3.2.7. Application of Amines and Amino Alcohols in the Palladium Catalyzed *α*-Arylation

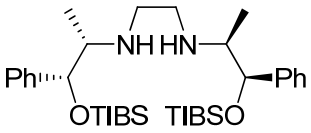
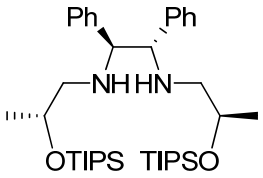
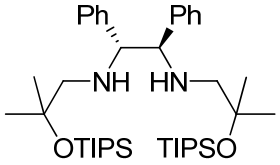
Amino alcohols have been explored as ligands in nickel-catalyzed Suzuki Reactions of unactivated alkyl halides, including secondary alkyl chlorides, with aryl boronic acids[138] and Hiyama reactions of activated and unactivated secondary alkyl halides.[139] But there was no report so far in exploiting these simple amino alcohols and diamines in the palladium catalyzed *α*-arylation reaction. An attempt was made to use diamines, amino alcohols and hydroxy protected diamines in the palladium catalysed intramolecular *α*-arylation reaction. The results are summarized in Table 20.

Norephedrine gave a yield of 29% with an *ee* of 13%. The yield of the product was doubled when *N*-methylated norephedrine was employed (Table 20, entry 3). This indicated the influence of the methyl group on the catalytic metal complex as well as a confirmation about the attachment of an amino group to the palladium centre.

Table 20: Application of amines and amino alcohols in the palladium catalyzed *α*-arylation[a]

Entry	Ligand	Yield [%]	*ee* [%]	Config.
1[b]		24	–	–
2[c]	 **51**	29	13	*R*

3[c]		55	–	*R*
4	 **56**	53	10	*S*
5	 **68**	50	4	*S*
6[c]	 **69**	27	–	–
7[c]	 **71**	72	7	*S*
8	 **72**	42	20	*S*

9	 **73**	45	15	*S*
10	 **77**	55	0	–
11	 **78**	43	20	*R*

[a] Reaction conditions: Pd:L is 1:2 for experiments 1,5 and 8-11 while for the rest is 1:1, $Pd(OAc)_2$, 60 °C, 1,4-dioxane, 3 equiv. LiO^tBu, 40h. [b] 80 °C, 56h. [c] Reaction was carried out for 20h.

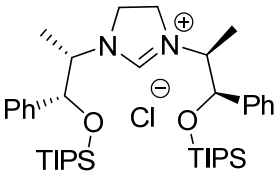
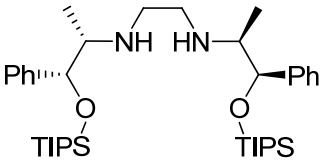
Among the bis-hydroxy diamines employed in the reaction, diamine **56** gave the highest yield of 53% with 10% *ee* of the product. Bis-hydroxy diamine **68** gave similar results. There was a drop in yield when **69** was applied (Table 20, entry 6). The next step was to employ diamines with hydroxy groups protected with sterically different silylating reagents. Bis-hydroxy protected diamine **71** gave the highest yield of 72% with a low *ee* of 7%. By introducing less bulky TBDMS protecting groups on the oxygen atoms, the *ee* was improved from 7% to 20% accompanied with a drop in yield. On the other hand diamine **73** with bulky TIBS groups could result in 45% yield and 15% *ee* of the product. A maximum of 20% *ee* was also achieved by applying diamine **78** (Table 20, entry 11).

2.3.2.8. Investigation of the Metal Source

As there were some results published on intermolecular α-arylation of ketones by using Ni[140] we also used to sort out metals other than palladium. Bis-hydroxy protected diamine

71 was selected as it gave a high yield of 72%. $Cu(OTf)_2$ gave no results. Only traces of the product were recovered when $Ni(cod)_2$ was applied as a metal source (Table 21, entries 3-5).

Table 21: Investigation of metal source[a]

Entry	Ligand/Ligand Precursor	Metal Source	Yield [%]	*ee* [%]
1		$Pd(OAc)_2$	95	45
2	**91**	$Pd_2(dba)_3$	90	65
3		$Pd(OAc)_2$	72	7
4	**71**	$Cu(OTf)_2$	–	–
5[b]		$Ni(cod)_2$	traces	–

[a] Reaction conditions: Pd:L 1:2 for experiments 1-2 and 1:1 for 3-5 in 1,4-dioxane, 10 mol% ligand, 60 °C, 3 equiv. LiO^tBu, 24h; [b] At 85 °C no product then at 60 °C for 24h.

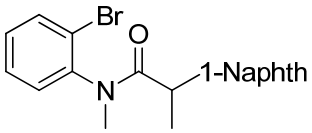
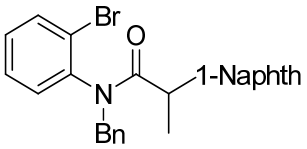
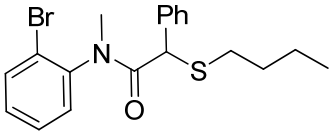
Monodentate imidazolinium carbene precursor **91** was investigated by changing the source of palladium from $Pd(OAc)_2$ to $Pd_2(dba)_3$. It was found that this change could lead to an improvement in *ee* from 45% to 65% (Table 21, entries 1 and 2).

2.3.2.9. Scope of Substrate

According to the model shown in Scheme 49a, a six-membered intermediate is formed when palladium oxidatively adds to the substrate. The relative position of the substituents on the α-carbon of the substrate with respect to ligand orientation determines the configuration of the newly formed stereogenic centre. In order to evaluate the effect of substituents of the α-carbon and nitrogen of the amide substrate, a number of substrates have been screened Substrate **134** having 1-naphthyl as substituent showed a yield of 75% with 31% *ee* of the

product. The methyl at the nitrogen atom of the substrate was replaced by a benzyl group and this substrate resulted in a moderate yield of 59% with 31% *ee*.

Table.22: Scope of substrate[a]

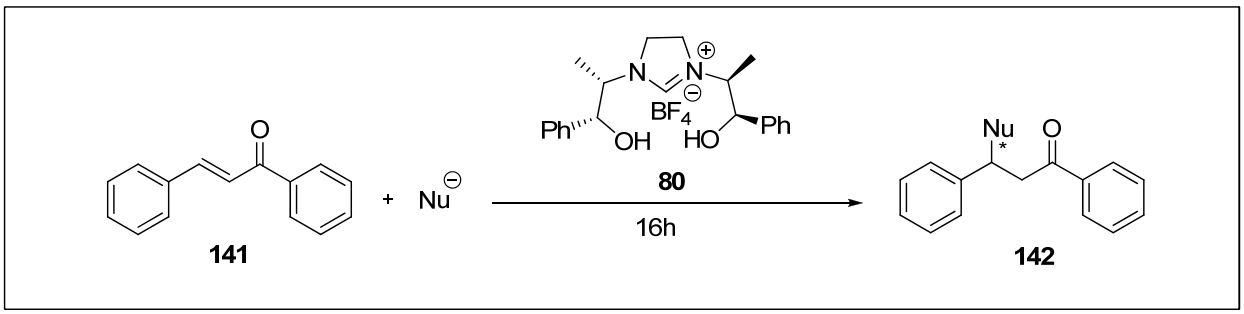
Entry	Substrate	Yield [%]	*ee* [%]	Config.
1	 **134**	75	31	*S*
2	 **136**	59	31	*S*
3	 **138**	–	–	–

[a] Reaction conditions: Pd:L 1:2, 1,4-dioxane, 10 mol% salt **91**, 80 °C, 24h; 3 equiv. LiO^tBu and $Pd(OAc)_2$for entries 1 and 2 while for entry 3 $Pd_2(dba)_3$ and 1.5 equiv. NaO^tBu.

Due to the importance of oxindoles with heteroatoms at the stereogenic centre in medicinal chemistry such as the potent growth hormone secretagogue SM-130686,[141] the clinical candidate AG-041R as gastrin/CCK-B[142] receptor antagonist and SSR-149415 as a drug under clinical trial for treatment of anxiety and depression,[143] a recent publication deals with the enantioselective oxindoles formation with new chiral centres bearing alkoxy and amino groups.[98] Therefore, the new substrate **138** was prepared which could give rise to oxindole bearing a sulfur heteroatom at the stereogenic centre. So far, no product was reported and optimization of the reaction conditions is required.

2.3.3. Asymmetric Michael Addition to Chalcone

The enantioselective Michael addition represents one of the most intensively investigated fields in organic synthesis.[144] However, Michael additions to acyclic enones catalyzed by *N*-heterocyclic carbene ligands did not give satisfactory results yet.[74] The bis-hydroxy incorporating imidazolinium carbene precursor **80** was tested in the 1,4-conjugate addition of different nucleophiles to chalcone **141** (Scheme 50).



Scheme 50

2.3.3.1. Michael Addition of Dimethylmalonate to Chalcone

The most common metal used for the dimethylmalonate addition to chalcone is copper. Calcium was also reported to catalyze the asymmetric Michael addition in combination with chiral BINOL.[145] Because of the importance of calcium being environment friendly, cheaper and readily available, calcium in combination with chiral ligand precursor **80** was applied in the dimethylmalonate addition to chalcone.

The reactions were carried out by using different calcium sources, bases and solvents. A maximum of 19% *ee* was observed when the reaction was carried out in toluene/EtOH (Table 23, entry 2). The reaction was not giving any *ee* when it was performed in toluene without the addition of EtOH. A low yield of 18% was observed when THF was used as solvent. By changing the base from KO^{t}Bu to KHMDS, yield was improved to 68% (Table 23, entries 3 and 5). The same yield of 68% was obtained when the reaction was carried out in toluene by employing CaH_2 or $CaCl_2$ (Table 23, entries 5 and 6). However, a solvent effect on the yield of the product was observed when CaH_2 was used in THF probably due to the better solubility of CaH_2 in THF (Table 23, entries 5 and 7).

Table 23: Michael addition of dimethylmalonate to chalcone

Entry	Salt	Solvent	Base	Yield [%]	*ee* [%]
1	-			13	0
2	$CaCl_2$	Toluene+EtOH	KO^{t}Bu	29	19
3		Toluene		41	0
4		THF		18	0
5	CaH_2	Toluene	KHMDS	68	0
6	$CaCl_2$			68	0
7	CaH_2	THF		34	0

2.3.3.2. Michael Addition of Diethylmalonate to Chalcone

In the diethylmalonate addition to chalcone different parameters of the reaction were varied for the improvement in yield and *ee* of the product. The chiral ligand precursor **80** along with $Cu(OTf)_2$ gave a yield of 73% without any asymmetric induction. The yield was improved to 81% when $Sr(NO_3)_2$ was used as metal source in the reaction. A blank reaction employing $Sr(NO_3)_2$ gave an excellent yield of 92% (Table 24, entry 5). The change of base from KO^{t}Bu to NaH resulted in 76% yield and 20% *ee* of the product (Table 24, entry 6). In order to enhance the *ee* of the product, the reaction was carried out at –20 °C but no improvement was observed. Furthermore, lowering of temperature reduced the yield to 62% but had no influence on the *ee* (Table 24, entry 10). $BaCl_2$ gave an excellent yield of 85% without any *ee*.

Table 24: Michael addition of diethylmalonate to chalcone[a]

Entry	Salt	Base	t [°C]	Yield [%]	*ee* [%]
1	$Cu(OTf)_2$	KO^tBu	rt	73	0
2	$Ni(acac)_2$			12	0
3	$CaCl_2$			27	8
4	$Sr(NO_3)_2$			81	0
5[b]				92	–
6		NaH		76	20
7			–20	87	13
8	$BaCl_2$			85	0
9[c]	-			94	0
10	$Sr(NO_3)_2$		–78 - –40	62	

[a] Reaction conditions: 3 equiv. base. M:L ratio was 1:2 for experiments 1-2 while 1:1 for the rest, solvent was toluene for experiments 1-5 and THF for 6-10; [b] without ligand, after 16h, base was added; [c] without metal salt.

2.3.3.3. Addition of Other Michael Nucleophiles to Chalcone

For evaluating the effect of steric crowding of the ester groups, di*iso*propyl and di*tert*butyl malonate esters were added to chalcone. Bothe nucleophiles gave excellent yields of 85% and 82% respectively but no *ee* was observed.

The aniline was tested but only traces of the product were recovered. The Michael addition of Et_2Zn was also performed employing imidazolinium salt **80** in combination with different metal salts. $Ni(acac)_2$ proved to be the best metallic salt as it gave a yield of 99% (Table 25, entry 6). The yield dropped to 68% when the reaction was carried out at –78 °C using

KHMDS as base. The reaction with $Ni(acac)_2$ gave a yield of 5% when the base was absent in the reaction mixture (Table 25, entry 8).

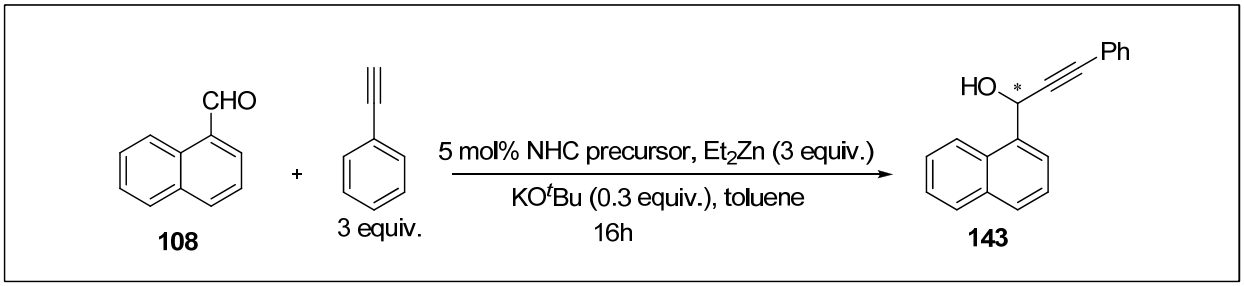
Table 25: Addition of Michael nucleophiles to chalcone[a]

Entry	Nucleophile	Metal	Yield [%]	*ee* [%]
1[b]	Di*iso*propylmalonate	$Sr(NO_3)_2$	85	0
2[c]	Di*tert*butylmalonate		82	
3[d]	Aniline	–	traces	–
4	Et_2Zn	$Cu(OTf)_2$	12	36
5		CuI	17	0
6		$Ni(acac)_2$	99	0
7[e]			68	0
8[f]			5	0

[a] Reaction conditions: rt, 10 mol% ligand precursor **80**, 3 equiv. KO^{t}Bu, M:L 1:1, solvent was THF for experiments 1-2 and toluene was for the rest; [b] at rt for overnight and then –20 °C for 10h; [c] –78 °C for 24h, –40 °C for 24h, –20°C for 16h; [d] ligand precursor **81** without metal was applied; [e] at –78 °C by using KHMDS base; [f] without base.

2.3.4. Synthesis of Optically Active Propargylic Alcohol

Optically active propargylic alcohols are important precursors for the synthesis of natural products, pharmaceuticals, and macromolecules.[146,147,148] It is easy to prepare alkynyl-metal reagents functioning as good carbon nucleophiles due to the acidity of a terminal alkynyl proton. Therefore, the phenylacetylene addition to 1-naphthaldehyde catalyzed by the *in situ* generated carbene ligand in combination with metal salt was carried out (Scheme 51).

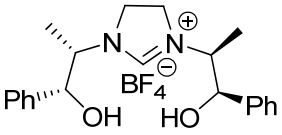
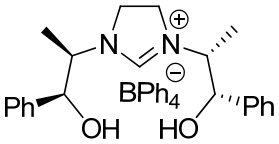
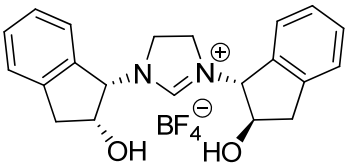


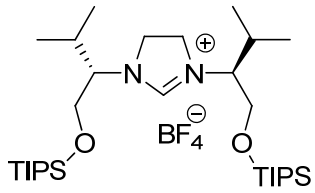
Scheme 51

2.3.4.1. Screening of Ligand Precursors

For the alkynylation of 1-naphthaldehyde, bis-hydroxy imidazolinium salts were tested first. Ligand precursor **80** gave a yield of 78% with 16% *ee*. The yield was reduced to 30% with an *ee* of 15% when ligand precursor **81**, differing in counter anion from **80**, was employed (Table 26, entry 2). The yield was further reduced to 11% when salt **114** was applied in the reaction. Then bis-hydroxy protected salt **98** was tested and a slight improvement in the *ee* was observed (Table 26, entry 4). The results are summarized in Table 26.

Table 26: Screening of ligand precursors

Entry	Ligand Precursors	Yield [%]	*ee* [%]
1	 **80**	78	16
2	 **81**	30	15
3	 **114**	11	7

4		67	23

98

2.3.4.2. Investigation of Metal Salt

Since the nature of the metal employed in the alkynylation reaction has an influence on the reaction outcome, different metal salts in combination with ligand precursor **80** were tested. It was observed that when diethylzinc was used alone without any cometallic ion, the highest yield was of 78% with an *ee* of 16%. Although titanium tetra*iso*propoxide improved the *ee* slightly it resulted in a decrease in the yield from 78% to 40%. A yield of 43% was observed when $Cu(OTf)_2$ was used as cometallic ion in combination with Et_2Zn (Table 27, entry 2).

Table 27: Effect of metal salt

Entry	Salt	Yield [%]	*ee* [%]
1	Et_2Zn	78	16
2	Et_2Zn+$Cu(OTf)_2$	43	19
3	Et_2Zn+$Ti(^iPrO)_4$	40	26

2.3.4.3. Effect of Concentration of Imidazolinium Salt

The effect of ligand loading on the outcome of the reaction was monitored by employing imidazolinium salt **80**. A 5 mol% ligand loading gave 78% yield and 16% *ee*. An increase in the concentration of ligand did not improve the results. So it can be concluded that change in the concentration of salt **80** did not have any influence on the outcome of the reaction.

Table 28: Effect of concentration of imidazolinium salt

Entry	Imidazolinium Salt [mol%]	Yield [%]	*ee* [%]
1	5	78	16
2	10	80	18
3	20	80	15

2.3.4.4. Effect of Temperature

In order to improve the enantioselectivity, the temperature was varied. By lowering the temperature to 0 °C, an *ee* of 14% was observed. The yield reached to 15% with a slight improvement in the *ee* when the reaction was carried out at −20 °C (Table 29, entry 3).

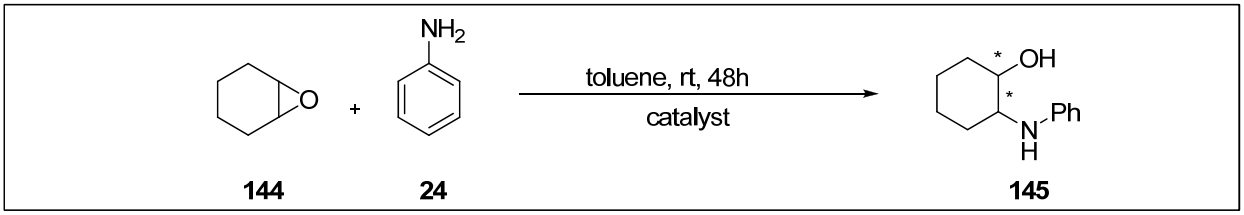
Table 29: Effect of temperature

Entry	t [°C]	Yield [%]	*ee* [%]
01	rt	78	16
02	0	62	14
03	–20	15	22

2.3.5. Ring Opening of Epoxides:

Asymmetric ring opening of meso-epoxides with aromatic amines is of particular interest because the resulting chiral *β*-amino alcohols have wide applications in the synthesis of pharmaceutically active compounds and chiral auxillaries/ligands.[149]

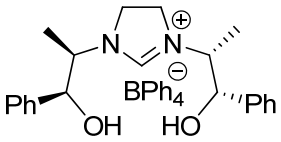
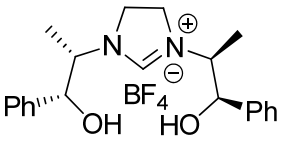
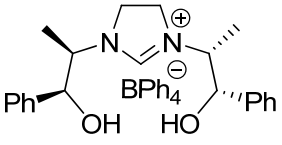
The ring opening of epoxide with aniline (Scheme 52) was catalyzed efficiently with norephedrine based imidazolinium salt **81** furnishing the product in 70% yield.



Scheme 52

A blank reaction was performed with $NaBPh_4$ and the yield was 7% and hence excluding the possibility of a $NaBPh_4$ catalyzed reaction. This reaction (Table 30, entry 1) qualifies as an organocatalytic process since no metal cations were necessary to catalyze the reaction. The salt with a BF_4 anion gave just traces of the product. In order to improve the yield and *ee* of the product, salt **81** was used with a metal salt but yield dropped to 50% with no enantioselectivity. The results are summarized in Table 30.

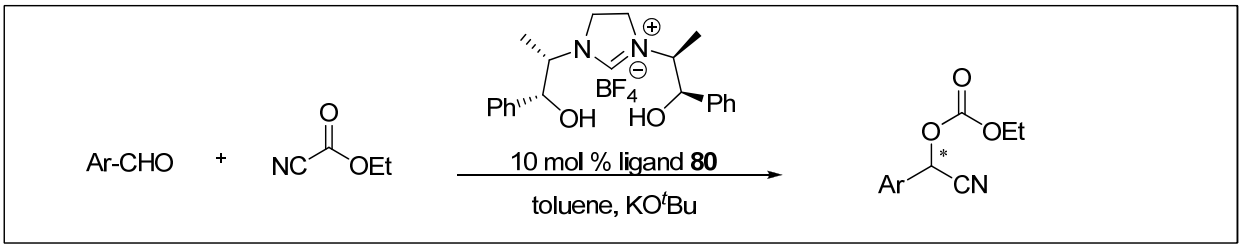
Table 30: Ring opening of epoxide

Entry	Catalyst	Yield [%]	*ee* [%]
1	 **81**	70	0
2	$NaBPh_4$	7	0
3	 **80**	traces	–
4[a]	 **81**	50	0

[a] $Sc(OTf)_3$, KO^tBu

2.3.6. Asymmetric Cyanoformylation of Aldehydes

Optically active cyanohydrins serve as starting materials for many natural products.[150] The trimethylsilyl cyanide (TMSCN) or hydrogen cyanide (HCN) are used as cyanide sources in reactions with carbonyl compounds.[151, 152] Now cyanoformate esters, acetyl cyanide or diethyl cyanophosphonate are good alternatives to the volatile and hazardous cyanide sources. Many research groups have used these alternatives in the asymmetric cyanation reaction successfully.[153, 154] With our catalytic system, ethyl cyanoformate was added to the aromatic aldehydes employing chiral ligand precursor **80** and different metal sources.



Scheme 53

Ti(^{i}PrO)$_4$ was applied first as precatalyst along with chiral salt **80** in the cyanoformylation reaction of benzaldehyde with ethyl cyanoformate. The reaction gave 50% yield with no *ee*. Then, Cu(OTf)$_2$ with a M:L ratio of 1:2 was applied with 1-naphthaldehyde as the substrate. The reaction proceeded with a yield of 57% and 9% *ee* of the product at rt. At –20 °C, the yield improved to 80% with a lower *ee* of 5%. The results are summarized in Table 31.

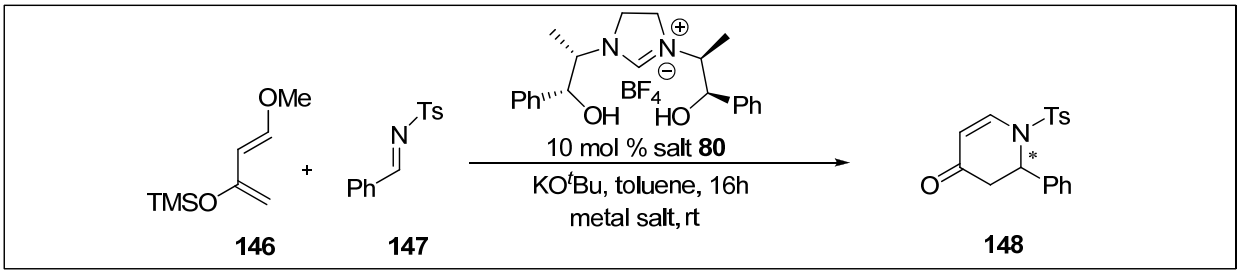
Table 31. Asymmetric ethyl cyanoformylation to aldehydes

Entry	Substrate	Metal Salt	t [°C]	Yield [%]	*ee* [%]
1	Benzaldehyde	Ti(^{i}PrO)$_4$	rt	50	0
2	1-Naphthaldehyde	Cu(OTf)$_2$		57	9
3			–20°C	80	5

2.3.7. Asymmetric Aza Diels-Alder Reaction:

Six-membered nitrogen containing heterocylcles are key units in medicinal chemistry and interesting intermediates in organic synthesis. The catalytic enantioselective aza-Diels-Alder reaction of electron rich dienes with aldimines is conceptually an extremely powerful strategy for the construction of this type of structures with high enantiopurity.

We have chosen Danishefsky' diene and tosyl imine in order to evaluate our catalytic system (Scheme 54).



Scheme 54

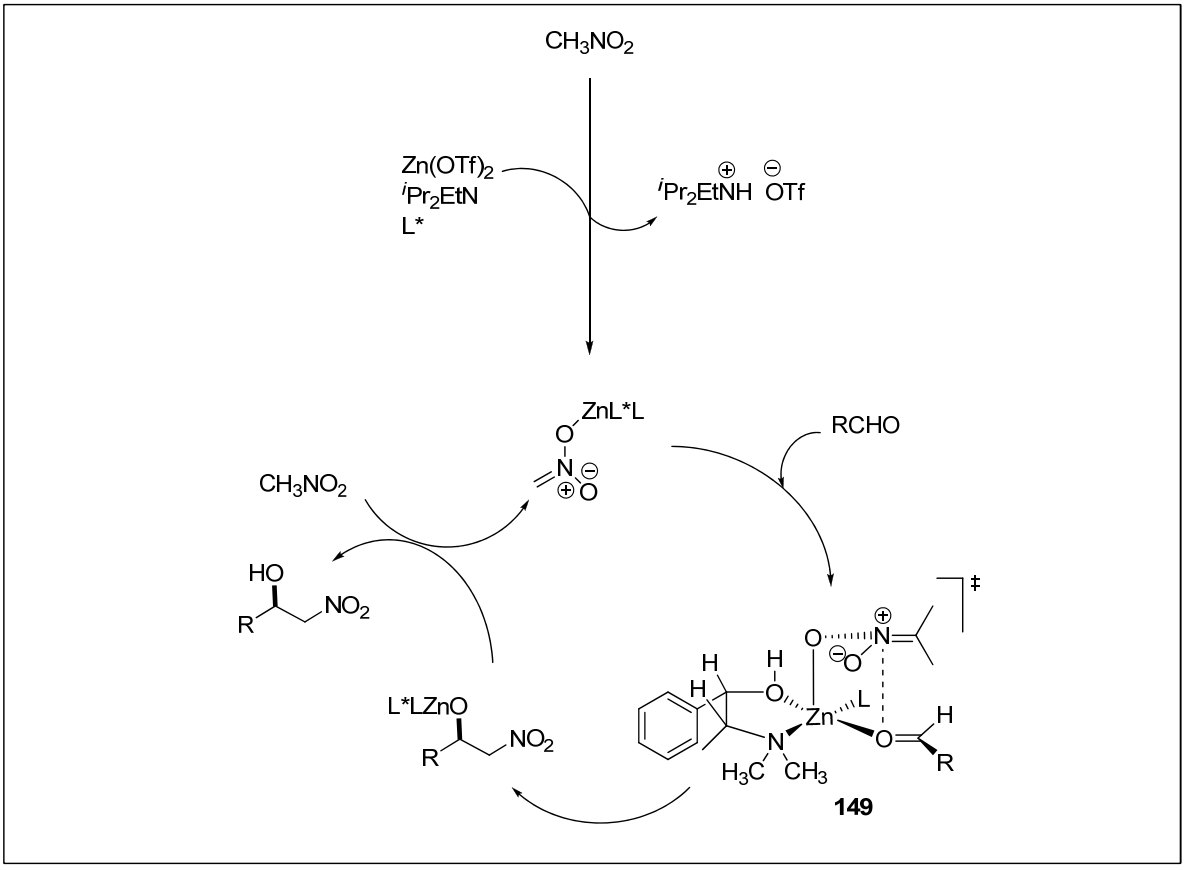
The reason for selecting the tosyl imine is that the tosyl group decreases the electron density at the double bond, making the imine more reactive towards the diene. $Cu(OTf)_2$ and $Ti(^iPrO)_4$ were tested for the described system. Both metallic salts gave yields of 50% and 40% respectively with no *ee*. The salt to ligand ratio was 1:2. Toluene was used as solvent and the reaction was quenched after 16h stirring at room temperature. The results are summarized in Table 32.

Table 32: Scope of aza Diels-Alder reaction

Entry	Salt	Yield [%]	*ee* [%]
1	$Cu(OTf)_2$	50	0
2	$Ti(^iPrO)_4$	40	0

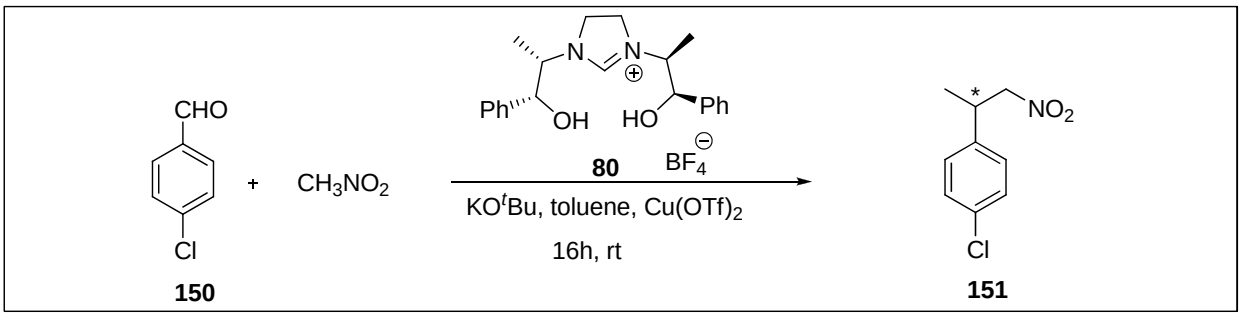
2.3.8. Asymmetric Henry Reaction

The Henry reaction constitutes a fundamental carbon-carbon bond forming reaction in organic chemistry, which has been used for the construction of numerous useful compounds. The nitro group of theses products can undergo a Nef reaction, reduction to an amino group, or nucleophilic displacement.[155] This reaction has been reported previously by the groups of Shibasaki,[156] Torst,[157] and Evans.[158] They have applied metal-based bifunctional chiral catalysts. In 2005, Palomo *et al*.[159] used chiral amino alcohols as ligands in combination with $Zn(OTf)_2$, achieving excellent yields and *ee*s. They have proposed the reaction pathway (Scheme 55) in which transition state **149** explains the formation of the major enantiomer.



Scheme 55

As the catalytic asymmetric Henry reaction has been successfully implemented only in a very few cases, the attempts were exerted to evaluate the efficiency of our catalytic system (Scheme 56).



Scheme 56

It was found and expected in the reaction of *p*-chlorobenzaldehyde with nitromethane, that by adding triethylamine the yield would increase. Indeed the yield doubled from 22% to 47%. In both cases, only a racemate was formed.

Table 33: Effect of base

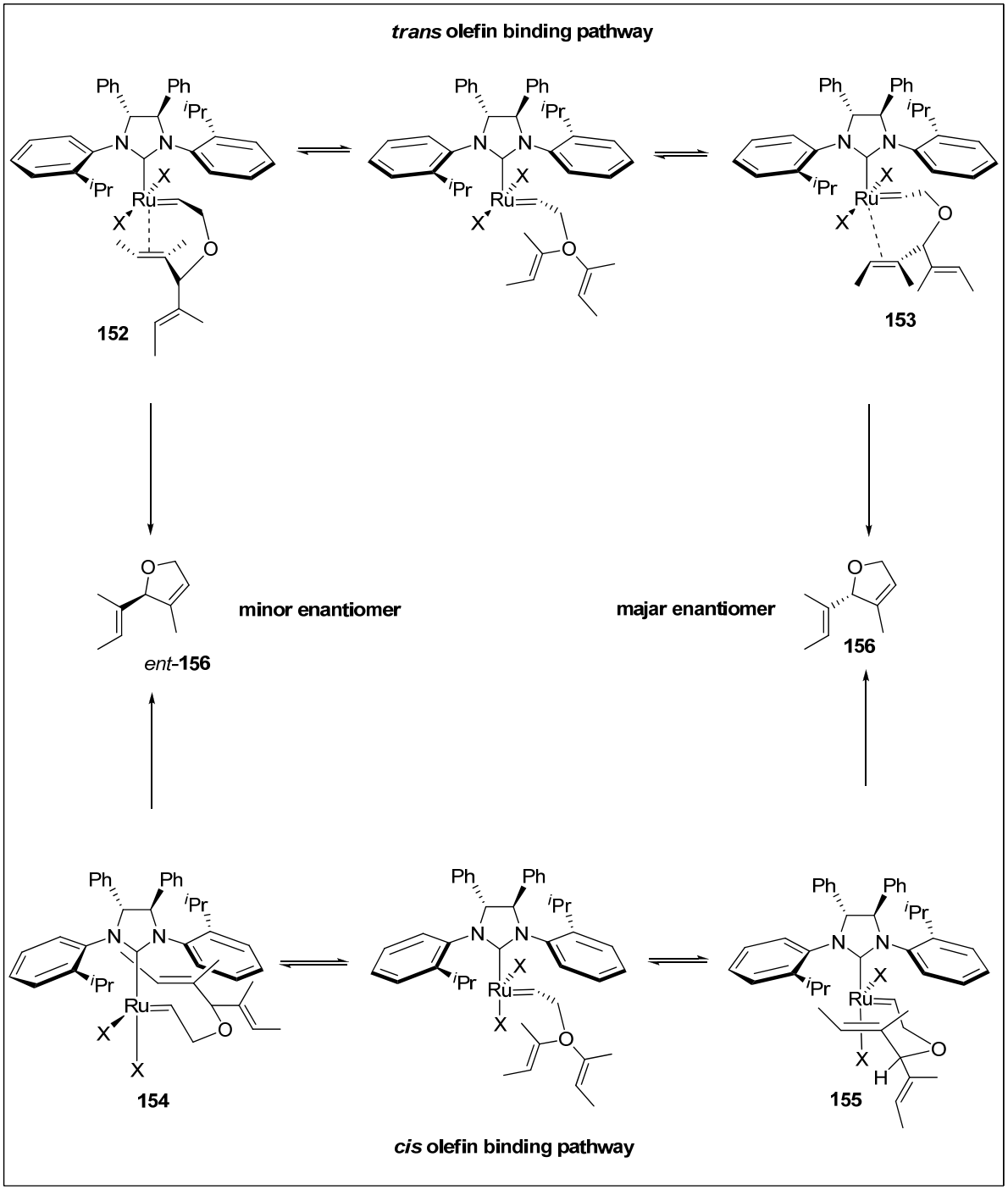
Entry	Base	Yield [%]	*ee* [%]
01	–	25	0
02	Et_3N	47	0

2.3.9. Asymmetric Ring-Closing Olefin Metathesis

Metal-catalyzed olefin metathesis is a powerful technique for C-C bond formation.[160] Ruthenium-based olefin metathesis has attracted the attention due to the greater functional group tolerance and simple handling of ruthenium catalysts. Theoretical[161] and experimental studies[162] were being carried out in order to understand the mechanism of olefin metathesis reactions. The proposed pathways for the major product in ARCM reaction are shown in Scheme 57.

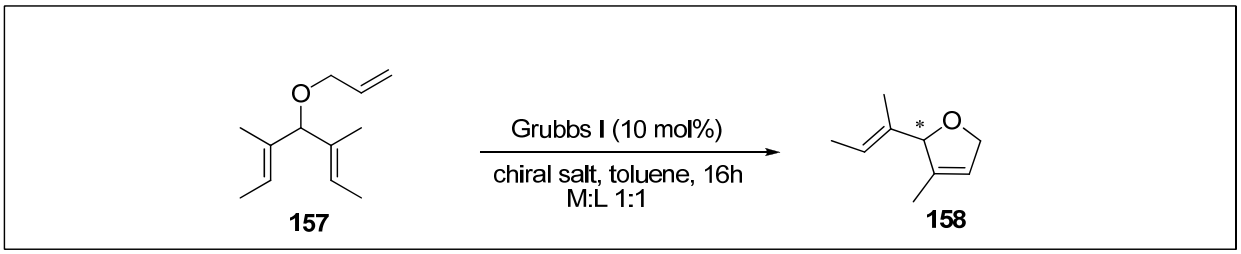
According to the proposed model, a ruthenium alkylidene complex is formed from the least-substituted triene. Then this alkylidene complex binds one of the diastereotopic olefins. There is still no clarity about the position of coordinated olefin relative to the NHC ring. Recent studies suggest the olefin binding *trans* to the NHC and the observed stereochemistry can be justified through *trans* binding. This *trans*-binding model (upper pathway) was also supported by computational studies.[157a] In the *trans* olefin binding pathway, it was assumed

that alkylidene is lying underneath the isopropyl group due to the tilt of the *ortho*-substituted *N*-aryl ring, instead of being underneath the C-H bond (structure **152**). This favored positioning of alkylidene leads to the product **156**, the major enantiomer. The *cis*-binding hypothesis was reinforced by the fact that enantiomeric excess of the product improved when a larger halide ligand like iodide was introduced. [157a]



Scheme 57

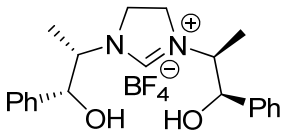
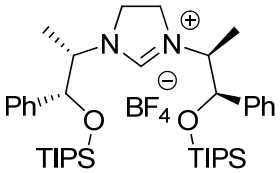
The ligand precursors **80**, **90** and **122** were tested for the system shown in Scheme 58.

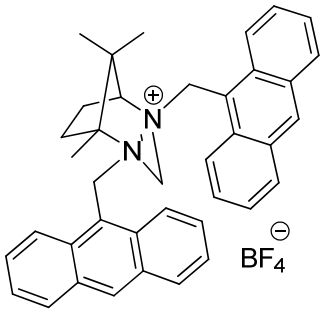


Scheme 58

A blank reaction employing Grubbs I in the absence of a chiral environment was carried out in order to obtain racemic product for comparison. The racemate was obtained in 62% yield when the reaction was carried out at 40 °C in toluene. The ligand precursor **80** incorporating hydroxy groups was applied with Grubbs I at rt. The reaction did not occur. Then the reaction was carried out by applying ligand precursor **90**. The reaction was stopped after 16h but no product was recovered. Another ligand precursor **122** was also applied in the reaction under the same conditions but no product formed. The results are summarized in Table 34.

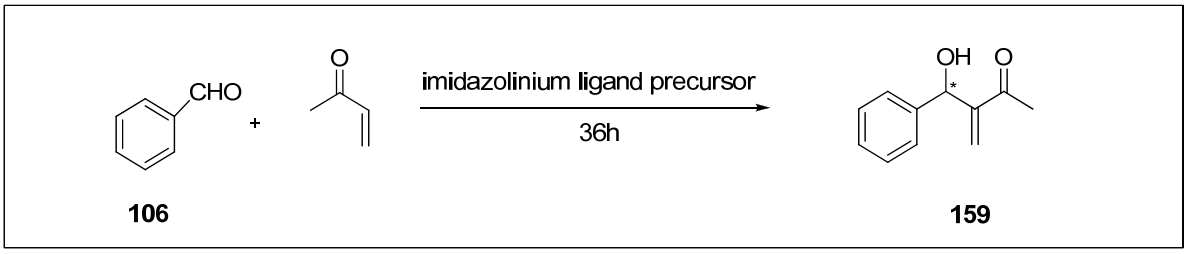
Table 34: Asymmetric ring-closing metathesis reaction

Entry	Ligand Precursor	t [°C]	Yield [%]	*ee* [%]
1	-	40	62	–
2	 **80**	rt	–	–
3		40	–	–

	90		
4		–	–
	122		

2.3.10. Baylis-Hillman Reaction

The Baylis Hillman reaction is the addition of aldehyde to *α*,*β*-unsaturated carbonyl compounds resulting in the formation of *α*-methylene-*β*-hydroxycarbonyl compounds. The reaction is useful in providing intermediates for the synthesis of several natural products.[163] The reaction needs a Lewis base catalyst for initiation. The enolate formed by the addition of the nucleophile to the Michael acceptor is trapped by the aldehyde and proton transfer followed by the release of the nucleophile resulting in the formation of the product. The limitations of this reaction include long reaction time and polymerization of carbonyl compounds.

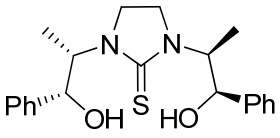
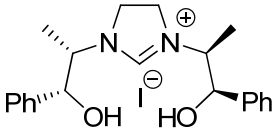


Scheme 59

Two ligand precursors were tested for the Baylis Hillman reaction and results are summarized in Table 35. No product formed when ligands **103** and **83** were employed. In each case 2 equiv. of the benzaldehyde was used. It was anticipated that the thiourea or the

iodide ion function as Lewis base in this reaction. That both can act as Lewis bases is known.

Table 35: Screening of ligand/Precursor

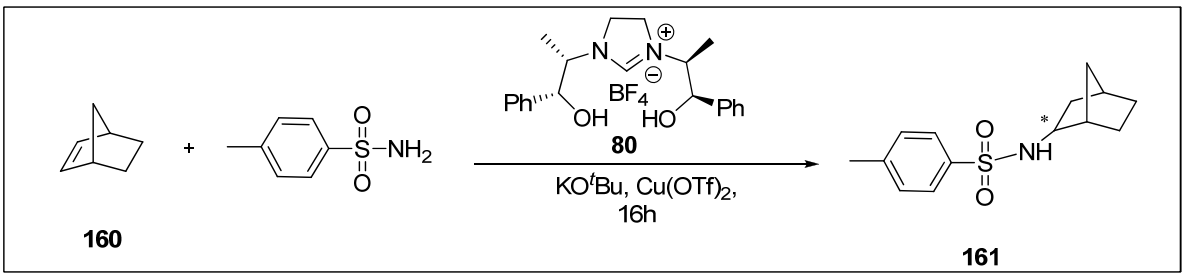
Entry	Ligand/Precursor	Solvent	Yield [%]	*ee* [%]
1[a]	 **103**	Toluene	–	–
2[b]	 **83**	Acetonitrile	–	–

[a] 20 mol% of ligand **103**; [b] 1equiv. of ligand **83**

2.3.11. Asymmetric Hydroamination Reaction

The hydroamination reaction is the addition of the N-H bond to an alkene. The C-N bond is found in many chiral key building blocks and pharmaceutical compounds.[164] The enantioselective addition of aromatic amines to vinylarenes, dienes or norbornene has been achieved successfully by chiral late transition metal catalysts.[165] However, a few chiral catalysts have been developed for the hydroamination process with high enantioselectivity.[166] The Intermolecular hydroamination reactions catalyzed by copper complexes have been reported by Leighton *et al*. in 2006.[167]

The *in situ* generated chiral *N*-heterocyclic carbene/copper complex was tested in the addition of $TsNH_2$ to the strained norbornene (Scheme 60).



Scheme 60

The initial results were not satisfactory. The blank reaction gave only traces of the product. The reactions carried out at room temperature gave no product. Then the reaction was carried out at 75 °C with a change of M:L precursor ratio from 1:1 to 1:2, no product was recovered from the reaction mixture. The reaction carried out in 1,4-dioxane did not proceed as well. The results are summarized in Table 36.

Table 36: Attempts for the optimization of hydroamination reaction

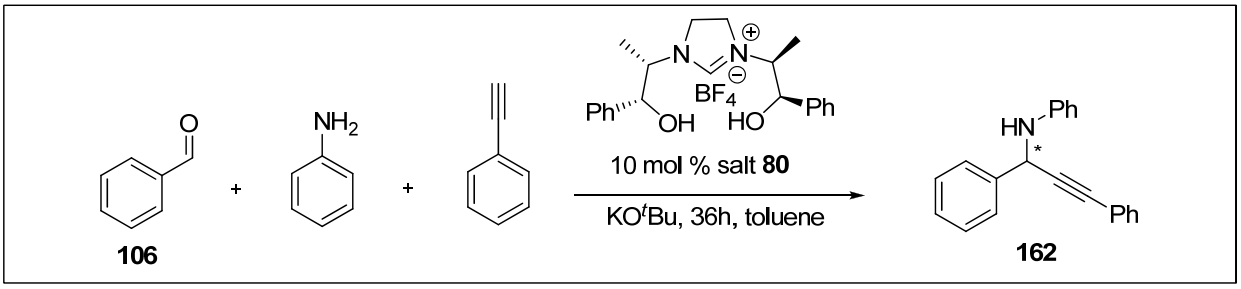
Entry	t [°C]	M:L	Solvent	Yield [%]	*ee* [%]
1	75	–	1,4-Dioxane	traces	–
2	rt	1:1	Toluene	–	–
3	75	1:2		–	–
4			1,4-Dioxane	–	–

2.3.12. Three Component Condensation Reaction

One pot multi-component reactions (MCRs) offer an advantage of incorporating several diversified elements into the product.[168] One example of such type of reaction is the three component coupling of aldehydes, alkynes and amines (A^3-coupling).[169] The propargylamines obtained from this coupling reaction are important precursors for biologically active compounds such as β-lactams, isosteres and drug molecules.[170] The metal catalysts used for the multi-component A^3-coupling reactions include Ag salts,[171] Au

salts,[172] Au-salen complexes,[173] Cu salts,[174] Ir complexes,[175] Hg_2Cl_2[176] and Cu/Ru bimetallic systems.[177] Recently, a silica-immobilized NHC-Cu complex was reported to catalyze the reaction effectively.[178]

The chiral NHC precursor **80** was applied for the reaction shown in Scheme 61. Both $Cu(OTf)_2$ and CuI were tested for a long time of 36h but no reaction took place. The results are summarized in Table 37.



Scheme 61

Table 37: Attempts for one-pot three-component reaction

Entry	Salt	Salt:[NHC]	Yield [%]	*ee* [%]
1	$Cu(OTf)_2$	1:2	–	–
2	CuI	1:2	–	–

2.3.13. Imidazolinium Salts as Chiral Shift Reagents

A rapid and convenient method for determining the enantiomeric excess of chiral compounds is by employing chiral shift reagents or chiral solvating reagents in NMR spectroscopy. This method avoids the derivatization of those chiral compounds that can not be run directly on chiral HPLC. The chiral recognition ability of imidazolinium-based ionic liquids was reported in 2002.[179] Amongst a wide variety of chiral shift reagents imidazolinium salts incorporating hydroxy groups were also reported to show stereodiscrimination when interacting with racemic Mosher's carboxylate salt.[180]

The newly synthesized salts were investigated for their ability to interact with Mosher's carboxylate, by examination of differences in the chemical shifts of the MeO group and the

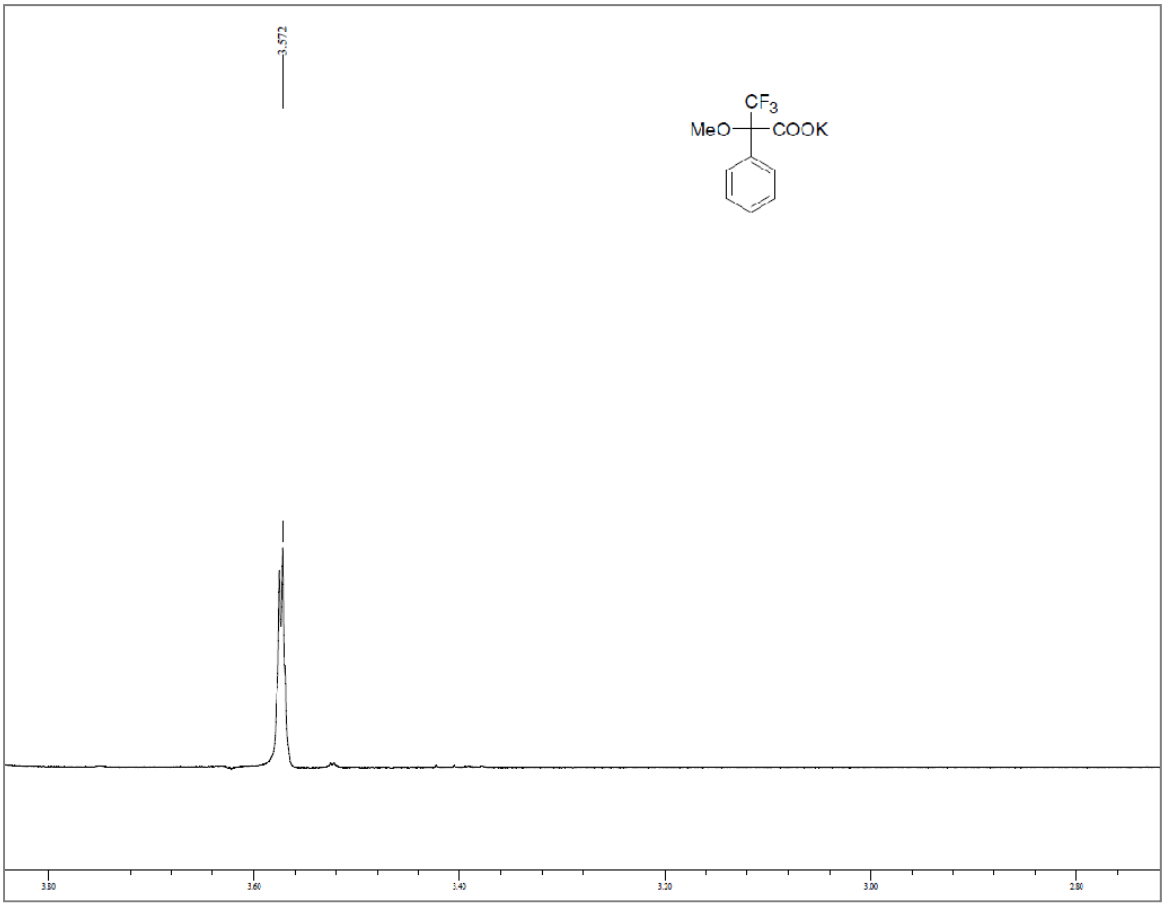
CF_3 group of the two enantiomers of Mosher's carboxylate. In order to assign the signals of the corresponding enantiomers, enantioenriched (12% *ee*) Mosher's carboxylate potassium salt was mixed with the chiral imidazolinium salts with a 1:1 ratio. The mixture was dissolved in [D_6] acetone and ^{1}H and ^{19}F NMR spectra were recorded. The results are summarized in Table 38.

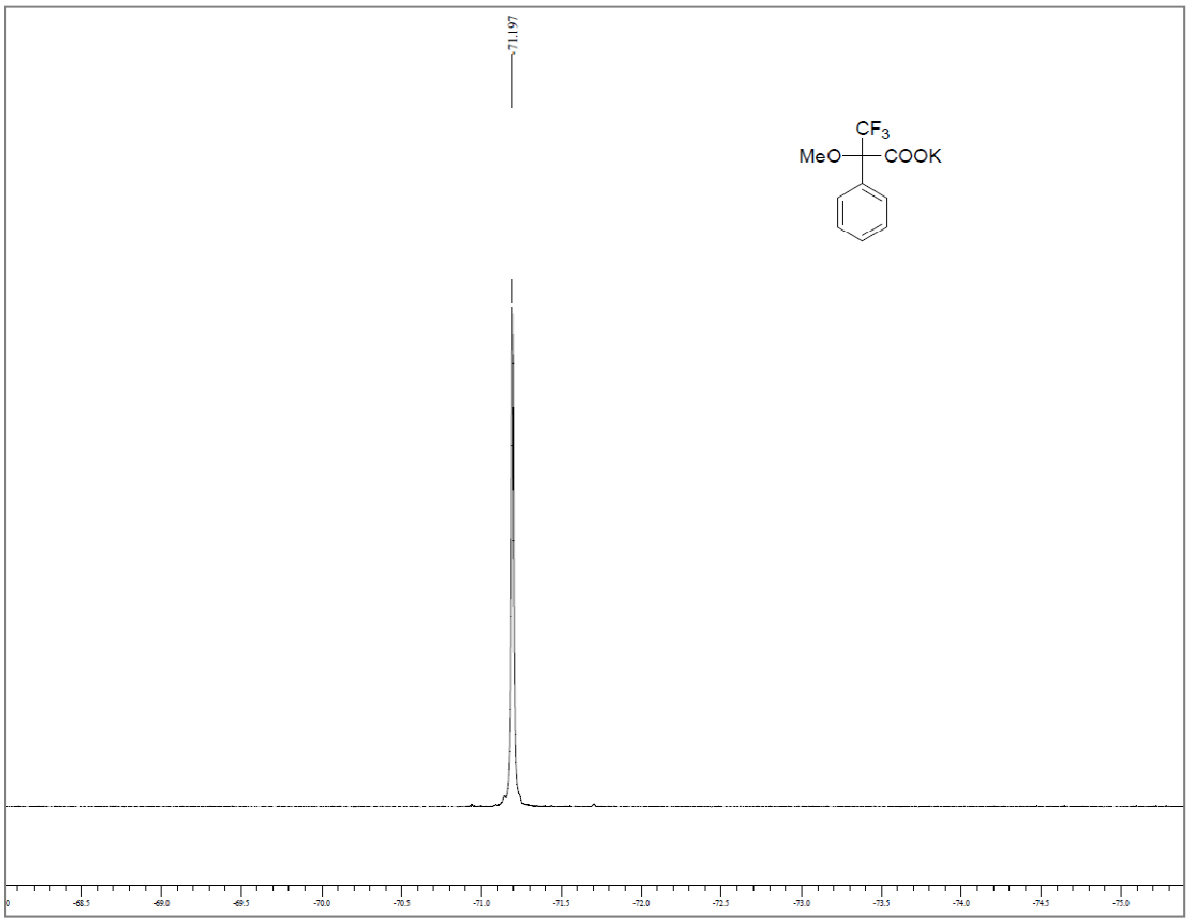
The methoxy group of Mosher's salt showed a singlet at 3.57 Hz and the CF_3 group displayed a singlet at –71.19 Hz in ^{19}F-NMR. In general, by mixing the two salts together reshuffling of ion pairs would occur. The enantiopure imidazolinium cation would interact with each of the two enantiomeric anions of Mosher's carboxylate resulting in the formation of diastereomeric ion pairs. Since diastereomers are different compounds both physically and chemically, therefore each diastereomer should show theoretically different chemical shift values. Salt **84** and **83** having Br and I as counter anions respectively showed a splitting of 12 Hz in ^{1}HNMR and 117 Hz in ^{19}F NMR each (Table 38, entries 3-4). Whereas salt **85** having the same cation as that of salts **84** and **83** but a chloride anion did not display any splitting in ^{1}H NMR and ^{19}F NMR. It can be postulated that the anions influence the interaction of these chiral cations with the Mosher's carboxylate salt. Salts **86** and **89** showed no splitting at all while salt **88** showed a splitting of 22 Hz in ^{19}F NMR and salt **87** displayed a splitting of 4 Hz in ^{1}H NMR. The spectra of Mosher's carboxylate and salts **83-85** are shown in Figure 3.

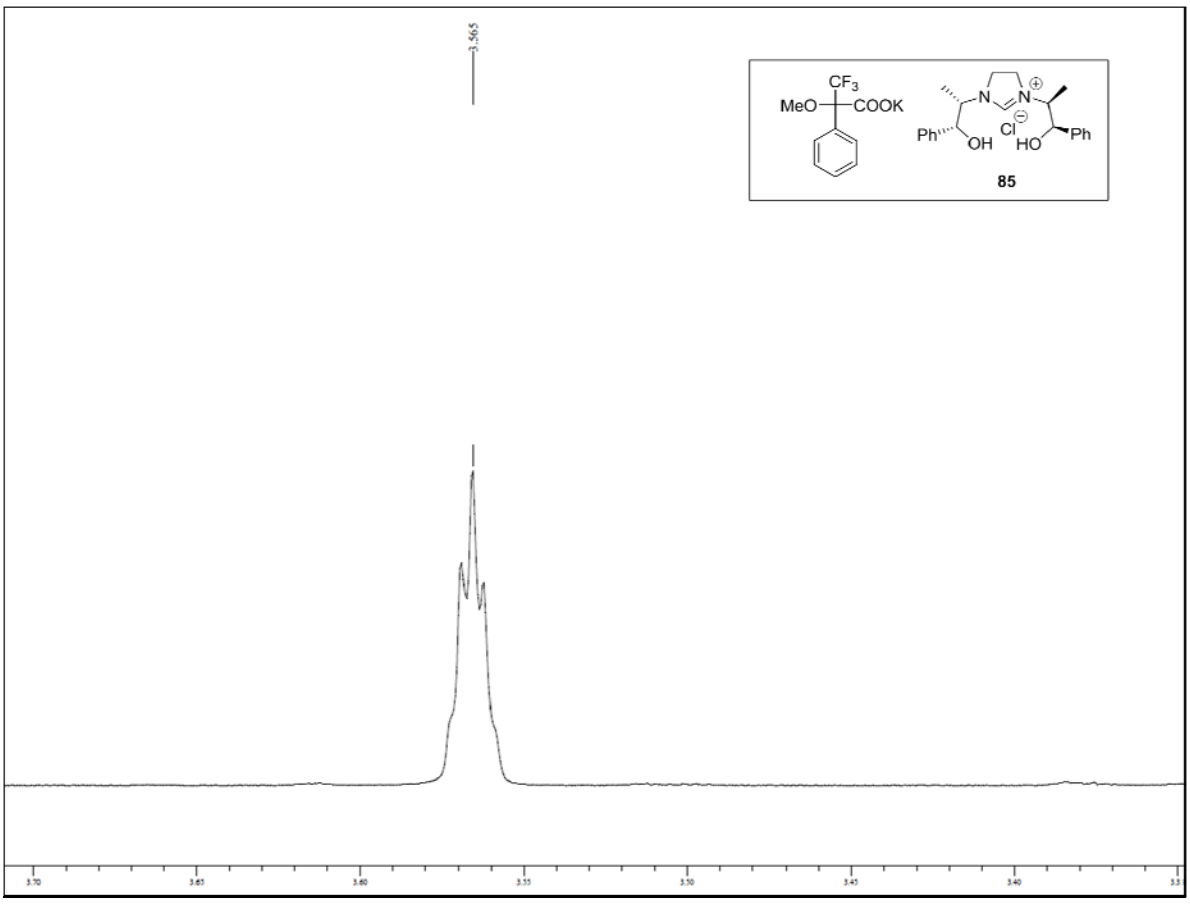
Table 38: Chemical shifts δ of Mosher's carboxylate in ppm and $\Delta\delta$ values in Hz (400 MHz ^{1}H-NMR, 375 MHz ^{19}F-NMR).

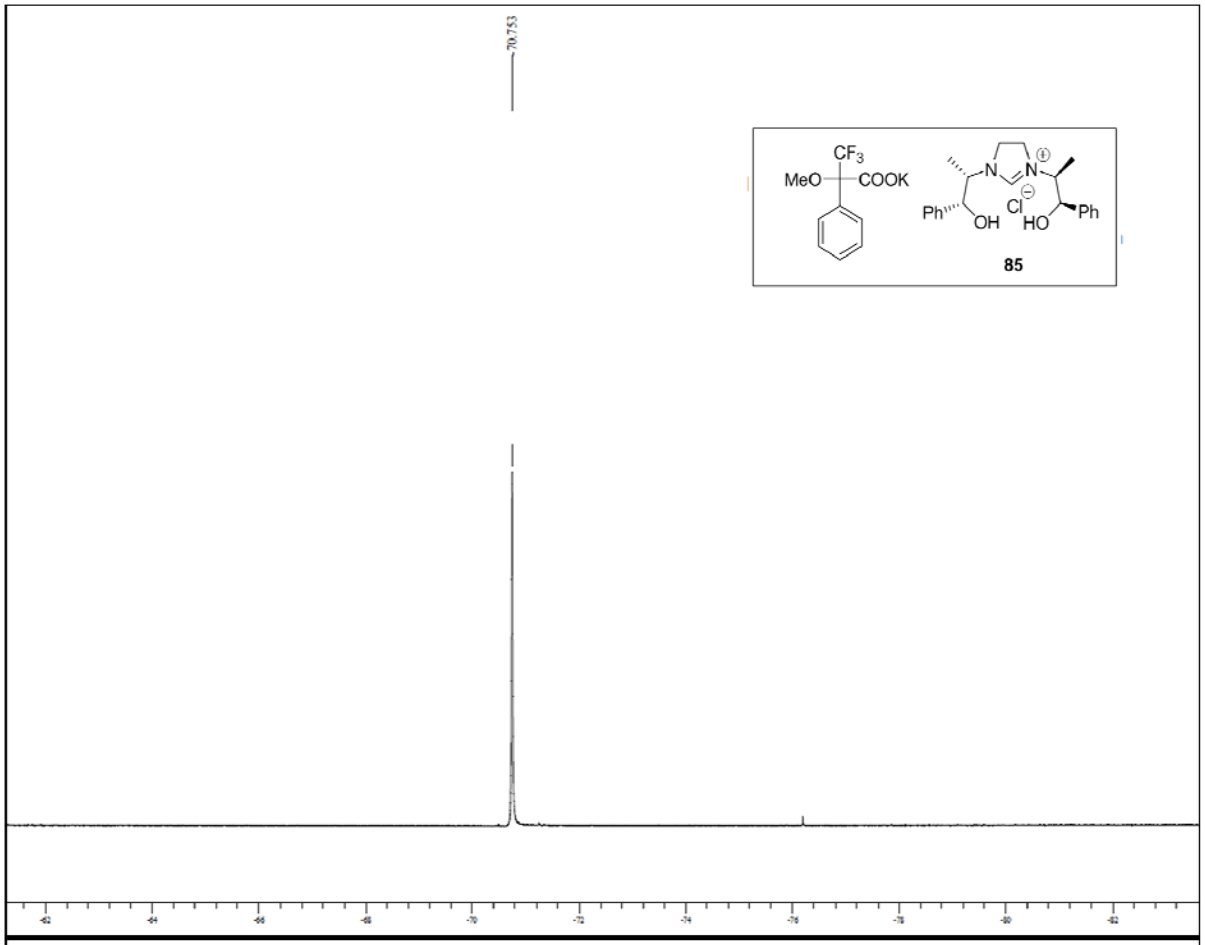
Entry	Salt	δ(1H) (*S*)/(*R*)	$\delta(^{19}F)$ (*S*)/(*R*)	$\Delta\delta(^1H)$	$\Delta\delta(^{19}F)$
1	–	3.57 / 3.57	–71.19/–71.19	0	0
2	**85**	3.56 / 3.56	–70.75/–70.75	0	0
3	**84**	3.57 / 3.54	–70.73/–71.04	12	117

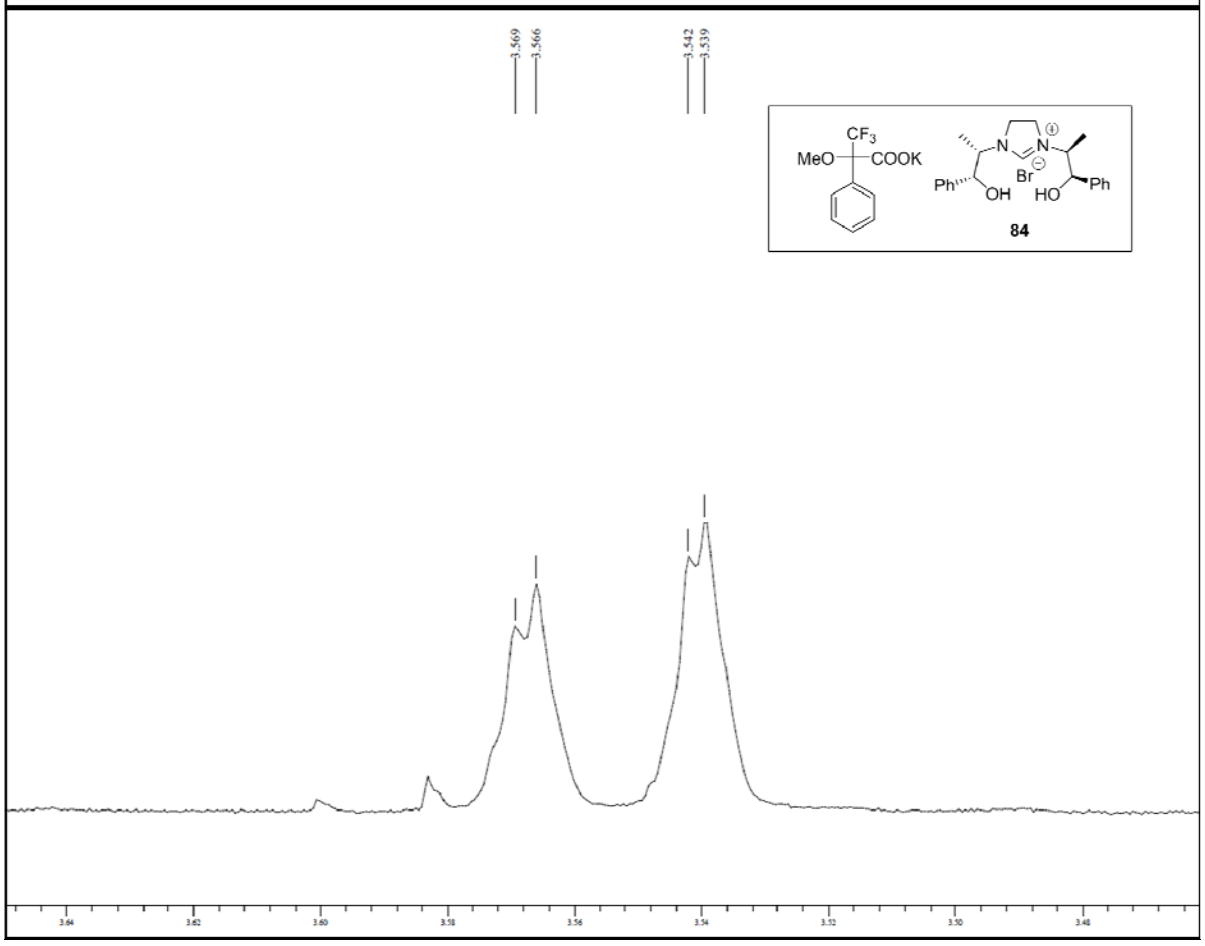
4	**83**	3.56 / 3.53	–70.68/–70.99	12	117
5	**86**	3.56 / 3.56	–71.06/–71.06	0	0
6	**87**	3.60 / 3.61	–71.17/–71.17	4	0
7	**88**	3.60 / 3.60	–70.97/–71.03	0	22
8	**89**	3.62 / 3.62	–71.07/–71.07	0	0

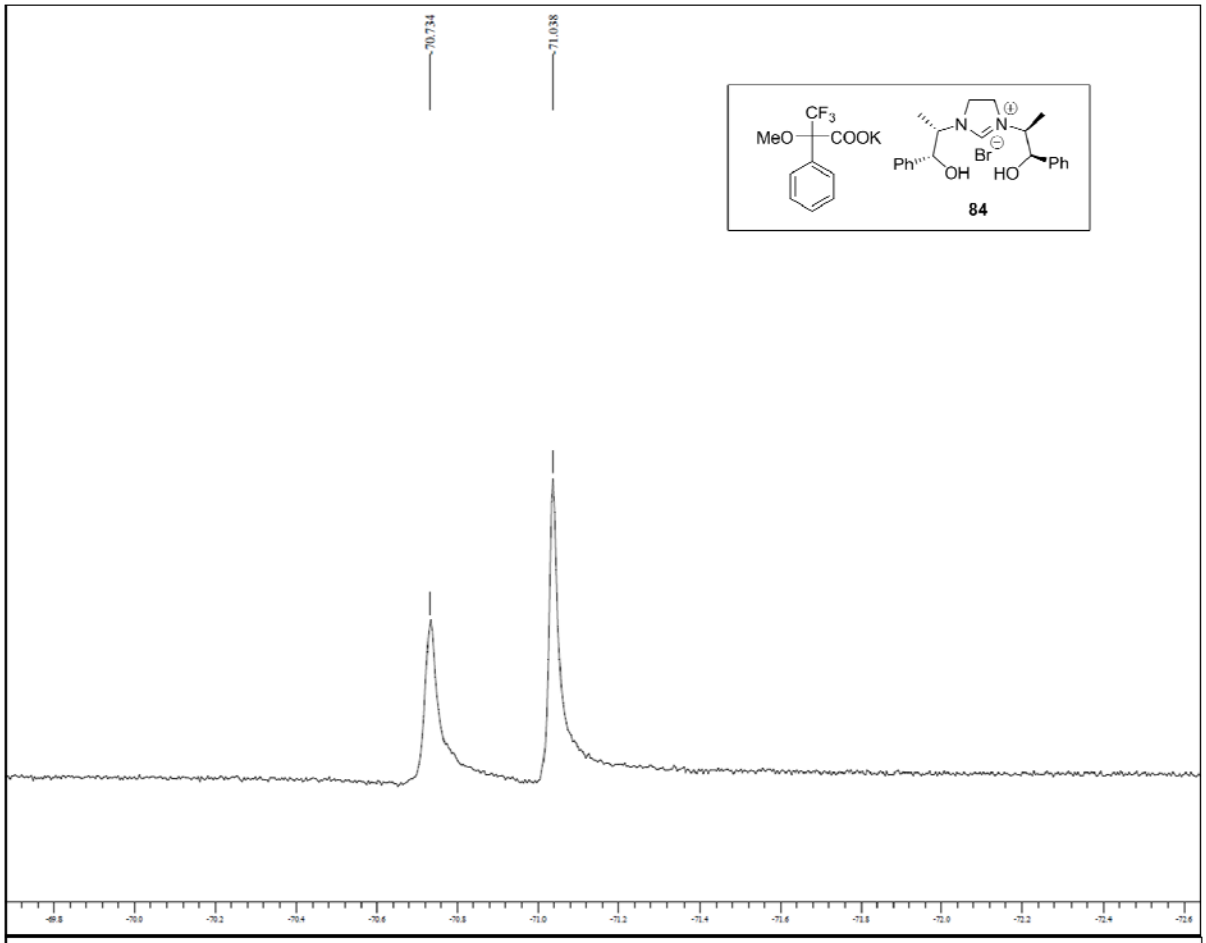


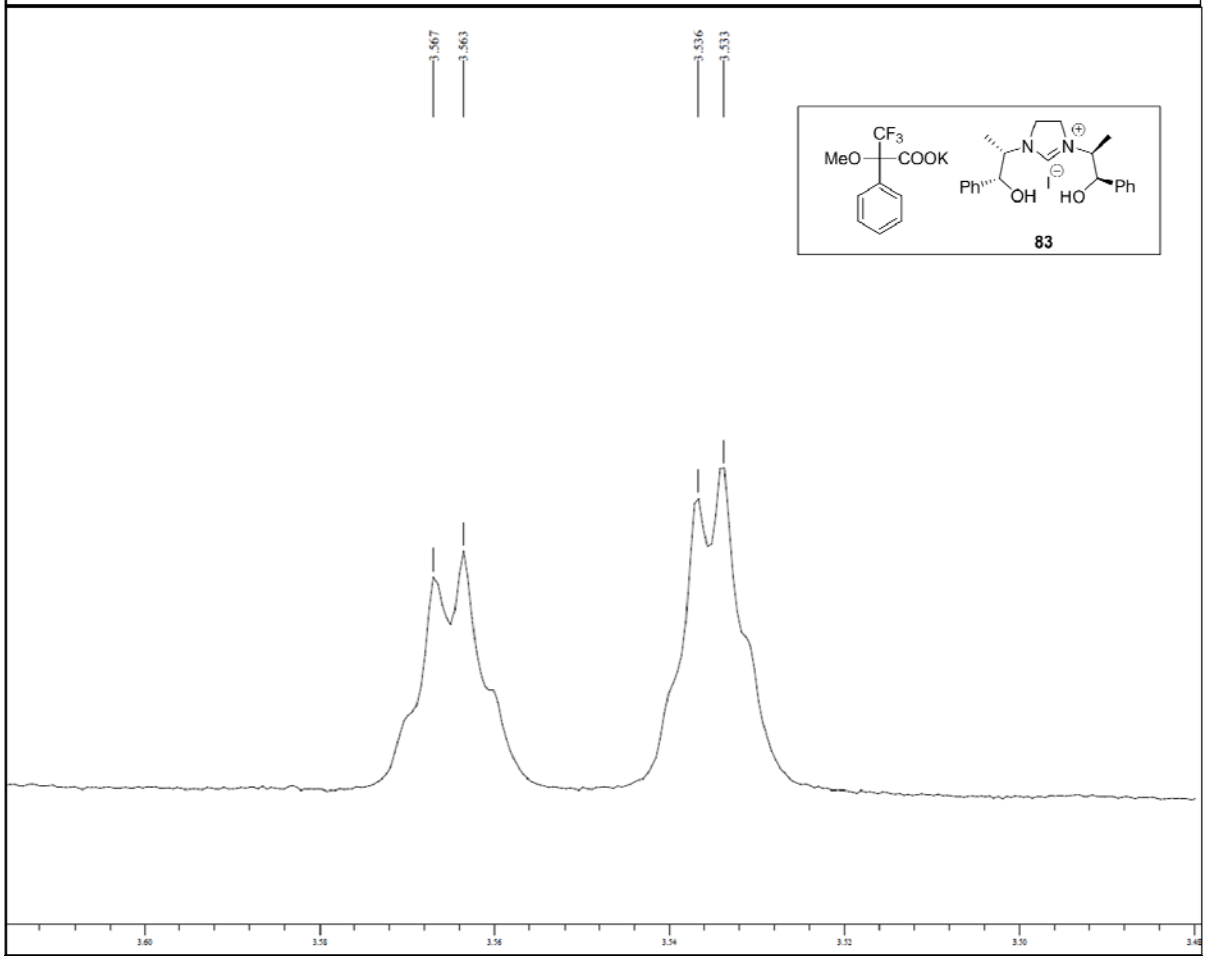

71.197
CF3
MeO
COOK


3.565
CF3
MeO
COOK
Ph
OH
Cl
HO
Ph
85


-70.753
CF3
MeO
COOK
Ph
OH
N
N
Cl
HO
Ph
85


3.569
3.566
3.542
3.539
CF3
MeO
COOK
Ph
OH
N
N
Br
HO
Ph
84


-70.734
-71.038
CF3
MeO
COOK
Ph
OH
Br
HO
Ph
84


3.567
3.563
3.536
3.533
CF3
MeO
COOK
Ph
OH
I
HO
Ph
83

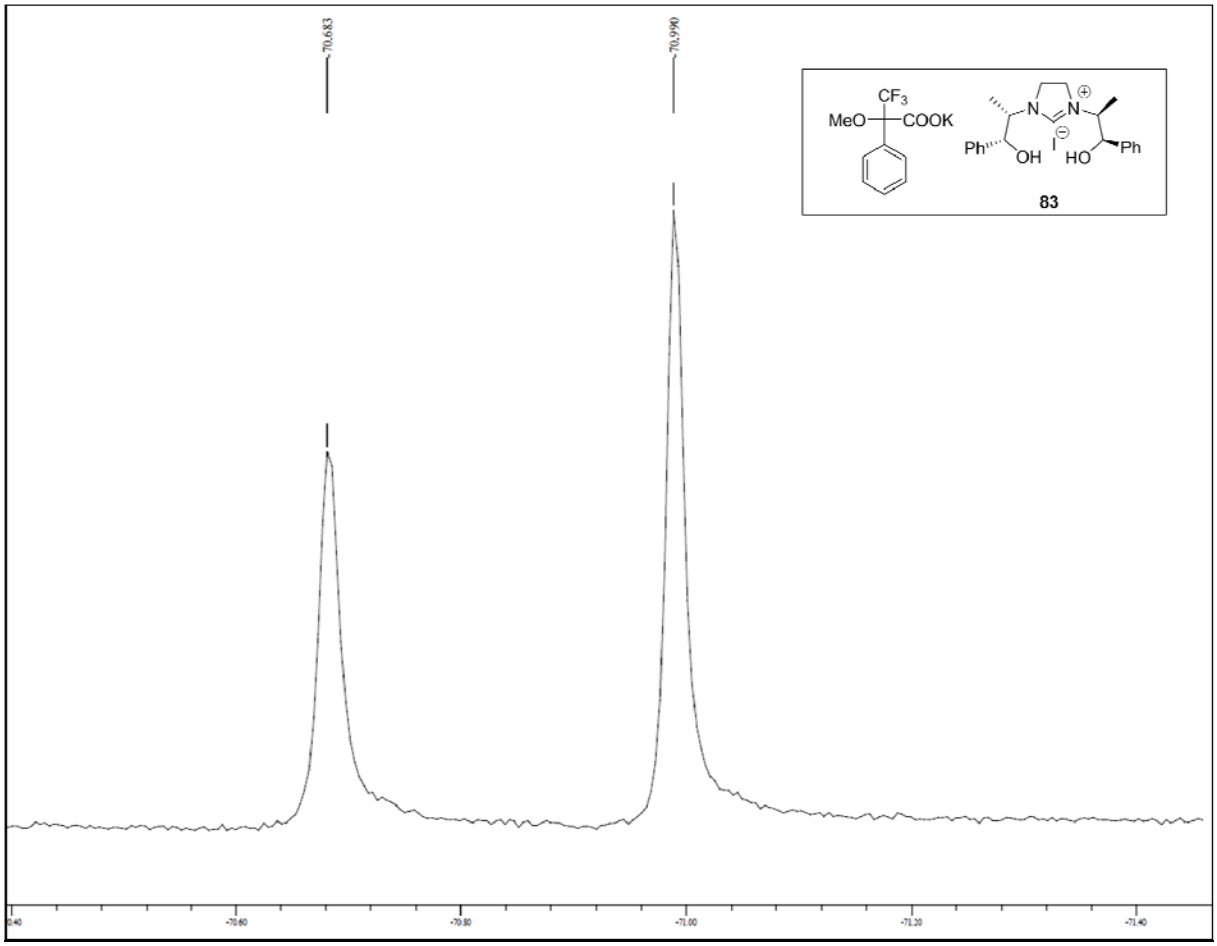
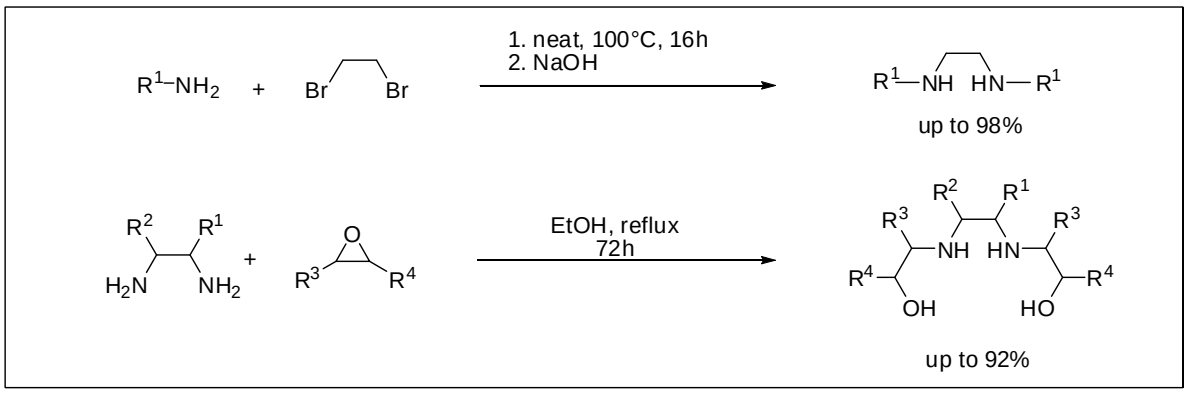


Figure 3

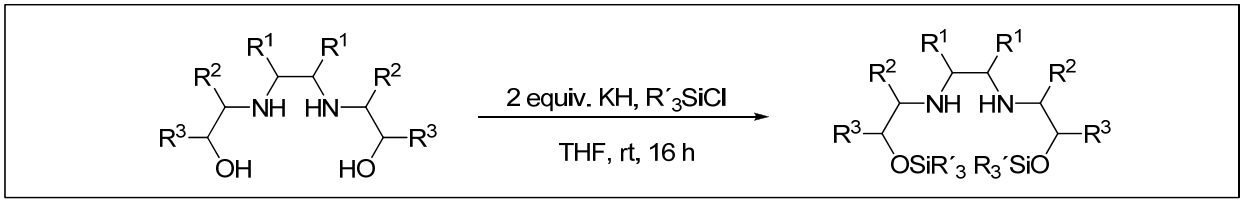
2.4. Summary and Outlook

The presented work began with the synthesis of C_2-symmetric diamines by two routes. The first route involved the direct alkylation of commercially-available chiral amino alcohols. The alkylated diamines were obtained in good to excellent yields. The second route was the regioselective ring opening of epoxides. The yields of the C_2-symmetric diamines ranged from moderate to excellent level (Scheme 62).



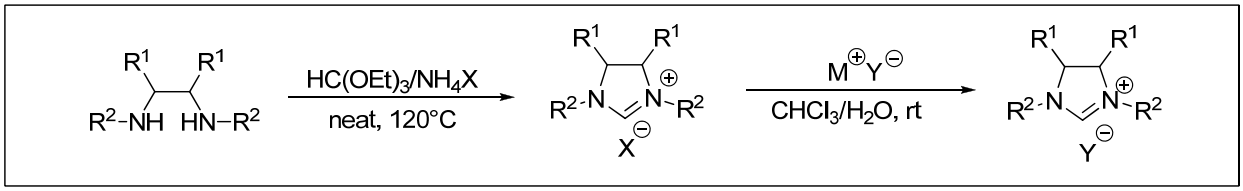
Scheme 62

Next the the protection of hydroxy groups of previously synthesized amino alcohols with different silylating reagents was described. Mono- and bis-hydroxy protected diamines were obtained with moderate yields but in high purities (Scheme 63).



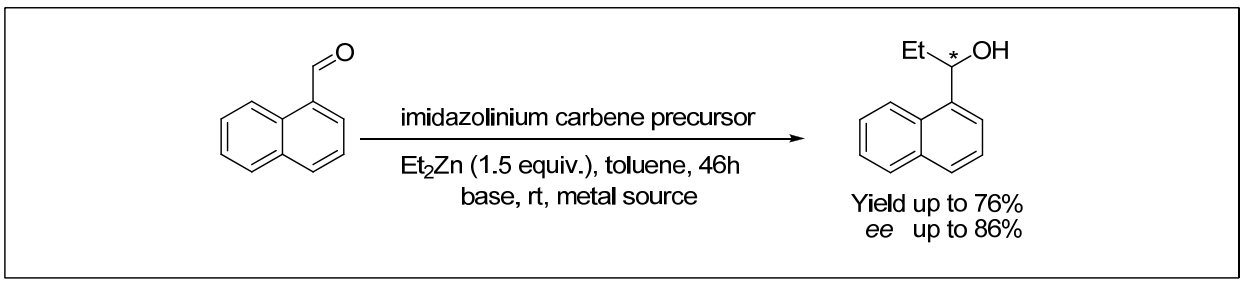
Scheme 63

The diamines were applied in the synthesis of imidazolinium salts by direct reaction with ortho-esters in the presence of an acid source. The properties of these salts were then modified by using different counter anions. One thiourea precursor has been synthesized from norephedrine based amino alcohol (Scheme 64).



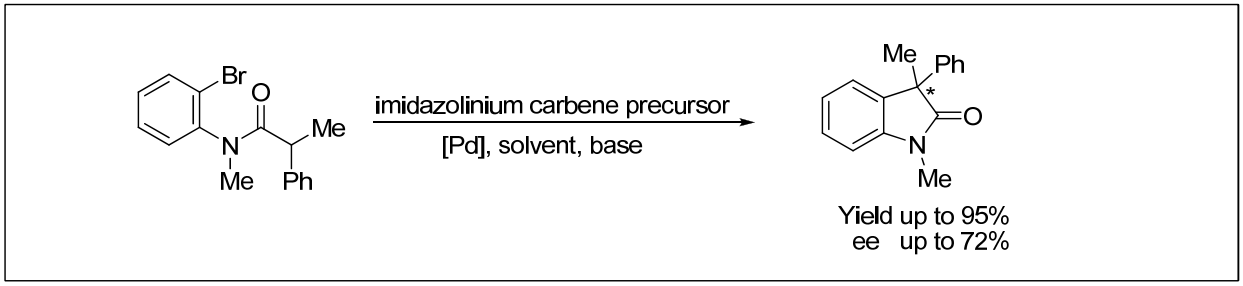
Scheme 64

The salts were applied in different asymmetric catalytic reactions. The asymmetric diethylzinc addition to aldehydes was illustrated. Optically active secondary alcohols were obtained in high yields with high enantioselectivities. The optimization of this reaction involved screening a number of new ligands with different metallic salts, metal to ligand ratio and several other reaction conditions. This extensive optimization led to understand the behaviour of the ligands under different reaction conditions, indicating a tridentate ligand and ^{t}BuOH is coordinating the metal cation. It was found that copper gave the highest *ee* in the reaction, which is remarkable since it is normally used for the 1,4 addition of diethylzinc to unsaturated carbonyl compounds (Scheme 65).



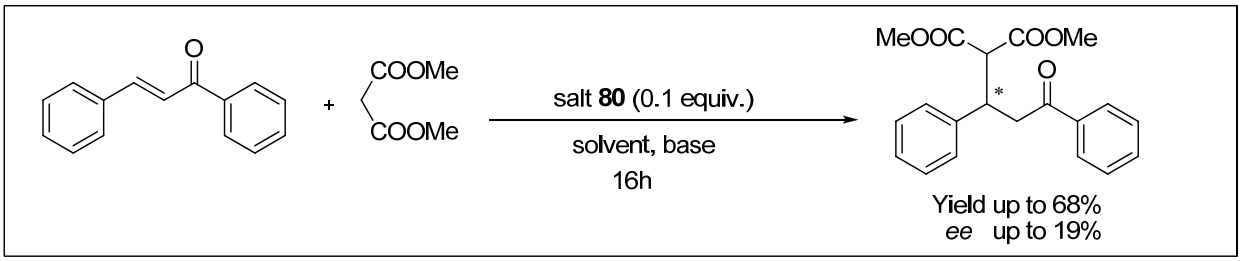
Scheme 65

Then the asymmetric intramolecular *α*-arylation of amides was described. The reaction was optimized by varying a number of conditions. The easy accessible carbene precursors were giving an *ee* of up to 72% with nearly quantitative yields. Furthermore, it was also found for the first time that the use of amino alcohols and bis-hydroxy protected diamines as ligands were resulting in the formation of the products in good yield, although in low enantiomeric excess (Scheme 66).



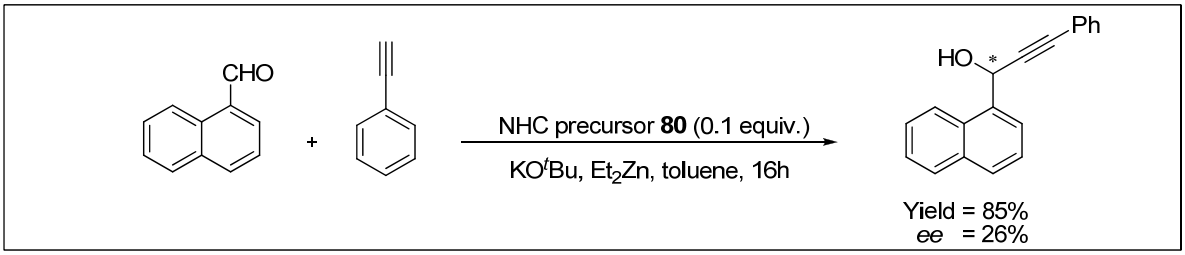
Scheme 66

The asymmetric Michael addition was discussed in section 2.3.3. The reactios were carried out by employing different metal sources, nucleophiles, solvents and bases. In the dimethylmalonate addition to chalcone, the catalyst consisting of ligand precursor **80** and environment friendly calcium metal gave a maximum *ee* of 19%. The other malonate ester nucleophiles gave excellent yields but with very low enantioselectivities (Scheme 67).



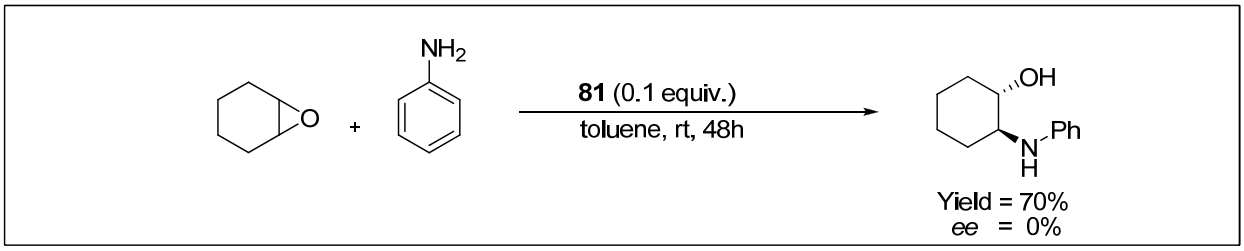
Scheme 67

Propargylic alcohols were obtained with a maximum yield of 85% and 26% *ee*. The detailed optimization of this reaction was described in the section 2.3.4 (Scheme 68).



Scheme 68

The asymmetric ring opening of epoxides was carried out by employing salt **81** as an organocatalysts. The yield obtained in the reaction was 70% but no *ee* was observed (Scheme 69).



Scheme 69

The newly synthesized carbene precursors were also applied in other reactions like ARCM, Henry reaction, cyanoformylation of aldehydes, aza Diels-Alder reaction, Baylis-Hillman reaction, hydroamination reaction, and one pot three component reactions.

The evaluation of imidazolinium salts as chiral shift reagents was described in the last section of this chapter. Imidazolinium salts **83** and **84** having iodide and bromide as counter anions showed a maximum splitting of 12 Hz in ^{1}H NMR and 117 Hz in ^{19}F NMR.

In conclusion, chiral imidazolinium salts are having remarkable applications in the area of asymmetric synthesis. There is still a room for these NHC ligands to be applied in several other reactions. The bis-hydroxy protected imidazolinium salts could be tested further in reactions like asymmetric hydrogenation, asymmetric hydrosilylation, Heck, Suzuki and Stille-couplings. Furthermore, new imidazolinium ligands with greater steric bulk next to the *N*-substituents could be synthesized and tested providing promising results.

2.5. References

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3. Experimental

3.1. General experimental

- **Melting points**

  Melting points were taken with an apparatus after Dr. Tottoli and are uncorrected.

- **IR**

  Infrared spectra were recorded on a Bruker Vektor 22 FTIR spectrometer. KBr pellets in case of solid compounds and as thin films between NaCl plates in cases of oils and liquids.

- **^{1}H-NMR**

  ^{1}H-NMR spectra were acquired at ambient temperature on a Bruker AMX. 400 (400 MHz) and a Bruker AC 200F (200 MHz) in the deuteriated solvents as stated. Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard.

- **^{13}C-NMR**

  ^{13}C-NMR spectra were recorded at ambient temperature on a Bruker AMX 400 (100 MHz) and a Bruker AC 200F (50 MHz) in the deuteriated solvents. Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard.

- **^{19}F-NMR**

  ^{19}F-NMR spectra were recorded at ambient temperature on a Bruker AMX 400 (378 MHz).

- **LR-MS**

  Mass spectra (EI) were recorded with a Hewlett Packard 5989B at 70 eV. Mass spectra (ESI) were recorded on Hewlett Packard MS LC/MSD Series 1100 MSD.

- **HR-MS**

  High resolution mass spectra were measured on Bruker Daltonik Tesla-Fourier Transform-Ion Cyclotron Resonance-Massspektrometer mit Electrospray-Ionisierung by Dr. Dräger at the Institute of Organic Chemistry, University of Hannover.

- **Elemental analysis**

  Elemental analyses were carried out by the Microanalytical Laboratory of the Institut fur Pharmazeutische Chemie der Technische Universitat Braunschweig on “Elemental Analyzer” Model 1106 from the “Carlo Erba Instrumentazione” company.

- **Chromatography**

  Flash column chromatography[181] was performed on Sorbisil C-60. Reactions were monitored by TLC with Merck Silica gel 60 F254 plates.

- **HPLC Analysis**

  HPLC analyses was carried out using a Daicel CHIRALPACK OD-H and Daicel CHIRALPACK AD-H columns with a Waters 510 Pump system, an ISCO Model UA-5 UV/VIS Detector (254 nm) and a Waters 410 Differential Refractometer.

3.2 Commercially available compounds

(*S*)-(+)-2-Amino-1-propanol, (*S*)-(−)-2-Amino-3-phenyl-1-propanol, 2-Bromo-N-methylanilin, *tert*butylmagnesium chloride (2M in diethyl ether), di*iso*propylmalonate, *iso*butylmagnesium bromide (2M in diethyl ether), *iso*butylmagnesium chloride (2M in ether) lithium *tert*butoxide (1M in hexane), methylmagnesium bromide (3M in diethyl ether), diethylzinc (1M in hexane) and Copper(II)trifluoromethanesulfonate were purchased from Aldrich.

Chlorotri*iso*propylsilane, *tert*butyldimethylchlorosilane and 1-naphthaldehyde were purchased from Merck. 1-Naphtaldehyde was distilled when stayed in the shelf for longer time.

L-(+)-α-Phenylglycinol, D-(+)-norephedrine and L-(−)-norephedrine were purchased from Fluka.

Diethylzinc (1M in toluene), isobutylene oxide, (+)-(*R*)-propylene oxide were purchased from Acros.

The reactions in water were carried out with distilled water.

rac-Mosher's acid was purchased from Lancaster.

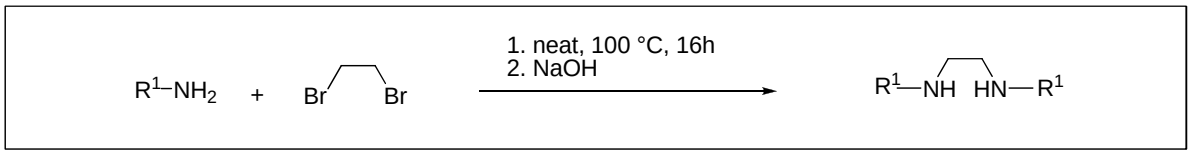
All the other reactions were performed in oven dried glassware under a nitrogen atmosphere.

Absolute EtOH and MeOH were purchased from Merck. Pentane, hexane and benzene were distilled from P_2O_5. Et_2O, Dioxane, THF and Toluene were distilled from sodium. MeCN and CH_2Cl_2 were distilled from CaH_2.

3.3. Preparation of C_2-Symmetric Diamines

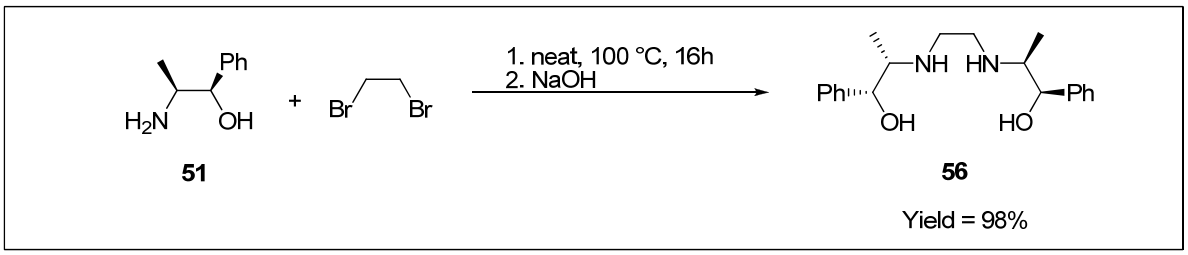
3.3.1. By Alkylation with Dibromoethane

General Procedure for the Preparation of Diamines by Alkylation with Dibromoethane



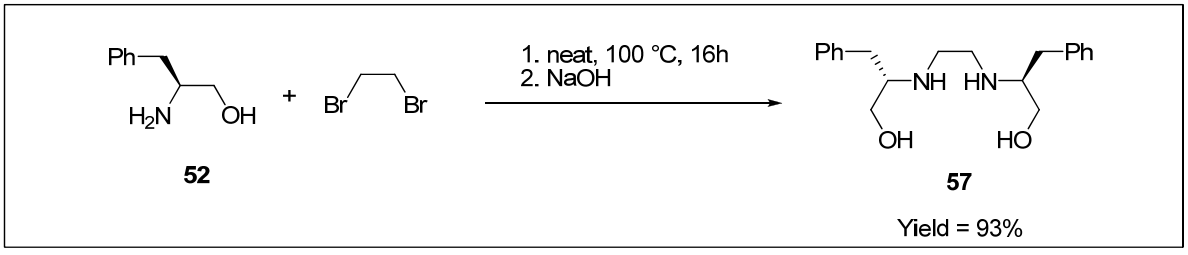
An amino alcohol (1.00 mmol) was added in a dried flask under nitrogen. Dibromoethane (43µl, 0.50 mmol) was added via syringe under nitrogen. The reaction mixture was heated at 100°C for 16h. The mixture was then cooled to room temperature. After dissolving the solid in water, the aqueous phase was washed with chloroform. The aqueous phase was basified with 2M NaOH and the diamine was extracted with chloroform (3×5 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the bis-amino alcohol.

(–)-(1*R*,1'*R*,2*S*,2'*S*)-2,2'-(Ethane-1,2-diylbis-(azanediyl))-bis-(1-phenylpropan-1-ol) (56)



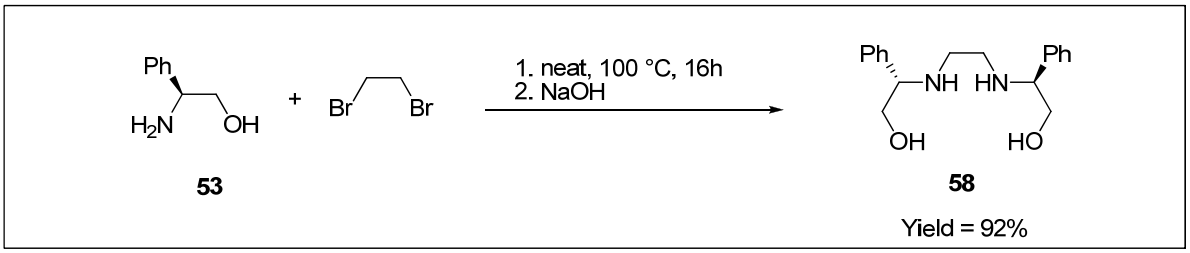
Prepared from (–)-norephedrine (3.00 g, 19.84 mmol) and dibromoethane (0.85 mL, 9.92 mmol), after basification with NaOH as a yellow solid (3.18 g, 98%). Spectral data were consistent with literature values.[182]

(–)-(2*S*,2'*S*)-2,2'-(Ethane-1,2-diylbis(azanediyl))-bis-(3-phenylpropan-1-ol) (57)



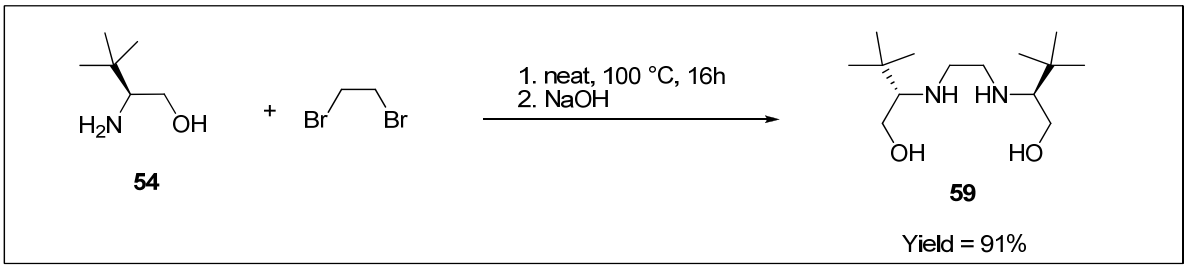
Prepared from (–)-(*S*)-2-amino-3-phenyl-1-propanol (0.30 g, 1.98 mmol) and dibromoethane (86.0 µl, 0.99 mmol), after basification with NaOH as a yellow solid (0.30 g, 93%). Spectral data were consistent with literature values.[183]

(+)-(2*S*,2'*S*)-2,2'-(Ethane-1,2-diylbis(azanediyl))-bis-(2-phenylethanol) (58)



Prepared from (+)-(*S*)-phenylglycinol (0.30 g, 2.19 mmol) and dibromoethane (95.0 µl, 1.09 mmol), after basification with NaOH as a yellow oil (0.30 g, 92 %). Spectral data were consistent with literature values.[184]

(*S*)-2-(2-((*S*)-1-Hydroxymethyl-2-methyl-propylamino)-ethylamino)-3-methyl-butan-1-ol (59)

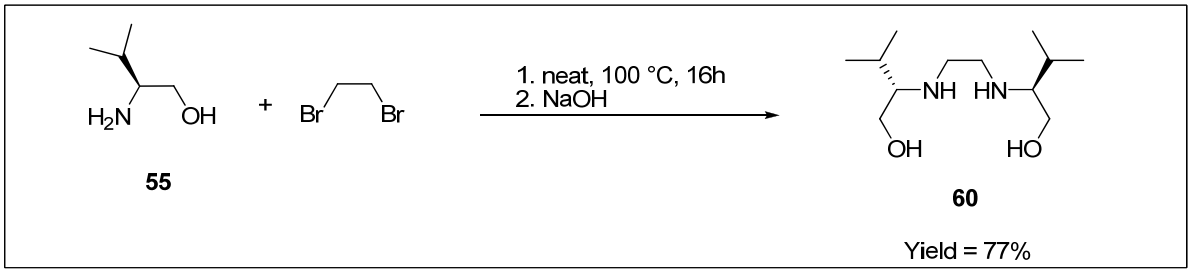


Prepared from L-*tert*leucinol (2.00 g, 17.10 mmol) and dibromoethane (740 µL, 8.55 mmol), after basified with 2M NaOH (8.55 mL, 17.10 mmol) as a white solid (2.01 g, 91%). For the purpose of elemental analysis, the diamine was crystallized from EtOH.

- **mp**: 53 °C.
- $[\alpha]^{22}_{D}$ = +53.8 (c = 0.34, $CHCl_3$).
- **IR (KBr)**: 3314, 2958, 2873, 1467, 1052, 452 cm^{-1}.
- **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.71 (dd, *J* = 3.52, 10.6 Hz, 2 H, -CH_2OH), 3.55-3.42 (m, 2 H, -CH_2OH), 3.08 (d, *J* = 8.6 Hz, 2 H, 2x –NH-C*H*-), 2.73 (d, *J* = 8.6 Hz, 2 H, -NH-CH_2-), 2.34 (dd, *J* = 3.52, 10.6 Hz, 2 H, -NH-CH_2-), 0.97 (s, 18 H, 2x -CH-C(CH_3)$_3$).
- **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 67.9, 62.9, 49.7, 34.4, 27.2.

- **MS (EI)**: *m/z* 261 (M^++H, 10%), 229 (15), 203 (25), 144 (25), 130 (100), 100 (50), 86 (50), 74 (40), 57 (45).
- **Anal**.: Calcd for $C_{14}H_{32}N_2O_2$: C, 64.57; H, 12.39; N, 10.76 found: C, 64.44; H, 12.54; N, 10.88.
- **HRMS** (ESI): Calcd. for $C_{14}H_{33}N_2O_2$: 261.2542, found: 261.2546.

(*S*)-2-(2-((*S*)-1-Hydroxymethyl-2-methyl-propylamino)-ethylamino)-3-methyl-butan-1-ol (60)



55 **60**

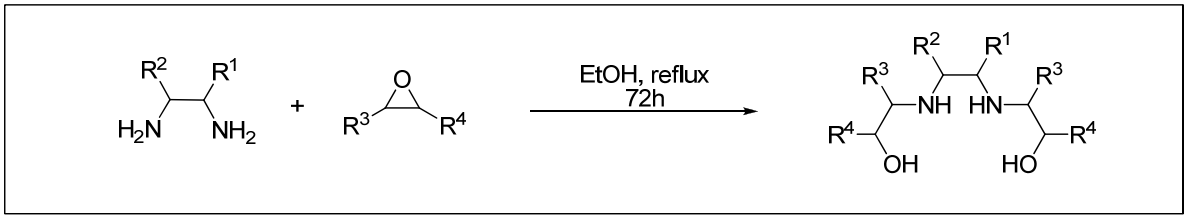
Yield = 77%

From L-valinol (1.23 g, 11.90 mmol) and dibromoethane (513 µL, 5.95 mmol), basified with 2M NaOH (5.10 mL, 10.20 mmol) as a yellow oil (1.06 g, 77%).

- $[\alpha]^{22}_{D}$ = +14.3 (c = 0.65, $CHCl_3$).
- **IR (neat)** 3314, 2958, 2873, 1467, 1052, 452 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 3.67-3.59 (m, 2 H, -C*H*$_2$OH), 3.42-3.33 (m, 2 H, -C*H*$_2$OH), 2.90-2.50 (m, 4 H, 2x -NH-C*H*$_2$-), 2.40-2.25 (m, 2 H, 2x -NH-C*H*-), 1.90-1.70 (m, 2 H, 2x -CH-C*H*$(CH_3)_2$), 1.01-0.85 (m, 12 H, 2x -CH(C*H*$_3)_2$).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 65.2, 62.0, 47.4, 29.4, 20.1, 18.7.
- **MS (ESI)**: *m/z* 233.3 (MH^+, 100%).

3.3.2. Preparation of Diamines by Ring Opening of Epoxides

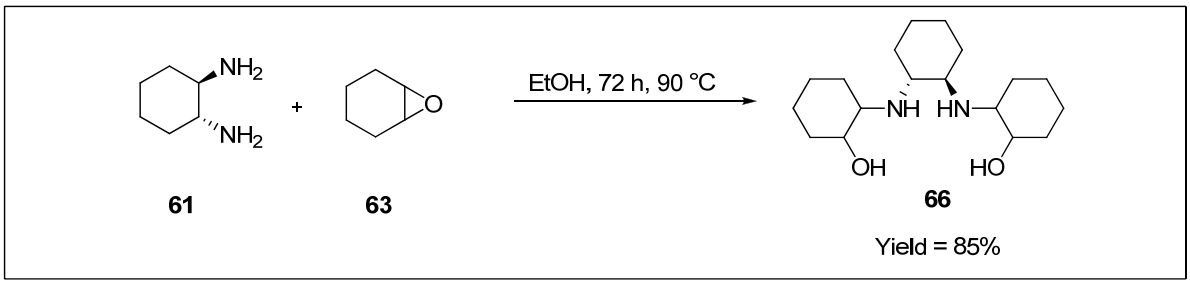
General Procedure for the Preparation of Diamines by Ring Opening of Epoxides



To a stirred solution of chiral 1,2-diphenyl-1,2-ethanediamine (0.21 g, 1.0 mmol) in anhydrous ethanol (5 mL) via a syringe was added epoxide (3.0 mmol) drop wise under an

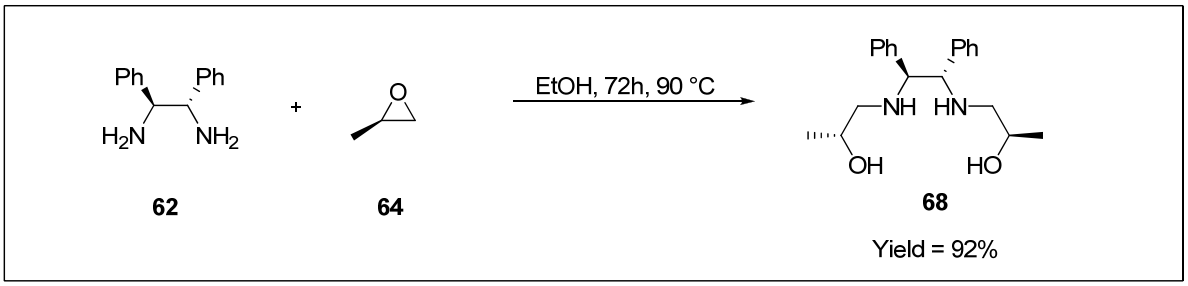
inert atmosphere at room temperature. Upon complete addition, the mixture was heated at reflux for 46h. After refluxing, the mixture was cooled to room temperature whereupon the solvent was evaporated to give a white solid. The solid was dissolved in water. The aqueous phase was acidified to pH 2 with 2M hydrochloric acid and the aqueous layer extracted with chloroform (3×5 mL) which was discarded. The aqueous layer was then basified to pH 11 with 2M aqueous sodium hydroxide and was again extracted with chloroform (3×5 mL). The combined organic layers were dried (Na_2SO_4) filtered and evaporated, resulting in a white crystalline solid.

_N,N´_-Bis-(2-hydroxycyclohexyl)-_trans_-cyclohexane-1,2-diamine (66)



This compound was prepared from (−)-(*R*,*R*)-1,2-diamime cyclohexane (2.0 g, 17.51 mmol) and cyclohexeneoxide (7.2 mL, 70.04 mmol), by following the general procedure as brown oil with an improved yield (4.66 g, 85%). Spectral data were consistent with literature values.[185]

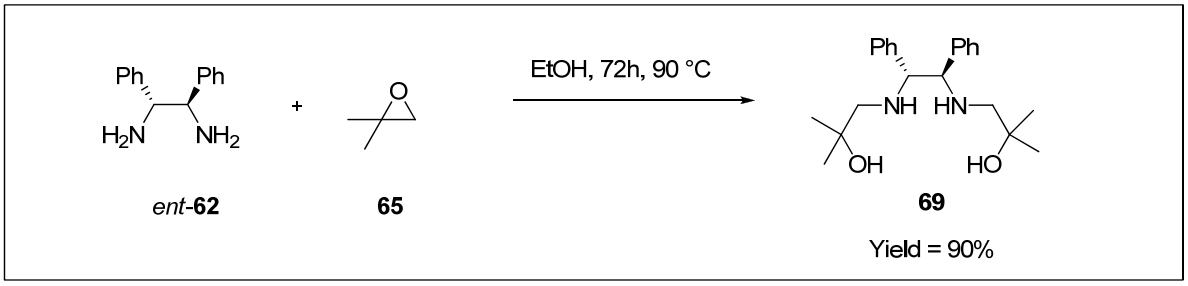
(−)-(*S,S*)-1,2-Diphenyl-*N,N*′-bis-((*R*)-2-hydroxyethyl)-3-methyl)ethylenediamine (68)



The amino alcohol was synthesized from (−)-(1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine (0.20 g, 0.94 mmol) and (+)-(*R*)-propylene oxide (0.20 mL, 2.83 mmol) by following the general procedure as a white crystalline solid (0.287 g, 93%).

- **mp**: 119 °C.
- **$[\alpha]^{D}_{22}$** = –30 (c = 1.0, $CHCl_3$).
- **IR (KBr)**: 3303, 2961, 2909, 1646, 1454, 1126, 1051, 864, 772, 700, 625, 575 cm^{-1}.
- **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.07-6.94 (m, 10 H, 10x Ar-*H*), 3.80-3.70 (m, 2 H, 2x -C*H*-OH -), 3.63 (s, 2 H, 2x Ar-C*H*-NH-) 2.43-2.16 (m, 4 H, 2x -NH-CH_2-), 0.98 (d, *J* = 5.4 Hz, 6 H, 2x -CH-CH_3).
- **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 140.7, 128.0, 127.7, 127.0, 68.3, 65.9, 54.3, 20.5.
- **MS (ESI)**: *m*/*z* = 351 [M+Na].
- **HRMS (ESI)**: calcd for $C_{21}H_{29}N_2O_2$ [M+H]: 329.2229; found 329.2229.

(+)-(*R*,*R*)-1,2-Diphenyl-*N*,*N*′-bis-(2-hydroxy-2-methyl-propyl)-ethylenediamine (69)



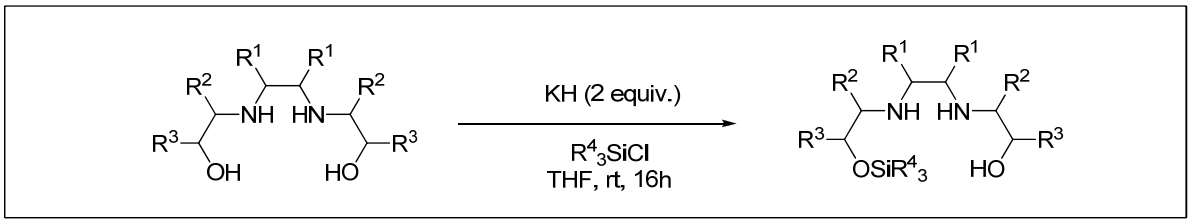
The amino alcohol was synthesized from (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (0.10 g, 0.47mmol) and isobutylene oxide (0.13ml, 1.41 mmol), by following the general procedure as a white crystalline solid (0.148g, 90%).

- **mp**: 123 °C.
- **$[\alpha]^{D}_{22}$** = +13 (c = 0.5, MeOH).
- **IR (KBr)**: 3302, 2962, 2907, 1455, 1405, 1164, 1127, 896, 845, 764, 699, 580 cm^{-1}.
- **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 7.26-6.98 (m, 10 H, 10x Ar-*H*), 3.69 (s, 2 H, 2x Ar-C*H*-NH-) 2.36 (s, 6 H, 2x -NH-CH_2, 2x -O*H*), 1.17 (s, 6 H, -CH_2-C(CH_3)$_2$), 1.13 (s, 6 H, -CH_2-C(CH_3)$_2$).
- **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 141.0, 128.0, 127.6, 127.0, 69.9, 69.6, 58.1, 27.4, 27. 3.
- **MS (ESI)**: *m*/*z* = 379 (70%) [M+Na], 357 (60) [M+H].
- **HRMS (ESI)**: calcd for $C_{21}H_{33}N_2O_2$ [M+H]: 357.2542; found 357.2542.

3.4. Synthesis of Hydroxy Protected Amines with Silyl Reagents

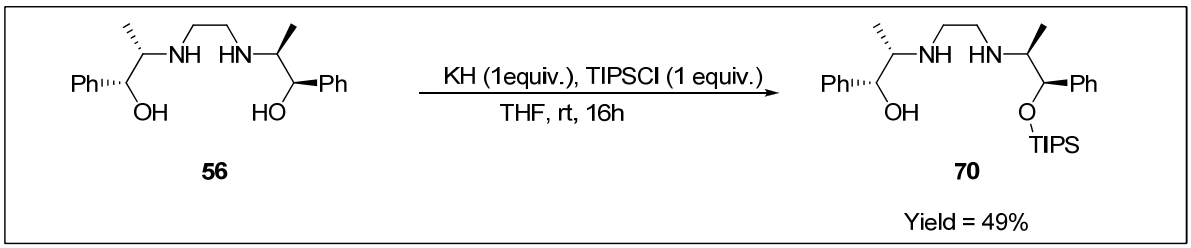
3.4.1. Synthesis of Monohydroxy Protected Diamine with Tri*iso*propylsilylchloride

General Procedure for the Preparation of Monohydroxy Protected Diamine



Bis-hydroxy-diamine (1 mmol) was transferred into a dry Schlenk tube equipped with a magnetic stirrer and a rubber septum. The tube was three times alternately evacuated and flushed with nitrogen. Potassium hydride (2.5 mmol of a 30% suspension in mineral oil) was then added followed by dry THF (1 mL). The suspension was stirred at room temperature until gas evolution ceased. Then tri*iso*propylsilylchloride (1 mmol) was added through the septum and a gas evolution was observed. The reaction mixture was stirred for 16h before it was quenched with water (2 mL). The aqueous layer was extracted three times with chloroform. The combined chloroform layers were dried over sodium sulphate and the solvent was removed *in vacuo* yielding the crude product which was purified by flash column chromatography (silica, 3% triethylamine/hexane).

(1*R*,2*S*)-2-[2-((1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenyl-ethylamino)-ethylamino]-1-phenyl-propoxy-tri*iso*propylsilane (70)



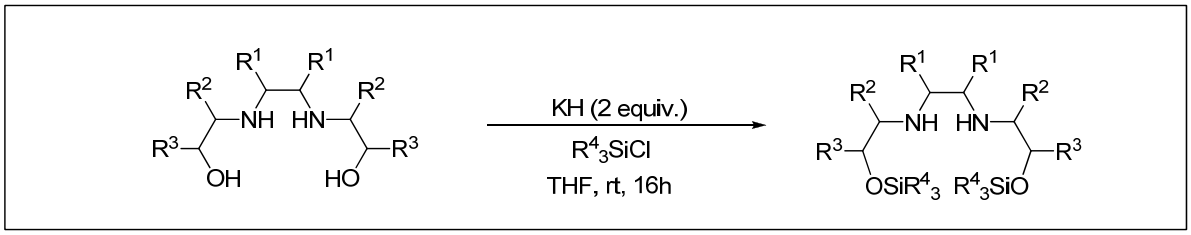
From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride (1equiv.) **70** as colorless oil (0.73 mmol, 0.357 g, 50%);

- $[\alpha]^{D}_{22} = -17$ (c = 1.6, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3684, 3620, 3020, 2976, 2401, 1522, 1423, 1216, 1047, 929, 772, 669, 627 cm^{-1}.

- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.26-7.15 (m, 10H, 10x Ar-*H*), 4.71 (dd, *J* = 3.6, 20.8 Hz, 1H, -C*H*-OH), 4.61 (d, *J* = 5.0 Hz, 1H, -C*H*-OTIPS), 3.57 (bs, 3H, 2x -N*H*, -O*H*), 2.78-2.58 (m, 6H, 2x -NH-C*H*-, -NH-(CH_2)$_2$-NH-), 1.09-0.67 (m, 27H, TIPS-*H*, 2x -NH-CH-CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 142.4, 141.3, 128.0, 127.2, 126.0, 78.9, 73.4, 59.9, 58.5, 46.9, 46.0, 18.0, 16.0, 12.4, 10.3.
- **MS (ESI)**: *m/z* 485.5 (MH^+, 100%).
- **HRMS (ESI)**: calcd for $C_{29}H_{48}N_2O_2Si$ [M+H]: 485.3563, found 485.3571.

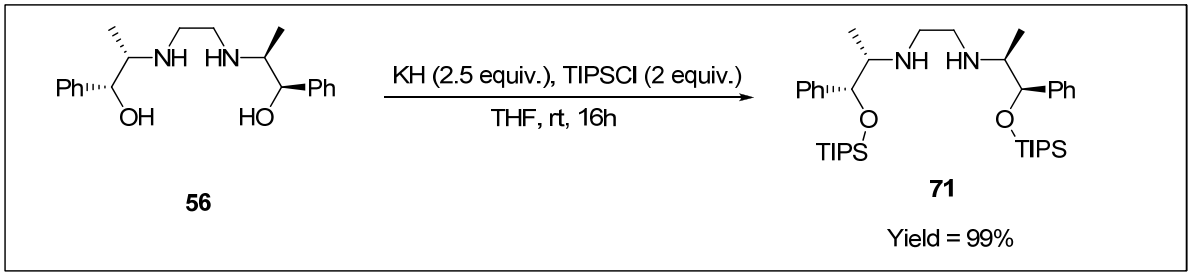
3.4.2. Synthesis of Bis-Hydroxy Protected Diamines

General Procedure for Preparation of Bis-Hydroxy Protected Diamines



Bis-hydroxy diamine (1 mmol) was transferred into a dry Schlenk tube equipped with a magnetic stirrer and a rubber septum. The tube was three times alternately evacuated and flushed with nitrogen. Potassium hydride (2.5 mmol of a 30% suspension in mineral oil) was then added through the open septum, followed by dry THF (1 mL). The suspension was stirred at room temperature until gas evolution ceased. Then trialkylsilyl chloride (2 mmol) was added through the septum and a gas evolution was observed. The reaction mixture was stirred for 16h before it was quenched with water (2 mL). The aqueous layer was extracted three times with chloroform, the combined chloroform layers were dried over sodium sulphate and the solvent was removed *in vacuo* yielding the crude product which was purified by flash column chromatography (silica, 3% triethylamine/hexane).

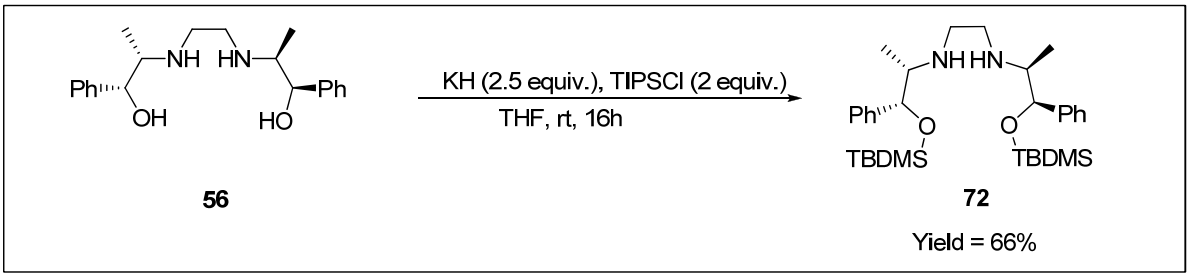
(1*R*,2*S*)-2-[2-((1*S*,2*R*)-2-Tri*iso*propylsiloxy-1-methyl-2-phenyl-ethylamino)-ethylamino]-1-phenyl-propoxy-tri*iso*propylsilane (71)



From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride, **71** as colorless oil (0.99 mmol, 0.634 g, 99%):

- **$[\alpha]_D^{24}$** = –25 (c = 0.97, $CHCl_3$)
- **IR (NaCl)**: ν_{max}= 2943, 2891, 2867, 1463, 1370, 1094, 1062, 1207, 997, 919, 883, 819, 701, 681, 449, 408 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ= 7.32-7.20 (m, 10H, 10x Ar-*H*), 4.72 (d, *J* = 3.6 Hz, 2H, 2x -C*H*-OTIPS), 2.80 - 2.49 (m, 6H, 2x -NH-C*H*-, -NH-(CH_2)$_2$-NH-) 1.12 - 0.98 (m, 48H, 2x TIPS-*H*, 2x -NH-CH-CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ= 142.9, 127.8, 127.2, 78.8, 59.9, 47.5, 18.0, 15.9, 12.5.
- **MS (ESI)**: *m/z* 641.4 (MH^+, 100%).
- HRMS (ESI): calcd for $C_{38}H_{68}N_2O_2Si_2$ [M+H]: 641.4898, found 641.4892.

(1*R*,2*S*)-2-[2-((1*S*,2*R*)-2-*tert*Butyldimethylsiloxy-1-methyl-2-phenyl-ethylamino)-ethylamino]-1-phenyl-propoxy- *tert*butyldimethylsilane (72)



56 **72**

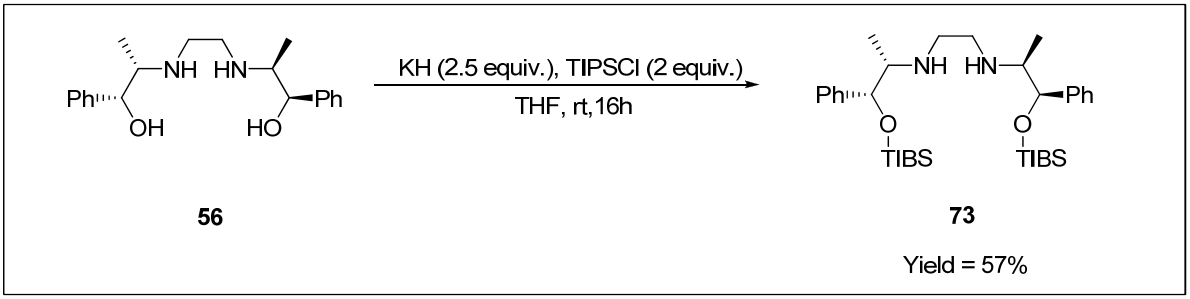
Yield = 66%

From the corresponding bis-hydroxy diamine and *tert*butyldimethylsilylchloride, **72** as colorless oil (0.20mmol, 0.112g, 66%).

- **$[\alpha]_D^{24}$** = –42 (c = 0.42, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2976, 2896, 2401, 1522, 1474, 1424, 1216, 1047, 929, 774, 669, 627 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.42-7.51 (m, 10H, 10x Ar-*H*), 4.74 (d, *J* = 4.0 Hz, 2H, 2x -C*H*-OTIPS), 2.90 - 2.69 (m, 6H, 2x -NH-C*H*-, -NH-(CH_2)$_2$-NH-) 1.08 - 1.17 (m, 24H, 2x Si-*tert*butyl-*H*, 2x -NH-CH-CH_3). –0.018 (s, 6H, 2x Si-CH_3), –0.242 (s, 6H, 2x Si-CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 143.1, 127.8, 127.0, 126.7, 76.9, 59.7, 47.0, 25.8, 15.2, -4.5, -4.9.
- **MS (ESI)**: *m/z* 557.3 (MH^+, 100%).

- **HRMS (ESI)**: calcd for $C_{32}H_{56}N_2O_2Si_2$ [M+H]: 557.3959, found 557.3961.

(1*R*,2*S*)-2-[2-((1*S*,2*R*)-2-Tri*iso*butylsiloxy-1-methyl-2-phenyl-ethylamino)-ethylamino]-1-phenyl-propoxy- tri*iso*butylsilane (73)



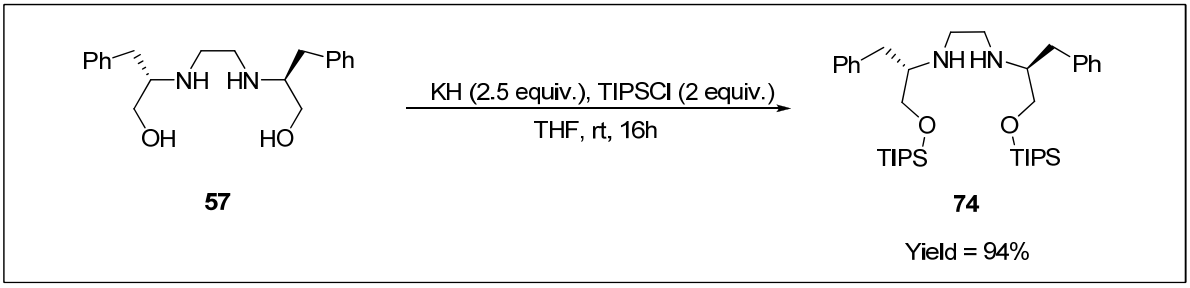
56 **73**

Yield = 57%

From the corresponding bis-hydroxy diamine and tri*iso*butylsilylchloride, **73** as colorless oil (0.40 mmol, 0.287 g, 57%).

- $[\alpha]^{D}_{22} = -22$ (c = 1.5, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2956, 2401, 2361, 1522, 1424, 1216, 1046, 929, 772, 670, 588 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.31-7.23 (m, 10H, 10x Ar-*H*), 4.57 (d, *J* = 4.0 Hz, 2H, 2x -C*H*-OTIBS), 2.73 - 2.52 (m, 6H, 2x -NH-C*H*-, -NH-(C*H*$_2$)$_2$-NH-), 1.77- 1.73 (m, 6H, 6x -CH$_2$-C*H*(CH$_3$)$_2$), 0.98 (d, *J* = 2.0, 6H, 2x -CH-C*H*$_3$), 0.92 (d, *J* = 3.2, 18H, 6x -CH-(C*H*$_3$)$_2$), 0.88 (d, *J* = 3.2, 18H, 6x -CH-(C*H*$_3$)$_2$), 0.55 (d, *J* = 3.4, 12H, 6x -Si-C*H*$_2$-).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 142.9, 127.8, 127.0, 76.3, 59.6, 47.1, 26.4, 25.7, 24.0, 15.6.
- **MS (ESI)**: *m/z* 725.5 (MH^+, 100%).
- **HRMS (ESI)**: calcd for $C_{44}H_{80}N_2O_2Si_2$ [M+H]: 725.5837, found 725.5814.

(*S*)-2-[2-((*S*)-1-Tri*iso*propylsiloxymethyl-phenylethylamino)-ethylamino]-3-phenylpropoxy-tri*iso*propylsilane (74)

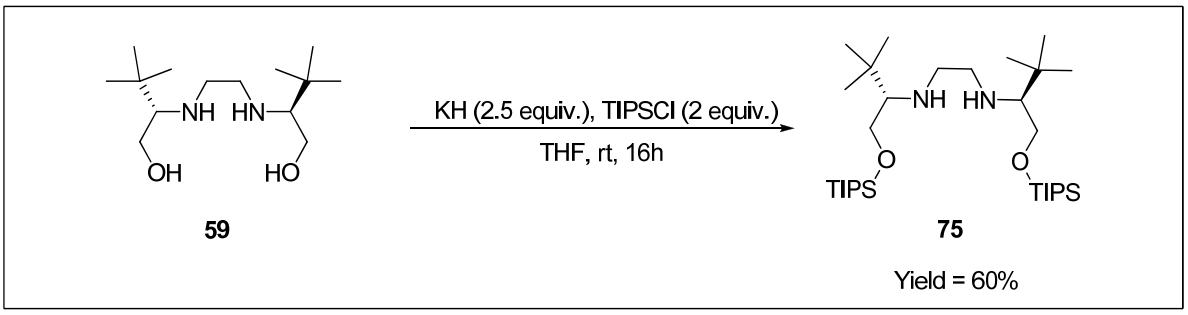


57 **74**

Yield = 94%

From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride, **74** as colorless oil (0.94 mmol, 0.602 g, 94%); The compound was used without further purification in the next step.

(*S*)-2-[2-((*S*)-1-Tri*iso*propylsiloxymethyl-2-dimethyl-propylamino)-ethylamino]-3,3′-dimethyl-butoxy-tri*iso*proplylsilane (75)



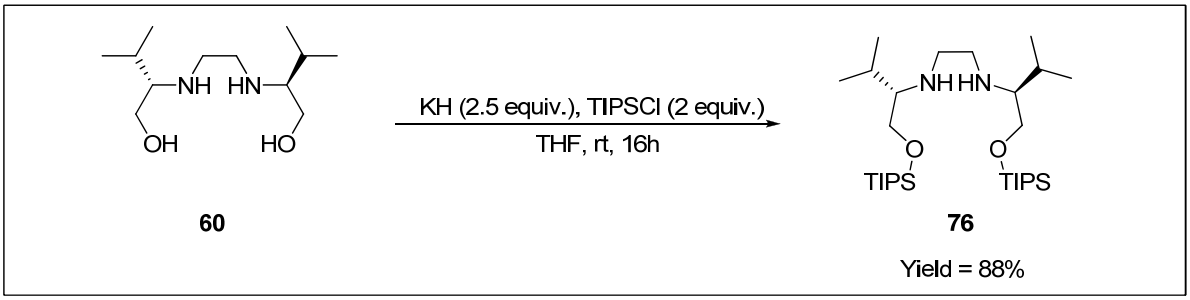
59 **75**

Yield = 60%

From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride, **75** was prepared as colorless oil (0.43 mmol, 0.246 g, 43 %.).

- $[\alpha]^{D}_{22} = -7$ (c = 0.73, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 2866, 1732, 1463, 1390, 1362, 1332, 1101, 997, 919, 883, 810, 682 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ =3.75 (ddd *J* = 4.6, 10.4, 4.7 Hz, 4H, 2x -O-C*H*$_2$-), 2.79 (dd *J* = 8.24, 7.0 Hz, 4H, -NH-(C*H*$_2$)$_2$-NH-) 2.15 (t, *J* = 4.8 Hz, 2H, 2x -NH-C*H*-) 1.56 (bs, 2H, 2x N*H*), 1.12 - 0.98 (m, 42H, 2x TIPS-*H*), 0.94 (s, 18H, 2x *t*Bu-*H*).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 68.7, 63.2, 50.6, 34.3, 27.4, 18.1, 11.9.
- **MS (ESI)**: *m/z* 573.5 (MH^+, 100%).
- **HRMS (ESI)** calcd for $C_{32}H_{72}N_2O_2Si_2$ [M+H]: 573.5211, found 573.5232.

(*S*)-2-[2-((*S*)-1-Tri*iso*propylsiloxymethyl-2-dimethyl-propylamino)-ethylamino]-3-methyl-butoxy-tri*iso*propylsilan (76)



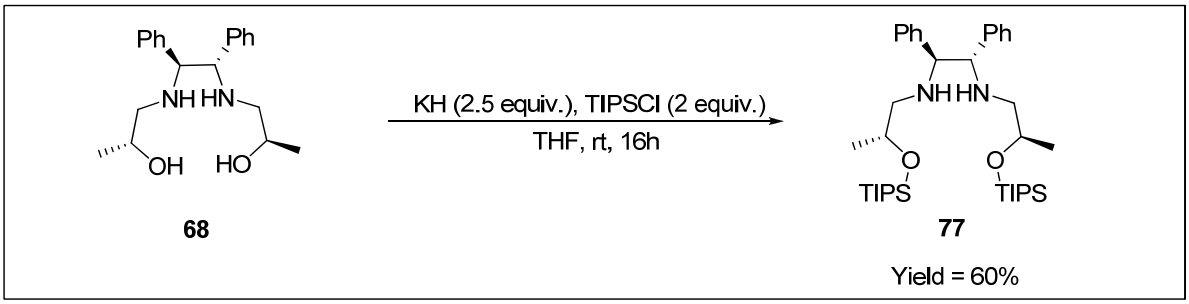
60 **76**

Yield = 88%

From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride, **76** colorless oil (0.88 mmol, 0.48 g, 88 %).

- **$[\alpha]^{D}_{22}$** = –6 (c = 0.8, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 2957, 2867, 1464, 1108, 883, 682, 439 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 3.70 (dd *J* = 9.9, 5.4 Hz, 4H, 2x -O–C*H*$_2$-), 2.74 - 2.53 (m, 4H, -NH-(C*H*$_2$)$_2$-NH-), 2.29 (dd *J* = 10.9, 5.4 Hz, 2H, 2x -NH-C*H*-), 1.86 - 1.69 (m, 2H, 2x -C*H*(CH_3)$_2$), 1.55 (bs, 2H, 2x N*H*), 1.05 - 0.92 (m, 42H, 2xTIPS-*H*), 0.85 (d *J* = 6.8 Hz, 12H, 4x C*H*$_3$).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 64.9, 63.1, 48.5, 28.82, 18.9, 18.6, 18.1, 12.0.
- **MS (ESI)**: *m/z* 545.4 (MH^+, 100%).
- **HRMS(ESI)**: calcd for $C_{30}H_{68}N_2O_2Si_2$ [M+H]: 545.4898, found 545.4917.

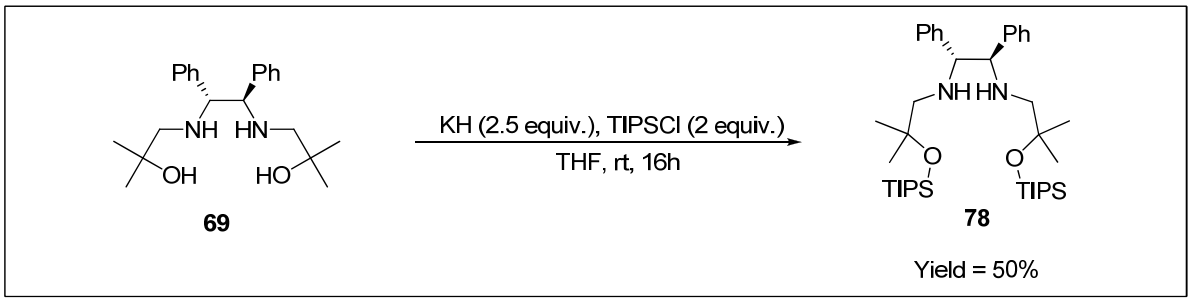
(–)-(1*S*,2*S*)-1,2-Diphenyl-*N*,*N*′-bis-((*R*)-2-(tri*iso*propyl-silyloxy)-propyl)-ethane-1,2-diamine (77)



From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride, **77** as colorless oil (0.23 mmol, 0.148 g, 60%).

- **$[\alpha]^{D}_{22}$** = –3 (c = 0.23, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2971, 2867, 1522, 1426, 1216, 1047, 757, 669, 628 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.25-6.96 (m, 10H, 10x Ar-*H*), 4.0 (dd, *J* = 5.4, 11.4 Hz, 2H, 2x Ar-C*H*-NH-), 3.58 (s, 2H, 2x -C*H*-OTIPS), 2.48-2.31 (m, 4H, 2x -NH-C*H*$_2$-), 1.17 (d, *J* = 6.2, 6H, 2x -CH-C*H*$_3$), 1.06-0.84 (m, 42H, 2x TIPS-*H)*.
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 141.6, 127.9, 127.6, 126.5, 69.3, 68.2, 55.4, 21.9, 18.0, 12.4.
- **MS (ESI)**: *m/z* 641.0 (MH^+, 100%).
- **HRMS (ESI)**: calcd for $C_{38}H_{68}N_2O_2Si_2$ [M+H]: 641.4898, found 641.4908.

(+)-(1R, 2R)-*N*,*N*′-Bis-(2-methyl-2-tri*iso*propylsilyloxy)-propyl)ethane-1,2-diamine (78)

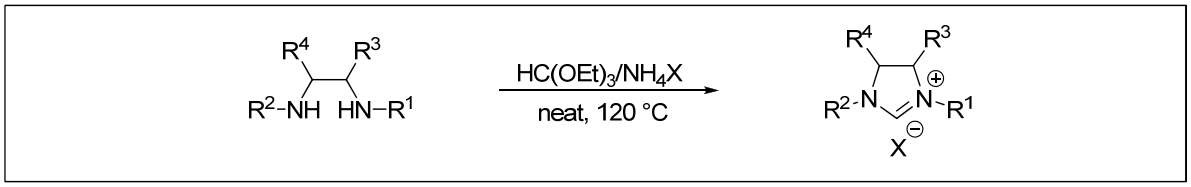


From the corresponding bis-hydroxy diamine and tri*iso*propylsilylchloride, **78** as colorless oil (0.96 mmol, 0.646 g, 50%).

- **$[\alpha]^{D}_{22}$** = +4 (c = 0.3, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2361, 1216, 1046, 929, 757, 669, 589 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.25-7.01 (m, 10H, 10x Ar-*H*), 3.60 (s, 2H, 2x Ar-C*H*-NH-), 2.30 (s, 4H, 2x -NH-CH_2-), 1.25 (bs, 2H, 2x -N*H*-), 1.23 (d, *J* = 2.0, 12H, 2x -CH_2-CH-(CH_3)$_2$), 1.05-1.00 (m, 42H, 2x TIPS-*H*).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 142.1, 127.9, 127.6, 126.4, 73.9, 69.7, 60.3, 28.4, 18.3, 13.3.
- **MS (ESI)**: *m/z* 669.2 (MH^+, 100%).
- **HRMS (ESI)**: calcd for $C_{40}H_{72}N_2O_2Si_2$ [M+H]: 669.5211, found 669.5206.

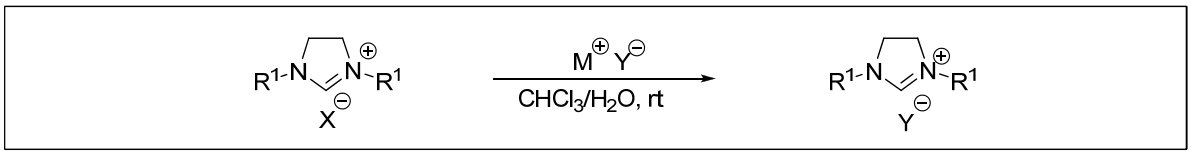
3.5. Synthesis of Imidazolinium Salts

General Procedure for the Preparation of Imidazolinium Salts



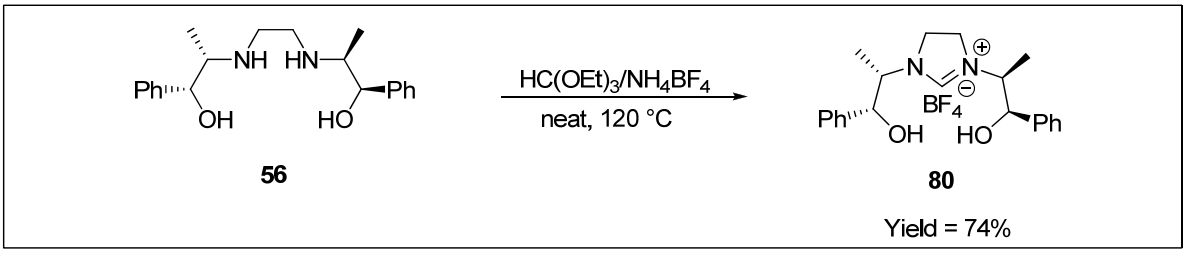
Bis-hydroxy diamine (1 mmol) was put into a pressure vessel. Ammonium tetrafluoroborate (1 mmol, 1.04 g) was added and the vessel was flushed with nitrogen. Triethyl*ortho*formate (1 mmol, 1.65 mL) was added and the vessel was sealed. The mixture was heated to 120 °C for the indicated time. After that the crude solid was either recrystallized from dry ethanol or purified via column chromatography (CH_2Cl_2:MeOH 20:1).

Gerneral Procedure for Counter Anion Metathesis



Imidazolinium tetrafluoroborate (1.0 mmol) was dissolved in CH_2Cl_2 (5 mL) in a flask. Sodium tetraphenylborate (1.0 mmol) and water (5 mL) were added sequentially. The reaction mixture was stirred for 16h. Afterwards the organic phase was separated, washed three times with water, dried (Na_2SO_4) and solvent was evaporated under reduced pressure. The product was dried *in vacuo* to provide the corresponding imidazolinium tetraphenylborate.

(−)-1,3-Bis-((1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-imidazolinium tetrafluoroborate (80)

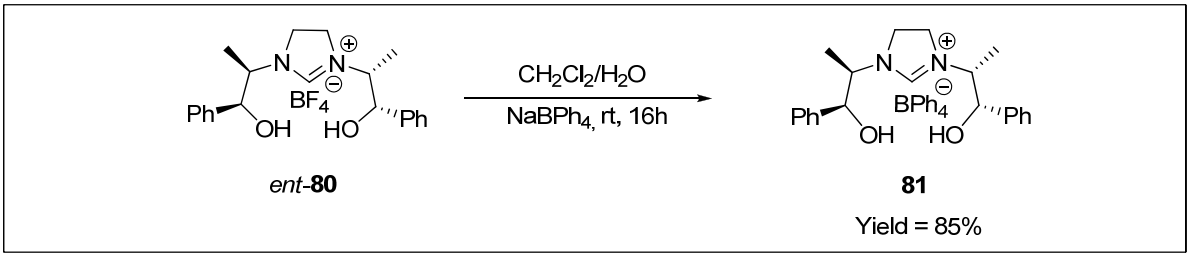


56 **80**

Yield = 74%

Prepared from **56** (500 mg, 1.52 mmol), NH_4BF_4 (156 mg, 1.52 mmol) and $CH(OEt)_3$ (250 µL, 1.52 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5h. After removing the ethanol, the crude was washed with hexane, diethyl ether and dichloromethane giving the title compound as a white solid (481 mg, 74%). Spectral data were consistent with literature values.[87]

(+)-1,3-Bis-((1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl)-imidazolinium tetraphenylborate (81)



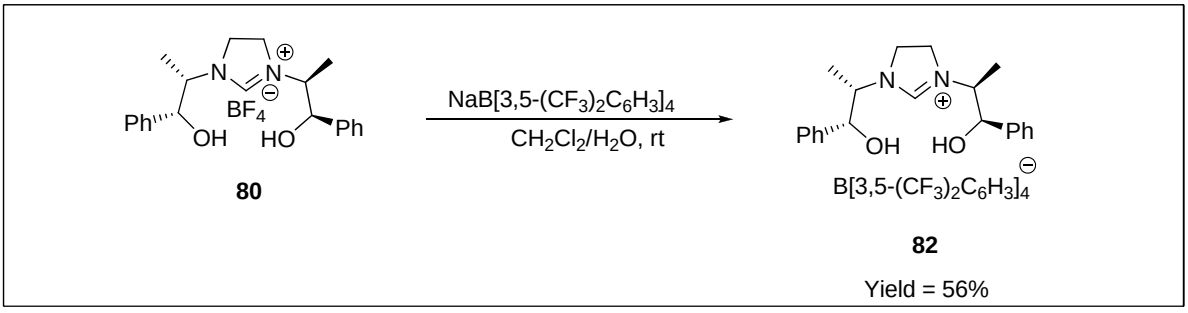
ent-**80** **81**

Yield = 85%

From *ent*-**80** (100 mg, 0.24 mmol) and $NaBPh_4$ (80.0 mg, 0.24 mmol) in a mixture of CH_2Cl_2 (5 mL) and H_2O (5 mL) as a yellow gummy compound (131 mg, 85%).

- **$[\alpha]^D_{22}$** = +8 (c = 1.0, MeOH).
- **IR (NaCl)**: 3332, 2924, 2832, 1639, 1451, 1028, 736, 705 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.27 (s, 1 H, -N-C*H*-N-), 7.42-7.33(m, 20 H, 20x Ar-*H*), 6.96-6.77 (m, 10 H, 10x Ar-*H*), 5.04 (d, *J* = 4.0 Hz 2 H, 2x -C*H*-OH), 4.11-4.00 (m, 6 H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 1.24 (d, *J* = 7.0 Hz, 6 H, 2x -N-CH CH_3).
- **^{13}C-NMR** (50 MHz, $(CD_3)_2CO$) δ = 157.1, 137.0, 134.1, 129.2, 128.7, 126.0, 125.9, 122.2, 74.5, 60.3, 47.2, 12.9.
- **MS (ESI)**: *m*/*z* = 339 [M].

1,3-Bis-((1*S*,2*R*)-2-hydroxy-2-phenylpropan-1-yl)-imidazolinium tetrakis-(3,5-bis-(trifluoromethyl)-phenyl)-borate (82)

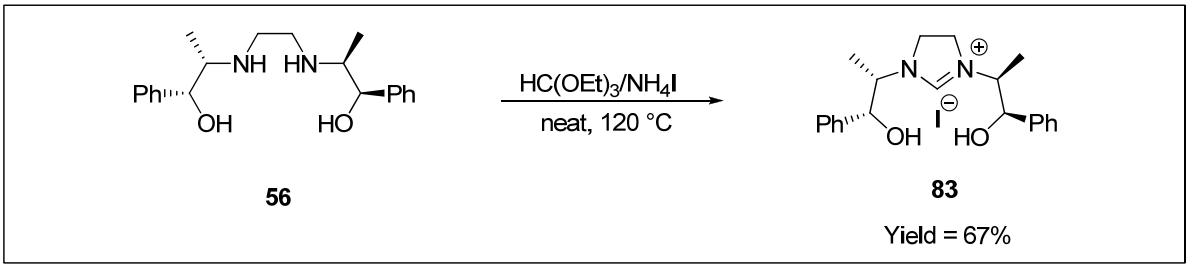


From 1,3-bis-((1*S*,2*R*)-2-hydroxy-2-phenylpropan-1-yl)-imidazolinium tetrafluoroborate **80** (200 mg, 0.47 mmol) and $NaB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (416 mg, 0.47 mmol) in a mixture of CH_2Cl_2 (5 mL) and water (5 mL) as a brown oil (477 mg, 84%).

- **$[\alpha]^D_{22}$** = –53.2 (c = 0.5, $CHCl_3$).
- **IR (KBr)** 1641, 1356, 1279, 1124, 682 cm^{-1}.
- **^{1}H-NMR** (400 MHz, acetone-*d6*) δ = 8.33 (s, 1 H, -N-C*H*-N-), 7.08 (s, broad, 8 H, -B-Ar-*H*), 7.69 (broad s, 4 H, -B-Ar-*H*), 7.50-7.30 (m, 10 H, 10x Ar-*H*), 5.20-5.05 (m, 2 H, 2x -C*H*-OH), 4.25-4.05 (m, 6 H, 2x -N-C*H*-, -N-(CH_2)$_2$-NH-), 2.88 (broad s, 2 H, 2x -O*H*), 1.29 (d, *J* = 8.1 Hz, 6 H, 2x –N-CH CH_3).
- **^{13}C-NMR** (100 MHz, acetone-*d6*) δ = 161.7 (q, *J* = 49.5 Hz), 156.4, 140.9, 134.6, 129.3 (q, *J* = 28.4 Hz, 128.4, 127.9, 126.2 124.5 (q, *J* = 269.8 Hz, 117.6, 73.8, 59.6, 52.5, 47.8, 47.6, 12.1.

- **MS (ESI)**: *m/z* 339.2 (M^+, 100%).
- **HRMS (ESI)** calculated for $C_{21}H_{27}N_2O_2^+$: 339.2073, found: 339.2079.

(–)-3-Bis-((1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-imidazolinium iodide (83)



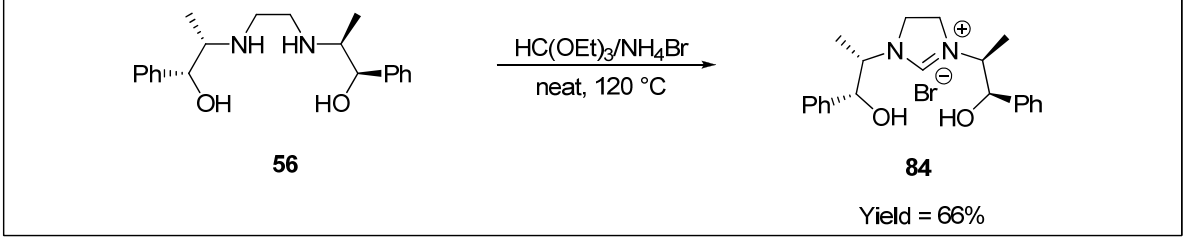
56 **83**

Yield = 67%

Prepared from **56** (200 mg, 0.61 mmol), NH_4I (88.3 mg, 0.61 mmol) and $CH(OEt)_3$ (100 µL, 0.61 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5 h. After removal of the solvent, the crude was washed with hexane and diethyl ether giving the title compound as a white crystalline solid (189 mg, 67%). The compound **83** was recrystallized in acetone for X-ray crystallography.

- **mp**: 184 °C.
- $[\alpha]^{D}_{22}$ = –4 (c = 0.3, MeOH).
- **IR (KBr)**: 3438, 3236, 1650, 1496, 1262, 1138, 1029, 1016, 753, 704 cm^{-1}.
- **^{1}H-NMR** (200 MHz, CD_3OD) δ = 7.90 (s, 1 H, -N-C*H*-N-), 7.16-7.08 (m, 10 H, 10x Ar-*H*), 4.61 (s, 2 H, 2x -C*H*-OH), 3.72-3.60 (m, 6 H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 1.00 (d, *J* = 7.0 Hz, 6 H, 2x -N-CH CH_3).
- **^{13}C-NMR** (50 MHz, CD_3OD) δ = 157.8, 142.1, 129.6, 129.1, 127.5, 75.2, 60.9, 47.2, 13.5.
- **MS (ESI)**: *m/z* = 339 [M].
- **HRMS (ESI)**: calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073, found 339.2072.

(–)-1,3-Bis-((1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-imidazolinium bromide (84)



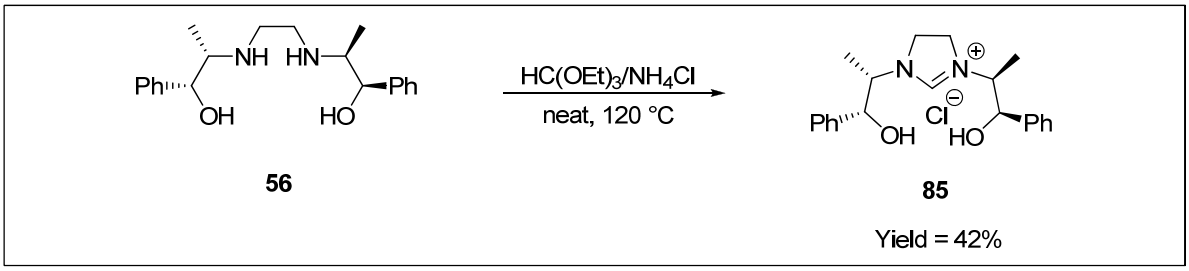
56 **84**

Yield = 66%

Prepared from **56** (100 mg, 0.30 mmol), NH_4Br (32.2 mg, 0.33 mmol) and $CH(OEt)_3$ (56 µL, 0.34 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 12h. After removal of the solvent, the crude was washed with hexane and diethyl ether giving the title compound as a yellow crystalline solid (84 mg, 66%).

- **mp**: 148 °C.
- **$[\alpha]^{D}_{22}$** = –17 (c 1.0, MeOH).
- **IR (KBr)** 3344, 1647, 1266, 1151, 753, 704 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.51 (s, 1 H, -N-C*H*-N-), 7.28-7.04 (m, 10 H, 10x Ar-*H*), 5.68 (d, *J* = 4.0 Hz, 2 H, 2x -C*H*-OH), 5.10 (br. s, 2 H, 2x -O*H*) 4.09-3.86 (m, 6 H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 0.85 (d, *J* = 7.0 Hz, 6 H, 2x -N-CH CH_3).
- **^{13}C NMR** (50 MHz, $(CD_3)_2CO$) δ = 157.2, 142.3, 128.9, 127.7, 126.8, 72.3, 60.3, 48.8, 11.1.
- **MS (ESI)**: *m*/*z* = 339 [M].
- **HRMS (ESI)**: calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073, found 339.2070.

(–)-3-Bis-((1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-imidazolinium chloride (85)



56 **85**

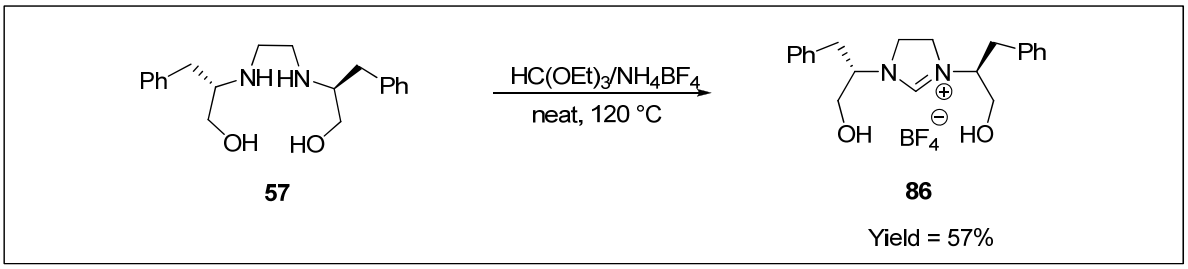
Yield = 42%

Prepared from **56** (300 mg, 0.91 mmol), NH_4Cl (48.8 mg, 0.91 mmol) and $CH(OEt)_3$ (148 µL, 0.91 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 16h. After removal of the solvent, the crude was washed with hexane, diethyl ether and chloroform giving the title compound as a white crystalline solid (143 mg, 42%).

- **mp**: 199 °C.
- **$[\alpha]^{D}_{22}$** = –16 (c 0.4, MeOH).
- **^{1}H-NMR** (200 MHz, CD_3OD) δ = 7.90 (s, 1 H. -N-C*H*-N-), 7.17-7.08 (m, 10 H, 10x Ar-*H*), 4.61 (d, *J* = 4.4 Hz, 2 H, 2x -C*H*-OH), 3.71-3.59 (m, 6 H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 1.07 (d, *J* = 7.0 Hz, 6 H, 2x -N-CH CH_3).
- **^{13}C-NMR** (50 MHz, CD_3OD) δ = 156.3, 140.6, 128.1, 127.6, 126.0, 73.7, 59.4, 47.0, 11.9.

- **MS (ESI)**: *m*/*z* = 339 [M].
- **HRMS (ESI)**: calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073, found 339.2073.

(−)-1,3-Bis-((*S*)-1-(hydroxymethyl)-2-methylbenzyl)-imidazolinium tetrafluoroborate (86)



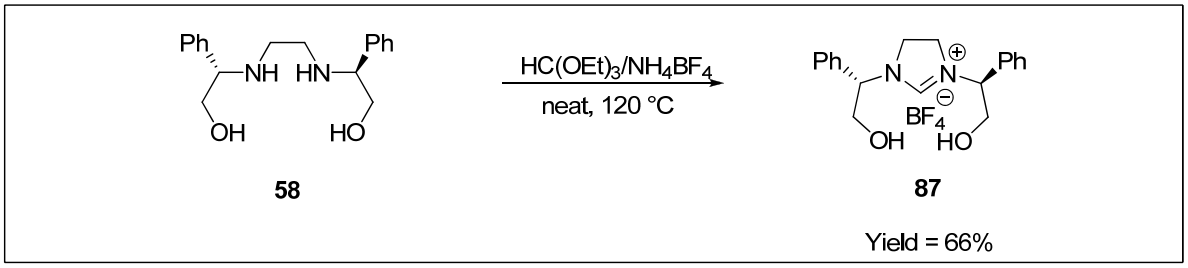
57 **86**

Yield = 57%

Prepared from **57** (200 mg, 0.61 mmol), NH_4BF_4 (68.6 mg, 0.67 mmol) and $CH(OEt)_3$ (109 µL, 0.67 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5h. After removal of the solvent, the crude was washed with hexane and diethyl ether giving the title yellow gummy compound. (147 mg, 57%).

- $[\alpha]^{D}_{22}$ = –71 (c =1.0, $CHCl_3$).
- **IR (NaCl)**: 3054, 2987, 1422, 1265, 896, 739 cm^{-1}.
- **^{1}H NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.16 (s, 1 H, -N-C*H*-N-), 7.20-7.14 (m, 10 H, 10x Ar-*H*), 3.57-3.95 (m, 12 H, 2x –CH_2O*H*, 2x –N-C*H*-, -N-(CH_2)$_2$-N-), 2.84 (m, 4 H, 2x -CH-CH_2-Ar).
- **^{13}C NMR** (50 MHz, $(CD_3)_2CO$) δ = 158.6, 137.9, 129.9, 129.6, 127.7, 62.8, 61.3, 46.9, 35.6.
- **MS (ESI)**: *m*/*z* = 339 [M].
- **HRMS (ESI)**: calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073, found 339.2075.

(+)-1,3-Bis-((*S*)-1-(hydroxymethyl)-2-methylphenyl)-imidazolinium tetrafluoroborate (87)



58 **87**

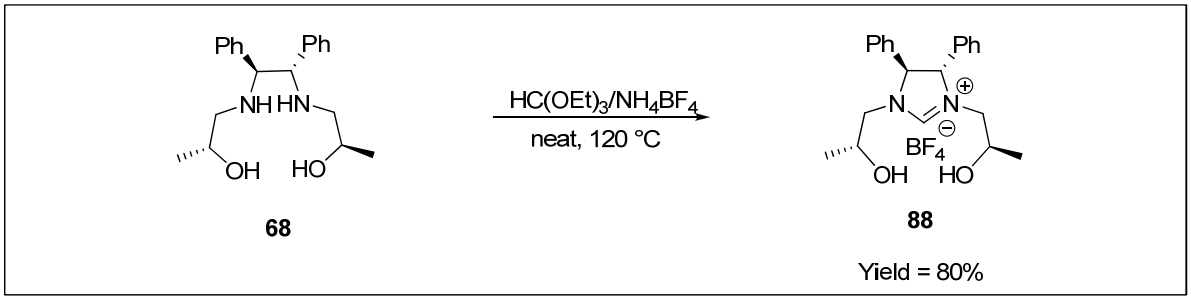
Yield = 66%

Prepared from **58** (100 mg, 0.33 mmol), NH_4BF_4 (53.8 mg, 0.49 mmol) and $CH(OEt)_3$ (83 µL, 0.49 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 16h.

After removal of the solvent, the crude was washed with hexane and diethyl ether giving the yellow oil (87 mg, 66%).

- **$[\alpha]^{D}_{22}$** = +65 (c = 0.65, MeOH).
- **IR (NaCl)**: 3054, 2987, 1422, 1265, 896, 739 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.74 (s, 1 H, -N-C*H*-N-), 7.33-7.24 (m, 10 H, 10x Ar-*H*), 4.97-4.91 (m, 2 H, 2x -N-C*H*-Ar), 4.54 (s, br, 2 H, 2x -O*H*), 3.90-3.82 (m, 8 H, 2x –CH_2OH, -N(CH_2)$_2$-N-).
- **^{13}C-NMR** (50 MHz, $(CD_3)_2CO$) δ = 158.5, 135.5, 129.9, 129.7, 128.7, 64.9, 62.1, 47.4.
- **MS (ESI)**: *m*/*z* = 311 [M].
- **HRMS (ESI)**: calcd for $C_{19}H_{23}N_2O_2^+$ 311.1760, found 311.1761.

(–)-(4*S*,5*S*)-Diphenyl-1,3-bis-((*R*)-2-hydroxyethyl)-3-methyl)-imidazolinium tetrafluoroborate (88)

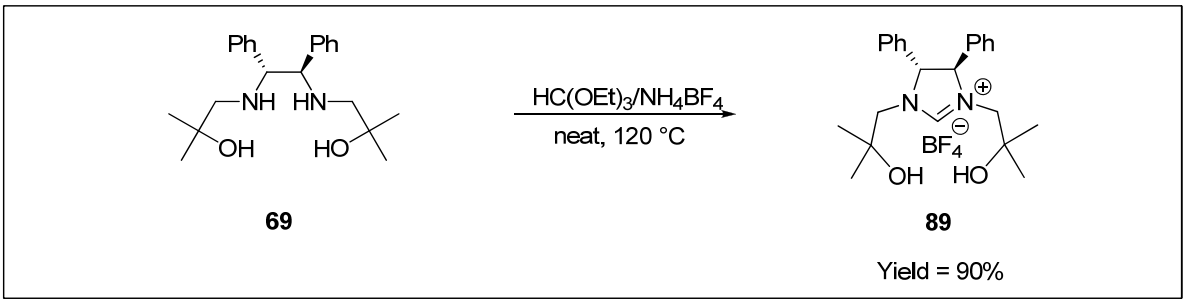


Prepared from **68** (104 mg, 0.32 mmol), NH_4BF_4 (35.8 mg, 0.35 mmol) and $CH(OEt)_3$ (58 µL, 0.35 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 5h. After the removal of solvent, the crude product was washed with hexane and diethyl ether giving the white crystalline compound **88** (143 mg, 80%).

- **mp**: 118 °C.
- **$[\alpha]^{D}_{22}$** = –51 (c = 1.2, $CHCl_3$).
- **IR (KBr)**: 3346, 2971, 1640, 1458, 1211, 1083, 763, 702, 625, 522 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.72 (s, 1 H, -NC*H*-N-), 7.44-7.33 (m, 10 H, 10x Ar-*H*), 4.48 (d, *J* = 5.6 Hz, 2 H, 2x N-C*H*-Ar), 4.01 (s, br, 2 H, 2x -C*H*-CH_3), 3.52-3.06 (m, 4 H, 2x -N-CH_2-), 1.03 (d, *J* = 6.2 Hz, 6 H, 2x -CH-CH_3).
- **^{13}C-NMR** (50 MHz, $(CD_3)_2CO$) δ = 160.1, 136.9, 130.4, 128.6, 73.4, 63.2, 53.5, 20.9.

- **MS (ESI)**: *m*/*z* = 339 [M].
- **HRMS (ESI)**: calcd for $C_{21}H_{27}N_2O_2^+$ 339.2073, found 339.2064.

(+)-(4*R*,5*R*)-Diphenyl-1,3-bis-(2-hydroxy-2-methylpropyl)-imidazolinium tetrafluoroborate (89)



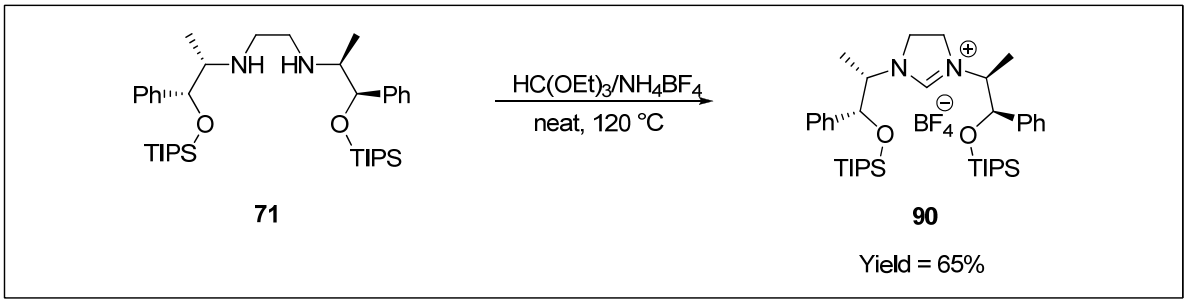
69 **89**

Yield = 90%

Prepared from **69** (150 mg, 0.42 mmol), NH_4BF_4 (47.5 mg, 0.46 mmol) and $CH(OEt)_3$ (78 µL, 0.46 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 12h. After removal of the solvent, the crude was washed with hexane and diethyl ether giving the white crystalline compound (170 mg, 90%).

- **mp**: 108 °C.
- $[\alpha]^{D}_{22}$ = +150 (c = 1.1, MeOH).
- **IR (KBr)**: 3355, 2976, 1638, 1457, 1379, 1159, 1061, 763, 702, 625 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.84 (s, 1 H, -NC*H*-N-), 7.44-7.33 (m, 10 H, 10x Ar-*H*), 5.43 (s, 2 H, 2x N-C*H*-Ar), 3.68-3.61 (m, 4 H, -N-CH_2-) 3.14 (s, 1 H, -O*H*), 3.07 (s, 1 H, -O*H*) 1.18 (s, 6 H, -C(CH_3)$_2$), 1.10 (s, 6 H, -C(CH_3)$_2$).
- **^{13}C-NMR** (50 MHz, $(CD_3)_2CO$) δ = 157.2, 142.3, 128.9, 127.7, 126.8, 72.3, 60.3, 48.8, 11.1.
- **MS (ESI)**: *m*/*z* = 367 [M].
- **HRMS (ESI)**: calcd for $C_{23}H_{31}N_2O_2^+$ 367.2386, found 367.2383.

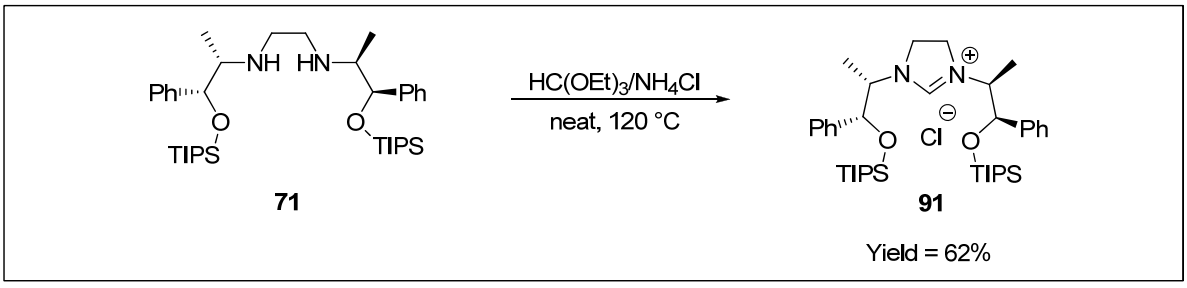
1,3-Bis-((1*S*,2*R*)-2-tri*iso*propylsilyloxy-1-methyl-2-phenyl-ethyl)-4,5 dihydro-3H-imidazol-1-ium tetrafluoroborate (90)



From **71**, ammonium tetrafluoroborate and triethyl*ortho*formate as yellow soild (0.65 mmol, 0.422 g, 65 %);

- **mp**: 82 °C.
- **[α]$^{D}_{22}$** = −30 (c = 0 52, CH_3OH).
- **IR (KBr)**: ν_{max}= 3423, 2946, 2868, 1646, 1464, 1261, 1098, 882, 818, 706, 682 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.42 - 7.24 (m, 11H, 10x Ar-*H*, -N-C*H*-N-), 4.72 (d *J* = 3.6 Hz, 2H, 2x -C*H*-OTIPS), 4.00 - 3.15 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 0.96 - 0.85 (48H, m, 2x TIPS-*H*, 2x -N-CH-CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 155.6, 137.9, 127.8, 127.4, 126.1, 78.9, 60.1, 47.4, 16.9, 13.9, 11.1.
- **MS (ESI)**: *m/z* 651.5 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{39}H_{67}N_2O_2Si_2$ [M]: 651.4741, found 651.4745.

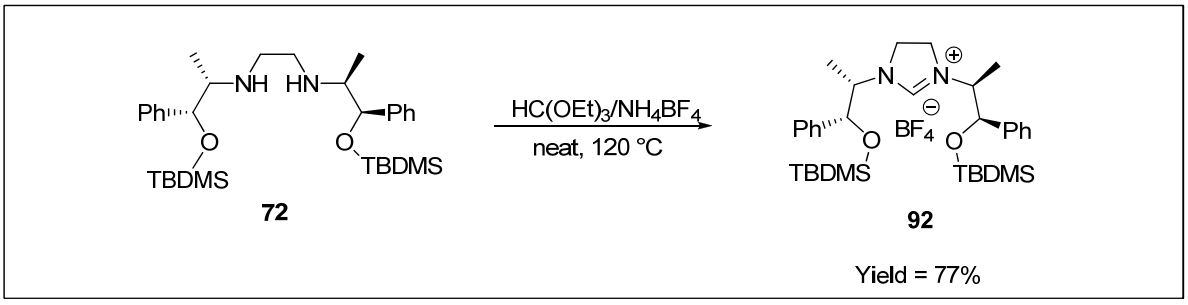
1,3-Bis-((1*S*,2*R*)-2-tri*iso*propylsilyloxy-1-methyl-2-phenyl-ethyl)-4,5 dihydro-3H-imidazol-1-ium chloride (91)



From **71**, ammonium chloride and triethyl*ortho*formate as a white crystalline soild (0.11 mmol, 0.073 g, 62 %).

- **mp**: 237 °C.
- **$[\alpha]^{D}_{22}$** = −30 (c = 0.52, CH_3OH).
- **IR (KBr)**: ν_{max}= 2943, 2865, 1641, 1512, 1269, 1098, 883, 829, 711, 677, 651, 564 cm^{-1}.
- **^{1}H-NMR** (200 MHz, CD_3OD) δ = 7.45 - 7.30 (m, 11H, 10x Ar-*H*, -NC*H*N-), 4.84 (d, *J* = 5.0 Hz, 2H, 2x -C*H*-OTIPS), 3.99 - 3.56 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 1.30 (d, *J* = 7.0 Hz, 6H, 2x -N-CH-CH_3), 1.07 - 0.95 (m, 42H, 2x TIPS-*H*,).
- **^{13}C-NMR** (50 MHz, CD_3OD) δ = 157.4, 140.7, 129.7, 128.4, 78.8, 62.2, 47.4, 18.4, 16.0, 11.1.
- **MS (ESI)**: *m/z* 651.2 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{39}H_{67}N_2O_2Si_2$[M]: 651.4741, found 651.4734.

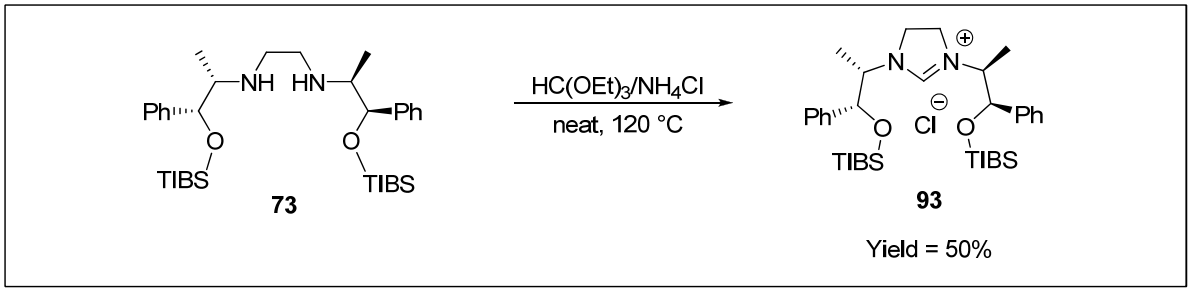
1,3-Bis-((1*S*,2*R*)-2-*tert*butyldimethylsilyloxy-1-methyl-2-phenyl-ethyl)-4,5 dihydro-3H-imidazol-1-ium tetrafluoroborate (92)



From **72**, ammonium tetrafluoroborate and triethyl*ortho*formate as white crystalline soild (0.17 mmol, 0.116 g, 77%);

- **mp**: 76 °C.
- **$[\alpha]^{D}_{22}$** = −6 (c = 0.26, CH_3OH).
- **IR (KBr)**: ν_{max}= 3423, 2956, 2929, 2858, 1647, 1514, 1261, 1089, 862, 843, 780, 755, 681, 502 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.65 (s, 1H, -N-C*H*-N-) 7.43-7.30 (m, 10H, 10x Ar-*H*), 4.75 (d, *J* = 2.2 Hz, 2H, 2x -C*H*-OTBDMS), 3.90 - 3.55 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 1.34 (d, *J* = 3.6 Hz, 6H, 2x -N-CH-CH_3) 0.89 (s, 18H, -Si-C(CH_3)$_3$), 0.07 (s, 6H, 2x -Si-CH_3), -0.17 (s, 6H, 2x Si-CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 156.6, 139.7, 128.5, 126.8, 77.1, 60.7, 47.5, 25.8, 18.0, 13.9, -4.7, -5.1.
- **MS (ESI)**: *m/z* 567.2 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{33}H_{55}N_2O_2$ [M]: 567.3802, found 567.3806.

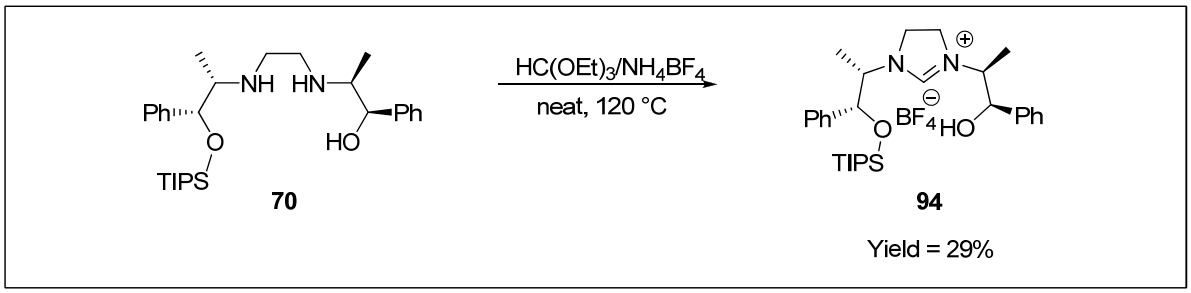
1,3-Bis-((1*S*,2*R*)-2-tri*iso*butylsilyloxy-1-methyl-2-phenyl-ethyl)-4,5 dihydro-3H-imidazol-1-ium chloride(93)



From **73**, ammonium chloride and triethyl*ortho*formate as yellow oil (0.20 mmol, 0.158g, 50%)

- $[\alpha]^{D}_{22} = -20$ (c = 0.25, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2976, 2401, 1423, 1216, 1046, 929, 768, 669 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.77 (s, 1H, -N-C*H*-N-) 7.28-7.20 (m, 10H, 10x Ar-*H*), 4.67 (d, *J* = 4.6 Hz, 2H, 2x -C*H*-OTIBS), 3.98 - 3.50 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 1.63 - 1.23 (m, 12H, 2x -N-CH-CH_3, 6x -Si-CH_2-C*H*(CH_3)$_2$), 0.82 - 0.75 (m, 36H, 6x -Si-CH_2-CH(CH_3)$_2$, 0.45- 0.42 (m, 12H, 6x -Si-CH_2-CH(CH_3)$_2$).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 157.0, 138.7, 127.5, 127.4, 126.0, 76.7, 59.5, 46.1, 25.4, 24.5, 23.0, 13.2.
- **MS (ESI)**: *m/z* 735.3 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{45}H_{79}N_2O_2$ [M]: 735.5680, found 725.5701.

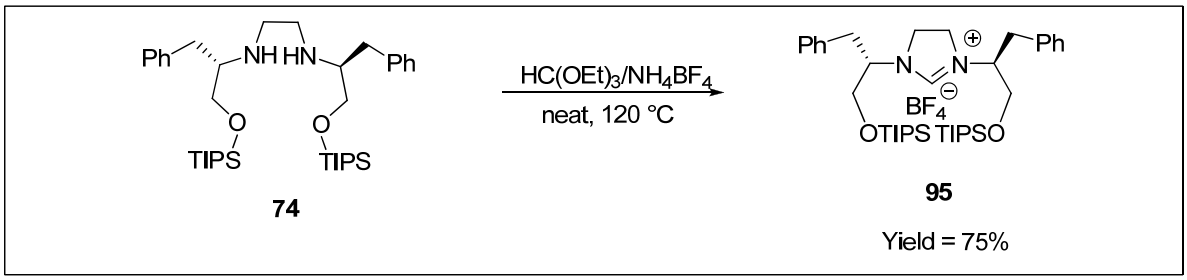
(–)-3-((1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-1-((1*R*,2*S*)-1-phenyl-1-(tri*iso*propylsilyloxy)propan-2-yl)-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate (94)



From **70**, ammonium tetrafluoroborate and triethyl*ortho*formate as white solid (0.16 mmol, 0.093g, 29%);

- **mp**: 95-96 °C.
- **$[\alpha]^{D}_{22}$** = –66 (c = 1, $CHCl_3$).
- **IR (KBr)**: ν_{max}= 3539, 3278, 3094, 2946, 2867, 1647, 1605, 1455, 1392, 1274, 1200, 1097, 1064, 989, 920, 882, 816, 701, 681, 493 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.38-7.24 (m, 11H, 10x Ar-*H,* -N-C*H*-N), 5.02 (d, *J* = 2.8, 1H, -C*H*-OH), 4.81 (d, *J* = 3.8 Hz, 1H, -C*H*-OTIPS), 4.03-3.71 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 3.47 (s, 1H, -CH-O*H*), 1.33-0.90 (m, 27H, TIPS-*H*, 2x –N-CH-CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 155.1, 139.7, 138.8, 128.5, 128.3, 126.9, 125.8, 77.6, 71.9, 60.8, 59.4, 49.1, 47.8, 17.9, 15.1, 12.1, 11.5.
- **MS (ESI)**: *m/z* 495.4 (M^+, 100%); [M+H].
- **HRMS (ESI)**: calcd for $C_{30}H_{47}N_2O_2Si$ [M]: 495.3407, found 495.3404.

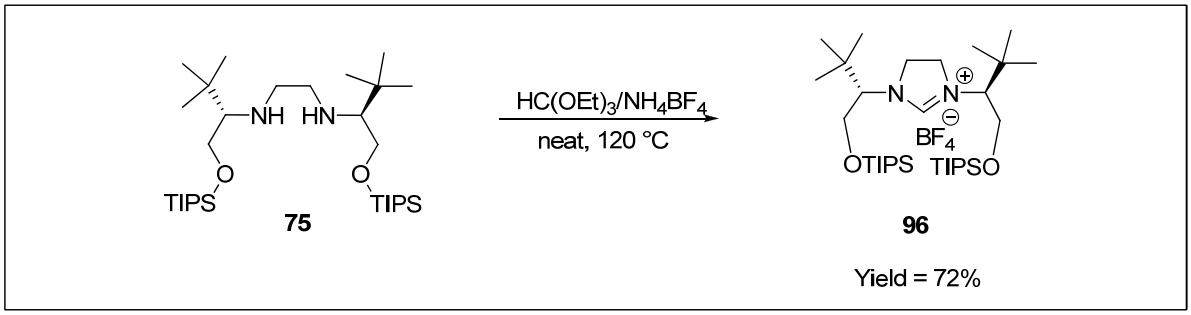
1,3-Bis-((*S*)-1-phenyl-3-(tri*iso*propylsilyloxy)propan-2-yl)-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate (95)



From **74**, ammonium tetrafluoroborate and triethyl*ortho*formate as yellow oil (0.66 mmol, 0.43 g, 75%).

- **$[\alpha]^{D}_{22}$** = –52 (c = 0.62, CH_3OH).
- **IR (KBr)**: ν_{max}= 2944, 2866, 1640, 1576, 1462, 1255, 1061, 883, 784 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.12 (s, 1H, -N-C*H*-N-), 7.30 - 7.14 (m, 10H, 10x Ar-*H*), 4.08 - 4.00 (m, 4H, 2x -OCH_2-*),* 3.95 - 3.79 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-N-), 2.96 (d, *J* = 7.7 Hz, 4H, 2x -CH_2-Ph), 1.20 - 0.85 (42H, m, 2x TIPS-*H*).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 157.1, 135.9, 129.0, 128.8, 127.2, 67.9, 63.6, 61.6, 50.7, 47.0, 34.8, 25.6, 17.9 11.7.
- **MS (ESI)**: *m/z* 651.5 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{39}H_{66}N_2O_2Si_2$ [M]: 650.4663 found, 650.4670.

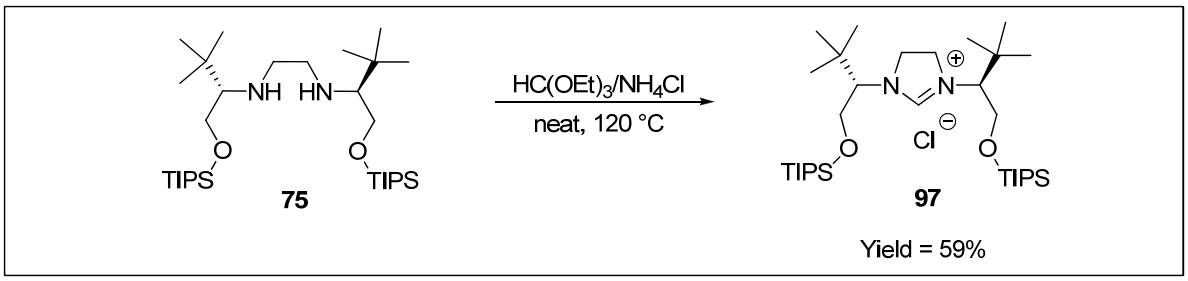
1,3-Bis-((*S*)-3,3-dimethyl-1-(tri*iso*propylsilyloxy)butan-2-yl)-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate (96)



From **75**, ammonium tetrafluoroborate and triethyl*ortho*formate as pale brown solid (0.72 mmol, 0.421 g, 72%).

- **mp**: 145 °C.
- **$[\alpha]^{D}_{22}$** = +40 (c = 0.58, $CHCl_3$).
- **IR (KBr)**: ν_{max}= 3423, 2960, 2867, 1638, 1465, 1193, 1094, 1071, 1015, 882, 808, 752, 690 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.44 (s, 1H, -N-C*H*-N-), 4.15 - 3.84 (m, 8H, 2x -O-CH_2-, -N-(CH_2)$_2$-N-), 3.69 - 3.65 (m, 2H, 2x -N-C*H*-), 1.10 - 0.90 (m, 60H, 2x TIPS-*H*, 2x *t*Bu-*H*).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 161.1, 69.3, 59.2, 47.3, 33.9, 27.4, 18.0, 11.8.
- **MS (ESI)**: *m/z* 583.5 (*M*+, 100%).
- **HRMS (ESI)**: calcd for $C_{33}H_{71}N_2O_2Si_2$ [M]: 583.5054, found 583.5062.

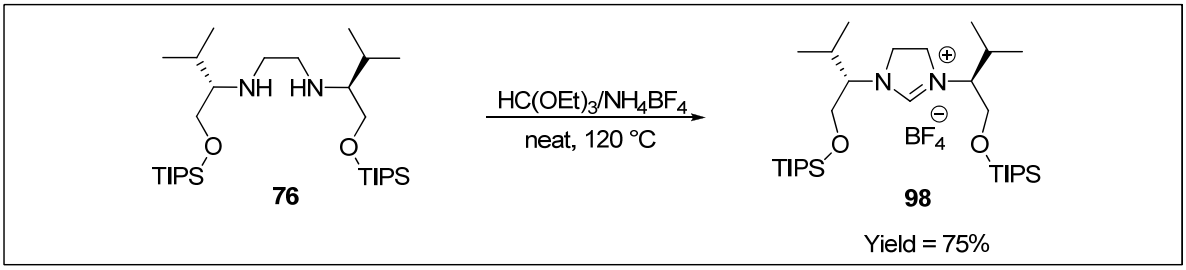
1,3-Bis-((*S*)-3,3-dimethyl-1-(tri*iso*propylsilyloxy)butan-2-yl)-4,5-dihydro-1H-imidazol-3-ium chloride (97)



From **75**, ammonium chloride and triethyl*ortho*formate as reddish gum (0.79 mmol, 0.477 g, 59%).

- **$[\alpha]^{D}_{22}$** = +20 (c = 0.65, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2973, 2401, 1630, 1522, 1423, 1216, 1047, 929, 756, 669, 627, 532 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 10.05 (s, 1H, -N-C*H*-N-), 4.04 - 3.94 (m, 10H, 2x -O CH_2-, -N-(CH_2)$_2$-N-, 2x -N-C*H*-), 1.10 - 0.98 (m, 60H, 2x TIPS-*H*, 2x *t*Bu-*H*).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 162.0, 68.7, 59.8, 47.7, 34.1, 27.6, 18.0, 11.7.
- **MS (ESI)**: *m/z* 583.3 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{33}H_{71}N_2O_2Si_2$ [M]: 583.5053, found 583.5051.

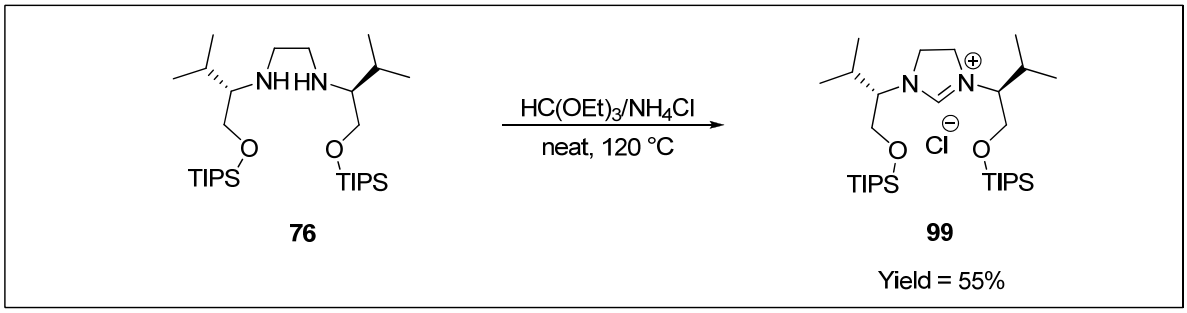
1,3-Bis-((*S*)-3-methyl-1-(tri*iso*propylsilyloxy)-butan-2-yl)-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate (98)



From **76**, ammonium tetrafluoroborate and triethyl*ortho*formate as yellow oil (0.75 mmol, 0.416 g, 75%).

- **$[\alpha]^{D}_{22}$** = –2.2 (c 0.45, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 2954, 2867, 1647 1465, 1390, 1253s, 1057, 882, 780, 686 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.36 (s, 1H, -N-C*H*-N), 4.15 - 3.85 (m, 8H, 2x –O-CH_2-, -N-(CH_2)$_2$-N-), 3.56 - 3.45 (m, 2H, 2x -N-C*H*-), 2.09 - 1.90 (m, 2H, 2x -C*H*(CH_3)$_2$), 1.08 - 0.95 (m, 54H, 2x TIPS-*H*, 4x CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 157.7, 65.7, 61.3, 45.2, 25.3, 18.7, 18.1, 17.0, 10.8.
- **MS (ESI)**: *m/z* 555.4 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{31}H_{67}N_2O_2Si_2$ [M]: 555.4741, found 555.4747.

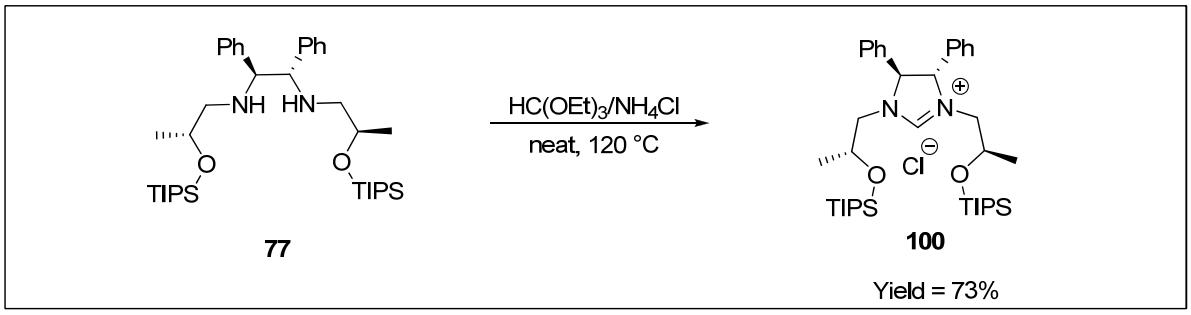
1,3-Bis-((*S*)-3-methyl-1-(tri*iso*propylsilyloxy)butan-2-yl)-4,5-dihydro-1H-imidazol-3-ium chloride (99)



From **76**, ammonium chloride and triethyl*ortho*formate as yellow oil (0.19 mmol, 0.110 g, 55%).

- $[\alpha]^{D}_{22} = -8$ (c 6.3, $CHCl_3$).
- **IR (NaCl)**: ν_{max}= 3621, 3020, 2965, 2869, 2401, 1635, 1513, 1465, 1392, 1216, 1108, 1048, 928, 882, 757, 669, 588 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 10.39 (s, 1H, -N-C*H*-N-), 4.01 - 3.46 (m, 10H, 2x –O-CH_2-, -N-(CH_2)$_2$-N-, 2x -N-C*H*-), 2.19 - 2.09 (m, 2H, 2x -C*H*(CH_3)$_2$), 1.08 - 0.98 (m, 54H, 2x TIPS-*H*, 4x CH_3).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 159.9, 65.9, 63.7, 46.7, 26.1, 19.8, 19.1, 18.0, 11.7.
- **MS (ESI)**: *m/z* 555.0 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{31}H_{67}N_2O_2Si_2$ [M]: 555.4741, found 555.4745.

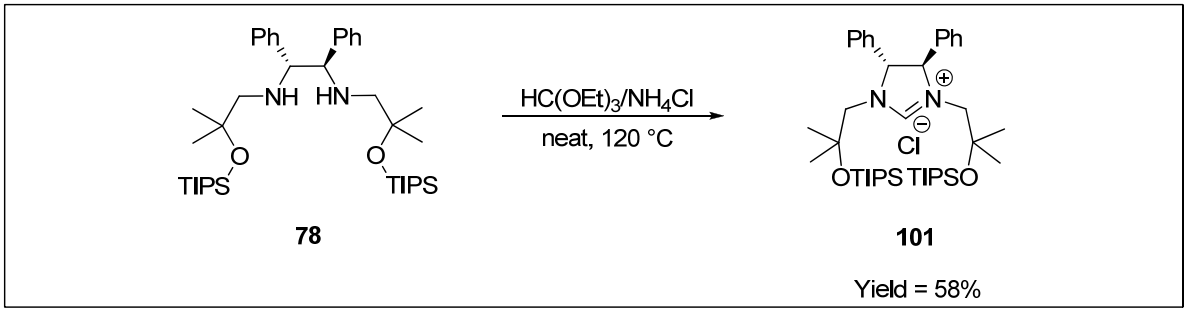
(4*S*,5*S*)-4,5-Diphenyl-1,3-bis-((*R*)-2-(tri*iso*propylsilyloxy)propyl)-4,5-dihydro-1H-imidazol-3-ium chloride (100)



From **77**, ammonium chloride and triethyl*ortho*formate as white solid (0.22 mmol, 0.155 g, 73%).

- **mp**: 74 °C.
- **$[\alpha]^{D}_{22}$** = –103 (c = 0.33, $CHCl_3$).
- **IR (KBr)**: ν_{max}= 3442, 2943, 2866, 1641, 1466, 1382, 1307, 1226, 1162, 1070, 985, 885, 757, 698, 626 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 10.71 (s, 1H, -N-C*H*-N-), 7.49-7.22 (m, 10H, 10x Ar-*H*), 5.12 (s, 2H, 2x Ar-C*H*-N-), 4.05-3.95 (m, 4H, 2x -C*H*-OTIPS), 3.22-3.02 (m, 4H, 2x -N-CH_2-), 1.24 (d, *J* = 6.2, 6H, 2x -CH-CH_3), 0.96-0.83 (m, 42H, 2x TIPS-*H*).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 160.6, 135.0, 129.9, 126.6, 74.1, 67.9, 53.3, 45.6, 21.6, 17.9, 12.7, 8.7.
- **MS (ESI)**: *m/z* 651.0 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{39}H_{67}N_2O_2Si_2$ [M]: 651.4741, found 651.4738.

(4R,5R)-1,3-Bis-(2-methyl-2(tri*iso*propylsilyloxy)propyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-3-ium chloride (101)



78 **101**

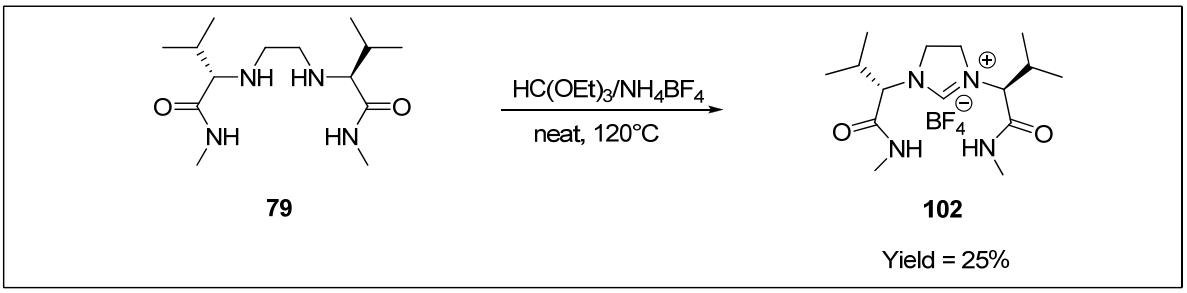
Yield = 58%

From **78**, ammonium chloride and triethyl*ortho*formate as a white crystalline solid (0.27 mmol, 0.197 g, 58%).

- **mp**: 170 °C.
- **$[\alpha]^{D}_{22}$** = +85 (c = 0.33, CH_2Cl_2).
- **IR (KBr)**: ν_{max}= 3410, 2968, 2867, 1635, 1452, 1375, 1235, 1160, 1043, 1014, 882, 821, 704, 671, 520 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 11.28 (s, 1H, -N-C*H*-N-), 7.44-7.11 (m, 10H, 10x Ar-*H*), 4.08 (d, *J* = 14.2, 2H, -N-CH_2), 3.12 (d, *J* = 14.2, 2H, -N-CH_2), 1.21- 0.76 (m, 54H, 2x TIPS-*H*, 2x –C-(CH_3)$_2$).
- **^{13}C-NMR** (50 MHz, $CDCl_3$) δ = 156.2, 135.8, 129.9, 127.9, 125.6, 74.2, 73.4, 57.4, 29.6, 28.4, 18.2, 13.3.

- **MS (ESI)**: *m/z* 679.0 (M^+, 100%).
- **HRMS (ESI)**: calcd for $C_{41}H_{71}N_2O_2Si_2$ [M]: 679.5054, found 679.5053.

(–)-1,3-Bis-((*S*)-3-methyl-1-(methylamino)-1-oxobutan-2-yl)-imidazolinium tetrafluoroborate (102)



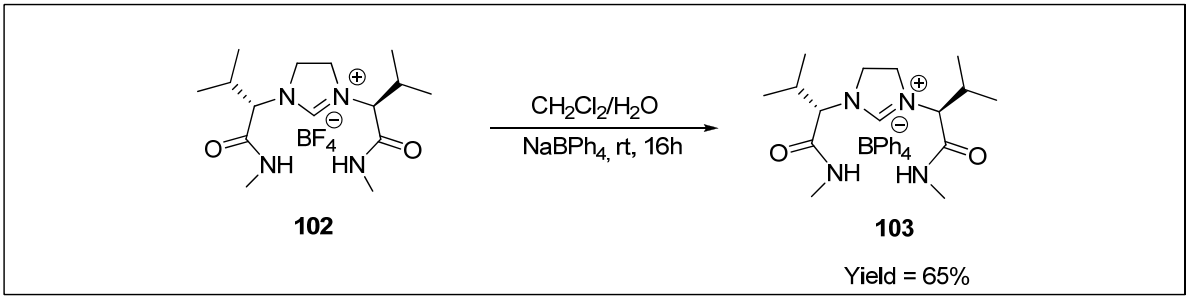
79 **102**

Yield = 25%

Prepared from **79** (126 mg, 0.44 mmol), NH_4BF_4 (49.6 mg, 0.484 mmol) and $CH(OEt)_3$ (53 µL, 0.48 mmol). The reaction mixture was heated to 120 °C in a sealed vessel for 6h. After removal of the solvent, the crude product was washed with hexane, diethyl ether, ethyl acetate and dichloromethane giving the title compound as a white solid (43 mg, 25%).

- **mp**: 209 °C
- $[\alpha]^{D}_{22}$ = –2 (c = 0.25, MeOH).
- **IR (KBr)**: 3315, 3109, 2969, 2360, 1661, 1568, 1411, 1299, 1164, 1064, 642 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $(CD_3)_2CO$) δ = 8.6 (s, 1 H, -N-C*H*-N-), 4.26-3.99 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$), 2.76 (s, 3H, -NH-CH_3), 2.73 (s, 3H, -NH-CH_3), 2.37-2.22 (m, 2H, 2x -C*H*(CH_3)$_2$), 0.97 (d, *J* = 6.0 Hz, 12 H, 2x CH(CH_3)$_2$).
- **^{13}C-NMR** (50 MHz, $(CD_3)_2CO$) δ = 167.3, 157.8, 66.4, 47.5, 28.0, 25.5, 18.6.
- **MS (ESI)**: *m/z* = 297.2 [M].

(–)-1,3-Bis-((*S*)-3-methyl-1-(methylamino)-1-oxobutan-2-yl)-imidazolinium tetraphenylborate (103)



102 **103**

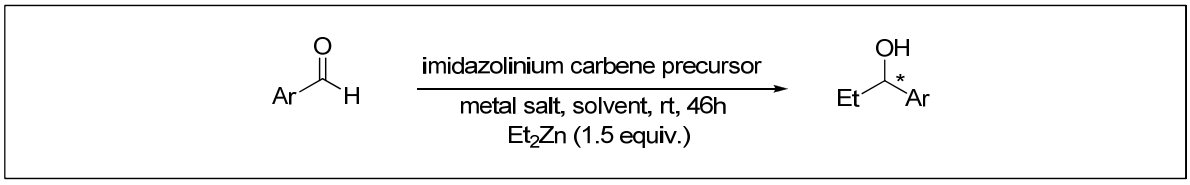
Yield = 65%

From **102** (31.0 mg, 0.08 mmol) and $NaBPh_4$ (27.6 mg, 0.08 mmol) in a mixture of CH_2Cl_2 (5 mL) and H_2O (5 mL) as a yellow gummy compound (32.5 mg, 65%).

- **$[\alpha]^{D}_{22}$** = –3 (c = 0.25, CH_2Cl_2).
- **IR (NaCl)**: 3055, 2986, 2360, 1685, 1541, 1422, 1265, 896, 740, 705 cm^{-1}.
- **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.35-6.96 (m, 21 H, -N-C*H*-N-, 2x Ar-*H*), 4.99-4.97 (s, 2H, 2x -N*H*-), 3.55-2.67 (m, 6H, 2x -N-C*H*-, -N-(CH_2)$_2$-), 2.75 (s, 3H, -NH-CH_3), 1.93-1.89 (m, 2H, 2x -C*H*(CH_3)$_2$), 0.79 (d, *J* = 6.4 Hz, 12 H, 2x CH(CH_3)$_2$).
- **^{13}C-NMR** (50 MHz, ($CDCl_3$) δ = 166.6, 156.3, 136.0, 128.7, 127.8, 126.1, 122.6, 66.9, 47.6, 29.2, 26.4, 18.5.
- **MS (ESI)**: *m*/*z* = 297.1 [M].

3.6. Application of the Catalysts

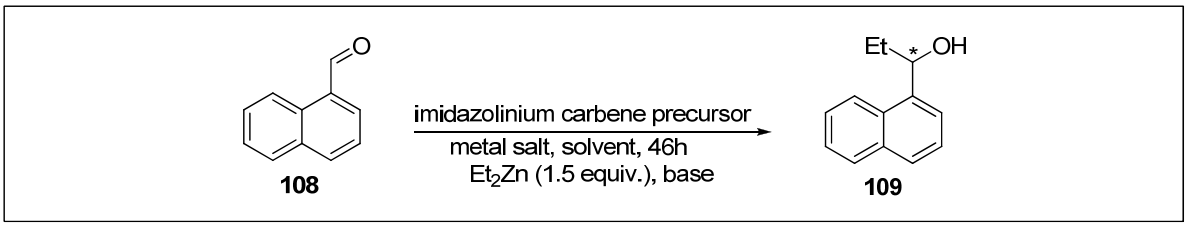
3.6.1. Asymmetric Et_2Zn Addition to Aldehydes



General Procedure for the Et_2Zn Addition to Aldehydes

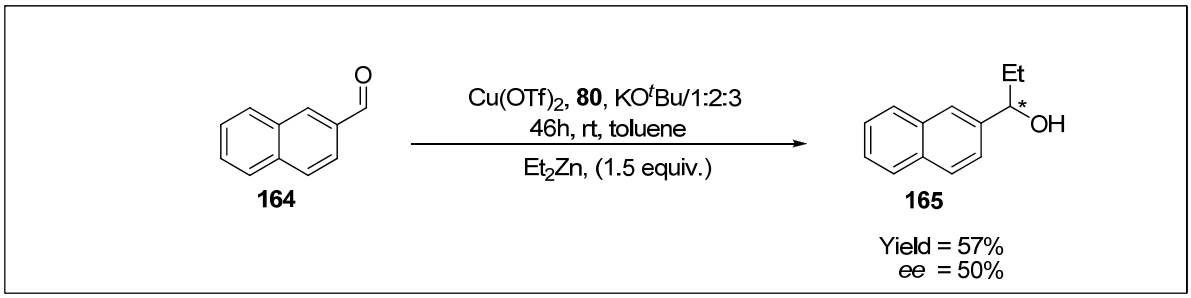
An imidazolinium salt (0.017 mmol) and KO^{t}Bu (6.1 mg, 0.051 mmol) were placed in a dry Schlenk flask and dry toluene (1 mL) was added. After stirring the mixture for 30 min, $Cu(OTf)_2$ (3.2 mg, 0.009 mmol) was added and left to stir for 1h. Aldehyde (0.35 mmol) was added and the mixture was stirred for 5 min. Then Et_2Zn (0.5 mL of a 1 M solution in hexane) was added dropwise. The mixture was stirred at rt for 46h, quenched by the addition of 1 N HCl (1mL) and extracted with Et_2O (3×5 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (petroleum ether/ethyl acetate, 9:1) to give the corresponding alcohol.

(*R*)-1-(1-Naphthyl)-propan-1-ol (109)



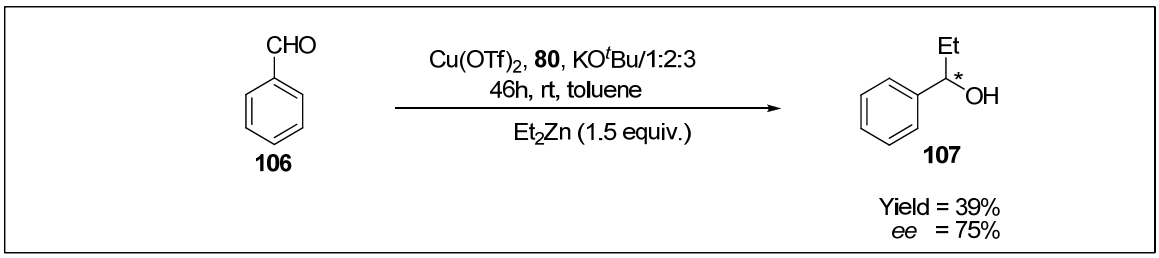
$[\alpha]^{D}_{22}$ = +35 (c = 0.30, $CHCl_3$). For catalysts, bases, yields, and *ee*s see Table 5-12. Spectral data were consistent with literature values.[176,186] 73% *ee* (*R*) by HPLC analysis [OD-H; ^{i}PrOH/hexane, 5:95; 0.4 mLmin^{-1}; t_1(*S*) = 35.7 min, t_2(*R*) = 67.6 min].

(*R*)-1-(2-Naphthyl)-propan-1-ol (165)



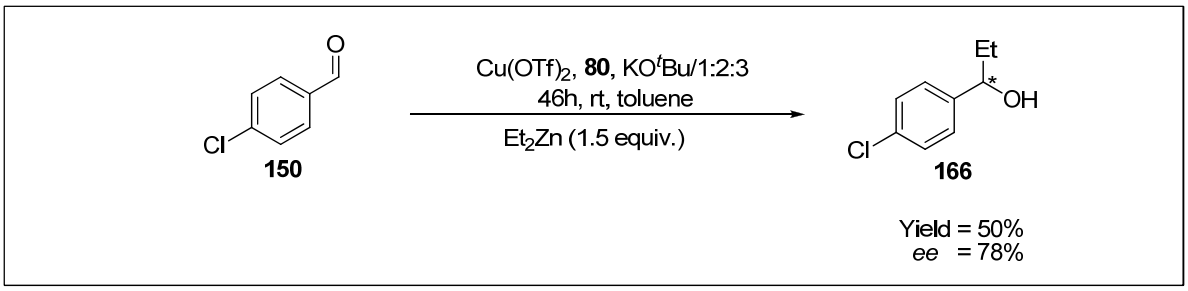
Yield = 57%; $[\alpha]^{D}_{22}$ = +29 (c = 0.50, $CHCl_3$). 50% *ee* (*R*) by HPLC analysis [OD-H; *i*PrOH/hexane, 10:90; 1.0 mLmin^{-1}; t_1(*S*) = 10.0 min, t_2(*R*) = 11.0 min]. Spectral data were consistent with literature values.[182]

(*R*)-1-Phenyl-1-propanol (107)



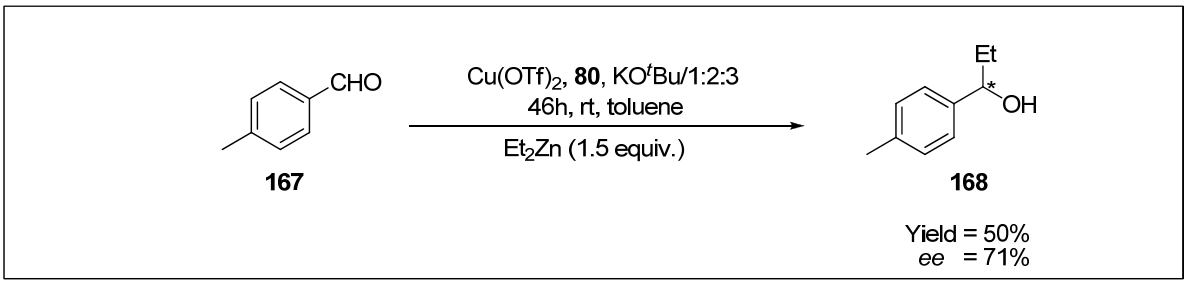
Yield = 39%; $[\alpha]^{D}_{22}$ = +36 (c = 0.50, $CHCl_3$). 75% *ee* (*R*) by HPLC analysis [OD-H; ^{i}PrOH/hexane, 5:95; 1.0 mLmin^{-1}; t_1(*R*) = 8.0 min, t_2(*S*) = 9.0 min]. Spectral data were consistent with literature values.[182]

(*R*)-1-(4-Chlorophenyl)-1-propanol.(166)



Yield = 60%; $[\alpha]^{D}_{22}$ = +28 (c = 1.33, $CHCl_3$). 78% *ee* (*R*) by HPLC analysis [OD-H; ^{i}PrOH/hexane, 2.5:97.5; 1.0 mLmin^{-1}; t_1(*S*) =11.8 min, t_2(*R*) = 12.5 min]. Spectral data were consistent with literature values.[182]

(*R*)-1-(4-Methylphenyl)-1-propanol (168)

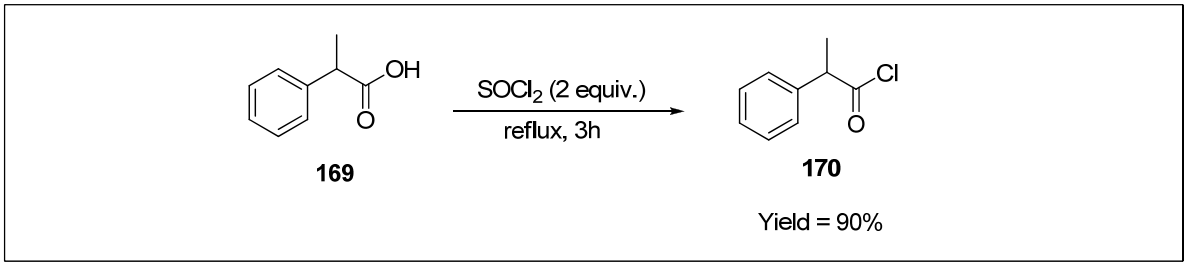


Yield = 50%; $[\alpha]^{D}_{22}$ = +32 (c = 1.0, $CHCl_3$). 71% *ee* (*R*) by HPLC analysis [OD-H; ^{i}PrOH/hexane, 0.1:99.9; 1.0 mLmin^{-1}; t_1(*R*) =67.7 min, t_2(*S*) = 85.0 min]. Spectral data were consistent with literature values.[182]

3.6.2. Asymmetric Intramolecular *α*-Arylation of Amides

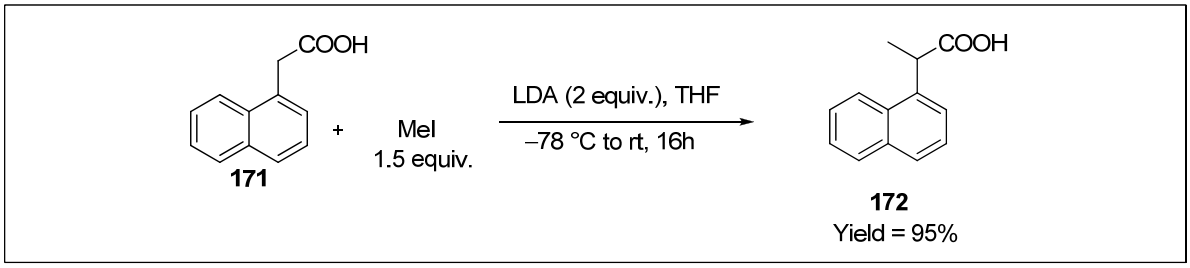
3.6.2.1. Preparation of Substrates

2-Phenylpropanoyl chloride (170)



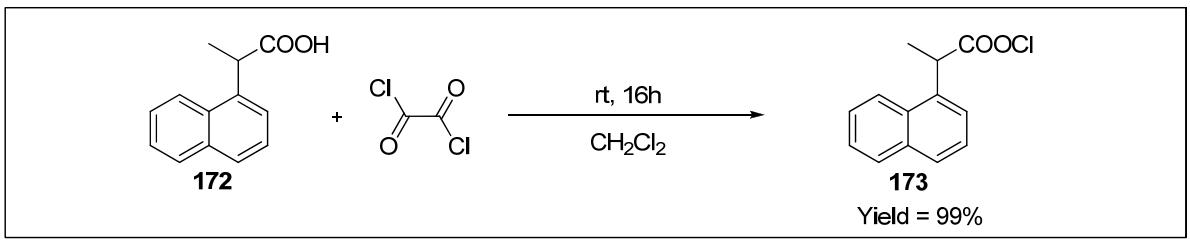
Thionyl chloride (5.3 mL, 73.04 mmol, 2 equiv.) was refluxed and 2-phenylpropionic acid **190** (5.0 mL, 36.52 mmol) was added to the solution dropwise over a period of 1h. Then the reaction mixture was refluxed for additional 3h. Most of the unreacted thionyl chloride was removed under reduced pressure. The residue was distilled and compound **191** was obtained at a bp of 90 °C/2.5 mbar as colorless oil (5.45 g, 90%). Spectral data were consistent with literature values.[187]

2-(1-Naphthyl) propionic acid (172)



A solution of LDA (27 mL, 26.85 mmol, 2 equiv.) was poured into the flask containing dry THF (150 mL) under nitrogen atmosphere. The temperature of the reaction mixture was cooled to –78 °C and 1-naphthylacetic acid (5.0 g, 26.85 mmol) was added in dry THF (30 mL) drop wise over 30 min. The mixture was stirred at 0 °C for 1h and recooled to –78 °C. To this solution methyl iodide (2.50 mL, 40.28 mmol, 1.5 equiv.) was added. Then the mixture was stirred overnight at rt and was quenched with water. The aqueous layer was extracted three times with diethylether. The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the product as a white solid (4.90 g, 95%). Spectral data were consistent with literature values.[188]

2-(1-Naphthyl) propanoyl chloride (173)



To a stirred solution of 2-(1-Naphthyl) propionic acid (2.0 g, 9.99 mmol,) in 50 mL CH_2Cl_2 was added $(COCl)_2$ dropwise. The solution was stirred at rt for overnight. The excess of $(COCl)_2$ was evaporated under reduced pressure and the product was obtained as colorless oil.

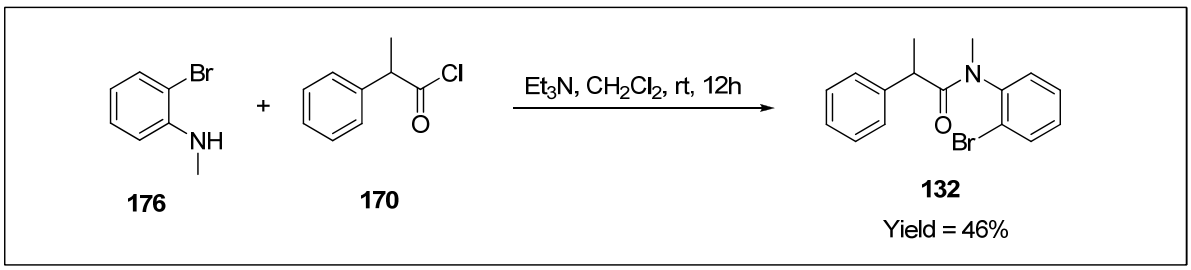
(2-Bromo-phenyl)-benzyl amine (175)

2-Bromo-aniline (1.5 g, 8.72 mmol) was dissolved in MeOH, and benzaldehyde (0.88 mL, 8.72 mmol) was added. After stirring for 4h under nitrogen, $NaBH_4$ (0.824 g, 21.8 mmol, 2.5 equiv.) was carefully added and the reaction mixture was allowed to stir overnight at room temperature. Then the reaction was quenched with 1M NaOH aqueous solution. The aqueous phase was extracted three times with diethylether and the combined organic phases were dried over sodium sulfate, filtered. The solvent was evaporated to give yellow oil. FCC with hexane/diethylether (9:1) gave the product as a colorless oil (0.645 g, 29%). Spectral data were consistent with literature values.[189]

3.6.2.2. General Procedure for the Preparation of 2-Bromoanilide Substrates

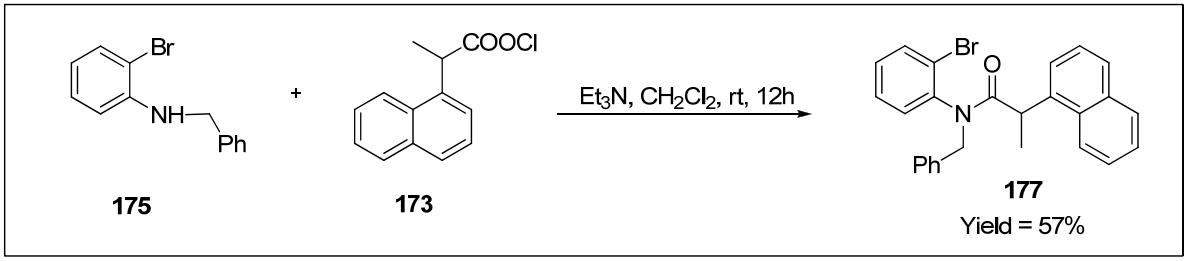
An acid chloride (1.2 equiv.) was dissolved in dry CH_2Cl_2. Triethylamine (1.5 equiv.) was added to the mixture followed by the addition of 2-bromoaniline (1.0 equiv.) The reaction was allowed to stir for 12h at rt. Then the reaction mixture was diluted with diethylether and quenched with saturated aqueous solution of NH_4Cl. The organic phase was washed with the brine solution and dried over sodium sulfate, filtered and concentrated. The resulting crude product was purified by FCC with hexane/ethyl acetate 9:1.

***N*-(2-Bromophenyl)-*N*-methyl-2-phenylpropanamide (132)**



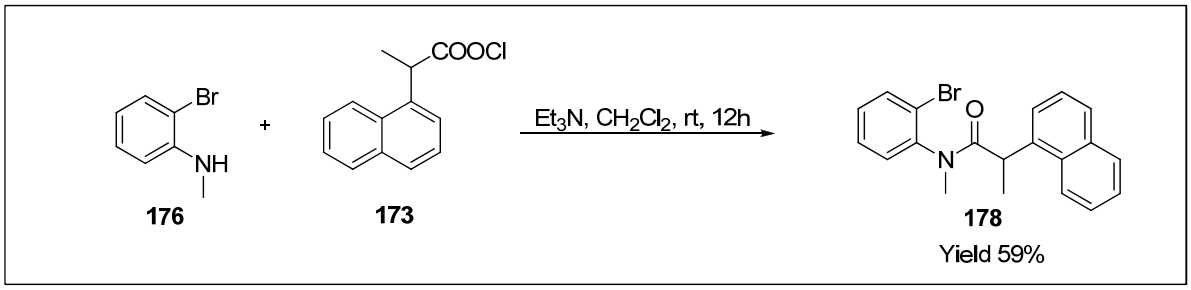
2-Bromo-*N*-methylaniline (0.21 mL, 1.80 mmol) was coupled with 2-phenylpropanoyl chloride (0.365 g, 2.165 mmol, 1.2 equiv.) to give the product as yellow oil (0.260 g, 46%). Spectral data were consistent with literature values.[98]

N-Benzyl-N-(2-bromophenyl)-2-(1-naphthyl) propanamide (177)



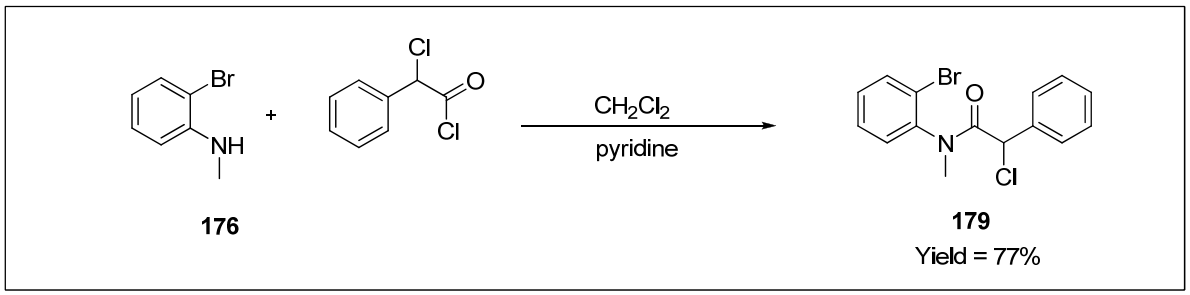
2-Bromo-*N*-benzylaniline (0.50 g, 1.90 mmol) was coupled with 2-(1-naphthyl) propanoyl chloride (0.45 g, 2.28 mmol, 1.2 equiv.) to give the product as a white solid (0.483 g, 57%). Spectral data were consistent with literature values.[98]

N-(2-Bromophenyl)-N-methyl-2-(1-naphthyl) propanamide (178)



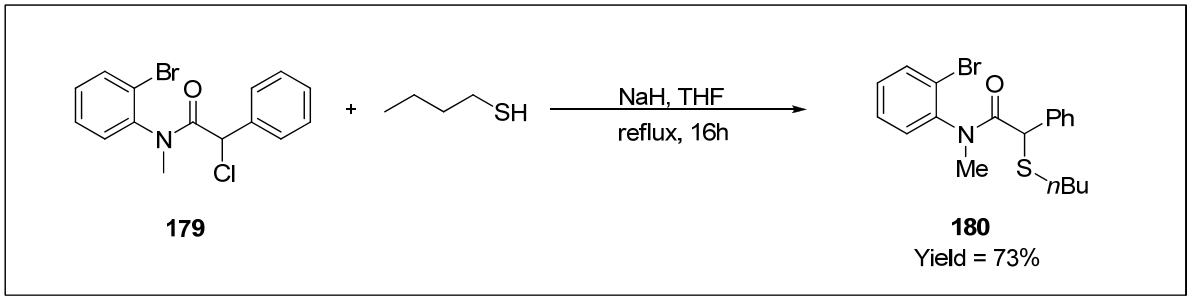
2-Bromo-*N*-methylaniline (0.22 mL, 1.90 mmol) was coupled with 2-(1-naphthyl) propanoyl chloride (0.50 g, 2.29 mmol, 1.2 equiv.) to give the product as a white solid (0.483 g, 57%). Spectral data were consistent with literature values.[98]

N-(2-Bromophenyl)-N-methyl-2-chloro-2-phenylacetamide (179)



2-Bromo-*N*-methylaniline (1 g, 5.37 mmol) was dissolved in dry CH_2Cl_2. Then pyridine (0.57 mL, 6.987 mmol, 1.3 equiv.) was added to the reaction mixture, followed by the addition of chlorophenylacetyl chloride (1.23 mL, 6.99 mmol, 1.3 equiv.). The mixture was stirred for 3h and then diluted with CH_2Cl_2. After washing with water, 1M NaOH and brine, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude was subjected to FCC (petroleum ether/ethyl acetate, 8:2) to give a yellow crystalline compound (1.41 g, 77%).[190]

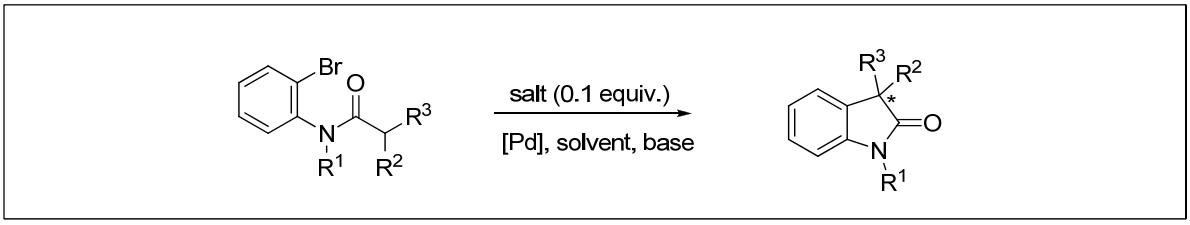
_N_-(2-Bromophenyl)-2-(butylthio)-_N_-methyl-2-phenylacetamide (180)



179 **180**
Yield = 73%

NaH (1 equiv., 60% in mineral oil) was added to a THF solution of *n*butane thiol (0.16 mL, 1.477 mmol, 1 equiv.) and stirred for 30 min at room temperature. Then *N*-(2 bromophenyl)-*N*-methyl-2-chloro-2-phenylacetamide (0.5 g, 1.476 mmol) was added to the reaction mixture under nitrogen. The reaction was refluxed overnight and then the mixture was washed with water, brine and extracted with CH_2Cl_2. The combined organic layers were filtered, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by FCC (petroleum ether/ethyl acetate, 8:2) to give a yellow oil (0.42 g, 73%).

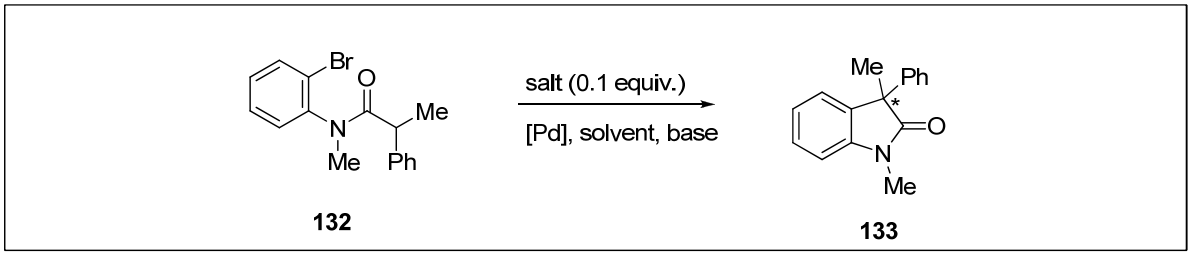
3.6.2.3. General Procedure for the Asymmetric Synthesis of Oxindoles



To the dried Schlenk, 2-bromoanilide (0.2 mmol), imidazolinium carbene precursor (0.02 mmol) and palladium salt (0.05 mmol) were added under nitrogen atmosphere. Then dry 1,4-dioxane (1 mL) was added and the mixture was stirred for 15 min. The base LiO^tBu (0.6 mmol) was added and the temperature of the reaction mixture was raised to 60 °C. After

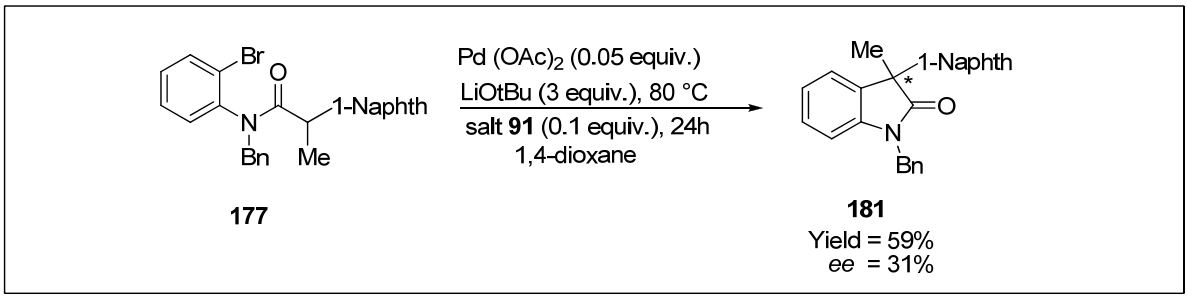
24h, the deep red reaction mixture was cooled down to room temperature and quenched with saturated NH_4Cl solution. The aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over sodium sulfate. Filtration and removal of the solvent in *vacuo* gave a crude yellow oil which was purified by column chromatography (hexane:ethyl acetate, 8:1) to give the desired oxindole as a colorless oil.

1,3-Dimethyl-3- phenyloxindole (133)



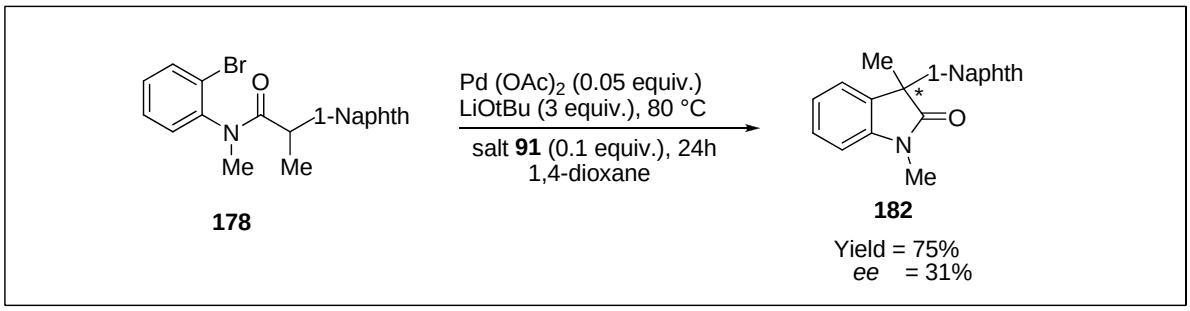
Colorless oil; For catalysts, bases, yields, and *ee* see Table 14-20. Spectral data were consistent with literature values.[98] 73 % *ee* (*S*) by HPLC analysis [OD-H; ^{i}PrOH:hexane, 2.5:97.5; 1.0 mL/min; t_1(*S*) = 12.3 min, t_2(*R*) = 14.7 min.

1-Benzyl-3-(1-naphthyl)-3-methyloxindole (181)



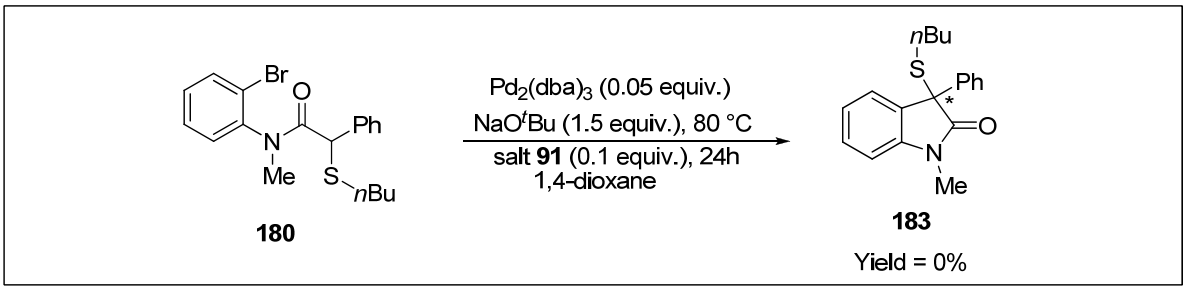
Colorless oil; Yield = 59%; Spectral data were consistent with literature values;[98] 31% *ee* (*S*) by HPLC analysis [OD-H; ^{i}PrOH/hexane, 2.5:97.5; 1.0 mLmin^{-1}; t_1(*S*) = 24.9 min, t_2(*R*) = 57.8 min].

1,3-Dimethyl-3-(1-naphthyl)-oxindole (182)



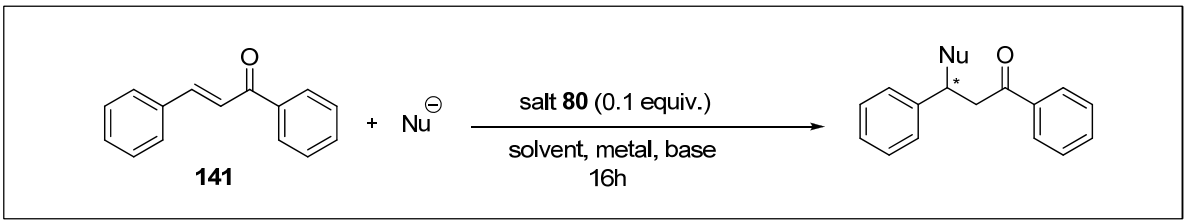
Colorless oil; Yield = 75%; Spectral data were consistent with literature values,[98] 31 % *ee* (*S*) by HPLC analysis [OD-H; ^{i}PrOH/hexane, 2.5:97.5; 1.0 mLmin^{-1}; t_1(*S*) = 35.7 min, t_2(*R*) = 67.6 min].

3-(Butylthio)-1-methyl-3-phenylindolin-2-one (183)



3.6.3. Michael Addition

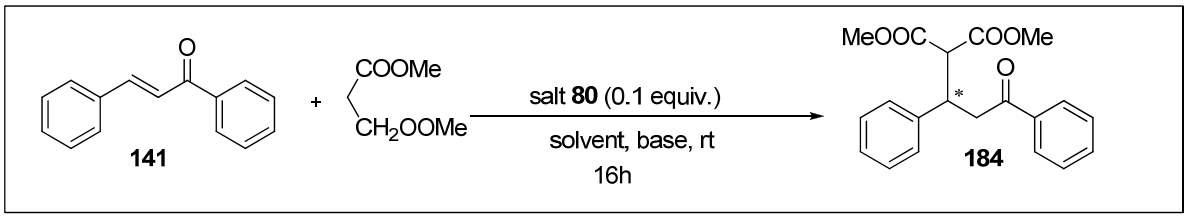
3.6.3.1. General procedure for the asymmetric Michael Addition to Chalcone



An imidazolinium salt **80** (7.5 mg, 0.017 mmol) and KO^{t}Bu (6.1 mg, 0.051 mmol) were placed in a dry Schlenk flask and dry toluene (1 mL) was added. After stirring the mixture for 30 min, metal salt (0.017 mmol) was added and left to stir for 30 min. Chalcone (73.0 mg, 0.35 mmol) was added and the mixture was stirred for 5 min. Then the nucleophile (0.385 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred at rt for 16h, quenched by the addition of 1N HCl (1mL) and extracted with Et_2O (3×5 mL). The

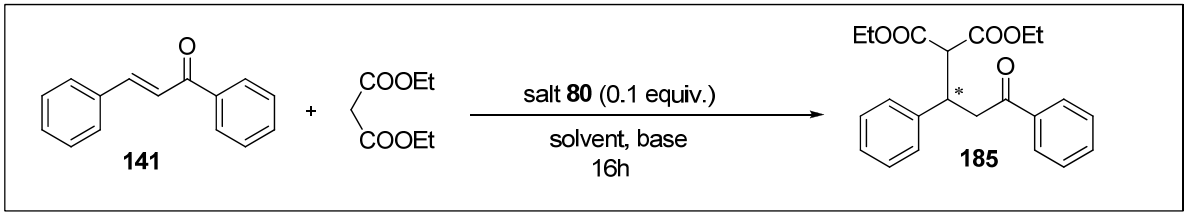
combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (petroleum ether/ethyl acetate, 9:1) to give the corresponding alcohol.

2-(3-Oxo-1,3-diphenylpropyl) malonic acid dimethyl ester (184)



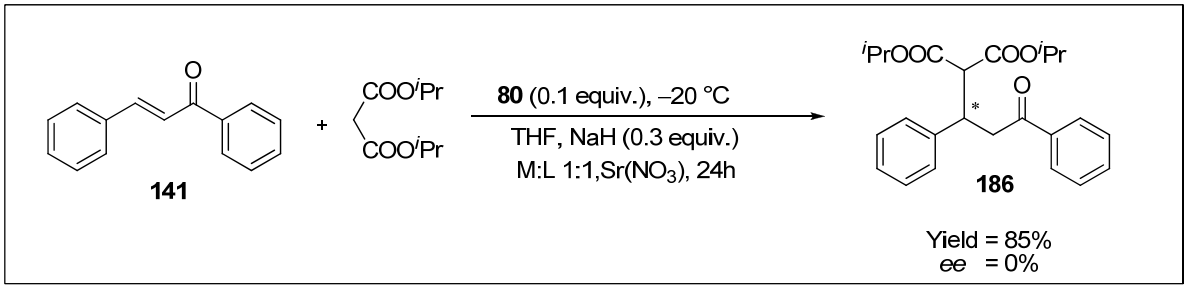
For yields, *ee*s, bases, catalysts, and solvents see Table 23. From chalcone (73.0 mg, 0.35 mmol) and dimethylmalonate (44.0 µL, 0.385 mmol, 1.1 equiv.), catalyzed by *in situ* generated carbene from salt **80** with a base (0.3 equiv.) and the metal salt (0.1 equiv.) in solvent (1 mL), as white solid. Spectral data were consistent with literature values.[191]

2-(3-Oxo-1,3-diphenyl-propyl)-malonic acid diethyl ester (185)



For yields, *ee*s, bases, catalysts, and solvents see Table 24. From chalcone (73.0 mg, 0.35 mmol) and diethylmalonate (58.4 µL, 0.385 mmol, 1.1 equiv.), catalyzed by *in situ* generated carbene from salt **80** with a base (0.3 equiv.) and the metal salt (0.1 equiv.) in solvent (1 mL), as white solid. Spectral data were consistent with literature values.[187]

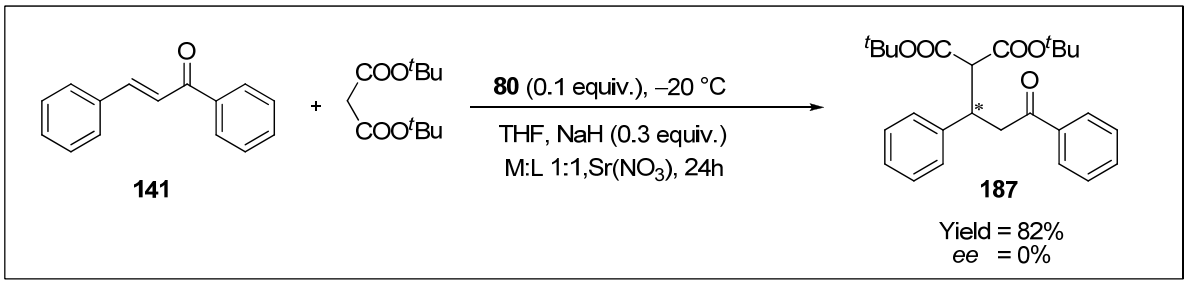
2-(3-Oxo-1,3-diphenyl-propyl)-malonic acid di*iso*propyl ester (186)



From chalcone ((73.0 mg, 0.35 mmol) and di*iso*propylmalonate (73.1 µL, 0.385 mmol, 1.1 equiv.), catalyzed by *in situ* generated carbene from salt **80** with NaH (0.3 equiv.) and

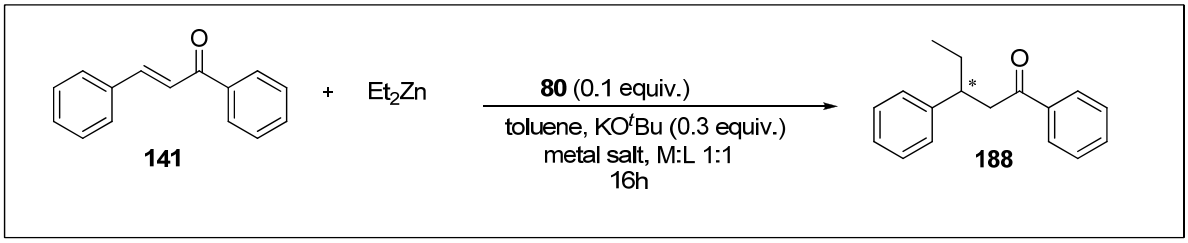
$Sr(NO_3)_2$ (0.1 equiv.) in THF (1 mL), as white solid (117.0 mg, 85%). Spectral data were consistent with literature values.[192]

2-(3-Oxo-1,3-diphenylpropyl)-malonic acid di-*tert*butyl ester (187)



From chalcone ((73.0 mg, 0.35 mmol) and di*tert*butylmalonate (87.0 µL, 0.385 mmol, 1.1 equiv.), catalyzed by *in situ* generated carbene from salt **80** with NaH (0.3 equiv.) and $Sr(NO_3)_2$ (0.1 equiv.) in THF (1 mL), as white solid (122.0 mg, 82%). Spectral data were consistent with literature values.[193]

1,3-Diphenylpentan-1-one (188)

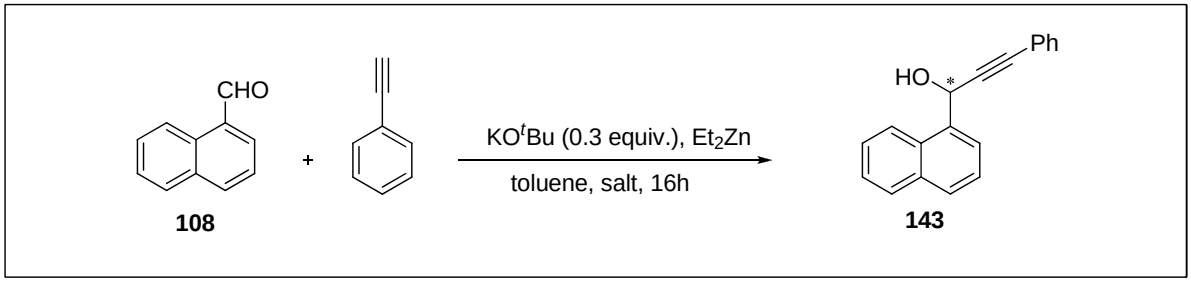


For yields, *ee*s, catalysts, and temperature see Table 25. From chalcone ((73.0 mg, 0.35 mmol) and diethylzinc (0.38 mL of 1 M solution in hexane, 0.385 mmol, 1.1 equiv.), catalyzed by *in situ* generated carbene from salt **80** with KO^{t}Bu (0.3 equiv.) and the metal salt (0.1 equiv.) in toluene (1 mL) as white solid. Spectral data were consistent with literature values.[194]

3.6.4. Synthesis of Optically Active Propargylic Alcohol

3.6.4.1. General procedure for the synthesis of optically active propargylic alcohol

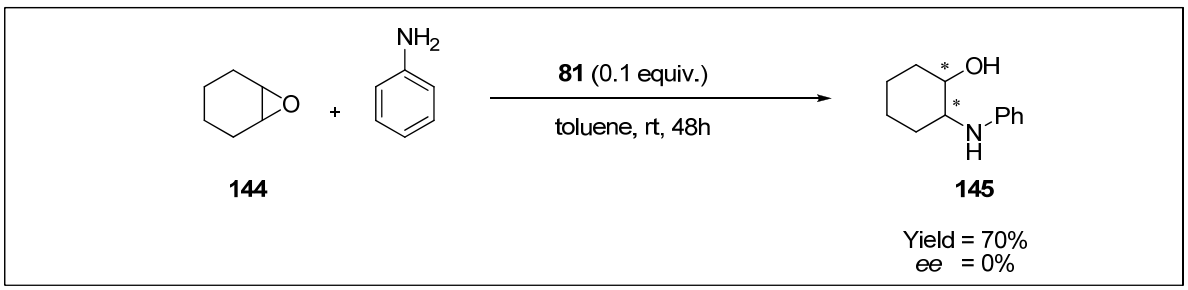
1-(1-Naphthyl)-3-phenylprop-2-yn-1-ol (143)



For yields, *ee*s, catalysts, and temperature see Tables 26-29 An imidazolinium salt (0.035 mmol) and KO^{t}Bu (12.2 mg, 0.105 mmol, 0.3 equiv.) were placed in a dry Schlenk flask and dry toluene (1 mL) was added. After stirring the mixture for 30 min, metal salt (1.05 mmol, 3equiv.) was added and left to stir for 30 min. 1-Naphthaldehyde (48.0 µL, 0.35 mmol) was added and the mixture was stirred for 15 min. Then phenylacetylene (110.0 µL, 1.05 mmol, 3.0 equiv.) was added drop wise. The mixture was stirred at rt for 16h quenched by the addition of 1N HCl (1mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography (petroleum ether/ethyl acetate, 9:1) to give the white solid. Spectral data were consistent with literature values.[195]

3.6.5. Asymmetric Ring Opening of Epoxides

2-(Phenylamino) cyclohexanol (145)

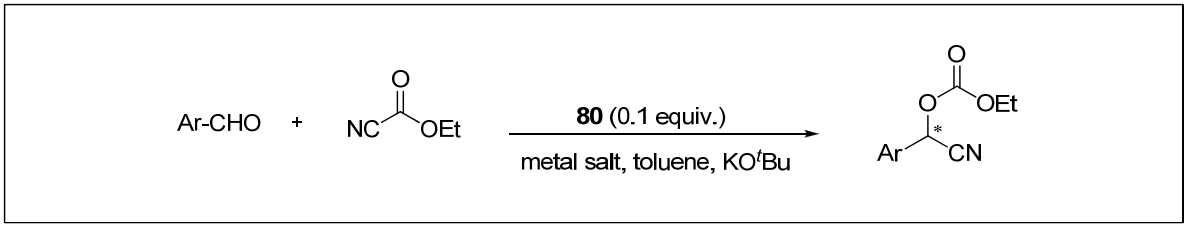


3.6.5.1. General Procedure for the Asymmetric Ring Opening of Epoxides

The imidazolinium salt **81** (23.0 mg, 0.035 mmol, 0.1 equiv.) was dissolved in dry toluene (1 mL) in a dry Schlenk flask under nitrogen. Then cyclohexene oxide (36.0 µL, 0.35 mmol, 1.0 equiv.) was added followed by the addition of aniline (35 µL, 0.385 mmol, 1.1 equiv.). The reaction mixture was stirred for 48h at rt. The reaction was quenched with water and extracted with CH_2Cl_2, filtered, dried (Na_2SO_4) and concentrated under reduced pressure.

The crude product was purified by FCC (petroleum ether/EtOAc, 9/1) giving title compound (47.0 mg, 70%). Spectral data were consistent with literature values.[196]

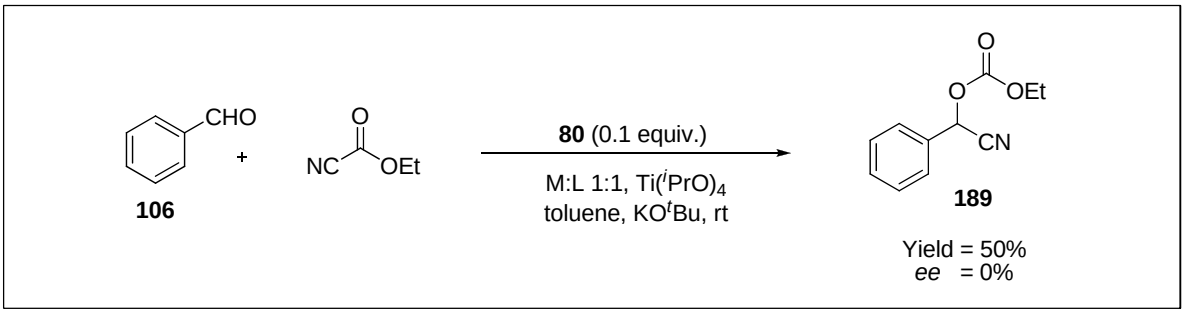
3.6.6. Asymmetric Cyanoformylation of Aldehydes



3.6.6.1 General Procedure for the Asymmetric Cyanoformylation of Aldehydes

The imidazolinium carbene precursor **80** (15.0 mg, 0.035 mmol, 0.1 equiv.) was added into a dry Schlenk flask under nitrogen. The base KO^{t}Bu (12.2 mg, 0.105 mmol, 0.3 equiv.) was added followed by toluene (1 mL) as solvent. The mixture was allowed to stir for 30 min. The metal salt (0.1 equiv.) was added and stirring was continued for another 15 min. Then aldehyde (0.35 mmol) was added into the reaction mixture. This was followed by ethyl cyanoformate (38 µL, 0.385 mmol, 1.1 equiv.). The contents were stirred for 46h and the residue was purified by silica gel column chromatography (petroleum ether/diethyl ether, 9/1). Spectral data were consistent with literature values.[197]

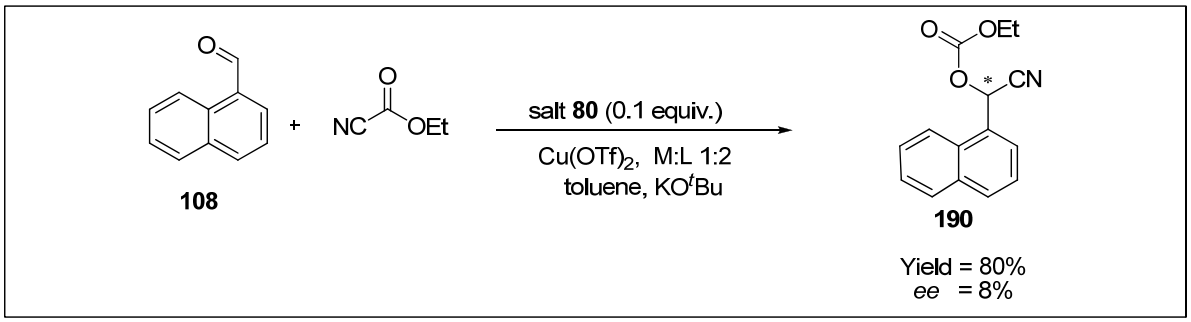
2-Ethoxycarbonyloxy-2-phenyl-acetonitrile (189)



From benzaldehyde (35.0 µL, 0.35 mmol) and ethyl cyanoformate (38.0 µL, 0.385 mmol, 1.1 equiv.), catalyzed by *in situ* generated carbene from salt **80** (15.0 mg, 0.035 mmol, 0.1

equiv.) with KO^{t}Bu (12.2 mg, 0.105 mmol, 0.3 equiv.) and Ti(^{i}PrO)$_4$ (12.0 µL, 0.035 mmol, 0.1 equiv.) in toluene (1 mL), as a colorless oil (36.2 mg, 50.0%). Spectral data were consistent with literature values.[198]

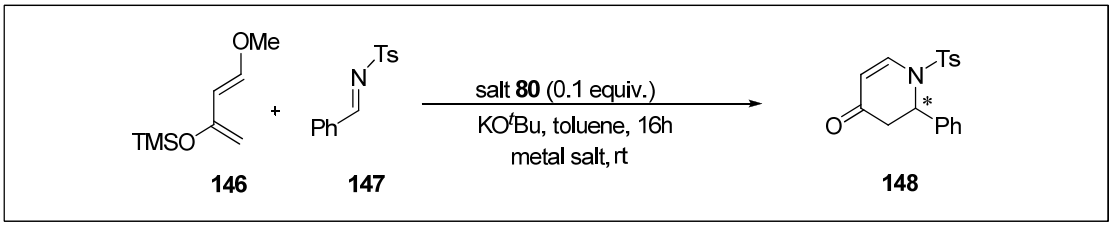
2-Ethoxycarbonyloxy-2-(1-naphthyl) acetonitrile (190)



From 1-naphthaldehyde (48.0 µL, 0.35 mmol) and ethyl cyanoformate (38.0 µL, 0.525 mmol, 1.5 equiv.), catalyzed by *in situ* generated carbene from salt **80** (15.0 mg, 0.035 mmol, 0.1 equiv.) with KO^{t}Bu (12.2 mg, 0.105 mmol, 0.3 equiv.) and Cu(OTf)$_2$ (6.4 mg, 0.035 mmol, 0.1 equiv.) in toluene (1 mL) at –20 °C, as a colorless oil (71.0 mg, 80.0%). $[\alpha]^D_{22}$ = –0.57 (c = 3.5, $CHCl_3$); Spectral data were consistent with literature values.[199]

3.6.7. Asymmetric Aza Diels-Alder Reaction

2-Phenyl-1-tosyl-2,3-diyhydropyridin-4(1*H*)-one (148)



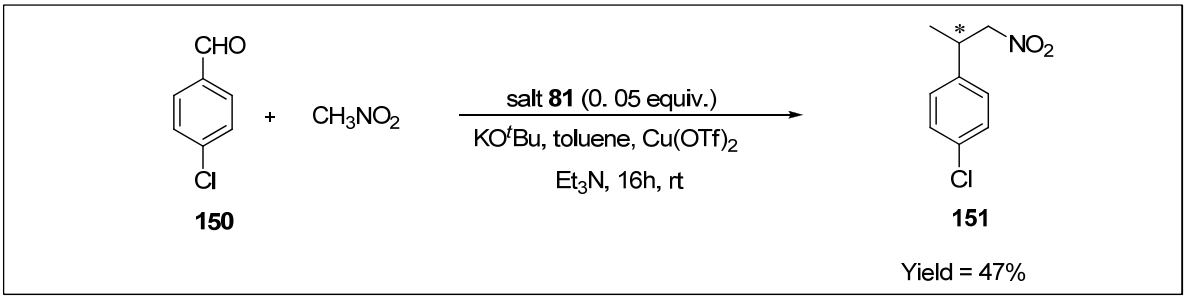
3.6.7.1. General Procedure for the Asymmetric Aza Diels-Alder Reaction

The imidazolinium carbene precursor **80** (7.7 mg, 0.017 mmol, 0.05 equiv.) was added into a dry Schlenk flask under nitrogen. The base KO^{t}Bu (6.1 mg, 0.051 mmol) was added followed by toluene (1 mL) as solvent. The mixture was allowed to stir for 30 min. Then a metal salt (0.025 equiv.) was added and stirring was continued for another 15 min. The imine **147** (90.8 mg, 0.35 mmol) was added into the reaction mixture. After stirring for 5 min, the Danishefsky's diene (110 µL, 0.525 mmol, 1.5 equiv.) was added. The reaction was stirred at room temperature for 16h. Then the reaction was quenched with trifluoroacetic acid,

extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. FCC (petroleum ether/EtOAc, 9/1) gave the white solid. For the different metal salts employed see Table 32. Spectral data were consistent with literature values.[200]

3.6.8. Asymmetric Henry Reaction

1-Chloro-4-(1-nitropropan-2-yl) benzene (151)



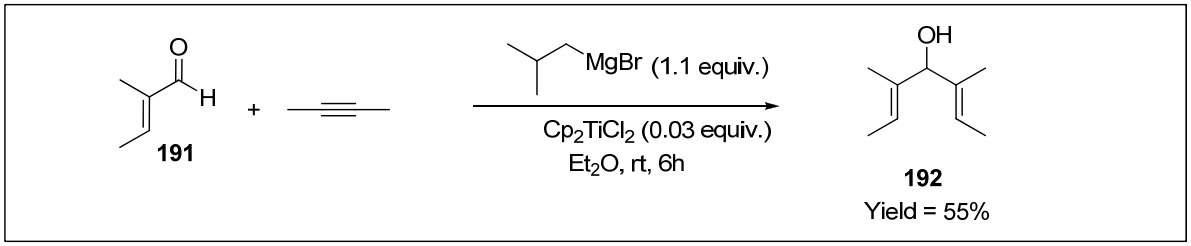
3.6.8.1. General Procedure for the Asymmetric Henry Reaction

The imidazolinium carbene precursor **80** (7.7 mg, 0.017 mmol, 0.05 equiv.) was added into a dry Schlenk flask under nitrogen. The base KO^{t}Bu (6.1 mg, 0.051 mmol, 0.15 equiv.) was added followed by toluene (1 mL) as solvent. The mixture was allowed to stir for 30 min. $Cu(OTf)_2$ (6.3 mg, 0.017 mmol, 0.05 equiv.) was added and stirring was continued for another 15 min. Then *p*-chlorobenzaldehye (49.2 mg, 0.35 mmol) was added into the reaction mixture. After stirring for 5 min, CH_3NO_2 (21.0 µL, 0.385 mmol, 1.1 equiv.) was added. The base Et_3N (2.4 µL, 0.0175 mmol) was added subsequently. The reaction was stirred at room temperature for 16h. Then the reaction was quenched with aqueous NH_4Cl, extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. FCC (petroleum ether/EtOAc, 9/1) gave the white solid (33.3 mg, 47%). Spectral data were consistent with literature values.[155]

3.6.8. Asymmetric Ring-Closing Olefin Metathesis

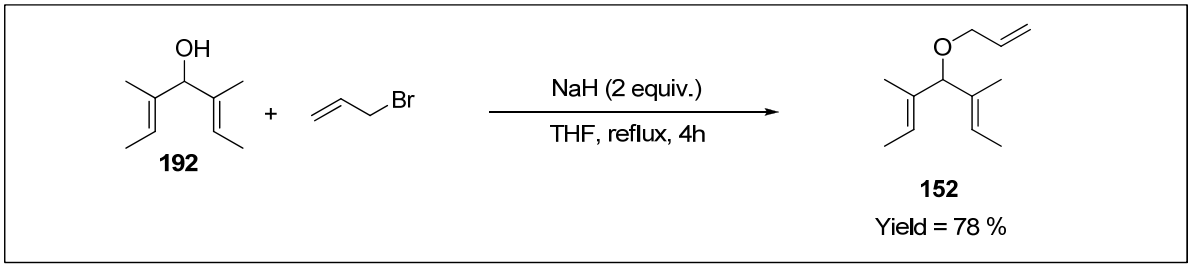
3.6.8.1. Preparation of Starting Material for the Asymmetric Metathesis Reactions

(2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-0l (192)



2-Butyne (5.2 mL, 66.0 mmol) and *iso*butylmagnesium bromide (2.0M in diethyl ether, 30.6 mL, 61 mmol) were added in 60 mL Et_2O in a dry flask under nitrogen. Then titanocene dichloride (412.7 mg, 1.65 mmol) was added to the reaction mixture. *Trans*-2-methyl-2-butenal (5.30 mL, 54.8 mmol) was added slowly. The mixture was stirred at room temperature for 4h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether (3×75 mL), and the organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to give a brown oil. The crude product was purified by FCC (hexane/ethyl acetate, 9/1) to give a yellow oil which was further distilled (Kugelrohr, 1 torr, 120 °C) to give a colorless oil (4.27 g, 56%). Spectral data were consistent with literature values.[201]

(2*E*,5*E*)-4-(Allyloxy)-3,5-dimethylhepta-2,5-diene (152)



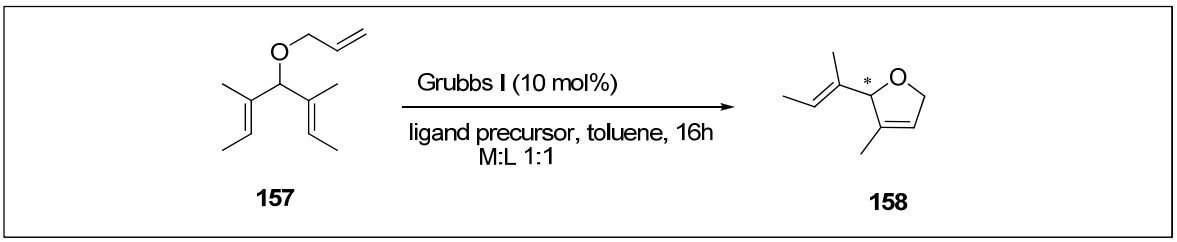
NaH (350.0 mg, 8.74 mmol, 60% in oil) was added in THF (10 mL) into a dry Schlenk. Alcohol **192** (613 mg, 4.37 mmol) was added dropwise to the suspension. The mixture was refluxed for 15 min and then allowed to cool to rt. Allyl bromide (0.92 mL, 10.92 mmol, 2.5

equiv.) was added and the mixture was again refluxed for 4h. The reaction was quenched with aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to an oil which was purified by flash chromatography (1% ethyl acetate in hexane) to give **152** (611 mg, 78%) as a colorless oil. Spectral data were consistent with literature values.[196]

3.6.8.2. General Procedure for Asymmetric Ring-Closing Olefin Metathesis

An imidazolinium carbene precursor **80** (15.0 mg, 0.035 mmol, 0.1 equiv.) was added into a dry Schlenk flask under nitrogen. The base KO^{t}Bu (12.2 mg, 0.105 mmol, 0.3 equiv.) was added followed, by toluene (1 mL) as solvent. The mixture was allowed to stir for 30 min. The Grubbs I catalyst (28.8 mg, 0.035 mmol, 0.1 equiv.) was added and stirring was continued for another 15 min. Then triene (63.1 mg, 0.35 mmol) was added into the reaction mixture. The contents were stirred for 24h and the residue was purified by silica gel column chromatography (2% diethyl ether in pentane).

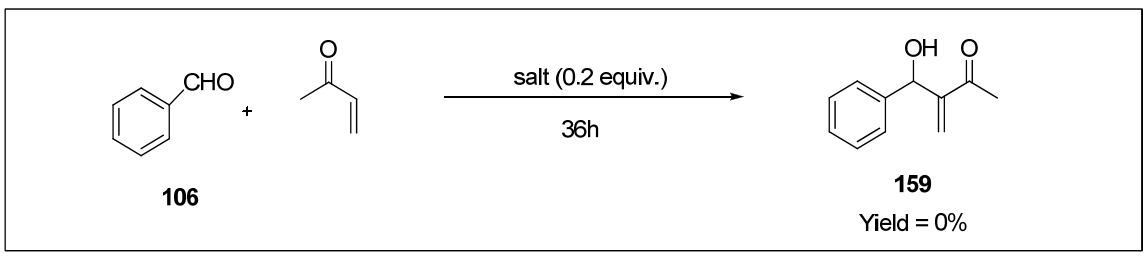
(*E*)-2-(But-2-en-2-yl)-3-methyl-2,5-dihydrofuran (158)



This reaction was performed to obtain the racemate. From triene (32.0 mg, 0.176 mmol) and Grubbs I (14.5 mg, 0.0176 mmol, 0.1 equiv.) in toluene at 40 °C for 24h to give pale yellow oil (15.2 mg, 62%). Spectral data were consistent with literature values.[196]

3.6.9. Baylis-Hillman Reaction

3-(Hydroxy (phenyl) methyl)-but-3-en-2-one (159)

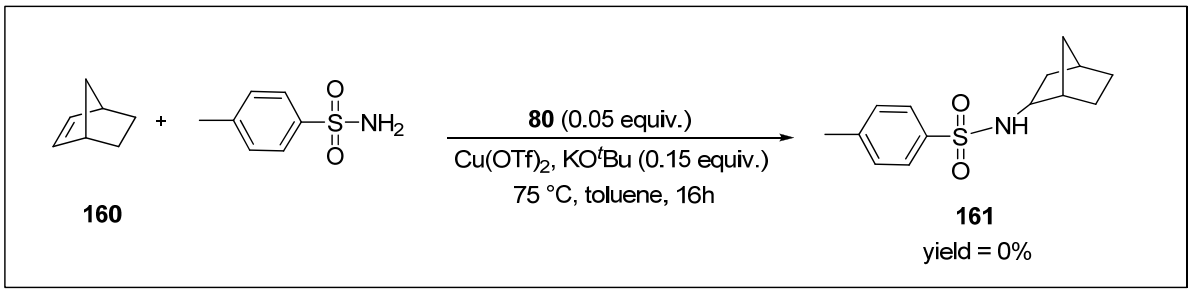


3.6.9.1. General Procedure for the Baylis-Hillman Reaction

An imidazolinium salt (0.2 equiv.) was placed into a Schlenk flask under nitrogen and was dissolved in toluene (1 mL). Then benzaldehyde (47 µL, 0.47 mmol, 2 equiv.) and but-3-en-2-one (18 µL, 0.24 mmol) were added sequentially. The reaction was allowed to stir for 36h at room temperature. Afterwards the crude mixture was filtered and columned but no product was obtained. For the ligands employed see Table 35.

3.6.10. Asymmetric Hydroamination Reaction

_N_-(-Bicyclo [2.2.1] heptan-2-yl)-4-methylbenzenesulfonamide (161)



160 **161**

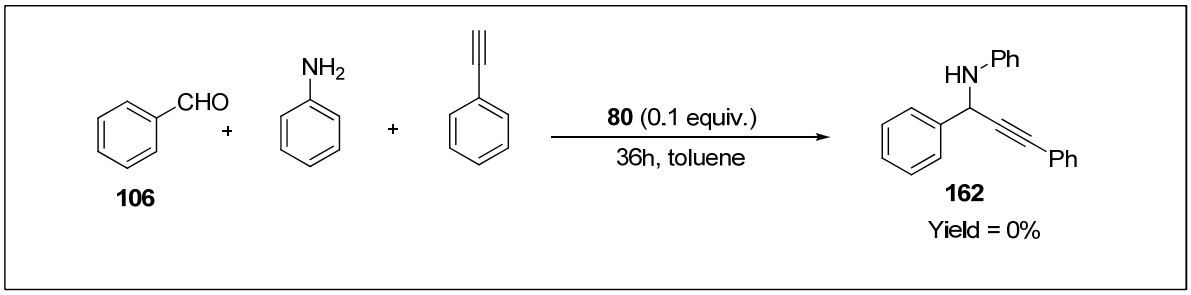
yield = 0%

3.6.10.1. General Procedure for the Hydroamination Reaction

The imidazolinium salt **80** (7.7 mg, 0.017 mmol, 0.05 equiv.) was added into a dry Schlenk flask under nitrogen. KO^{t}Bu (6.1 mg, 0.051 mmol, 0.15 equiv.) was added followed by toluene (1 mL) as solvent. The mixture was allowed to stir for 30 min. $Cu(OTf)_2$ (6.3 mg, 0.017 mmol, 0.05 equiv.) was added and stirring was continued for another 15 min. Then norbornene **160** (33.0 mg, 0.35 mmol) was added into the reaction mixture. After stirring for another 5 min, $TsNH_2$ (60.0 mg, 0.385 mmol, 1.1 equiv.) was added. The reaction was stirred at 75 °C for 16h. No progress of the reaction was observed by monitoring the TLC.

3.6.11. Three Component Condensation Reaction

_N_-(1,3-Diphenyl-2-propynyl) aniline (162)

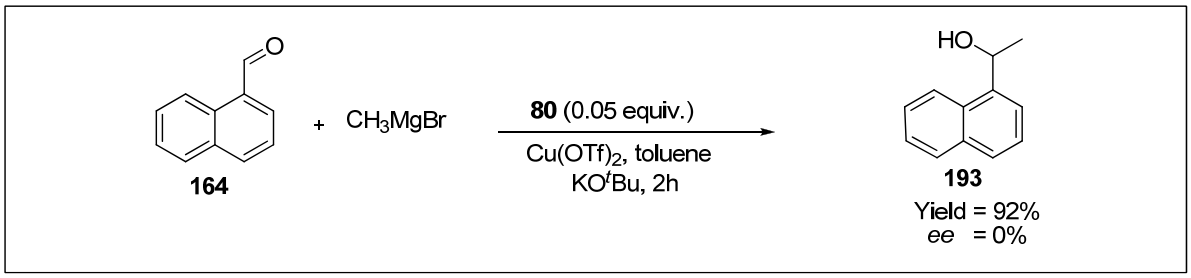


3.6.11.1. General Procedure for A^3-Coupling Reaction

The imidazolinium salt **80** (7.7 mg, 0.017 mmol, 0.1 equiv.) and KO^{t}Bu (6.1 mg, 0.051 mmol, 0.15 equiv.) were dissolved in toluene (1 mL) in a dry Schlenk flask under nitrogen. The mixture was allowed to stir for 30 min. $Cu(OTf)_2$ (6.3 mg, 0.017 mmol, 0.05 equiv.) was added and stirring was continued for another 15 min. Then benzaldehyde (36.0 µL, 0.35 mmol), aniline (32.0 µL, 0.35 mmol) and phenylacetylene (58.0 µL, 0.53 mmol) were added into the reaction mixture. The reaction was stirred at rt for 24h. No progress of the reaction was observed by monitoring the TLC. The crude mixture was filtered and columned but no product was isolated.

3.6.12. Addition of Grignard Reagent to 1-Naphthaldehyde

1-(Naphthalen-1-yl) ethanol (193)

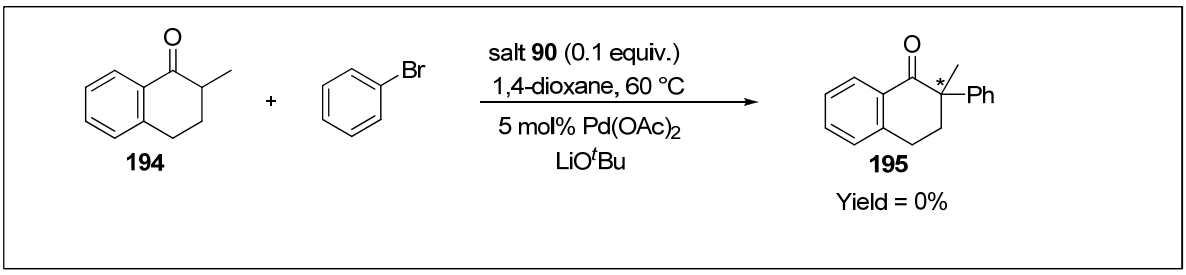


To the dry Schlenk flask were added salt **80** (7.5 mg, 0.05 equiv.), KO^{t}Bu (6.1 mg, 0.051 mmol, 0.15 equiv.) followed by toluene (1 mL). After 30 min stirring, $Cu(OTf)_2$ (6.3 mg, 0.175 mmol, 0.05 equiv.) was added and the mixture was allowed to stir for 15 min. Then 1-naphthaldehyde (48.0 µL, 0.35 mmol) and CH_3MgBr (170 µL, 1.5 equiv.) were added subsequently. The contents were stirred for 2h. The reaction was quenched with 1N HCl, extracted with CH_2Cl_2, filtered, dried (Na_2SO_4) and the solvent was removed under reduced

pressure. The crude was purified by FCC (petroleum ether/EtOAc, 9/1) to give title compound (56.0 mg, 92%). Spectral data were consistent with literature values.[202]

3.6.13. Asymmetric Intermolucluar *α*-Arylation Reaction

2-Methyl-2-phenyl-3,4-dihydronaphthalen-1(2*H*)-one (195)



3.6.13.1. General Procedure for the Intermolucluar *α*-Arylation Reaction

To the dried Schlenk, substrate **194** (32.1 mg, 0.2 mmol), the imidazolinium carbene precursor **90** (14.8 mg, 0.02 mmol) and $Pd(OAc)_2$ (4.6 mg, 0.02 mmol) were added under nitrogen. 1,4-Dioxane (1 mL) was added followed by the addition of bromobenzene (42.1 µL, 0.4 mmol, 2 equiv.) and the mixture was stirred for 15 min. Then LiO^tBu (0.6 mmol) was added and the temperature of the reaction mixture was raised to 60 °C. The contents were stirred for 24h. No product was observed while monitoring the reaction by TLC. The reaction mixture was discarded.

3.7. Imidazolinium Salts as Chiral Shift Reagents

3.7.1. Preparation of Racemic Potassium Mosher´s Carboxylate

Racemic Mosher's acid (302.0 mg, 1.29 mmol) was dissolved in water (1 mL) and a solution of KOH (72.0 mg, 1.29 mmol) in water (3 mL) was added. The mixture was stirred at rt for 15 min and water was removed under reduced pressure. The remaining solid was further dried under high vacuum to give the potassium Mosher's carboxylate salt as a white solid (351.0 mg, quant.).

3.7.2. NMR Experiment with the Racemic Mosher's Acid Salt

The Mosher's acid salt (1.0 mmol) and the corresponding imidazolinium salt (1.0 mmol) were dissolved in acetone-d_6 and the ^{1}H-NMR and ^{19}F-NMR spectra were recorded at rt. For results see Table 38.

3.8. References

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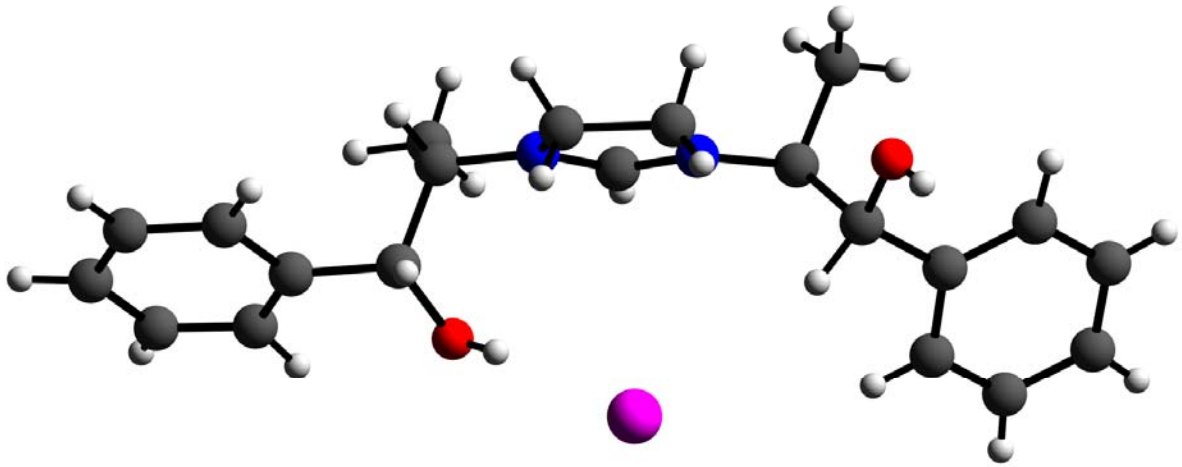
A. Appendix

A1. X-ray structure of (–)-3-Bis-((1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-imidazolinium iodide (83)

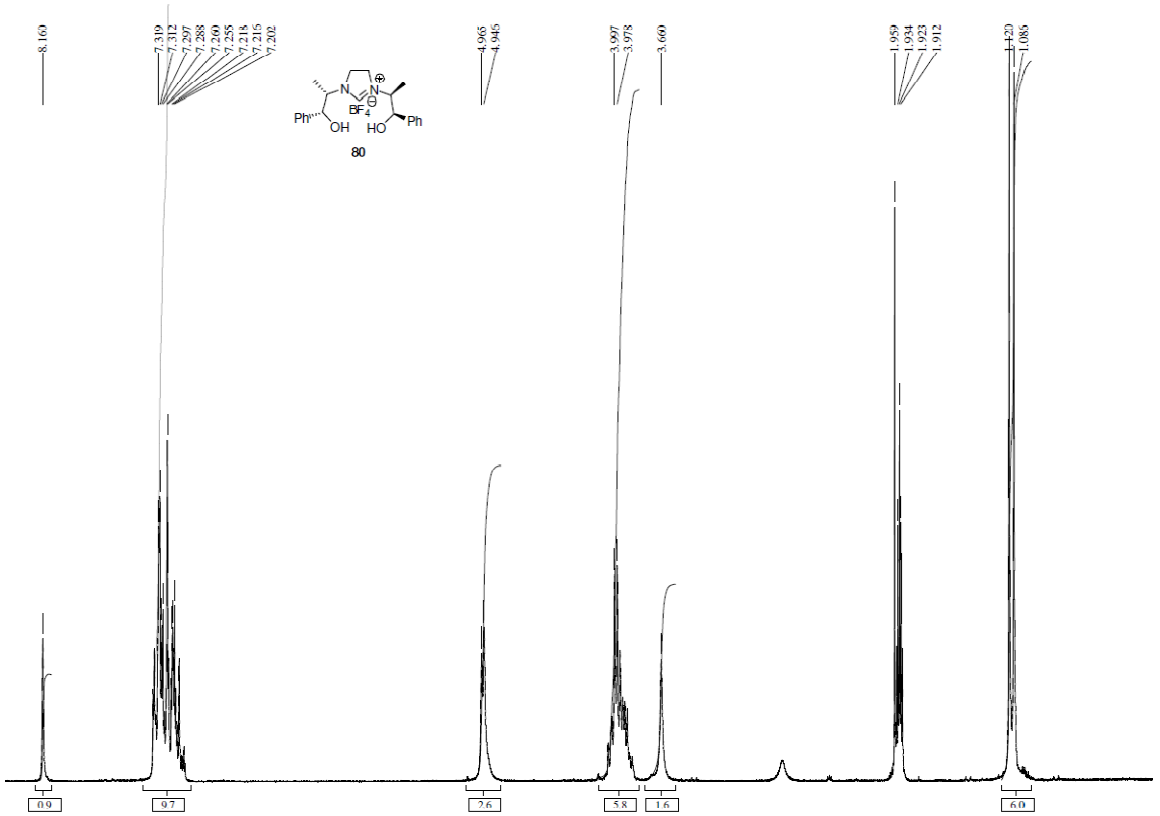


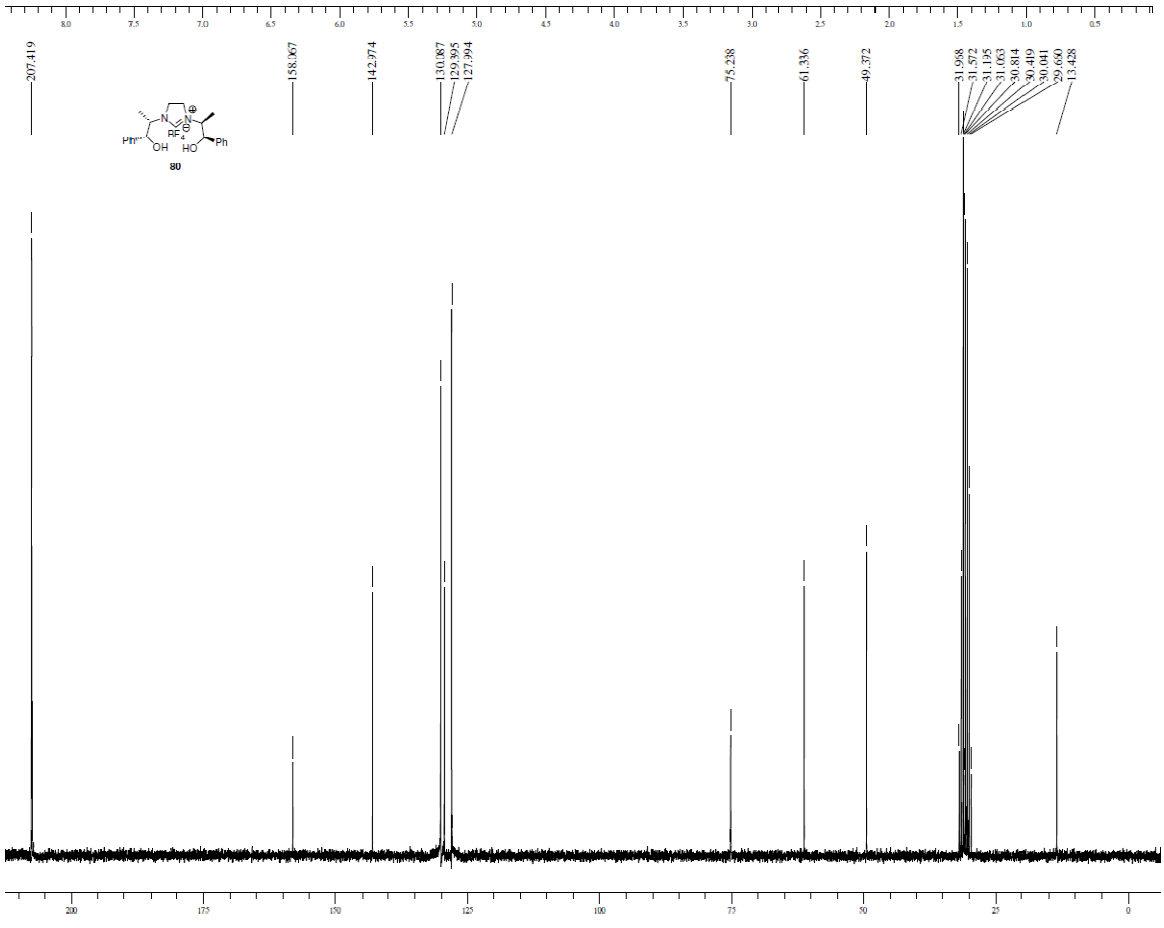
Kristalldaten für $C_{21}H_{27}IN_2O_2$

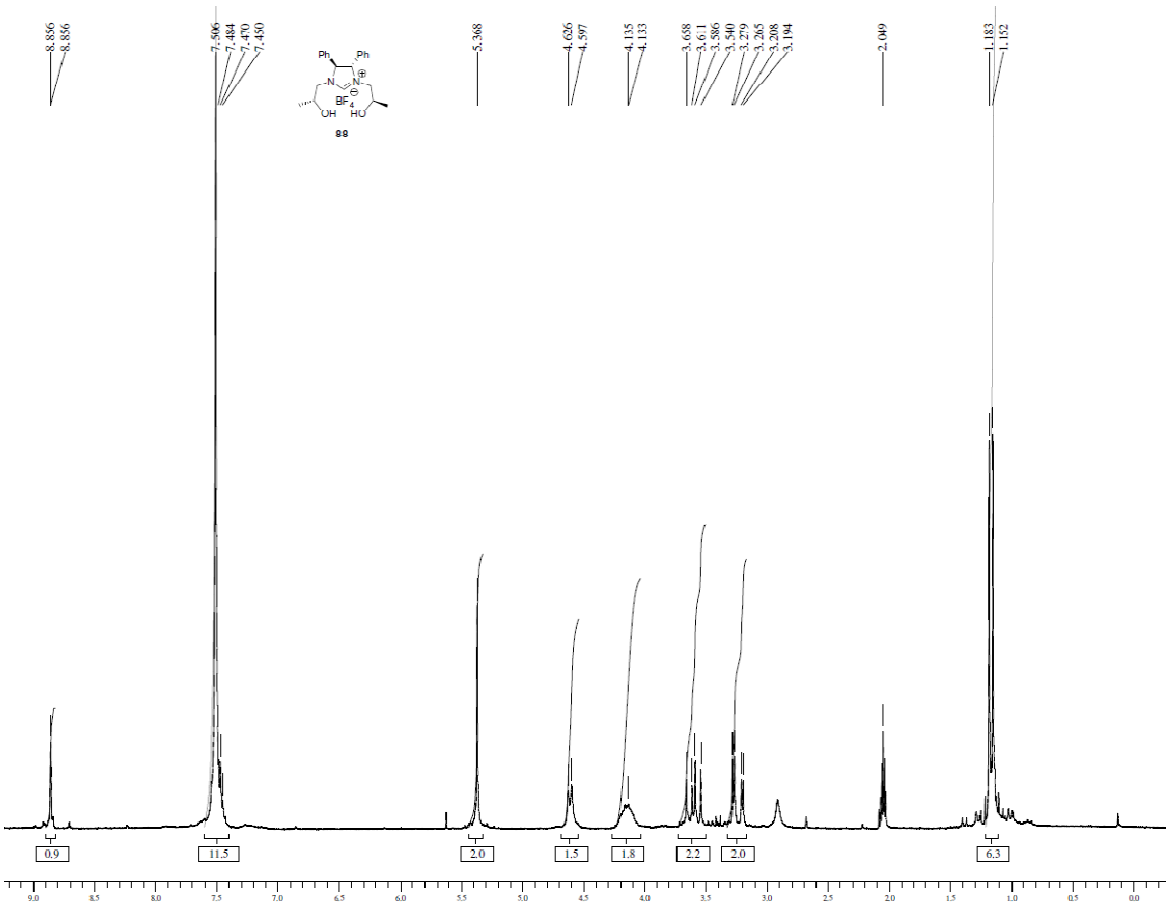
Kristallsystem	orthorhombisch
Raumgruppe	$P2_12_12_1$ (Nr. 19)
a / Å	7,759(1)
b / Å	10,508(1)
c / Å	25,567(1)
V / Å^3	2084,5(2)

Goof	1,021
x-Flack	0,0092
*R*1 (all Daten)	0,0381
*wR*2 (all Daten)	0,0781

A2. NMR Spectras of Selected Compounds



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3.611
3.586
3.540
3.279
3.265
3.208
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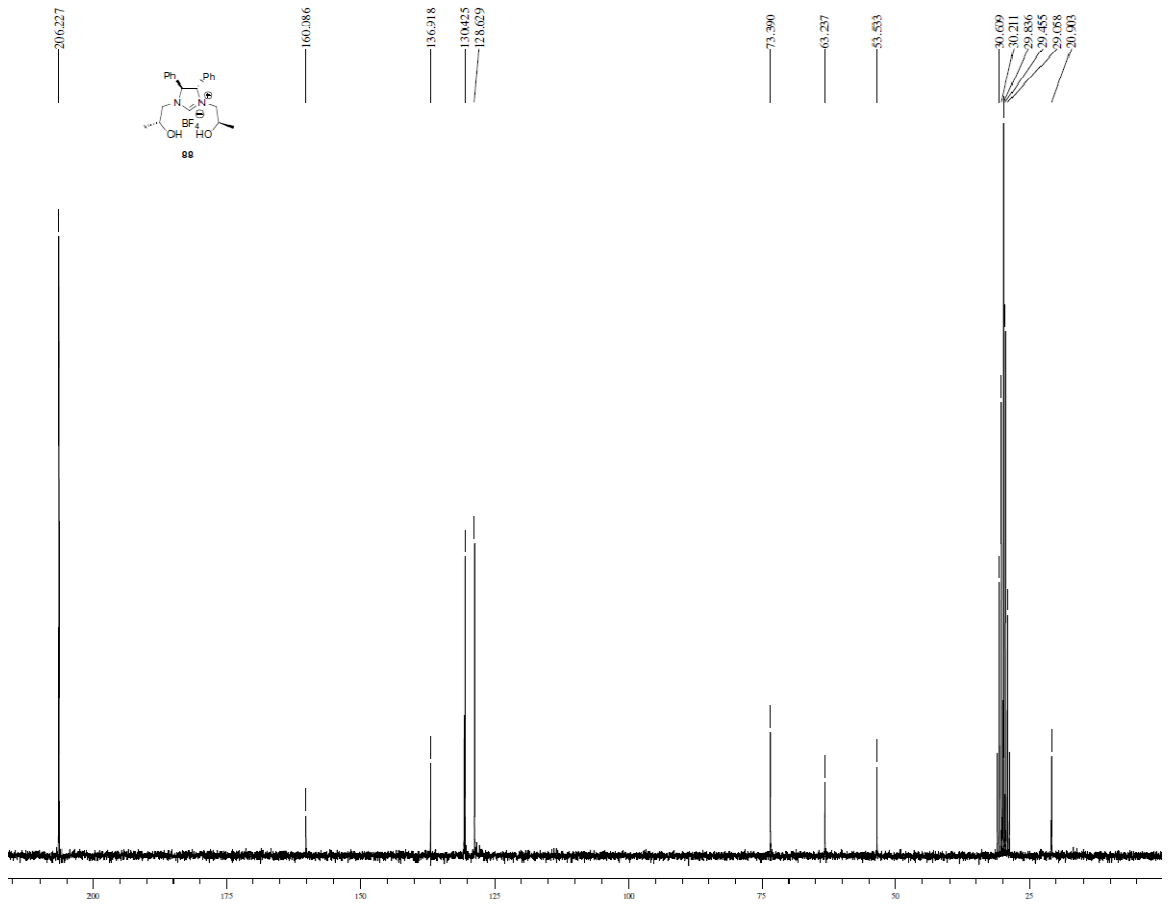
1.5
1.8
2.2
2.0
6.3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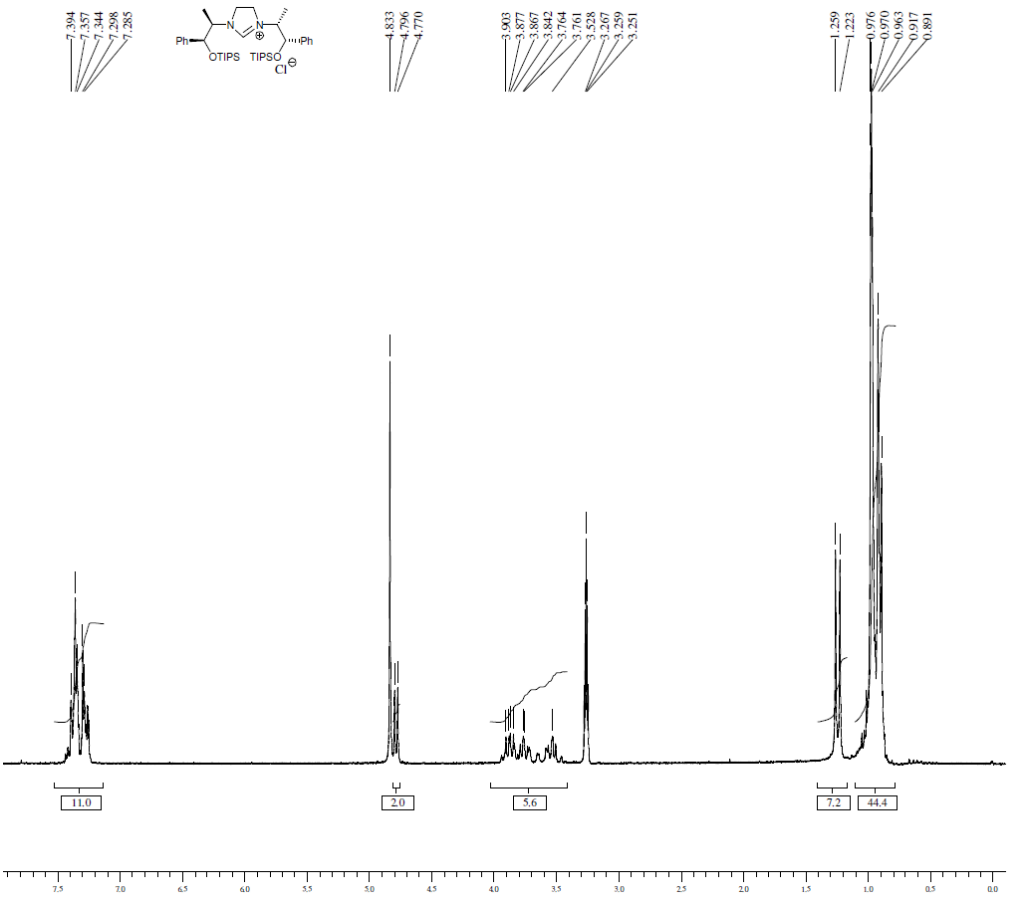
29.058
20.903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3.764
3.761
3.528
3.267
3.259
3.251
1.259
1.223
0.976
0.970
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7.2
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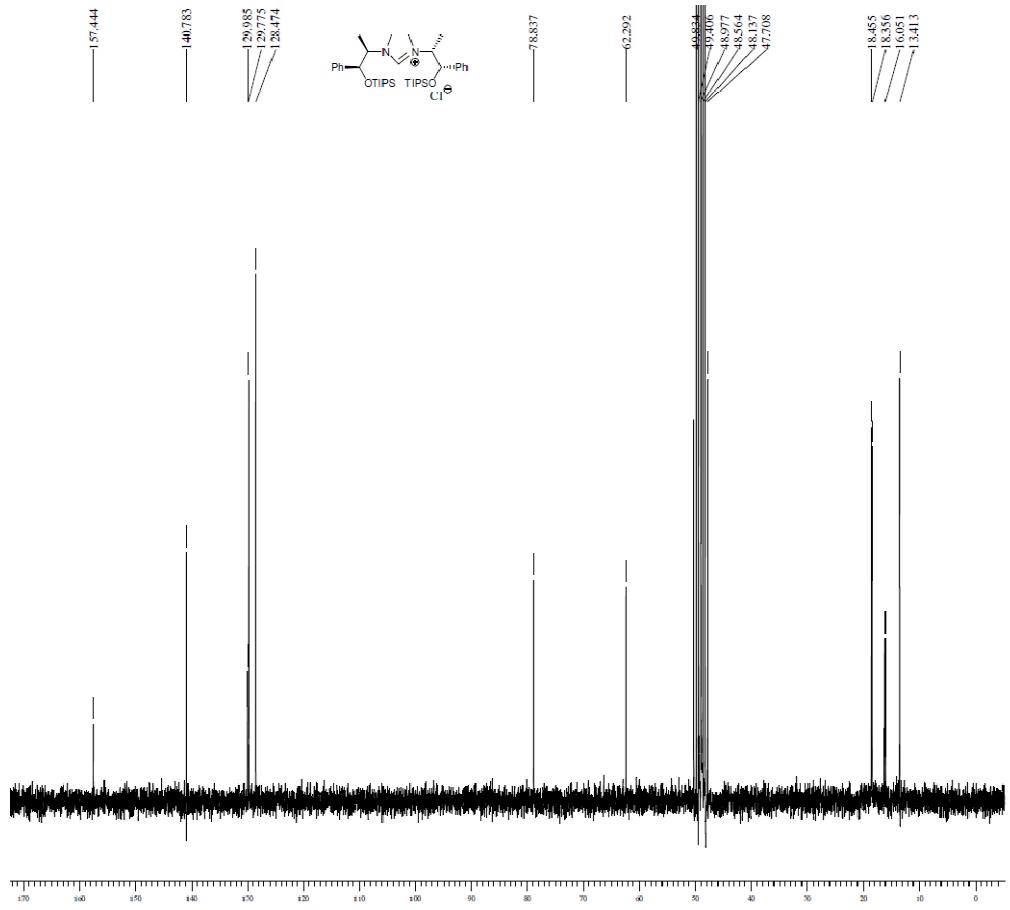
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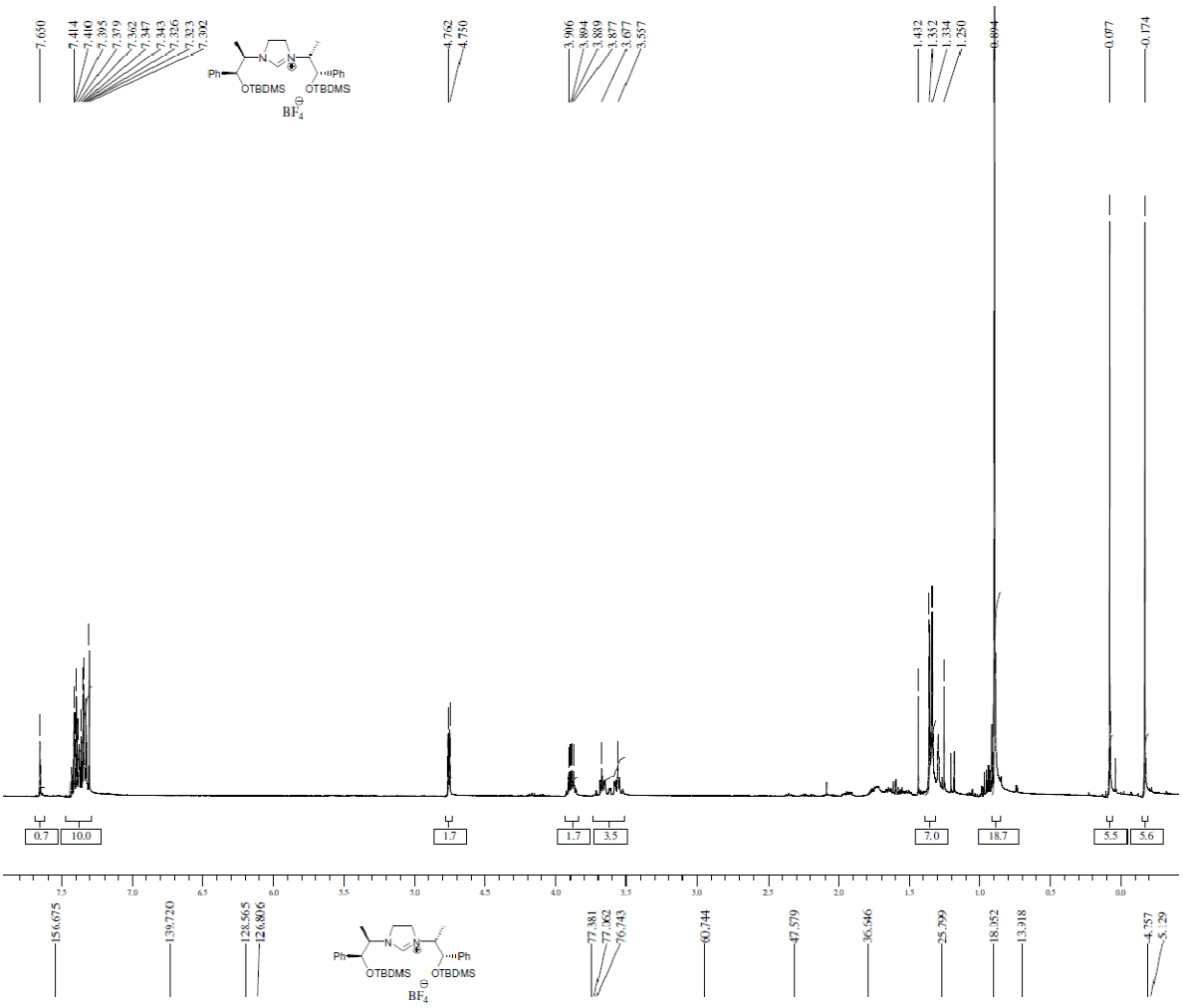
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0.174
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OTBDMS
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1.7
3.5
7.0
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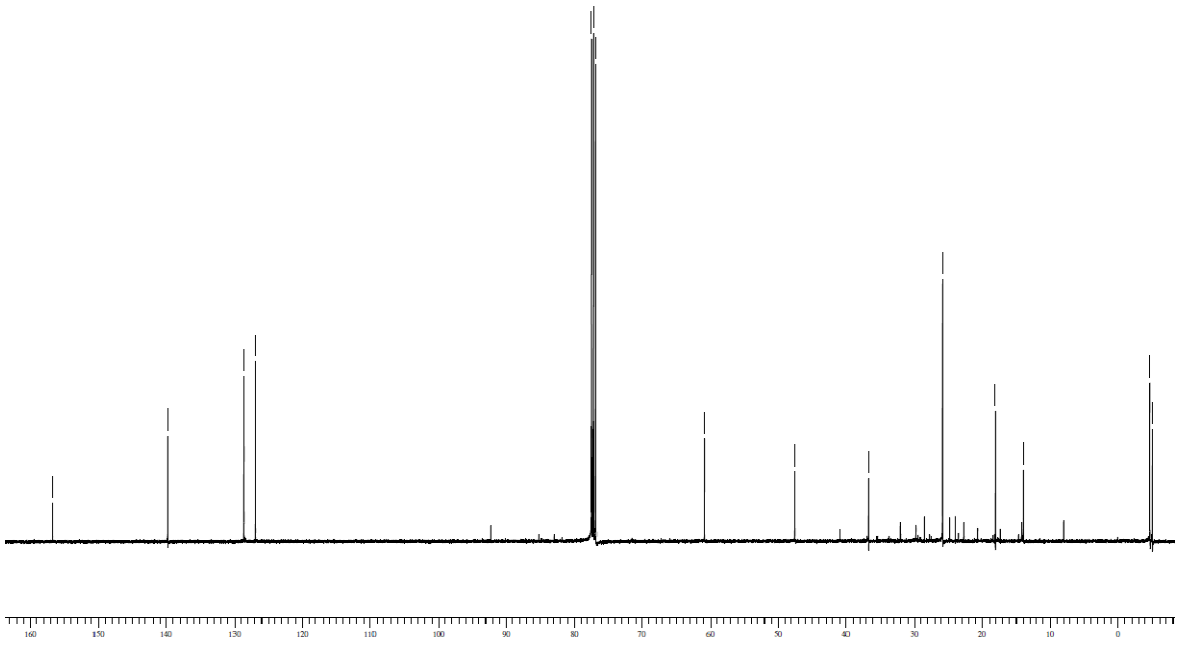

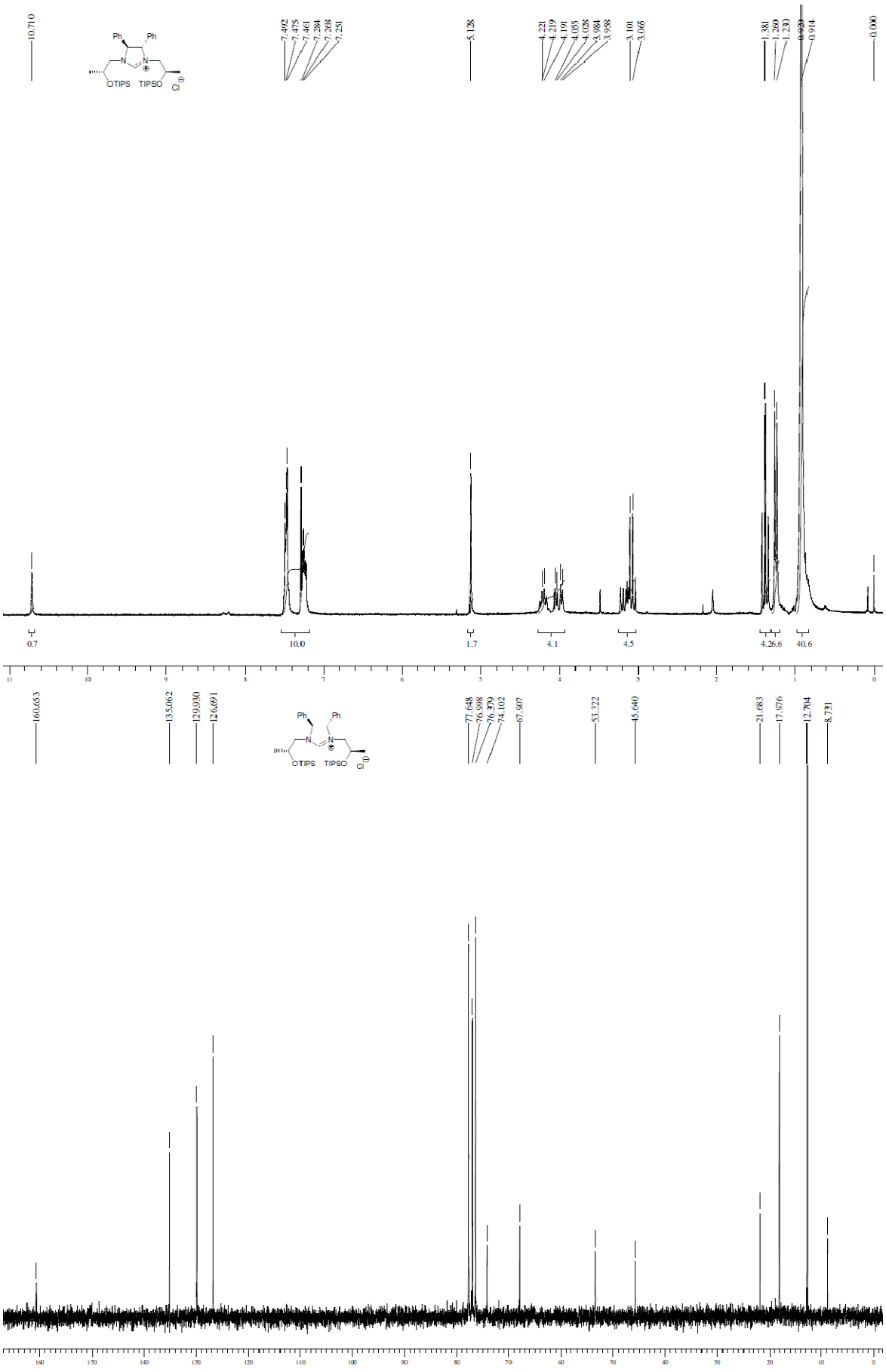
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3.065
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Ph
Ph
OTIPS
TIPSO
Cl
0.7
10.0
1.7
4.1
4.5
4.26.6
40.6
160.653
135.062
129.930
126.691
77.648
76.998
76.379
74.102
67.907
53.322
45.640
21.683
17.576
12.704
8.731

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ORGANIC CHEMIST

Education

2006-May 2009, **PhD Scholar**, Clausthal University of Technology, Germany
PhD in Synthetic Organic chemistry.Topic: Development of Novel Chiral Imidazolinium Salts and Their Application in Asymmetric Catalysis
Supervisor: Prof. Dr. René Wilhelm

2003-2006, **Research Fellow**, HEJ Research Institute of Chemistry, University of Karachi, Pakistan
Project: Isolation and characterization of Natural Products from *Auranella congolensis*

1999-2001, **M.Sc, Chemistry** *(1st Division)* University of the Punjab, Pakistan
Project: Oxidation of Thiosemicarbazid and Allyl Thiourea in Neutral and Acidic.Media

1999-1997, **B.Sc** *(1st Division, GPA 3.93/4.0, with distinction)* Govt. College Lahore, Pakistan

1997-1999, **F.Sc** *(1st Division)* Board of Secondary Education, Lahore, Pakistan

Achievements/Awards

- Ph.D scholarship awarded by Higher Education Commission, Pakistan.
- Merit scholarship awarded by Govt. of Punjab in M.Sc.
- 2nd position in B. Sc securing certificate of distinction.
- Merit scholarship conferred by Govt. College Lahore during graduate studies.
- Joint Secretary of Blood Donor Society at Govt. College, Lahore.

Research Experience

- Worked for three years on isolation and characterization of natural products at HEJ Research Institute of Chemistry, University of Karachi.
- Worked for one year in an R&D and Q.C. section in Ittehad Chemicals (pvt.) Ltd. Lahore, Pakistan.

Publications

- Easily Accessible Chiral Imidazolinium Salts Bearing Two Hydroxy-Containing Substituents as Shift Reagents and Carbene Precursors. Vaclav Jurcik, Mazhar Gilani and René Wilhelm, ***Eur. J. Org. Chem.***, 2006, 5103-5109.

- New Enantiopure Imidazolinium Carbene Ligands Incorporating Two Hydroxy Groups for Lewis Acid Catalyzed Diethyl Zinc Addition to Aldehydes. Mazhar Gilani and René Wilhelm, ***Tetrahedron: Asymmetry***, 2008, 19, 2346-2352.

- New Imidazolinium Salts and Amines from Amino Alcohols and Their Application in the Palladium Catalyzed Intramolecular Asymmetric α-Arylation, Mazhar Gilani, Christian Torborg and René Wilhelm (Manuscript submitted).

Experience in Techniques/Instruments

Chromatographic Techniques (FCC, Chiral HPLC, GC), NMR (1D, 2D), UV, Mass Spectrometry, IR Spectroscopy