ASYMMETRIC DIETHYLZINC ADDITION TO N-SULPHONYL AND N-PHOSPHINOYL ARYLALDIMINES

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Design of new chiral ligands for asymmetric synthesis is important. The ligand should be economical and efficient in enantioselective transformations. For the synthesis of some natural products and biologically active compounds, optically active amines are used as important intermediates. For this reason, it is significant to develop new catalyst system which can produce optically active amines in an economical and efficient way. Our group developed PFAM ligands and used successfully for the enantioselective synthesis of organic compounds. In this work, these ligands were tested as chiral catalysts for enantioselective synthesis of amines. N-sulphonyl and N-phosphinoyl imines synthesized from aromatic aldehydes were used as the starting material for enantioselective diethylzinc addition reaction in the presence of copper salt and PFAM ligands. By improving the known procedure, N-benzylidine sulphonylaldimine was obtained in excellent yield (98%). Asymmetric diethylzinc addition reaction to N-sulphonyl and N-phosphinoyl aryldimines provided chiral amines in up to 81% enantioselectivity and 99% yield.

Keywords: Asymmetric synthesis, diethylzinc addition, N-sulphonyl and N-phosphinoyl aryldimines, chiral ligand

Anahtar kelimeler: Asimetrik sentez, dietilçinko katılması, N-sulfonoil ve N-fosfinoil arilaldimin, kiral ligand
To my beloved family...
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LIST OF ABBREVIATIONS

Ar : Aryl (also argon)
δ : Chemical shift in parts per million downfield from tetramethylsilane
J : Coupling constant
DABCO : Diazabicyclo[2.2.2]octane
1,2-DCE : 1,2-dichloroethane
DIPEA : Diisopropylethylamine
dr : Diastereomeric ratio
Fc : Ferrocenyli
FAM : Ferrocenyl substituted Aziridinyl Methanol
HMPA : Hexamethylphosphoramide
KPH2 : Potassium diphenylphosphide
L : Ligand
mp : Melting point
MS : Molecular sieves
PFAM : Phosphino Ferrocenyl Aziridinyl Methanones and Methanols
POFAM : Phosphineoxy Ferrocenyl Aziridinyl Methanones and Methanols
Rf : Retention factor (TLC)
& : Retention time (in HPLC)
TMEDA : Tetramethylethylenediamine
TMS : Tetramethylsilane, also Trimethylsilyl
CHAPTER 1

INTRODUCTION

1.1. Synthetic approaches for chiral compounds

The biological activity of many pharmaceutical compounds, agricultural chemicals, flavors, fragrances and materials is related to the absolute configuration of molecules [1]. The demand of the synthesis of enantiomerically pure compounds has displayed a sharp increase in recent years. The explicit reasons to wish to obtain one enantiomer in pure are;

- unenviable hazardous properties of other enantiomer
- ecological risk of inactive enantiomer
- redundant economical loss

In particular, Limonene has found in two enantiomeric form. While (R)-Limonene has orange flavor, (S)-Limonene has lemon flavor and irritant. Similarly, although (R)-Fluazifob butyl is used as herbicide, (S) form of it is inactive (Figure 1).

![Chemical Structures of Limonene and Fluazifob Butyl](image)

Figure 1. A pair of enantiomers having different properties
Realizing the significance of the formation of a single enantiomer, several methodologies to generate enantiomerically enriched compounds were derived in history. Single enantiomer has been obtained either via transformation from enantiomerically enriched precursor or from chirality pool of nature by indirect methods or via kinetic resolution from racemic mixture.

However, all these methods suffer from significant disadvantages which are necessity of finding suitable precursors and use of them in stoichiometric amounts and giving maximum yield of 50% for desired enantiomer respectively [2]. Due to the drawbacks mentioned above, new methodology was generated to obtain one pure enantiomer easily, with high variety and in good yields which is asymmetric catalysis.

1.1.1. **Asymmetric catalysis**

By definition, asymmetric catalysis is a methodology used to obtain optically active substances in pure form from symmetrical precursors via use of chiral compounds (catalysts, ligands or auxiliaries) as a reaction intermediate [3]. Among all the other plausible approaches to get enantiomerically pure compounds, asymmetric catalysis is an ideal and the most elegant method having various advantages. The large quantity of desired enantiomer could be synthesized. It is not only economical but also ecological method to obtain single enantiomer. Chiral reagents utilized are necessary in small quantities and they could be used again without loss of chiral information input. The recovery of catalyst is plausible without requirement to any cleavage reaction. If two isomers of chiral reagent exist, it is possible to synthesize both enantiomers of the product.

To conduct asymmetric catalysis, chiral reagent participates in catalytic cycle for many times throughout the reaction and control the formation of single enantiomer. The representative figure displays the working principle of chiral catalyst *(Figure 2)*. Chiral reagent forms the intermediate complex with the substrate first followed by the reaction with reagent and resulted in formation of product selectively in one configuration. Chiral catalyst is released at the end of the reaction without loss of chiral information and participated in catalytic cycle many times [2].

![Catalytic cycle in asymmetric catalysis](image)

*S: Substrate  
R: Reagent  
P: Product  
C: Catalyst  
♦: optically active*
Chiral reagents used in asymmetric transformations are basically classified as biocatalysts, organocatalysts and metal catalysts (ligands) (Figure 3). Biocatalysts are generally enzymes or whole cells used mostly for industrial synthetic chemistry. They have been used in production of alcohol by fermentation process or cheese by enzymatic cleavage of milk proteins for hundreds of years. The range of biocatalytic application of biocatalysts has increased to provide the understanding of protein structure-function association over the past few decades [4]. Biocatalysts speed up the reaction like the other catalysts without influencing the thermodynamics of the reaction but they have unique features over traditional catalysts. They provide high selectivity which is either chiral (i.e. stereoselectivity), positional (i.e. regioselectivity) or functional group specific (i.e. chemoselectivity). This high selectivity provide various assistances such as limited or no need to use of protecting groups, diminished side reactions, separation ease and limited environmental drawbacks. They also offer high catalytic efficiency and mild working conditions which are significant for commercial applications. On the other hand, working in aqueous medium having high boiling point, limited scope and substrate or product inhibition are the drawbacks served by use of biocatalysts [5].

Organocatalysts are small organic compounds having low molecular weight and increase the reaction rate without containing a metal in their structures. They are cheap, readily available, robust, non-toxic, metal-free, environmental friendly and inert to moisture and oxygen. However, the reaction scope that organocatalysts are used is limited. In other words, they could not catalyze all types of reactions that the metal-catalysts are used [6]. The one having the widest scope of application in various chemical reaction giving high selectivities is metal catalyst.

![Figure 3. Chiral reagents used in asymmetric synthesis](image-url)
1.1.1.1. Metal catalysts (M+ Chiral ligands)

The mostly developed chiral catalysts so far are metal complexes of chiral organic ligands. Chiral ligands provide the preferential formation of one of the two plausible enantiomers in the reaction via modifying the reactivity and selectivity of the metal center. Based on this perception, many metal complexes provide high enantioselectivities in various types of reactions [7].

In history, first Knowles at Monsanto Company, St. Louis displayed that it is possible to transfer chirality to nonchiral substrate forming chiral product with enantiomeric excess via using chiral metal based catalyst in 1968. In mid-sixties, two different ligands were designed by different groups. Firstly, Osborn and Wilkinson was discovered rhodium complex, \([(PPh_3)_3RhCl]\), and tested in hydrogenation of unhindered olefins. Then, Horner and Mislow were discovered a methodology to synthesize optically active phosphines. By replacing the triphenylphosphine in Osborn and Wilkinson’s catalyst with the known chiral phosphine, Knowles succeeded in catalytic asymmetric hydrogenation of prochiral olefins in 15% ee (Figure 4) [8].

![Figure 4. Knowles’s catalytic asymmetric hydrogenation](image)

Although the enantiomeric excess obtained is too low, this study proved the probability to achieve catalytic asymmetric hydrogenation via using chiral ligand. Afterwards, Horner [9], Kagan [10], Morrison [11] and Bosnich obtained the similar results and they all contributed to the strike of new and significant area for not only for academic field but also in industrial research [8].

1.2. Asymmetric synthesis of chiral amines

Chiral amine synthesis is a significant area of interest as chiral amines act as a powerful pharmacophores for designing new pharmaceutical drugs. These are the result of their high density of structural information and inherit capability of H-bonding. However, synthesis of those amines could not be easy most of the times. This challenge is further become greater when the aim is to introduce nitrogen into a compound or advanced intermediate by simple procedure, preferentially at one step with complete enantio-, diastereo-, regio- and chemocontrol.
As a definition, chiral amine, that is better defined as α-chiral amine, is a nitrogen atom bearing an adjacent or stereogenic carbon atom except the α- and β- amino acids. Mainly, chiral amines have two significant structural properties. First, the nitrogen in their structures could be primary, secondary, tertiary and even quarternary (which is for quarternary ammonium salts). Second, α-stereogenic carbon could be secondary or tertiary. Via using different methods, the chiral amine having these properties could be obtained (Scheme 1). Among those, nucleophilic attack to azomethine carbon of imines is the most frequently applicable one. Within these reactions, the ones providing the formation of primary amine building blocks are mostly preferential one due to the flexible structure leading to easy synthetic design of pharmaceutical drugs and natural alkaloid products (Figure 5) [12-13].

Scheme 1. Nucleophilic addition to C=N double bond

Figure 5. Function of chiral primary amines to formation of complex chiral amine building blocks
1.2.1. Design of the synthesis of α-branched amines

1.2.1.1. Enantioselective synthesis of amines from imines

The catalytic enantioselective addition reactions of organometallic reagents to C=N double bonds of imines are basically significant processes that offer suitable and flexible routes to synthesis of optically active amines containing a chirality center at α-position.

Most of the chiral biologically active complex compounds contain α-branched optically active amines such as methoxyphenamine (β₂-adrenergic antagonist to cure asthma), repaglinide (used as hypoglycemic agent) and rivastigmine (used as an enzyme inhibitor for treatment of Alzheimer’s disease) (Figure 6) [14].

In history, the studies in enantioselective addition to C=N double bonds were conducted either in the presence of chiral auxiliaries or chiral ligands. Firstly, Takahashi and co-workers reported the pioneering work on asymmetric addition to imines derived from aldehydes and valinol or phenylglycinol via using organolithium reagents in presence of chiral auxiliary in 1982 (Scheme 2) [15-16]. The chiral auxiliary approach is a significant technology as it is practical. The easy cleavage of chiral auxiliary after the separation of the diastereomeric products results in the only one enantiomer in pure. The enantioselective addition of organometallic reagents to the C=N double bonds of imines by use of stoichiometric or catalytic amounts of a chiral ligand built up as a new strategy for synthesis of chiral amines containing alkaloids in past two decades. One of the practical advantages of the use of chiral ligands is recoverability of unchanged ligands after the reaction.
The first chiral ligand controlled enantioselective addition of organometallic reagents to imines reported by Tomioka and co-workers in 1990. The study was conducted using organolithium reagents and chiral amino ether ligand 1 as an activator (Scheme 3). In presence of 5 mol% of chiral ligand, addition product that is enriched amine was obtained by moderate enantioselectivity. By this study, the doors of the catalytic asymmetric synthesis of chiral amines via addition of organometallic reagents to imines were opened [17].

Then, Denmark and co-workers displayed the capability of asymmetric induction of their chiral ligands that are (-)-sparteine and bisoxazoline 2 in this reaction via using alkyl-lithium reagent and obtained good enantioselectivities (Scheme 4) [18].
In 1992, Soai and co-workers published the first catalytic enantioselective addition of dialkylzinc reagent to C=N double bond of N-(diphenylphosphinoyl) imines via use of chiral aminoalcohol 3 as a promoter and obtained high enantioselectivity. Interestingly, they reached good enantioselectivity in presence of even 10 mol% of chiral ligand although the yield was low (Scheme 5) [19].

The main perception for the working principle of this reaction in enantioselective way is the formation of active organometal-chiral ligand complexes from less reactive organometallic reagents in transition state. However, unlike the high enantioselectivities and yields obtained from asymmetric alkylation of aldehydes using organozinc reagents in presence of chiral amino alcohols, catalytic asymmetric addition of alkylmetals to imines provided low chemical yield and ee due to lower electrophilicity of azomethine carbon compared to the aldehyde. This has changed by the recent copper-catalyzed asymmetric addition of dialkylzinc to imines [20].
1.2.1.2. Reactivity of imines

The addition to imines has been difficult compared to corresponding carbonyl carbon of aldehyde due to lower electrophilic character of azomethine carbon. The poor electrophilicity is the result of the smaller electronegativity of nitrogen (Pauling 3.0) compared to that of oxygen (Pauling 3.5). This makes the C=N bond less polar than the C=O bond having dipole moment 0.9 D and 2.7 D respectively [13]. In addition, electronegativity difference also affects the stability of amide and hydroxide formed as a result of addition reactions (pK_a for H_2N-H ca. 38 and pK_a for HO-H ca. 16). Due to the reasons mentioned above, the addition reaction to C=O double bond is more favored thermodynamically than that to C=N double bond. In order to get addition product to imines, the low electrophilic azomethine carbon should be activated either by attachment of activating substituents on imine nitrogen, using more nucleophilic organometallic reagents or activation via Lewis acid. Both nonsubstituted and commonly used activated imines were displayed in Figure 7 with the corresponding aldehyde below [14].

![Figure 7](image-url)

**Figure 7.** Commonly used activated imines with natural atomic charges on carbonyl or azomethine carbon

The substituents on the imine nitrogen allow the negative charge stabilization by delocalization over aromatic rings or by electronegative oxygen atom in the structure followed by the formation of addition product.
1.2.1.3. Activation of diorganozinc reagents via different transition metal salts

The study conducted by Hoveyda and Snapper displayed the unconventional approach to catalytic asymmetric synthesis of α-branched amines via zirconium-catalyzed diethylzinc addition to α-anisidine derived imines in presence of Schiff base dipeptide ligands 4 in 2001. They obtained corresponding ethyl addition product in 82% yield and 93% enantioselectivity via using catalytic amount of chiral peptidic ligand (10 mol%) and zirconium salt (20 mol%) (Scheme 6) [21]. The drawbacks of this reaction are that zirconium salts are not readily available reagents and the significant excess amounts of dialkylzinc reagents are needed (6.0 equiv.).

![Scheme 6. Zr-Ligand complex catalyzed asymmetric diethylzinc addition to imines](image1)

Then, Nishimura and co-workers reported asymmetric rhodium catalyzed dimethylzinc addition to N-sulfonylarylimines via using chiral diene, (R,R)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod*) 5, as a ligand in 2006. This study is the first Rhodium catalyzed methyl transfer reaction. They reached excellent yields and enantioselectivities 82% and 97% respectively (Scheme 7). This reaction was also conducted via using different chiral ligands but the results were much lower as shown in Figure 8 [22].

![Scheme 7. First enantioselective Rh catalyzed methyl transfer reaction](image2)
By most of the previously mentioned methods, it was difficult to prepare starting materials and to deprotect the products to obtain chiral amines. Therefore, the methodology designed by Dahmen and Brase stated the catalytic asymmetric diethylzinc addition to formaldimines in presence of small amounts of N,O-ligand 6 even 1 mol % gave the addition product in excellent yield and enantioselectivity (93%). However, they faced with two significant problems. First one was the difficulties in catalytic cycle due to high reactivity of some imine substrates. Second was the tight coordination of products to zinc complexes resulted in isolation problems. (Scheme 8) [23].

Scheme 8. Catalytic asymmetric diethylzinc addition to formaldimines via N,O-ligand
1.2.1.4. Copper-catalyzed catalytic asymmetric diethylzinc addition to imines

The catalytic asymmetric addition of diethylzinc addition in presence of zinc alkoxide-copper complex and heavy transition metal-copper complexes was studied and the results obtained were high with respect to both yield and enantioselectivity. However, due to the unavailability, unstability of reagents, requirement of huge amounts of dialkylzinc reagents somehow and the catalytic turnover problems, they were not practical and applicable enough. Therefore, it is important to develop a methodology that is easily applicable in mild conditions to satisfy asymmetric addition of simple alkylmetals to imines via using catalytic amounts of chiral ligand. Designed methodology should also provide high chemical yield and enantioselectivity. To achieve this, the studies conducted on catalytic asymmetric addition of diethylzinc to imines in presence of chiral ligand-copper complex. Highly reactive imines containing electron withdrawing groups such as tosyl- and diphenylphosphinoyl- were used that provide easy cleavage under mild conditions after addition reaction by conserving chirality to obtain chiral amine building blocks [24].

1.2.1.4.1. Addition to N-sulphonylimine

One of the earliest studies in literature on asymmetric diethylzinc addition to N-sulphonylimines a was conducted by Fujihara and coworkers in presence of copper complexes of chiral phosphine and amidophosphine ligands in 2000 (Scheme 9). In this study, it was shown that representative chiral bisphosphine ligand, \((R)(+)-\text{BINAP} 7\) (20 mol %) gave the corresponding ethyl addition product b in 52% yield and 2% enantioselectivity, surprisingly. Then, \((-)\text{-DIOP} 8\) (20 mol %) was tested in corresponding reaction and slightly better results were obtained by 60% yield and 27% ee. They reached the best yield and enantioselectivity using \((S)(-)\text{-chiral amidophosphine derivative ligand 9 with 94% and 90% respectively (Figure 9). They also reported the formation of reduction product c in uncatalyzed reaction in absence of Cu (II) triflate and using toluene as a solvent in high yields. However, the amounts of c sharply decreased in copper-amidophosphine catalyzed reaction [24].

![Scheme 9](image_url)

**Scheme 9.** One of the earliest studies in literature on asymmetric diethylzinc addition to N-Sulphonylimines
Then, in 2002, the same group reported moderate enantioselectivities as a result of the asymmetric diethylzinc addition reaction with the chiral ligand \( 10 \) but excellent enantioselectivities via chiral ligand \( 9 \). This study showed the steric hindrance due to bulky groups on ligand and rigidity have the significant effects on enantioselectivity (Figure 10) [25].

After that, Li and coworkers used a series of copper complexes of chiral bidentate and tridentate bisoxazolines \( 11 \) in corresponding ethyl addition reaction in 2003. At optimized conditions, the tridentate ligand (10 mol %) gave the best results of 60% yield and 78% ee using CuOTf (10 mol%) at -20 °C in 31 hour. It was reported that the use of MS 4 Å increased both yield and enantioselectivity (Scheme 10) [26].
In the same year, Wang and coworkers displayed the catalytic activity of their chiral binaphthylthiophosphoramidate ligand **12** (6 mol %) in presence of Cu(I) (3 mol %) in asymmetric addition of diethylzinc (2.0 equiv.) to N-sulfonylimines. They reached the excellent yields (highest 93%) and enantioselectivities (highest 86%) via using Cu(MeCN)$_4$BF$_4$ salt. Under same conditions, the use of Cu(OTf)$_2$ provided same yield but slightly lower enantioselectivity (Scheme 11) [27].
In 2005, they also tested the new chiral ferrocenyl amidophosphine ligand 13 in corresponding reaction. The use of copper complex of the ligand derived to the formation of diethylzinc (3.0 equiv.) addition product in 94 % yield and 86 % ee at -5–0 °C. It was observed that the decrease in temperature to -20 °C lead to slight increase in ee up to 88% but sharp decrease in yield to 57% at a prolonged reaction time. In addition, compared to the results of Nagai and co-workers reported in 2002 using similar amidophosphine derived ligand 10 shown above, the positive effect of existence of bulky ferrocenyl group in structure of chiral ligand on asymmetric induction was proved (Scheme 12) [28].

Scheme 11. Asymmetric diethylzinc addition to N-sulphonylimines by chiral binaphthylthiophosphoramides

Scheme 12. New chiral amidophosphate-Cu complex catalyzed diethylzinc addition reaction
Finally, the recent reported study on the corresponding reaction was conducted by Suzuki and co-workers using N-Heterocyclic carbenes (NHCs) \[14\] as a ligand which was used firstly in asymmetric diethylzinc addition to enones and revealed ligand acceleration impact. As a result of reaction proceed at -5 °C, racemic product was obtained in good yield (83 %). Decreasing the reaction temperature didn't improve enantioselectivity and lowered the yield (Scheme 13) [29].

\[
\text{Ph—N}^-\text{Ts + Et₂Zn} \xrightarrow{\text{azolium salt (5 mol%), t-BuOK (5 mol%)}} \text{Et}^-\text{N—Ts}
\]

\[
\text{Cu(OTf)₂ (5 mol%), toluene, 24 h} \rightarrow 83\% \text{ yield, 1\% ee}
\]

**Scheme 13.** The recent reported study via using N-Heterocyclic carbenes (NHCs) in corresponding reaction

### 1.2.1.4.2. Addition to N-diphenylphosphinoylimine

One of the earliest studies conducted on catalytic asymmetric copper-ligand complex catalyzed diethylzinc addition to N-diphenylphosphinoylimines was reported by Charette and Boezio in 2002 (Scheme 14). They tested different ligands in corresponding reaction and obtained moderate to excellent yields and enantioselectivities. The ligands they tested and results are given in Figure 12. They reported the highest enantioselectivity with phosphine derivative (R,R)-Me-DuPHOS ligand \[15\] with 96% yield and 93% ee. Interestingly, when the Me- group in ligand was replaced by Et- group yield and ee were shaply decreased to 44% and 38% respectively. When they changed to i-Pr- group, the racemic product was obtained in trace amount [30].
Scheme 14. Catalytic asymmetric copper-ligand complex catalyzed diethylzinc addition to N-diphenylphosphinoylimines

Figure 12. Various ligands tested by Charette and Boezio in corresponding ethyl addition reaction

Then, in 2005, chiral diphosphine and thiophosphoramide 16 were tested by Chung and co-workers. They obtained good yields and enantioselectivities 80% and 85% respectively. They stated that they preferred to use Cu(OTf)$_2$ in the reaction as a transition metal salt due to its stability and greater convenience by handling compared to the other Cu salts (Scheme 15) [31].
After that, Wang and co-workers worked on the corresponding reaction via using ferrocenyl amino ketone derivative ligand 13 in 2006. They reached the highest result after the optimization studies as 60% yield and 78% ee which is lower than the result they obtained by using tosylimines in this reaction being highest 57% yield, 88% ee as shown in Scheme 12. They improved their result to 69% yield and 90% ee by using the N-diphenylphosphinoyl imine derived from $p$-Cl-benzaldehyde rather than benzaldehyde. They explained the good enantioselectivity of their ferrocenyl chiral ligand-copper complex as the unique, electron rich, rigid structure of ferrocene group [32].

Scheme 16. Enantioselective diethylzinc addition to N-phosphinoylimines via using ferrocenyl amidophosphine derivative ligand
Finally, novel chiral tert-butanesulfinylphosphine ligand 17 was tested by Liao and coworkers in copper-ligand complex catalyzed catalytic asymmetric diethylzinc addition to N-phosphinoylimines in 2008. They obtained the corresponding product in 89% yield and 92% enantioselectivity. However, they used high excess amounts of diethylzinc (4.0 equiv.) which was not preferred for this reaction. In addition, as a transition metal salt copper thiophene-2-carboxylate was tested but the product was obtained in slightly lower yield and enantioselectivity (82% and 80% respectively) (Scheme 17). During the course of derivatization studies, they obtained the highest enantioselectivity as 94% via using p-MeO-derivative of benzaldehyde in the synthesis of starting material N-diphenylphosphinoylimines [33].

Scheme 17. Hydrated Cu(II)-tert-butanesulfinylphosphine catalyzed asymmetric diethylzinc addition to N-diphenylphosphinoylimines.
1.3. Aim of work

Chiral amines are the significant small building blocks of many compounds used especially in pharmaceutical industry. Therefore, it is important to synthesize chiral amines in enantiomerically pure form with economical and efficient methodology. For this purposes, many procedures have been developed in literature. Among these, one of the most preferable methodology is the synthesis of chiral amines from imines by enantioselective reduction using diorganozinc compounds in presence of chiral ligands and copper-salts. In this study, we also aimed to use this methodology to synthesize chiral amines in enantiomerically pure forms. In doing so we have synthesized N-sulphonyl and N-phosphinoyl arylaldimines as the starting materials using literature procedures but in much better yields than the ones reported. We have used diethyl zinc as the alkyl source and tested different copper salts which are necessary for transmetallation. As the chiral ligands we have used phosphino ferrocenyl aziridinyl methanol (PFAM) and its keto form which were previously designed and synthesized in our group. In testing the performance of these ligands reaction conditions have been optimized by screening different solvents, additives, temperatures, and concentrations to get the chiral amine in high yield and enantioselectivity.
CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of imines

Imines are significant starting materials for the synthesis of chiral amines which are important biologically active compounds. Due to lower electrophilic character of azomethine carbon of imines, the addition is more difficult than their carbonyl analogues as mentioned in introduction part 1.2.1.2. To overcome this problem, imines are activated by tosyl (Ts-) and diphenyl phosphinoyl (Ph$_2$PO-) groups which are cleaved easily under mild conditions. The activation of imines by these groups made the addition easier. In this study, we preferred to use N-sulphonyl arylaldimines and N-phosphinoyl arylaldimines as starting materials for the asymmetric diethylzinc addition reaction.

Synthesis and purification of N-sulphonyl and N-phosphinoyl arylaldimines are difficult due to their high sensitivity to moisture, acidic and alkaline media. For synthesis of the corresponding imines, different methodologies were reported in literature. Chemla and coworkers used sodium p-toluenesulfinate in dilute formic acid [34], Jennings and Lovely used TiCl$_4$ and NEt$_3$ [35], Trost and Marrs used chloramine-T and tellurium metal [36]. In addition, Sisko and Weinreb stated a method for in situ generation of imines using Lewis acid by Kresze reaction [37]. Use of Amberlyst catalyst under Dean Stark conditions [38] is another way to synthesize corresponding imines. Through these methodologies, corresponding imines were synthesized not only under rough reaction conditions requiring the use of various expensive reagents but also in moderate to good yields. Therefore, it is significant to develop or improve methodology to synthesize the imines in mild conditions; with readily available reagents in high excellent yields. Herein, we report the improved methodology for the synthesis of N-benzylidine sulphonylaldimine in which corresponding imine was synthesized in better yields.
2.1.1. Improved methodology for synthesis of N-benzylidene sulphonylaldimine

\[
\text{Scheme 18. Improved methodology for synthesis of tosyl arylaldimines}
\]

N-benzylidene sulphonylaldimine 20 was synthesized by refluxing the benzaldehyde 18 and p-toluene sulfonamide 19 in toluene in presence of catalytic amount of TsOH during 2 hours (Scheme 18). p-toluenesulfonic acid protonates carbonyl oxygen of aldehyde therefore it becomes more electrophilic. Heating was performed at refluxing temperature of toluene. As a result, corresponding imine was obtained in excellent yield in pure form (98%). Excess amount of aldehyde was removed either by benzene azeotropy or recrystallization from DCM. This method is simple, practical and requires mild conditions compared to the literature methods. The other aldimines used in this study 21-28 were synthesized by adopting the literature procedure mentioned in the following part.

2.1.2. Derivatization studies of N-sulphonylaryl- and N-phosphinoyl arylaldimines

\[
\text{Scheme 19. Synthesis of N-sulphonylaryl- and N-phosphinoylaryl aldimine derivatives}
\]

Derivatives of N-sulphonyl- and N-phosphinoyl arylaldimines 21-28 were synthesized as shown in Scheme 19. In this synthesis, TiCl₄ was used as Lewis acid activator. After completeness of reaction, by appropriate workup procedure TiO₂ and triethylamine hydrochloride formed were removed. This reaction provided pure imines in moderate to high yields. For some derivatives, further purification was needed by either precipitation or recrystallization (see the experimental part). Literature procedure reported by Lovely and Jennings provides the reaction in 20 minutes. However, we observed that prolonged reaction time (2h) forms the aldimines in better yields (Table 1).
Table 1. Derivatives of N-sulphonylaryl- and N-phosphinoaryl aldimines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Derivatives of Arylaldimines</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-(4-methoxybenzylidene)-4-methylbenzenesulfonamide</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>N-(4-bromobenzylidene)-4-methylbenzenesulfonamide</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>N-(1-naphthylmethylene)-4-methylbenzenesulfonamide</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>N-(2-naphthylmethylene)-4-methylbenzenesulfonamide</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>N-benzylidene-P,P-diphenylphosphinic amide</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>N-(4-bromobenzylidene)-P,P-diphenylphosphinic amide</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>N-(2-naphthylmethylene)-P,P-diphenylphosphinic amide</td>
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</tr>
<tr>
<td>8</td>
<td>N-(4-methoxybenzylidene)-P,P-diphenylphosphinic amide</td>
<td>60</td>
</tr>
</tbody>
</table>

2.2. Synthetic pathway for PFAM ligands

PFAM ligands were previously synthesized by our group starting from ferrocene and acryloyl chloride [42]. Their catalytic activities were tested in similar types of reactions and good enantioselectivities were obtained. For this reason, we decided to test the performance of these ligands for asymmetric diethylzinc addition reaction to imines. Since phosphorous based chiral ligands were mostly performed well in literature, we preferred to use PFAM ligands rather than their oxidized form POFAM ligands.

2.2.1. Synthesis of acryloyl ferrocene

\[
\text{Fe} \quad \text{Cl} \quad \text{Me}_3\text{Al-AlCl}_3 \quad \text{DCM, 0°C} \quad \text{Fe}
\]

Scheme 20. Formation of acryloyl ferrocene from ferrocene and acryloyl chloride
Acryloyl ferrocene 31 was synthesized from ferrocene 29 and acryloyl chloride 30 in presence of strong Lewis acid mixture Me₃Al-AlCl₃ via Friedel-Crafts acylation reaction (Scheme 20) [39]. By this method, acryloyl ferrocene was obtained in excellent (99%) yield in pure form after simple extraction.

2.2.2. Bromination of acryloyl ferrocene

```
\[ \text{Fe} \quad \text{O} \quad \text{Br} \quad \text{DCM} \quad -78 \, ^\circ \text{C} \quad \text{Fe} \quad \text{O} \quad \text{Br} + \text{Fe} \quad \text{O} \quad \text{Br} \]
```

**Scheme 21.** Synthesis of dibromo- and monobromo- compounds from acryloyl ferrocene

The reaction of acryloyl ferrocene 31 with bromine in DCM at -78 °C resulted in dibromo-compound 32 in excellent yield (98%) as major product and mono-bromo compound 33 in trace amount as minor product (Scheme 21). This reaction yields the desired product 32 only by rapid addition of Br₂ solution to reaction medium. Under other circumstances, bromine either reacts with the cyclopentadienyl units of ferrocene group or forms iron salts. Reaction residue was easily removed by direct filtration of reaction mixture from short plague of silica column by using chloroform as an eluent.

2.2.3. Aziridination of α-bromo ferrocenyl alkene

```
\[ \text{Fe} \quad \text{O} \quad \text{Br} \quad \text{Et₃N} \quad \text{Fe} \quad \text{O} \quad \text{Br} \]
```

**Scheme 22.** Conversion of dibromo compound to α-bromo acryloyl ferrocene

By treating the dibromo compound 32 with anhydrous triethylamine, complete conversion to α-bromo acryloyl ferrocene 33 was achieved. Reaction proceeded in alkaline medium by simple HBr elimination (Scheme 22).
Aziridination of α-bromo compound 33 with chiral amino alcohol, (\(R\))-\((-\))-2 amino-1-butanol 36 resulted in two diastereomeric aziridine products 34 and 35 via Gabriel-Cromwell reaction (Scheme 23). These diastereomeric ferrocenyl aziridines were easily purified and separated by flash column chromatography on silica gel. Their colored appearance ease the visualization simply by naked eye and purification via flash column chromatography. As a result of this reaction, pure ferrocenyl aziridines were obtained in 50% and 45% yields, respectively.

### 2.2.4. Tosylation of ferrocenyl aziridinyl ketones

Aziridination of α-bromo compound 33 with chiral amino alcohol, (\(R\))-\((-\))-2 amino-1-butanol 36 resulted in two diastereomeric aziridine products 34 and 35 via Gabriel-Cromwell reaction (Scheme 23). These diastereomeric ferrocenyl aziridines were easily purified and separated by flash column chromatography on silica gel. Their colored appearance ease the visualization simply by naked eye and purification via flash column chromatography. As a result of this reaction, pure ferrocenyl aziridines were obtained in 50% and 45% yields, respectively.
In order to introduce phosphine group to our chiral ligands, conversion of hydroxyl group into better leaving group tosylate was required. To achieve this, alcohol derivatives of ferrocenyl aziridinyl ketones 34 and 35 were treated with tosylchloride in alkaline medium separately (Scheme 24). Corresponding tosylated ferrocenyl aziridinyl ketones 37 and 38 were obtained by addition-elimination reaction in 98% and 95% yields, respectively.

2.2.5. Phosphonylation of tosylated ferrocenyl aziridinyl ketones

For the synthesis of phosphino ferrocenyl aziridinyl ketones, tosylated compounds 37 and 38 were phosphonylated separately by following the procedure reported by Williams and co-workers [40]. Via this procedure, tosylate group was replaced with diphenylphosphine group via S_N_2 reaction. Corresponding products 39 and 41 were obtained in 68 % and 78% yields with their oxidized forms 40 (25 %) and 42 (20 %), respectively (Scheme 25).
2.2.6. Reduction of phosphonylated ferrocenyl aziridinyl ketones

Alcohol derivative of PFAM ligands 43-46 and their oxidized forms 47-50 were synthesized from their precursors 39 and 41 in moderate yields as shown in Scheme 26 via following the procedure reported by Yun and co-workers [41]. Absolute configurations of chiral PFAM ligands were assigned by making an analogy with the previously synthesized chiral FAM ligands. Ease of oxidation of phosphine group even by air makes isolation of 44 and 45 more difficult.

2.3. Asymmetric studies

Various metal salts and chiral ligands were tested for diethylzinc addition to N-sulphonyl and N-phosphinoyl arylaldimines by different groups. Among the metal salts, copper salts have advantages over the other transition metal salts as mentioned in introduction part. For this reason, we have used copper in testing the performance of our previously synthesized chiral phosphino ferrocenyl aziridinyl methanones (PFAM1-2) and phosphino ferrocenyl aziridinyl methanols (PFAM3-6) in diethylzinc addition to aldimes.


2.3.1. **Ligand screening studies**

![Chemical structure](image)

**Scheme 27.** Asymmetric diethylzinc addition to benzaldimine using **PFAM 1-2** and **PFAM 3-6** chiral ligands

For the ligand screening studies, keto (**PFAM 1-2**) and alcohol (**PFAM 3-6**) types of chiral ligands synthesized and purified previously were tested in reaction of enantioselective diethylzinc addition to N-sulphonyl and N-diphenylphosphinoyl arylaldimines. Ketone type **PFAM2** ligand gave the best result with 78% yield and 17% ee among six different chiral ligands (*Table 2, entry 2*). Although exact transition state is not known for this reaction, we proposed the possible transition state for this reaction as shown in *Figure 13*. Carbonyl oxygen and nitrogen in aziridine ring coordinated to Lewis acid EtZn which also had coordination with tosyl oxygens of N-sulphonyl arylaldimine. Phosphorous group of the ligand, on the other hand, was coordinated to CuEt where ethyl group transfer takes place selectively from the *si*-face of azomethine carbon. Though the proposed transition state is cyclic, due to low amount of copper salt it could be acyclic transition state.
Figure 13. Proposed 3D transition states for ethyl addition to aldimine

Table 2. Performance comparison of chiral ligands in corresponding reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand structures</th>
<th>Chiral ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>9</td>
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<tr>
<td>2</td>
<td><img src="image2.png" alt="Ligand 2" /></td>
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<td>17</td>
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<td><img src="image3.png" alt="Ligand 3" /></td>
<td>PFAM 3 (R, R, R)</td>
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<td>4</td>
</tr>
<tr>
<td>4</td>
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<td>PFAM 4 (S, R, R)</td>
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<td>n.d</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Ligand 5" /></td>
<td>PFAM 5 (S, S, R)</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Ligand 6" /></td>
<td>PFAM 6 (R, S, R)</td>
<td>28</td>
<td>4</td>
</tr>
</tbody>
</table>
2.3.2. Solvent screening studies

With the best performing ligand PFAM2, solvent screening studies were performed (Scheme 28). For this purpose, THF, DCM and 1,2-DCE were tested rather than toluene and results obtained were shown in Table 3 below. The highest enantioselectivity was obtained with toluene (Table 3, entry 4). The solvent effect on the yield of this reaction in absence of ligand is well documented in literature. In nonpolar solvents such as hexane and toluene, reduction product was obtained in high yields with trace amount of ethyl addition product at room temperature [43]. Therefore, we tested nonpolar solvents at lower temperatures.

In our conditions, toluene and 1,2-DCE were tested but hexane was not tested due to the solubility problem of ligand. The reaction in toluene gave the product with 78% yield and 17% ee. For the reactions in polar solvents such as DCM and THF, the yield of product was lower (Table 3, entries 1-2). Therefore, we proposed that non-polar solvents activated the diethylzinc and increased rate of formation of ethyl addition product. Although the yield obtained with 1,2-DCE was excellent (99%), the enantioselectivity was lower compared to toluene. As, polarity index of 1,2-DCE is 3.5 while it is 2.4 for toluene meaning 1,2-DCE was more polar compared to toluene.

Finally, it was decided to perform reaction in toluene which yielded the product with higher enantioselectivities via making diethylzinc activation better and maximizing the rate difference of catalyzed and background reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>1,2-DCE</td>
<td>99</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>78</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 3. Solvents tested in the corresponding reaction and their effects on yield and ee
2.3.3. Temperature and concentration screening studies

By using the best performing ligand and solvent, PFAM2 and toluene, temperature and concentration screening studies were performed (Scheme 29). When the temperature rised to 0 °C, product was formed in higher yields as expected but as a racemic mixture (Table 4, entry 1). Then, the temperature was decreased to -50 °C, it resulted in both decrease in yield and enantioselectivity (Table 4, entry 3). The reason for the change was interpreted to be based on collision theory. The rise in temperature causes the increase in kinetic energies of reactants and occurrence of high number of effective collisions resulted in higher yield. As the reaction rate increases, background reaction also takes place to form racemic product. Low enantioselectivity at low temperature, on the other hand, may result from the ineffective complexation of ligand and substrates with the metals at the transition state.

Subsequently, concentration effect on both yield and enantioselectivity was examined. Due to the same reasons mentioned for temperature effect, increase in temperature brought about the rise in yield while diminish in ee. In a similar way, reverse was true when the temperature was lowered (Table 4, entries 4-5). Finally, 0.2 M concentration and -20 °C temperature was chosen the best working conditions for this reaction.

Table 4. Temperature and molarity effects on corresponding reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Molarity</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.2</td>
<td>86</td>
<td>rac</td>
</tr>
<tr>
<td>2</td>
<td>-20</td>
<td><strong>0.2</strong></td>
<td><strong>78</strong></td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>-50</td>
<td>0.2</td>
<td>29</td>
<td>rac</td>
</tr>
<tr>
<td>4</td>
<td>-20</td>
<td>0.4</td>
<td>84</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>-20</td>
<td>0.1</td>
<td>52</td>
<td>6</td>
</tr>
</tbody>
</table>
2.3.4. Additive screening studies

\[
\begin{align*}
\text{N}^\text{Ts} & \quad + \quad \text{Et}_2\text{Zn} \quad \rightarrow \quad \text{HN}^\text{Ts} \\
& \quad \text{3.0 equiv.} \quad \text{PFAM 2 (10 mol\%)} \quad \text{Cu(OTf)}_2 \quad \text{Additive (20 mol\%)} \\
& \quad \text{-20 °C / Toluene}
\end{align*}
\]

Scheme 30. Circumstances in which the addive screening studies was performed

The aim of rapid catalytic cycle (Figure 14) via making decomplexation of Lewis acidic zinc complex easy, different bulky bases were used as additives in corresponding reaction with the optimized conditions (Scheme 31). For this purpose, diisopropyl ethylamine (DIPEA), triethylamine, hexamethylphosphoramide (HMPA), 1,4-diazabicyclo[2.2.2]octane (DABCO), methanol and tetramethylethylenediamine (TMEDA) were tested (Table 5). Among these additives, TMEDA was found to be the best performing additive by slightly decreasing yield but increasing the enantioselectivity (Table 5, entry 7). Further improvement in yield was achieved by the use of molecular sieves (MS) (Table 5, entry 8).

Table 5. Results of additive screening studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>78</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>DIPEA</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Et\textsubscript{3}N</td>
<td>59</td>
<td>rac</td>
</tr>
<tr>
<td>4</td>
<td>HMPA</td>
<td>58</td>
<td>rac</td>
</tr>
<tr>
<td>5</td>
<td>DABCO</td>
<td>74</td>
<td>rac</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>70</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>TMEDA</td>
<td>59</td>
<td>20</td>
</tr>
<tr>
<td>8\textsuperscript{a}</td>
<td>TMEDA</td>
<td>73</td>
<td>22</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction was carried out with 4 Å molecular sieves.
2.3.5. **Copper salt and amount screening studies**

![Scheme 31](image_url)

**Scheme 31.** Optimization studies with different copper salts and different amounts of reactants

Under the optimized reaction conditions reached so far, **Scheme 31**, copper salts and amount screening studies were performed. Since the enantioselective reaction proceeds via catalytic cycle basically based on transmetalation, type of the copper salt and its amount were significant for this reaction. Although exact catalytic cycle is not known, it seems to be that the reaction proceeds by the mechanism which is similar to the one for conjugate addition reactions. According to our proposed catalytic cycle, firstly, transmetalation takes place by transfer of ethyl group from Et₂Zn to CuOTf or Cu(OTf)₂ which has already complexed with chiral ligand. Then, the addition of ethyl group takes place to azomethine carbon of imine (**Figure 14**). Based on experimental results, increase in the amount of copper salt caused the rise in yield but decrease in ee (**Table 6, entry 2**). This result can be explained as the increase in the amount of copper salt increases the rate of background reaction. In other words, reaction was proceeded without participation of chiral ligand. When the amount of copper salt was reduced to 7 mol%, yield and ee was increased (**Table 6, entry 3**). Since the reaction is highly moisture sensitive, we wondered the impact of dryness of copper salt on both yield and ee. Therefore, copper salt was either benzene azeotroped or heated under vacuum by heat gun to remove moisture just before using. We observed sharp increase in ee up to 73% but slight decrease in yield to 56% (**Table 6, entries 4-5**). We interpreted this sharp increase as moisture deactivates both Et₂Zn and copper salt. Further decrease in the amount of copper salt caused sharp decrease in yield and slight decrease in ee (**Table 6, entry 6**). By replacing Cu(OTf)₂ with Cu(OAc)₂, the enantioselectivity decreased and yield increased slightly (**Table 6, entry 7**).
Figure 14. Catalytic cycle based on transmetallation

Table 6. Results of copper salt and amount screening studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper salt</th>
<th>Cu salt (mol %)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)$_2$</td>
<td>15</td>
<td>59</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)$_2$</td>
<td>30</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)$_2$</td>
<td>7</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>4$^a$</td>
<td>Cu(OTf)$_2$. Benzene</td>
<td>7</td>
<td>53</td>
<td>72</td>
</tr>
<tr>
<td>5$^b$</td>
<td>Cu(OTf)$_2$ (dried)</td>
<td>7</td>
<td>56</td>
<td>73</td>
</tr>
<tr>
<td>6$^b$</td>
<td>Cu(OTf)$_2$ (dried)</td>
<td>3,5</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>7$^b$</td>
<td>Cu(OAc)$_2$ (dried)</td>
<td>7</td>
<td>66</td>
<td>65</td>
</tr>
</tbody>
</table>

$^a$ Cu(OTf)$_2$ was benzene azeotroped.

$^b$ Cu(OTf)$_2$ was dried via heat gun
2.3.6. **Optimization studies at different amount of diethylzinc and ligand**

![Scheme 32](image)

For organometallic asymmetric reactions, the amount of ligand and metal is significant. Use of both of them at lower amounts is valuable and preferable. For this purposes, under optimum conditions (Scheme 32), we firstly tried to decrease the amount of Et₂Zn. When the amount of Et₂Zn was halved, the product was formed in same yield and slightly higher ee (Table 7, entry 2). Further decrease of diethylzinc resulted in sharp decrease in yield and ee (Table 7, entry 3). The reasons for this could be the decrease in Et₂Zn/Ligand ratio resulted in lower amount of ethyl source for addition and lower amount of Et₂Zn for complexation, respectively. Therefore, 1.5 equivalent of Et₂Zn was found to be the optimum amount for this reaction. Secondly, when the amount of ligand was halved, yield was increased up to 99% but ee was decreased sharply (Table 7, entry 4). Decrease in ee could be due to the same reason mentioned for Et₂Zn but increase in yield is because of the increase in rate of background reaction operating without ligand. Finally, increasing the amount of ligand affected both yield and ee negatively (Table 7, entry 5).

**Table 7. The impacts of diethylzinc and ligand amounts on yield and ee**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand equiv.</th>
<th>Et₂Zn equiv.</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>3.0</td>
<td>56</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td><strong>0.1</strong></td>
<td><strong>1.5</strong></td>
<td><strong>55</strong></td>
<td><strong>77</strong></td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>1.0</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>1.5</td>
<td>99</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>1.5</td>
<td>50</td>
<td>53</td>
</tr>
</tbody>
</table>
2.3.7. Reaction and diethylzinc addition time screening studies

In order to see the effect of time on yield and ee, reactions were carried out at different times. For the same reason, diethylzinc was also added at different times via syringe pump (Scheme 33). When reaction time was doubled, yield and ee both decreased with the formation of reduction product (Table 8, entry 2). By the decrease of the reaction time, since the reaction was not completed, yield was diminished sharply with slight decrease in ee (Table 8, entry 3). Dropwise addition of diethylzinc in 1h, product was formed in higher yield but lower ee. Lower yield can be attributed to the background reaction and lower ee can be the result of inadequate complexation time. Prolonged addition time provided almost the same yield with slight decrease in enantioselectivity (Table 8, entries 4-5). As a result of these studies, conditions mentioned in entry 1 were decided to be the best for this reaction.

When we changed the addition sequence of reagents, the product was obtained in lower yield but higher enantioselectivity. Under same conditions, increase in complexation time to 2 hours gave the product in low yield and ee (Table 8, entries 6-7).

After doing all these optimization studies, we decided to apply them to various arylaldimines.
Optimization studies based on reaction and Et₂Zn addition times

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time (h)</th>
<th>Et₂Zn addition time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>3</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>3</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>3</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>1</td>
<td>67</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>4.5</td>
<td>53</td>
<td>72</td>
</tr>
<tr>
<td>6a</td>
<td>21</td>
<td>3</td>
<td>42</td>
<td>81</td>
</tr>
<tr>
<td>7b</td>
<td>21</td>
<td>3</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

* a The order of addition of the reagents was Cu(OTf)₂-L-Et₂Zn (1 h mixing) followed by cooling of reaction mixture to -20 °C, TMEDA and dropwise addition of imine.
* b Same conditions with a were applied except prolonged complexation time to 2 h

2.3.8. Derivatization studies

![Scheme 34](image)

Scheme 34. Derivatization studies under optimized conditions

Derivatization studies were carried out under optimum conditions (Scheme 34). For this purpose, eight different derivatives of imines were synthesized from various aldehydes and amides. Firstly, p-methoxybenzylidene tosylimine 52, p-bromobenzylidene tosylimine 53, 1-naphthy tosylimine 54 and 2-naphyl tosylimine 55 were examined (Table 9, entries 2-5). Among these four arylaldimines, p-bromobenzylidene tosylimine gave the highest result with 50% yield and 56% ee (Table 9, entry 3).
This result revealed that tosylimines bearing electron withdrawing groups form the product in better enantioselectivity compared to the ones bearing electron donating groups. A simple explanation of this result is that the azomethine carbon of tosylimine is activated better by the phenyl ring bearing electron withdrawing groups resulted in higher ee compared to the ones bearing electron donating groups. On the other hand, among all tosylaldimines, N-benzyllidine tosylaldimine gave the best enantioselectivity (Table 9, entry 1).

Secondly, N-benzyllidine diphenylphosphinoylimine 56 and its derivatives 2-naphtyl diphenylphosphinoylimine 57, p-bromobenzyllidine diphenylphosphinoylimine 58, p-methoxybenzylidine diphenylphosphinoylimine 59 were also tested in corresponding reaction under same conditions. On contrary to tosyl aryldimines, products were obtained in trace amounts except the one derived from 2-naphtyl diphenylphosphinoylimine giving the product in 50% yield and 52% ee (Table 9, entry 6). The reason for the much lower yield could be that the experimental conditions which were not optimized specifically for the phosphinoyl aryldimines as in literature, most of the groups were studied either sulphonylimines or phosphinoylimines under totally different reaction conditions.

Table 9. Derivatives of imines tested in corresponding reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Yields (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (51)</td>
<td>Ts</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC_6H_4 (52)</td>
<td>Ts</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC_6H_4 (53)</td>
<td>Ts</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>1-naphtyl (54)</td>
<td>Ts</td>
<td>60</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>2-naphtyl (55)</td>
<td>Ts</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>2-naphtyl (57)</td>
<td>Ph_2PO</td>
<td>50</td>
<td>52</td>
</tr>
</tbody>
</table>
CHAPTER 3

CONCLUSION

Due to the significance of chiral amines as building blocks of many biologically active compounds, the development of new catalyst system producing chiral amines in high enantioselectivities has been essential. For this purpose, many studies have been conducted in literature to produce chiral amine building blocks in mild conditions.

In this study, previously synthesized PFAM ligands were tested in asymmetric diethylzinc addition to N-sulphonyl and N-phosphinoyl arylaldimines. For this purpose, firstly chiral ligands and corresponding imines were synthesized. It was difficult to synthesize pure imines due to their high sensitivity to moisture and silica gel. This study facilitated the improvement of the yield of the N-benzylidene sulphonylimine (98%) via modifying the procedure mentioned in literature. For the diethylzinc addition to aldimines under optimized reaction conditions, the highest enantioselectivity and yield were obtained by PFAM2 ligand. It was also found that the amount of copper salt is important. At higher amounts, yields are good but ee’s are low. At low concentration of copper, yield is low but ee is high. Clearly, at higher concentration of copper, background reaction is taking place considerably. Derivatization studies using various kinds of N-sulphonyl and N-diphenylphosphinoyl arylaldimines were also conducted. Sulphonylimines formed the product in acceptable yield but moderate ee except benzaldehyde which formed the product in good ee (being highest 81%). In the case of phosphinoyl arylaldimines, only 2-naphtyl derivative gave acceptable results, the others formed the product in very low yields. These results showed that the reaction conditions should be optimized for N-sulphonyl and N-phosphinoyl arylaldimines individually which is planned as the future work.
CHAPTER 4

EXPERIMENTAL

4.1. Generalities

4.1.1. General procedures

All reactions were carried out in flame dried glasswares under reduced pressure and charged with argon or nitrogen unless otherwise stated. Air and moisture-sensitive imines and chiral phosphorous containing ligands stored under inert atmosphere. They were transferred via syringe to reactor after dissolved in reaction solvent under inert medium. Commercial copper salts, Cu(OAc)$_2$ and Cu(OTf)$_2$ were benzene-azetroped or dried under vacuum via heating gun before to use. During the work-up procedure for the synthesis of derivatives of imines, TiO$_2$ was filtered through the Celite pad (Merck Celite 545) and washed with dichloromethane. They were further purified by recrystallization with proper dry mixture of solvents if needed. Ethyl addition products were purified via flash column chromatography on silica gel (E. Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). TLC analyses were performed on 250µm Silica Gel 60 F$_{254}$ plates. Spots indicating the product were visualized either by UV florescence at 254 nm or via using phosphomolybdic acid in ethanol as the coloring agent. Racemic compounds were prepared using EtMgBr in the absence of chiral ligand.

4.1.2. Materials

Solvents were dried with standard procedures and degassed with nitrogen. Aldehydes and amides used in preparation of imines were either distilled with proper reagents or dried under vacuum by heating before to use. Dichloromethane (DCM) and 1,2 dichloroethane (DCE) were distilled and dried over calcium hydride prior to use. Toluene was dried with sodium and charged with nitrogen. Tetrahydrofurane (THF) was dried over Na and benzophenone prior to use. Tetramethylethylenediamine (TMEDA) was distilled over sodium under vacuum and stored with potassium hydroxide pellets under inert atmosphere. N,N-diisopropylethylamine (DIPEA) was distilled under reduced pressure and stored over molecular sieves. Triethylamine (Et$_3$N) and diisopropylethylamine (Pr$_2$NET) were distilled and kept over NaOH pellets under Ar or N$_2$. 1,4-Diazabicyclo[2.2.2]octane (DABCO) was dried with benzene azetotropy prior to use. 4 Å molecular sieves were activated at high temperature just before the use.
4.1.3. Instrumentation

Enantiomeric excess of addition products were determined by chiral HPLC. Retention times were consistent with the literature but confirmed by the analysis of the racemic products. \(^1\)H- and \(^{13}\)C-NMR spectra were reported on a Brucker spectrospin Avance DPX-400 Ultra shield instrument at 400 MHz. \(^1\)H-NMR data are reported as chemical shifts (δ, ppm) relative to tetramethyldisilane (δ 0.00) with multiplicity (s = singlet, br = broad singlet, d = doublet, dd = doublet of doublet, ddd = doublets of doublets of doublet, dq = doublet of quartet, t = triplet, q = quartet, dt = doublet of triplet, p = pentet, sx = sextet, m = multiplet), coupling constant (Hz) and integration. \(^1\)H-NMR and \(^{13}\)C-NMR data are reported as chemical shifts. NMR samples were prepared in 1:1 CDCl\(_3\) solution. To measure optical rotations, Rudolph Research Analytical Autopol III Polarimeter was used. Measurements was performed in 1 dm cell and reported as [α]\(^{21}\)\(_D\) (c in 2.5 mg/mL solvent). For short term reactions performed at 0°C, reactor was placed in water-ice bath. For overnight reactions at -20°C and -50°C, reaction flask was placed in an ethanol or isopropanol bath cooled by cryostat (HAAKE EK90). Dropwise additions were performed by using syringe pump (New Era NE-300).

4.2. Imine synthesis

4.2.1. Synthesis of N-benzylidene-4-methylbenzenesulfonamide via Dean-Stark procedure

\[
\text{[Image of chemical structure]}
\]

Under inert atmosphere, \(p\)-toluenesulfonamide (29.2 mmol, 5.0 g) and benzaldehyde (35.04 mmol, 3.72 g) were dissolved in dry toluene (20.0 mL). Addition of 1-2 crystals of TsOH was followed by continuous reflux at boiling temperature of toluene during 2 hours. After 2 hours, \(^1\)H-NMR analysis of aliquot taken from reaction mixture indicated the complete conversion to product. Solvent was removed under vacuum and product was benzene azeotroped. Pure N-benzylidene-4-methylbenzenesulfonamide 20 was obtained in 98% yield as white solid. \(^1\)H-NMR (400 MHz) δ 9.04 (s, 1H), 7.94-7.89 (m, 4H), 7.63 (t, \(J = 7.66\) Hz, 1H), 7.49 (t, \(J = 7.90\) Hz, 2H), 7.35 (d, \(J = 7.90\) Hz, 2H), 2.44 (s, 3H). \(^{13}\)C-NMR (100 MHz) δ 170.6, 140.5, 135.4, 133.5, 131.7, 130.3, 130.2, 129.6, 128.5, 22.1.
4.2.2. Synthesis of derivatives of N-arylmethylsulfonamides and N-aryl(diphenyl)phosphinoylamides via using titanium tetrachloride

To ice-cooled solution of aldehyde (2.92 mmol, 1.0 equiv.), sulphonamide (2.92 mmol, 1.0 equiv.) and dry NEt$_3$ (8.96 mmol, 3.07 equiv.) in dry dichloromethane (10.0 mL), titanium tetrachloride (1.46 mmol, 1.61 mL) was added dropwise. The mixture was stirred during 2 hours at 0 °C (except for 21 that was stirred at room temperature during 4 hours). TiO$_2$ formed throughout reaction was removed by suction filtration through Celite using DCM as an eluent. Evaporation of DCM resulted in the solid mixture of the imine and triethylamine hydrochloride salt. To remove triethylamine hydrochloride salts were stirred with dry toluene (15 mL) for about 15 minutes and suction filtrated. Concentration of filtrate gave the corresponding imine product in moderate to high yields.

4.2.2.1. N-(4-methoxybenzylidene)-4-methylbenzenesulfonamide

The crude product 21 was precipitated from DCM with hexane for purification. Pure product was obtained as white crystalline solid (2.76 mmol, 0.80 g) in 95% yield. $^1$H-NMR (400 MHz) δ 8.95 (s, 1H), 7.88 (m, 2H), 7.33 (d, $J = 7.3$ Hz, 2H), 6.97 (d, $J = 8.1$ Hz, 2H), 3.89 (s, 3H), δ 2.43 (s, 3H); $^{13}$C-NMR (100 MHz) δ 169.2, 165.4, 133.7, 129.6, 127.9, 125.5, 114.7, 55.7, 21.5. All the data are consistent with the literature [35].

4.2.2.2. N-(4-bromobenzylidene)-4-methylbenzenesulfonamide

The crude product 22 was precipitated from DCM with hexane for purification. Product (1.18 mmol, 0.40 g) was obtained in 60% yield as a white solid. $^1$H-NMR (400 MHz) δ 8.98 (s, 1H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.5$ Hz, 2H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.36 (d, $J = 8.3$ Hz, 2H), 2.45 (s, 3H); $^{13}$C-NMR (100 MHz) δ 172.6, 132.6, 132.3, 130.3, 130.0, 129.5, 128.1, 129.6, 128.5, 21.5. All the data are consistent with the literature [35].
4.2.2.3. \(N\)-(1-naphthylmethylene)-4-methylbenzenesulfonamide

The crude product 23 was precipitated from DCM with petroleum ether for purification. Product was obtained as a light yellow solid (2.26 mmol, 0.70 g) in 79% yield. \(^1\)H-NMR (400 MHz) \(\delta\) 9.62 (s, 1H), 8.14 (dd, \(J=21.5\ Hz, J=8.4\ Hz\), 2H), 7.95 (m, 3H), 7.65 (m, 4H), 7.33 (dd, \(J=20.1\ Hz, J=8.2\ Hz\), 2H), 2.44 (s, 3H); \(^13\)C-NMR (100 MHz) \(\delta\) 170.0, 136.1, 135.4, 135.0, 133.9, 129.8, 129.1, 128.9, 128.0, 127.7, 126.9, 126.5, 125.1, 124.9, 124.3, 21.5. All the data are consistent with the literature [35].

4.2.2.4. \(N\)-(2-naphthylmethylene)-4-methylbenzenesulfonamide

The crude product 24 was precipitated from DCM with petroleum ether as light yellow powder. The product was further purified by performing recrystallization with chloroform and hexane. Pure imine was obtained as yellow needles (1.94 mmol, 0.60 g) in 66% yield. \(^1\)H-NMR (400 MHz) \(\delta\) 9.18 (s, 1H), 8.34 (s, 1H), 8.0 (d, \(J=8.8\ Hz, 1H\)), 7.9 (m, 6H), 7.61 (dt, \(J=25.7\ Hz, J=7.7\ Hz\), 2H), 2.44 (s, 3H); \(^13\)C-NMR (100 MHz) \(\delta\) 170.0, 136.1, 135.1, 134.9, 133.9, 129.8, 128.9, 128.0, 127.6, 127.4, 126.8, 126.4, 125.1, 124.7, 124.1, 21.6. All the data are consistent with the literature [35].

4.2.2.5. \(N\)-benzylidene-\(P,P\)-diphenylphosphinic amide

The crude product 25 was precipitated from DCM with hexane for purification. The product was obtained as a white solid (2.52 mmol, 0.77 g) in 60% yield. \(^1\)H-NMR (400 MHz) \(\delta\) 9.33 (d, \(J=34.2\ Hz, 1H\)), 8.10-7.90 (m, 6H), 7.56-7.41 (m, 9H); \(^13\)C-NMR (100 MHz) \(\delta\) 174.1, 136.1, 134.0, 133.8, 133.6 133.2, 132.5, 131.7, 130.2, 128.9, 128.4. All the data are consistent with the literature [35].
4.2.2.6. *N-(4-bromobenzylidene)-P,P-diphenylphosphinic amide*

The crude product 26 was precipitated from DCM with hexane for purification. The product was obtained as a white solid (1.46 mmol, 0.56 g) in 63% yield. \(^1\)H-NMR (400 MHz) δ 9.28 (d, \(J = 34.6\) Hz, 1H), 7.98-7.85 (m, 6H), 7.62 (m, 2H), 7.53-7.43 (m, 7H); \(^{13}\)C NMR (100 MHz) δ 172.4, 132.6, 132.3, 131.9, 131.6, 131.5, 131.4, 131.3, 128.7, 128.5, 128.4, 126.8. All the data are consistent with the literature [35].

![N-(4-bromobenzylidene)-P,P-diphenylphosphinic amide](image)

4.2.2.7. *N-(2-naphthylmethylene)-P,P-diphenylphosphinic amide*

The crude product 27 was recrystallized from benzene for purification. The product was obtained as a colorless powder (0.62 mmol, 0.22 g) in 28% yield. \(^1\)H-NMR (400 MHz) δ 9.47 (d, \(J = 33.0\) Hz, 1H), 8.34 (s, 1H), 8.22 (d, \(J = 8.5\) Hz, 1H), 8.02-7.88 (m, 7H), 7.64-7.54 (m, 2H), 7.53-7.43 (m, 6H); \(^{13}\)C-NMR (100 MHz) δ 173.8, 136.0, 134.2, 133.7, 133.0, 132.8, 132.0 131.8, 129.4, 128.9, 128.7, 128.5, 128.4, 127.0, 123.7. All the data are consistent with the literature [35].

![N-(2-naphthylmethylene)-P,P-diphenylphosphinic amide](image)

4.2.2.8. *N-(4-methoxybenzylidene)-P,P-diphenylphosphinic amide*

The crude product 28 was recrystallized from hexane by DCM for purification. The product was obtained as a colorless powder (1.37 mmol, 0.460 g) in 60% yield. \(^1\)H-NMR (400 MHz) δ 9.23 (d, \(J = 32.3\) Hz, 1H), 7.99-7.90 (m, 6H), 7.51-7.41 (m, 6H), 6.99 (d, \(J = 8.83\) Hz, 2H), 3.88 (s, 3H); \(^{13}\)C-NMR (100 MHz) δ 171.3, 171.2, 162.8, 132.6, 131.4, 130.9, 130.5, 130.4, 130.2, 130.1, 127.1, 126.9, 112.9, 54.1. All the data are consistent with the literature [35].

![N-(4-methoxybenzylidene)-P,P-diphenylphosphinic amide](image)
4.2.3. Chiral Ligand Synthesis and Characterization

4.2.3.1. Synthesis of acryloyl ferrocene

Acryloyl ferrocene 31 was synthesized by following the procedure given in literature [42].
$^1$H-NMR (400 MHz) $\delta$ 6.80 (dd, $J = 17.0$ Hz, $J = 10.3$ Hz, 1H), 6.42 (d, $J = 16.6$ Hz, 1H), 5.70 (d, $J = 10.0$ Hz, 1H), 4.80 (s, 2H), 4.55 (s, 2H), 4.16 (s, 5H).

4.2.3.2. Bromination of acryloyl ferrocene

Dibromo compound 32 was synthesized by following the procedure given in literature [42].
$^1$H-NMR (400 MHz) $\delta$ 4.79 (s, 1H), 4.68 (s, 1H), 4.61 (s, 1H), 4.34 (s, 5H), 4.23 (m, 1H), 3.76 (dd, $J = 9.8$ Hz, $J = 3.8$ Hz, 1H).
4.2.3.3. Synthesis of aziridino ketones

The aziridino ketones 34 and 35 were synthesized by following the procedure given in literature [42].

**34**: \(^1\)H-NMR (400 MHz) δ 4.92 (s, 1H), 4.84 (s, 1H), 4.51 (s, 2H), 4.21 (s, 5H), 3.75 (br, 2H), 2.68 (br, 1H), 2.32 (s, 1H), 2.23 (br, 1H) 1.66 (m, 4H), 0.98 (t, \(J = 7.2\) Hz, 3H); **35**: \(^1\)H-NMR (400 MHz) δ 4.82 (d, \(J = 12.97\) Hz, 2H), 4.46 (s, 2H), 4.14 (s, 5H), 3.68 (br, 2H), 2.49 (br, 1H), 2.26 (s, 1H), 2.14 (br, 1H), 1.79 (br, 1H), 1.67 (m, 1H), 1.57 (m, 1H), 1.45 (br, 1H), 0.93 (t, \(J = 7.25\) Hz, 3H).

4.2.3.4. Synthesis of tosylated aziridino ketone from aziridine 37

Tosylated product 37 was synthesized by following the procedure given in literature [42]. \(^1\)H-NMR (400 MHz) δ 7.63 (d, \(J = 8.1\) Hz, 2H), 7.22 (d, \(J = 8.0\) Hz, 2H), 5.02 (s, 1H), 4.87 (s, 1H), 4.56 (s, 2H), 4.20 (s, 5H), 4.14 (dd, \(J = 3.8\) Hz, \(J = 10.1\) Hz, 1H), 3.98 (dd, \(J = 7.7\) Hz, \(J = 10.0\) Hz, 1H), 2.82 (q, \(J = 3.1\) Hz, 1H), 2.39 (s, 3H, CH\(_3\)), 2.30 (s, 1H), 1.86 (m, 1H), 1.70 (d, \(J = 6.4\) Hz, 1H), 1.61 (m, 2H), 0.98 (t, \(J = 7.5\) Hz, 3H).
4.2.3.5. Synthesis of tosylated aziridino ketone from aziridine 38

![Tosylated ferrocenyl aziridino ketone 38](image)

Tosylated ferrocenyl aziridino ketone 38 was synthesized by following the procedure given in literature [42]. $^1$H-NMR (400 MHz) $\delta$ 7.80 (d, $J$ = 8.15 Hz, 2H), 7.35 (d, $J$ = 7.6 Hz, 2H), 4.86 (s, 2H), 4.51 (s, 2H), 4.17 (s, 5H), 4.11 (d, $J$ = 5.7 Hz, 2H), 2.51 (dd, $J$ = 3.0 Hz, $J$ = 6.4 Hz, 1H), 2.45 (s, 3H, CH$_3$), 2.22 (s, 1H), 1.91 (d, $J$ = 6.6 Hz, 1H), 1.83 (p, $J$ = 5.7 Hz, 1H), 1.59 (m, 2H), 0.95 (t, $J$ = 7.3 Hz, 3H).

4.2.3.6. Synthesis of phosphino aziridine 39 and phosphineoxy aziridine 40 from 37

![Phosphino aziridine 39 and phosphineoxy aziridine 40](image)

The phosphino aziridine 39 and its oxidized form 40 were synthesized by following the procedure given in literature [42]. 39: $^1$H-NMR (400 MHz) $\delta$ 7.34 (m, 4H), 7.23 (m, 6H), 4.77 (s, 2H), 4.43 (s, 2H), 4.08 (s, 5H), 2.32 (t, $J$ = 7.5 Hz, 2H), 2.27 (d, $J$ = 7.1 Hz, 1H), 1.74 (sx, $J$ = 7.2 Hz, 2H), 1.65 (d, $J$ = 6.6 Hz, 1H), 1.38 (sx, $J$ = 5.8 Hz, 1H), 0.94 (t, $J$ = 7.4 Hz, 3H); 40: $^1$H-NMR (400 MHz) $\delta$ 7.65 (m, 4H), 7.39 (m, 4H), 7.28 (m, 2H), 5.00 (s, 1H), 4.77 (s, 1H), 4.41 (s, 2H), 4.05 (s, 5H), 2.95 (dd, $J$ = 2.8 Hz, $J$ = 3.1 Hz, 1H), 2.51 (m, 2H), 2.31 (s, 1H), 2.04 (m, 1H), 1.81 (d, $J$ = 6.1 Hz, 1H), 1.61 (m, 1H), 1.53 (m, 1H), 0.82 (t, $J$ = 7.4 Hz, 3H).
4.2.3.7. Synthesis of phosphino aziridine \(41\) and phosphineoxy aziridine \(42\) from \(38\)

Phosphino aziridine \(41\) and its oxidized form \(42\) were synthesized by following the procedure given in literature [42]. \(41\): \(^1\)H-NMR (400 MHz) \(\delta\) 7.45 (m, 4H), 7.34 (m, 6H), 4.84 (s, 2H), 4.50 (s, 2H), 4.19 (s, 5H), 2.44 (m, 3H), 2.19 (s, 1H), 1.81 (p, \(J = 7.2\) Hz, 2H), 1.61 (d, \(J = 6.7\) Hz, 1H), 1.51 (sx, \(J = 6.3\) Hz, 1H), 1.01 (t, \(J = 7.4\) Hz, 3H); \(42\): \(^1\)H-NMR (400 MHz) \(\delta\) 7.86 (m, 2H), 7.75 (m, 2H), 7.50 (m, 6H), 4.82 (s, 2H), 4.51 (s, 2H), 4.17 (s, 5H), 2.67 (m, 2H), 2.60 (dd, \(J = 2.7\) Hz, \(J = 6.3\) Hz, 1H), 2.15 (septet, \(J = 5.5\) Hz, 1H), 1.90 (s, 1H), 1.83 (d, \(J = 6.7\) Hz, 1H), 1.69 (p, \(J = 7.3\) Hz, 2H). 0.94 (t, \(J = 7.4\) Hz, 3H).

4.2.3.8. Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols (\(R, R, R\)) from \(39\)

Phosphorous ferrocenyl aziridinyl methanol \(43\) and its oxidized form \(47\) were synthesized by following the procedure given in literature [42]. \(43\): \(^1\)H-NMR (400 MHz) \(\delta\) 7.34 - 7.23 (m, 10H), 4.29 (d, \(J = 4.3\) Hz, 1H), 4.19 (s, 1H), 4.16 (s, 1H), 4.11 (s, 5H), 4.08 (s, 1H), 2.46 (br, 1H), 2.09 (ddd, \(J = 7.7\) Hz, \(J = 6.3\) Hz and \(J = 5.1\) Hz, 2H), 1.81 (d, \(J = 3.3\) Hz, 1H), 1.66 (sx, \(J = 6.2\) Hz, 1H), 1.59 (sx, \(J = 7.1\) Hz, 1H), 1.53 (m, 1H), 1.33 (sx, \(J = 7.5\) Hz, 1H), 1.23 (d, \(J = 6.4\) Hz, 1H), 0.89 (t, \(J = 7.4\) Hz, 3H); \(47\): \(^1\)H-NMR (400 MHz) \(\delta\) 7.57 (q, \(J = 7.4\) Hz, 4H), 7.43-7.37 (m, 6H), 4.23 (s, 1H), 4.18 (s, 1H), 4.14 (s, 5H), 4.11 (s, 2H), 3.97 (s, 1H), 2.50 (br, 1H), 2.32-2.13 (m, 2H), 1.81 (s, 1H), 1.66 (m, 1H), 1.33 (d, \(J = 6.3\) Hz, 2H), 1.23 (d, \(J = 6.2\) Hz, 1H), 1.19 (s, 1H), 0.84 (t, \(J = 7.4\) Hz, 3H).
4.2.3.9. Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols ($S, R, R$) from 39

PFAM 44 and its oxidized form POFAM 48 were synthesized by following the procedure given in literature [42]. 44: $^1$H-NMR (400 MHz) $\delta$ 7.34 (m, 4H), 7.25 (m, 6H), 4.23 (s, 1H), 4.12 (s, 5H), 4.10 (s, 1H), 2.15 (s, 1H), 1.72 (d, $J = 3.2$ Hz, 1H), 1.59 (m, 1H), 1.52 (p, $J = 7.3$ Hz, 1H), 1.40 (q, $J = 6.0$ Hz, 1H), 1.27 (d, $J = 6.4$ Hz, 1H), 1.19 (m, 1H), 0.88 (t, $J = 7.3$ Hz, 3H); 48: $^1$H-NMR (400 MHz) $\delta$ 7.64 (dd, $J = 10.7$ Hz and $J = 4.7$ Hz, 4H), 7.41 (m, 6H), 4.24 (s, 1H), 4.17 (s, 1H), 4.13 (s, 1H), 4.07 (s, 2H), 3.90 (d, $J = 6.0$ Hz, 1H), 2.55 (m, 1H), 2.37 (m, 1H), 1.70 (br, 1H), 1.55 (m, 2H), 1.29 (d, $J = 7.1$ Hz, 2H), 1.20 (s, 1H), 0.81 (t, $J = 7.0$ Hz, 3H).

4.2.3.10. Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols ($S, S, R$) from 41

PFAM 45 and its oxidized form POFAM 49 were synthesized by following the procedure given in literature [42]. 45: $^1$H-NMR (400 MHz) $\delta$ 7.35 (m, 4H), 7.23 (m, 6H), 4.39 (s, 1H), 4.12 (s, 5H), 4.08 (s, 2H), 4.05 (s, 1H), 2.57 (s, 1H), 2.26 (d, $J = 6.4$ Hz, 2H), 1.60 (m, 4H), 1.44 (sx, $J = 6.1$ Hz, 1H), 1.09 (d, $J = 6.2$ Hz, 1H), 0.86 (t, $J = 7.3$ Hz, 3H); 49: $^1$H-NMR (400 MHz) $\delta$ 7.75 (dd, $J = 10.5$ Hz and $J = 3.5$ Hz, 2H), 7.67 (dd, $J = 10.3$ Hz and $J = 3.6$ Hz, 2H), 7.40 (m, 6H, Ph), 4.48 (s, 1H), 4.17 (s, 1H), 4.11 (s, 1H), 4.08 (s, 5H), 4.05 (s, 1H), 4.03 (s, 1H), 2.54 (m, 2H), 1.98 (p, $J = 5.4$ Hz, 2H), 1.78 (br, 1H), 1.54 (m, 2H), 1.23 (d, $J = 6.2$ Hz, 1H), 1.05 (d, $J = 6.0$ Hz, 1H), 0.80 (t, $J = 7.4$ Hz, 3H).
4.2.3.11. Synthesis of phosphino and phosphineoxy ferrocenyl aziridinyl methanols \((R, S, R)\) from 41

![Structures of PFAM 46 and POFAM 50](image)

PFAM 46 and its oxidized form POFAM 50 were synthesized by following the procedure given in literature [42]. 46: \(^1\)H-NMR (400 MHz) \(\delta\) 7.37 (s, 4H), 7.23 (s, 6H), 4.15 (s, 1H), 4.09 (s, 5H), 4.05 (s, 3H), 3.93 (d, \(J = 5.1\) Hz, 1H), 2.29 (m, 3H), 1.57 (t, \(J = 7.3\) Hz, 2H), 1.54 (s, 2H), 1.32 (m, 1H), 1.18 (d, \(J = 6.0\) Hz, 1H), 0.87 (t, \(J = 7.3\) Hz, 3H); 50: \(^1\)H-NMR (400 MHz) \(\delta\) 7.82 (dd, \(J = 7.4\) Hz and \(J = 3.3\) Hz, 2H), 7.73 (dd, \(J = 7.0\) Hz and \(J = 3.3\) Hz, 2H), 7.46 (ddd, \(J = 7.6\) Hz, \(J = 8.5\) Hz and \(J = 3.7\) Hz, 6H), 4.22 (s, 1H), 4.15 (s, 5H), 4.10 (s, 3H), 3.93 (d, \(J = 5.8\) Hz), 2.65 (br, 1H), 2.56 (q, \(J = 5.9\) Hz, 2H), 1.97 (p, \(J = 6.6\) Hz, 1H), 1.71 (ddd, \(J = 3.7\) Hz, \(J = 2.6\) Hz and \(J = 3.4\) Hz, 1H), 1.50 (p, \(J = 7.1\) Hz, 2H), 1.45 (d, \(J = 6.6\) Hz, 1H), 1.31 (d, \(J = 3.4\) Hz, 1H), 0.89 (t, \(J = 7.3\) Hz, 3H).

4.2.4. Asymmetric trials

4.2.4.1. General procedures for asymmetric diethylzinc addition to Arylaldimines

4.2.4.1.1. Optimized procedure A

In a 10 mL flame-dried reactor purged with nitrogen, Cu(OTf)$_2$ (7.0 mg, 0.020 mmol), 4 Å molecular sieves were added and dried under reduced pressure via heating. Toluene (3.5 mL) was added at room temperature. Then, chiral ligand 41 (13.0 mg, 0.026 mmol) was dissolved in toluene (0.5 mL) and reaction was stirred during 1 h at room temperature. After 1 h, imine (68.0 mg, 0.230 mmol) and TMEDA (8.0 μL, 0.04 mmol) were added respectively. After complete dissolution of imine, reaction mixture was cooled to -20 °C. Et$_2$Zn in 1.1 M toluene (0.47 mL, 0.34 mmol) was added dropwise in regular time interval during 3 h and reaction mixture was stirred overnight. Reaction was quenched with saturated NH$_4$Cl aqueous solution (4.0 mL). Organic phase was extracted two times with DCM (2 x 10.0 mL) and combined organic phase was dried over Na$_2$SO$_4$. Crude product was purified by flash column chromatography on silica gel by using 10:1 pentane-acetone eluent system. The pure product was obtained in moderate to good yields.
4.2.4.1.2. Optimized procedure B

In a 10 mL flame-dried schlenk tube purged with nitrogen, Cu(OTf)$_2$ (7.0 mg, 0.020 mmol), 4 Å molecular sieves were added and dried under reduced pressure via heating. Then, toluene (3.0 mL) and Et$_2$Zn (0.47 mL, 0.34 mmol), used from 1.1 M solution in toluene, were added respectively and reaction mixture was stirred for 1 h at room temperature. At the end of this period, TMEDA (8.0 µL, 0.04 mmol) was added and reaction mixture was cooled to -20 °C. Imine (68.0 mg, 0.230 mmol) was dissolved in toluene (1.0 mL) and added dropwise via syringe pump to the reaction mixture during 3 h. After stirring overnight, it was quenched with saturated NH$_4$Cl aqueous solution (4.0 mL). Aqueous phase was extracted two times with DCM (2 x 10.0 mL) and combined organic phase was dried over Na$_2$SO$_4$. Crude product was purified by flash column chromatography on silica gel by using 10:1 pentane-acetone eluent system.

The addition product was obtained in lower yields by following procedure B. The procedure A provided us to get products in higher yields with slight loss of ee. For this reasons, derivatization studies were performed by this procedure.

4.2.4.1.2.1. N-[1-phenylpropan-1-yl]-4-methylbenzenesulfonamide

Using procedure A 51 was obtained in 56% yield (27.0 mg, 0.09 mmol) and 77% ee. R$^=$ 0.40 (Pentan/Acetone= 5/1, colored black with phosphomolybdc acid in ethanol); white crystalline solid. Same compound was also synthesized by using procedure B in 42% yield and 81% ee determined by HPLC (Daicel Chiralcel OD column, UV detection at 254 nm, hexane/iPrOH= 10/1, 0.7 mL/min) t$^R$ = 29.8 min (R, minor) and 34.4 min (S, major); [α]$^D_{21}$ = -7.6 (c 0.25, CH$_2$Cl$_2$) for 43% ee (S). $^1$H-NMR (400 MHz) δ 7.54 (d, J= 7.9 Hz, 2H), 7.13 (d, J= 7.4 Hz, 2H), 6.92 (d, J= 7.9 Hz, 2H), 6.68 (d, J= 8.2 Hz, 2H), 4.69 (d, J= 7.0 Hz, 1H), 4.13 (q, J= 7.2 Hz, 1H), 3.74 (s, 3H), 2.37 (s, 3H), 1.74 (dq, J= 45.4 Hz, J= 8.3 Hz, 2H), 0.76 (t, J= 7.2 Hz, 3H); $^{13}$C-NMR (100 MHz) δ 142.9, 132.8, 129.2, 127.7, 127.2, 114.8, 113.7, 59.6, 55.3, 30.5, 21.4, 10.4. All the data are consistent with the literature [27].

4.2.4.1.2.2. N-[1-(4-methoxyphenyl)propan-1-yl]-4-methylbenzenesulfonamide

Using procedure B 52 was obtained in 43% yield (29.0 mg, 0.09 mmol); ee 43% (Daicel Chiralcel OD-H column, UV detection at 254 nm, hexane/iPrOH= 10/1, 0.6 mL/min) t$^R$ = 29.8 min (R, minor) and 34.4 min (S, major); [α]$^D_{21}$ = -7.6 (c 0.25, CH$_2$Cl$_2$) for 43% ee (S). $^1$H-NMR (400 MHz) δ 7.54 (d, J= 7.9 Hz, 2H), 7.13 (d, J= 7.4 Hz, 2H), 6.92 (d, J= 7.9 Hz, 2H), 6.68 (d, J= 8.2 Hz, 2H), 4.69 (d, J= 7.0 Hz, 1H), 4.13 (q, J= 7.2 Hz, 1H), 3.74 (s, 3H), 2.37 (s, 3H), 1.74 (dq, J= 45.4 Hz, J= 8.3 Hz, 2H), 0.76 (t, J= 7.2 Hz, 3H); $^{13}$C-NMR (100 MHz) δ 142.9, 132.8, 129.2, 127.7, 127.2, 114.8, 113.7, 59.6, 55.3, 30.5, 21.4, 10.4. All the data are consistent with the literature [27].
4.2.4.1.2.3. N-[1-(4-bromophenyl)propan-1-yl]-4-methylbenzenesulfonamide

R$_f$ = 0.41 (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, 50% yield (30.0 mg, 0.10 mmol); ee 56% (Daicel Chiralpak AS-H column, UV detection at 254 nm, hexane/PrOH= 75/25, 0.7 mL/min) $t_b = 30.7$ min ($R$, minor) and 54.8 min ($S$, major); $[\alpha]_D^{21} = -20.9$ (c 0.25, CH$_2$Cl$_2$) for 56% ee ($S$). $^1$H-NMR (400 MHz) $\delta$ 7.49 (d, $J = 7.9$ Hz, 2H), 7.26 (d, $J = 7.3$ Hz, 2H), 7.13 (d, $J = 7.9$ Hz, 2H), 6.88 (d, $J = 7.3$ Hz, 2H), 4.80 (d, $J = 7.0$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 1H), 2.38 (s, 3H), 1.70 (dq, $J = 45.0$ Hz, $J = 7.6$ Hz, 2H), 0.78 (t, $J = 7.5$ Hz, 3H); $^{13}$C-NMR (100 MHz) $\delta$ 141.2, 131.4, 129.3, 128.4, 126.9, 121.2, 59.2, 30.3, 21.4, 10.4. All the data are consistent with the literature [27].

4.2.4.1.2.4. N-[1-(1-naphthymethylene)propan-1-yl]-4-methylbenzenesulfonamide

$R_f$ = 0.52 (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, 60% yield (51.0 mg, 0.15 mmol); ee 26% (Daicel Chiralpak AD column, UV detection at 254 nm, hexane/PrOH= 85/15, 0.7 mL/min) $t_b = 19.1$ min ($S$, minor) and 24.2 min ($R$, major); $[\alpha]_D^{21} = -27.5$ (c 0.25, CH$_2$Cl$_2$) for 26% ee ($R$). $^1$H-NMR (400 MHz) $\delta$ 7.82- 7.23 (m, 9H), 6.88 (d, $J = 8.0$ Hz, 2H), 5.23 (d, $J = 7.7$ Hz, 1H), 5.04 (q, $J = 7.2$ Hz, 1H), 2.45 (s, 3H), 1.94 (dq, $J = 14.6$ Hz, $J = 4.3$ Hz, 2H), 0.85 (t, $J = 7.5$ Hz, 3H); $^{13}$C-NMR (100 MHz) $\delta$ 142.8, 142.6, 133.7, 131.3, 131.2, 130.6, 129.8, 129.1, 128.9, 128.7, 127.8, 127.3, 126.8, 126.7, 126.1, 126.0, 125.5, 125.2, 125.1, 123.9, 123.2, 122.6, 55.8, 45.4, 30.4, 21.2, 10.7. All the data are consistent with the literature [27].

4.2.4.1.2.5. N-[1-(2-naphthymethylene)propan-1-yl]-4-methylbenzenesulfonamide

$R_f$ = 0.47 (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, 30% yield (20.0 mg, 0.06 mmol); ee 12% (Daicel Chiralpak AD column, UV detection at 254 nm, hexane/PrOH= 85/15, 0.7 mL/min) $t_b = 21.5$ min ($S$, minor) and 29.0 min ($R$, major); $[\alpha]_D^{21} = -8.8$ (c 0.25, CH$_2$Cl$_2$) for 12% ee ($R$). $^1$H-NMR (400 MHz) $\delta$ 7.69-7.27 (m, 8H), 7.06 (dd, $J = 8.6$ Hz, $J = 1.84$ Hz, 1H), 6.84 (d, $J = 8.1$ Hz, 2H), 4.94 (d, $J = 7.6$ Hz, 1H), 4.28 (q, $J = 7.3$ Hz, 1H), 2.09 (s, 3H), 1.78 (dq, $J = 40.4$ Hz, $J = 7.53$ Hz, 2H), 0.76 (t, $J = 7.4$ Hz, 3H); $^{13}$C-NMR (400 MHz) $\delta$ 142.8, 142.6, 135.8, 128.5, 128.4, 127.7, 127.5, 127.0, 126.5, 126.0, 125.9, 124.9, 124.8, 124.7, 124.0, 122.6, 59.9, 46.4, 30.4, 21.5, 10.8. All the data are consistent with the literature [27].
4.2.4.1.2.6. N-[1-phenylpropyl]-P,P-diphenylphosphinic amide

\[
\text{TLC: } R_f = 0.33 \text{ (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, trace amount. Due to the low yields of both catalyzed and uncatalyzed reaction products, they could not be isolated in pure form, so characterization analysis could not be performed. All the data given are consistent with the literature [30].}
\]

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\]

4.2.4.1.2.7. N-[1-(2-naphthyl)propyl]-P,P-diphenylphosphinic amide

\[
R_f = 0.30 \text{ (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, 50\% yield (40.0 mg, 0.10 mmol); ee 56\% (Daicel Chiralpak AD column, UV detection at 254 nm, hexane/PrOH= 80/20, 1.0 mL/min) }\text{ t} = 10.3 \text{ min (R, minor) and 12.7 min (S, major); } [\alpha]_{D}^{21} = -4.8 \text{ (c 0.25, CH}_2\text{Cl}_2) \text{ 56\% ee (S). } \text{ } ^{1}H\text{-NMR (400 MHz) } \delta 7.91-7.75 \text{ (m, 3H), 7.65 (d, } J = 7.7 \text{ Hz, 2H), 7.47-7.22 \text{ (m, 10H), 6.91 (d, } J = 8.0 \text{ Hz, 2H), 5.04 (q, } J = 7.0 \text{ Hz, 1H), 4.97 (d, } J = 7.3 \text{ Hz, 1H), 1.96 (dq, } J = 14.4 \text{ Hz, } J = 3.5 \text{ Hz, 2H), 0.86 (t, } J = 7.5 \text{ Hz, 2H); } ^{13}C\text{-NMR (100 MHz) } \delta 133.2, 133.1, 133.1, 133.0, 131.7, 128.9, 128.8, 128.7, 58.1, 31.4 \text{ (JC-P= 4.8 Hz), 18.2 (JC-P= 5.3 Hz), 10.8. All the data are consistent with the literature [30]}.\]

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\]

4.2.4.1.2.8. N-[1-(4-bromophenyl)propyl]-P,P-diphenylphosphinic amide

\[
R_f = 0.32 \text{ (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, trace amount. Due to the low yields of both catalyzed and uncatalyzed reaction products, they could not be isolated in pure form, so characterization analysis could not be performed. All the data given are consistent with the literature [30]}.\]

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\text{58}
\]

4.2.4.1.2.9. N-[(1S)-1-(4-methoxyphenyl)propyl]-P,P-diphenylphosphinic amide

\[
R_f = 0.53 \text{ (Pentan/Acetone= 5/1, colored black with phosphomolybdic acid in ethanol); white crystalline solid, trace amount. Due to the low yields of both catalyzed and uncatalyzed reaction products, they could not be isolated in pure form, so characterization analysis could not be performed. All the data given are consistent with the literature [30]}.\]

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\text{59}
\]
4.2.4.2. General procedure for racemic addition reactions

In a 10 mL flame-dried reactor purged with nitrogen, imine (0.1 g), toluene (3.0 mL) were added and cooled to 0 °C. Then, EtMgBr (3.0 equiv.) was added dropwise followed by 2.5 h mixing. At the end of this, the reaction mixture was quenched with NaOH solution (1.0 M). Mixture was filtered through Celite and washed with DCM. Aqueous phase was extracted with DCM and combined organic layer was rinsed with saturated aqueous NaHCO₃ solution. Crude product was dried over MgSO₄ and concentrated under reduced pressure. Crude product was purified by flash column chromatography on silica gel using 10:1 pentane-acetone as an eluent.
REFERENCES


APPENDIX

NMR SPECTRA and HPLC CHROMATOGRAMS

Figure A. 1 $^1$H-NMR spectrum of compound 20

Figure A. 2 $^{13}$C-NMR spectrum of compound 20
Figure A. 3 $^1$H-NMR spectrum of compound 21

Figure A. 4 $^{13}$C-NMR spectrum of compound 21
Figure A. 5 $^1$H-NMR spectrum of compound 22

Figure A. 6 $^{13}$C-NMR spectrum of compound 22
Figure A. 7 $^1$H-NMR spectrum of compound 23

Figure A. 8 $^{13}$C-NMR spectrum of compound 23
Figure A. 9 $^1$H-NMR spectrum of compound 24

Figure A. 10 $^{13}$C-NMR spectrum of compound 24
Figure A. 11 $^1$H-NMR spectrum of compound 25

Figure A. 12 $^{13}$C-NMR spectrum of compound 25
Figure A. 13 $^1$H-NMR spectrum of compound 26

Figure A. 14 $^{13}$C-NMR spectrum of compound 26
Figure A. 15 $^1$H-NMR spectrum of compound 27

Figure A. 16 $^{13}$C-NMR spectrum of compound 27
Figure A. 17 $^1$H-NMR spectrum of compound 28

Figure A. 18 $^{13}$C-NMR spectrum of compound 28
Figure A. 19 $^1$H-NMR spectrum of compound 31

Figure A. 20 $^1$H-NMR spectrum of compound 32
Figure A. 21 $^1$H-NMR spectrum of compound 34

Figure A. 22 $^1$H-NMR spectrum of compound 35
Figure A. 23 $^1$H-NMR spectrum of compound 37

Figure A. 24 $^1$H-NMR spectrum of compound 38
Figure A. 25 $^1$H-NMR spectrum of compound 39

Figure A. 26 $^1$H-NMR spectrum of compound 40
Figure A. 27 $^1$H-NMR spectrum of compound 41

Figure A. 28 $^1$H-NMR spectrum of compound 42
Figure A. 29 $^1$H-NMR spectrum of compound 43

Figure A. 30 $^1$H-NMR spectrum of compound 47
Figure A. 31 $^1$H-NMR spectrum of compound 44

Figure A. 32 $^1$H-NMR spectrum of compound 48
Figure A. 33 $^1$H-NMR spectrum of compound 45

Figure A. 34 $^1$H-NMR spectrum of compound 49
Figure A. 35 $^1$H-NMR spectrum of compound 46

Figure A. 36 $^1$H-NMR spectrum of compound 50
Figure A. 37 $^1$H-NMR spectrum of compound 51

Figure A. 38 $^{13}$C-NMR spectrum of compound 51
Figure A. 39 $^1$H-NMR spectrum of compound 52

Figure A. 40 $^{13}$C-NMR spectrum of compound 52
Figure A. 41 $^1$H-NMR spectrum of compound 53

Figure A. 42 $^{13}$C-NMR spectrum of compound 53
Figure A. 43 $^1$H-NMR spectrum of compound 54

Figure A. 44 $^{13}$C-NMR spectrum of compound 54
Figure A. 45 $^1$H-NMR spectrum of compound 55

Figure A. 46 $^{13}$C-NMR spectrum of compound 55
Figure A. 47 $^1$H-NMR spectrum of compound 57

Figure A. 48 $^{13}$C-NMR spectrum of compound 57
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**Figure A. 49** HPLC chromatogram of compound 51

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**Figure A. 50** HPLC chromatogram of racemic compound 51
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Figure A. 51 HPLC chromatogram of compound 52

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Figure A. 52 HPLC chromatogram of racemic compound 52
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**Figure A. 53** HPLC chromatogram of compound 53

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**Figure A. 54** HPLC chromatogram of racemic compound 53
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**Figure A. 55** HPLC chromatogram of compound 54

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**Figure A. 56** HPLC chromatogram of racemic compound 54
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Figure A. 57 HPLC chromatogram of compound 55

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Figure A. 58 HPLC chromatogram of racemic compound 55
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**Figure A. 59** HPLC chromatogram of compound 57

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**Figure A. 60** HPLC chromatogram of racemic compound 57