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SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE E TECNOLOGIE CHIMICHE

INDRIZZO CATALISI

Synthesis of new Biaryl phosphepine ligands for asymmetric catalysis

PhD thesis of:
Satyajit Karandikar

Supervisor
Prof. Serafino Gladiali

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Mr. Satyajit Karandikar
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INTRODUCTION

1.1 *Asymmetric synthesis and catalysis*

Understanding and synthesizing chiral molecules are extremely important in the preparation of therapeutic drugs, as chirality can inherent different biological properties to the respective enantiomers. Different asymmetric synthetic tools are being employed in order to prepare chiral molecules. These methods include using of a chiral pool, or use of an chiral auxiliary and recently there has been an enormous interest and advances in performing enantioselective reactions by exploiting chiral catalyst.

1. Chiral pool synthesis: A more economical way of making compounds as single enantiomers is to manufacture them using an enantiomerically pure natural product as a *starting material*. This method is known as chiral pool strategy and relies on finding a suitable enantiomerically pure natural product that can be easily transformed into the target molecule.

2. Chiral auxiliary: An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material. A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only (or mostly) one isomer of the product. The chiral auxiliary is then removed by some simple reaction like hydrolysis leaving the product of the reaction as a single enantiomer. In this, although stoichiometric quantities are need, there is no waste, as all best known chiral auxiliaries are recycled.

3. Asymmetric catalysis: Small amounts of chiral, enantiomerically pure catalysts promote reactions and lead to the formation of large amounts of enantiomerically pure or enriched products. Mostly, three different kinds of chiral catalysts are employed:

a. Metal complexes modified with ***chiral ligands***
b. Chiral organocatalysts and
c. Biocatalysts.

Recently there has been an enormous growing interest in the use of ***chiral ligands*** *in order to selectively synthesize one enantiomer as the product, hence directing the reaction in enantioselective way.*

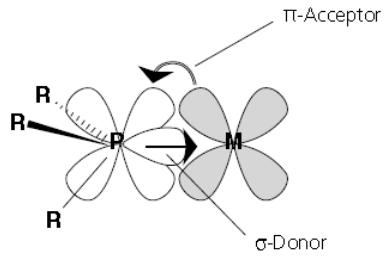
Chiral ligands are enantiopure organic compound which combines with a metal center by chelation to form a chiral catalyst. This catalyst engages in a chemical reaction and transfers its chirality to the reaction product which as a result is formed in a stereoselective mode. In an ideal reaction one equivalent of catalyst can turn over many more equivalents of reactant which enables the synthesis of a large amount of a hopefully enantiopure compound from achiral precursors with the aid of a very small (often expensive) chiral ligand. But more importantly, uses of *catalytic amounts* make them lucrative in order to synthesize biologically-important molecules from the industrial point of view.

1.2 *Phosphine ligands*

Phosphine ligands are utilised in the large majority of homogeneous catalysis with precious metals. The choice of right ligand can influence various reaction parameters like:

- ✓ The solubility of the active species
- ✓ The shielding and sterical properties of the catalyst
- ✓ The electron-density at the metal atom
- ✓ The reactivity of the catalyst in the catalytic cycle
- ✓ The lifetime and turnover-numbers of the catalyst
- ✓ The enantioselectivity of the reaction (with chiral ligands)

Phosphine ligands are usually strong σ-donor ligands and only weak π-acceptors, this effect can be increased with electron-donating groups in R, while electron with-drawing groups in R favour the π-acceptor backbonding.



A bulkier ligand (with large cone-angle) tends to have a higher dissociation rate than smaller ligands and electron-rich metal-centers tend to accelerate the "oxidative addition", a key-step in the catalytic cycle.

Many monodentate and bidentate phosphine ligands are now known. Also new ligands are being synthesized continuously in order to check their viability and selectivity in different reactions. As a fact, there is no 'one' universal ligand for all reactions. Only a small set of ligands or only one ligand, gives good result in one particular reaction. This gives rise to the increasing need of exploring new ligand molecules for its possible applications and performance in specific reactions. The

design of these new molecules, are based on the known chemical facts and catalyst mechanisms, as well as partly on the complexity of the molecule along with the simplicity of its preparation.

BINAP (**1**) is probably the most popular among chiral ligands. BINAP is used in organic synthesis for enantioselective transformations catalyzed by its complexes of ruthenium, rhodium, and palladium. Both (R)- & (S)- forms of BINAP are commercially available. As pioneered by Ryoji Noyori and his co-workers, Rh complexes of BINAP are useful for the synthesis of (-)-menthol. This synthetic method was industrialized by Takasago International Corporation. In part for this work, Noyori was awarded the 2001 Nobel Prize in Chemistry.

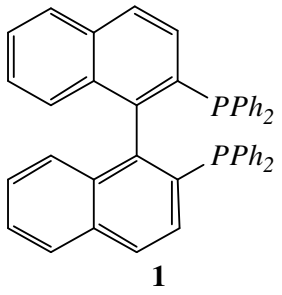


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Fig. 1.1 BINAP

BINAP is the paradigm of the class of chiral Biaryl Phosphine ligands. Such Biaryl class has axial chirality. Axial chirality is a special case of chirality in which the molecule does not have a stereogenic center but have an axis of chirality (**fig. 1.2**). It is an axis about which a set of substituents is held in a spatial arrangement which is not superposable on its mirror image. In Biaryls this axis of chirality is Aryl-Aryl bond where the rotation is restricted (fig. **1.2**).

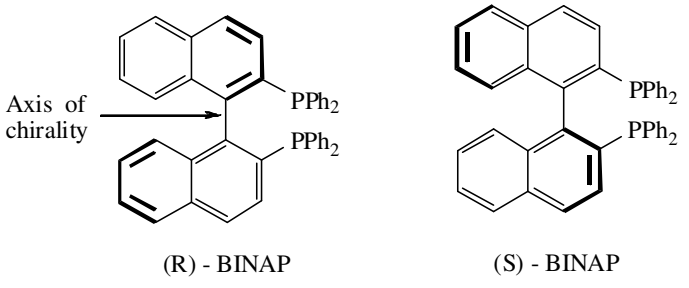


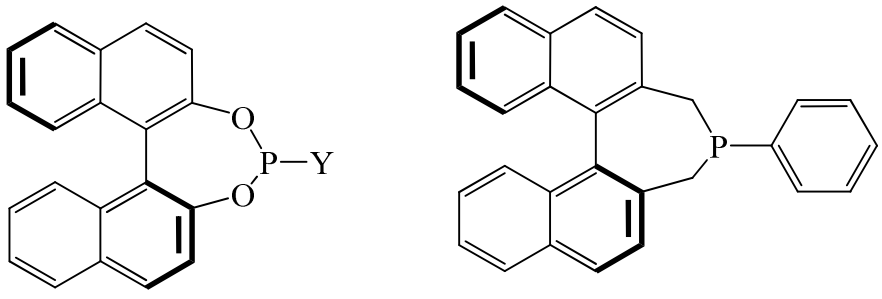
Fig. 1.2 Atropisemers of BINAP

BINAP is a bidentate Phosphine ligand having two P-atoms to chelate with the metal. There is an exhaustive list of bidentate phosphine ligands designed, published and commercially prepared for numerous applications. Bidentate phosphines are

preferred choice of ligand for its excellent results in catalysis. *But over the last few years, there has been an increasing interest in a range of monodentate P-donor ligands that are being explored and that have proved to equal or even outperform the analogue bidentate counterparts in some asymmetric reactions.* Also, chiral monodentate phosphines are easily accessible and tuneable than the bidentate analogues.

1.3 *Monodentate phosphepine ligands*

In 2000, Pringle *et al.*[1] reported that a monodentate biarylphosphonites of type **2a** as shown in Fig. **1.3**, outperform the analogous bidentate phosphonites in the asymmetric hydrogenation of enamides, in some cases. In a short lapse of time, this result was extended by individual findings of Reetz and his group[2] with type **2a** ligands, and groups of Vries & Feringa[3] with type **2b-c** ligands, respectively. These surprising results marked a major breakthrough in the field of enantioselective catalysis.



Y = R, RO, R_2N **2a-c**

Ph-BINEPINE **3a**

Fig. 1.3 Monodentate phosphepine ligands

These ligands **2a-c** share a range of common structural features: they all possess an endocyclic P-donor inserted in a seven-membered ring embedded in the C_2-symmetrical environment created by the binaphthalene scaffold. They all have P-atom connected to the diaryl template through two heteroatoms and they all have an axis of chirality. These type of monodentate phosphorus ligands **2a-c** showed interesting results in rhodium catalyzed asymmetric hydrogenation reactions.

The advent of astonishing results displayed by monodentate phosphorus ligands **2a-c**[1-3], made researchers take-up interest in exploring the plausible future applicability for monodentate phosphorus ligands.

Another class of monodentate phosphine ligands that contain P-donor inserted in a seven memebered ring with P-atom connected to diaryl template through a methylene are commonly known as phosphepines [4].

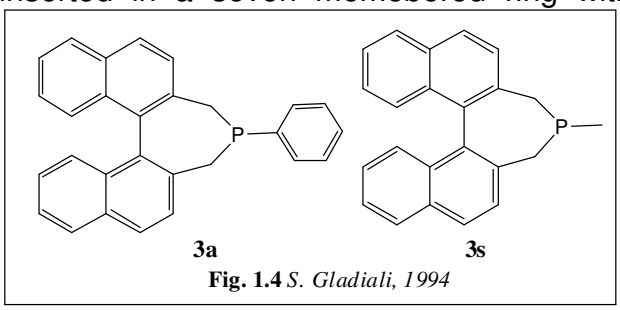
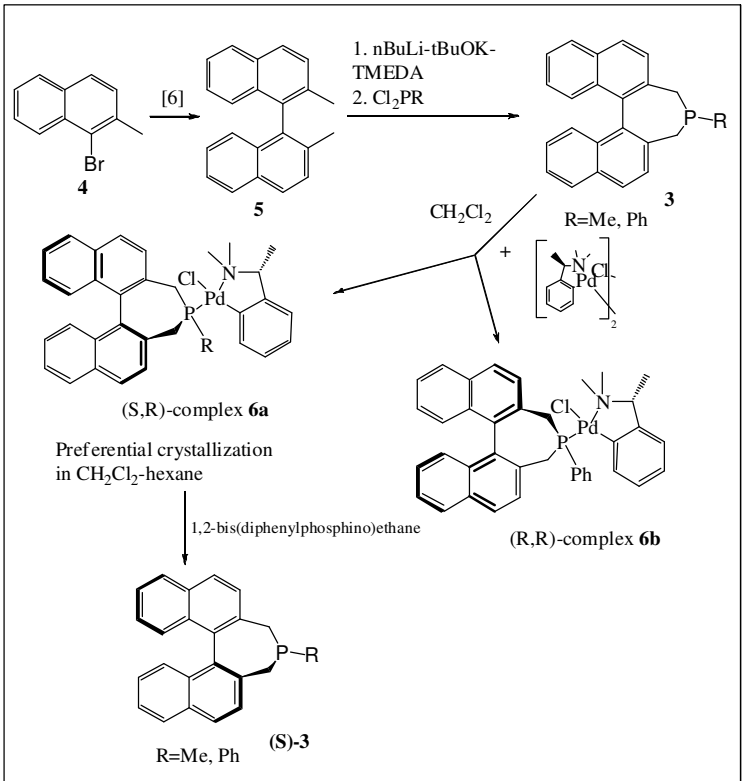


Fig. 1.4 *S. Gladiali, 1994*

BINEPINE **3a,3s**, are phosphepine ligands prepared in S. Gladiali's laboratory in 1994 [5], having the same basic structural features as of the binaphthol-core ligands **2a-c**. But, since the P-atom is connected through a methylene to the binaphalene template, BINEPINE **3** has a P-donor of comparably ***higher*** electron density.

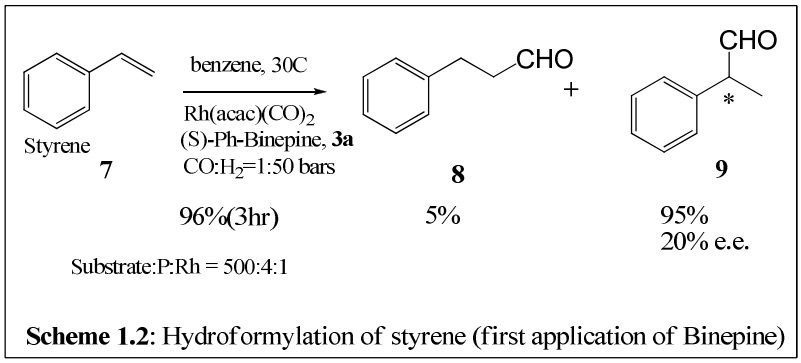
Initially, the synthesis of the BINEPINE was achieved in three steps as shown in **scheme 1.1**. 2,2'-dimethyl-1,1-binaphthyl **5**, was prepared by Ni-catalyzed coupling of 1-Bromo-2-methylnaphtalene[6]. Compound **5**, was then processed further as shown in this scheme to obtain the rac-Binepine.



Scheme 1.1: First synthesis of (S)-Ph-Binepine (**1994**, *S. Gladiali et. al*)

Racemic Binepine **3**, was then resolved via diastereomeric complex with chiral Pd-amine[7].

The ligand was tested as chiral inducer in the asymmetric hydroformylation of styrene in the presence of $Rh(acac)(CO_2)$ as the catalyst precursor, as shown in **scheme 1.2**.



Scheme 1.2: Hydroformylation of styrene (first application of Binepine)

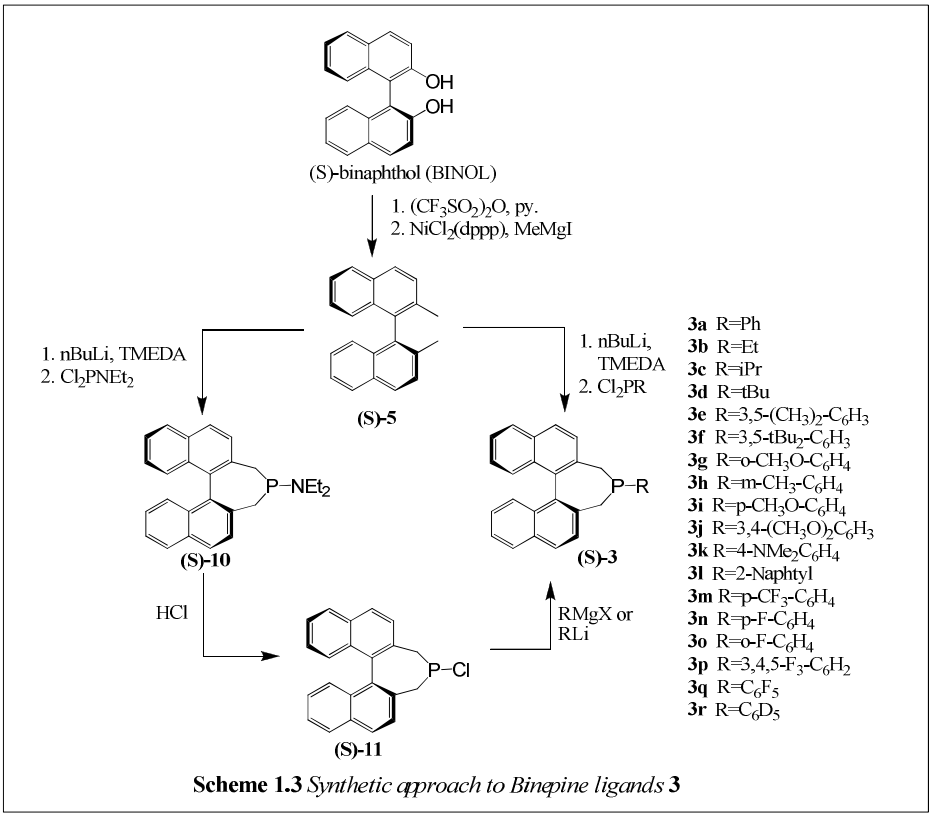
These preliminary results in asymmetric hydroformylation of styrene showed that, in comparison with triphenylphosphine, Ph-Binepine displayed the same catalytic activity but slightly more regioselectivity towards **9** (i.e. 95% with Ph-Binepine vs 83% with triphenylphosphine). Though the enantioselectivities were low, but 20% value was the highest at that time, obtained in Rh-catalyzed hydroformylation of styrene with chiral monodentate ligands.

P-donar ligands having a lower electron density and a higher π-acidity should affect negatively the rate of hydrogenation of enamides by Rhodium –phosphine complexes. This occurrence is because of the putative turn-over limiting step of the catalytic cycle that is oxidative addition of hydrogen[8]. Attributed to this fact, Binepine **3**, that has higher electron density over P-donor atom, is assumed to be a better ligand for Rh catalyzed hydrogenation of enamides over its analogues **2a-c**.

Attributed to the higher electron density on P-atom of phosphepines like Ph-BINEPINE **3a**, a large amount of work was resumed and initiated by different

research groups in the development of phosphepine-kind of ligands and exploring them in asymmetric hydrogenations, as well as in several other catalytic reactions. Ph-Binepine **3a**, was followed by independent research publications on the same subject by groups of Beller [9] and Zhang [10], almost at the same time. In a short time, this competition gave rise to the first interesting results of monodentate ligands having binaphthophosphepine motif, in the Rh-catalyzed hydrogenation of various olefins. This demonstrated the growing interests of the researchers in the unexplored phosphepine-kind ligands, and their potential usability in asymmetric catalysis.

Also, the commercial availability of enantiopure BINOL gave rise to a facile synthesis of 2,2'-dimethyl-1,1'-binaphtalene by Ni-catalyzed Kumada-coupling of BINOL ditriflate with methyl magnesium iodide (**Scheme 1.3**)[11]. This procedure allowed the preparation of the enantiopure starting material in more than 90% yield from BINOL.



Scheme 1.3 *Synthetic approach to Binepine ligands* **3**

It also served greatly in discarding 'resolution step' (**scheme 1.1**) of the racemic ligand, which could have been a limiting factor for any further investigation of the scope of this ligand in asymmetric catalysis.

Two different experimental methodologies were developed for the synthesis of BINEPINE ligands. The one-pot procedure originally executed for the preparation of **3a** involved deprotonation of the methyl groups with Schlosser base (BuLi-tBuOK-TMEDA) followed by direct quenching of the K bis-anion with dichlorophenylphosphine. In an alternative procedure, the di-lithium TMEDA-adduct obtained from the deprotonation of 2,2'dimethyl-1,1'binaphthalene is filtered off and separately reacted with the suitable phosphorus dielectrophile. This latter step-wise process was scaled-up to hundreds of grams. [8, 12]

Beller and his group synthesized and published a series of Binepine ligands with varying P-substitued groups as shown in **Fig 1.5**[8].

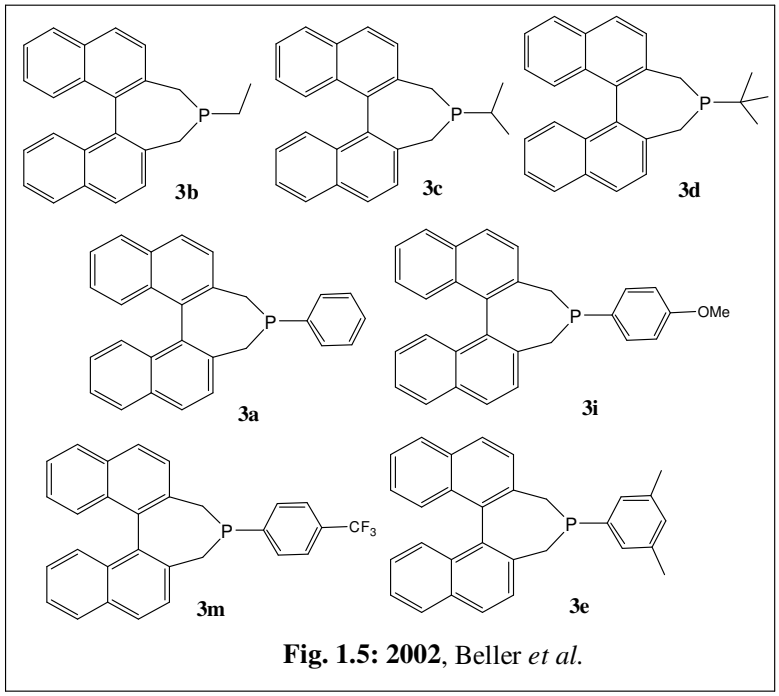
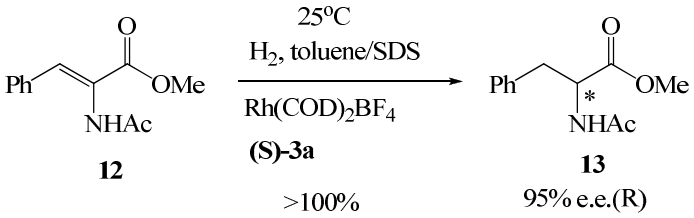


Fig. 1.5: 2002, Beller *et al.*

Ph-Binepine and other modified Binepines synthesized by Beller and his group were tried in asymmetric catalysis giving its first application in rhodium-catalyzed asymmetric hydrogenation of unsaturated carboxylic acid derivatives (**scheme 1.4**). The best e.e. was obtained by using Ph-Binepine, **3a** in this reaction. Enantioselectivities up to 95% e.e. for the hydrogenation of methyl α-acetamidocinnamate were obtained in the presence of **3a**. And it represented, one of

the highest enantioselectivities reported for asymmetric hydrogenation in the presence of monodentate phosphines.



Scheme 1.4: First Rh-catalyzed asymmetric hydrogenation **2002**, *Beller et. al.*

Even though more selective bidentate phosphine ligands were known for the above asymmetric hydrogenation reactions; this simple Ph-Binepine demonstrated selectivities close to the levels of known prominent chiral diphosphines.

While Zhang and his group synthesized phosphepine-related ligands as shown in **Fig 1.6**[10].

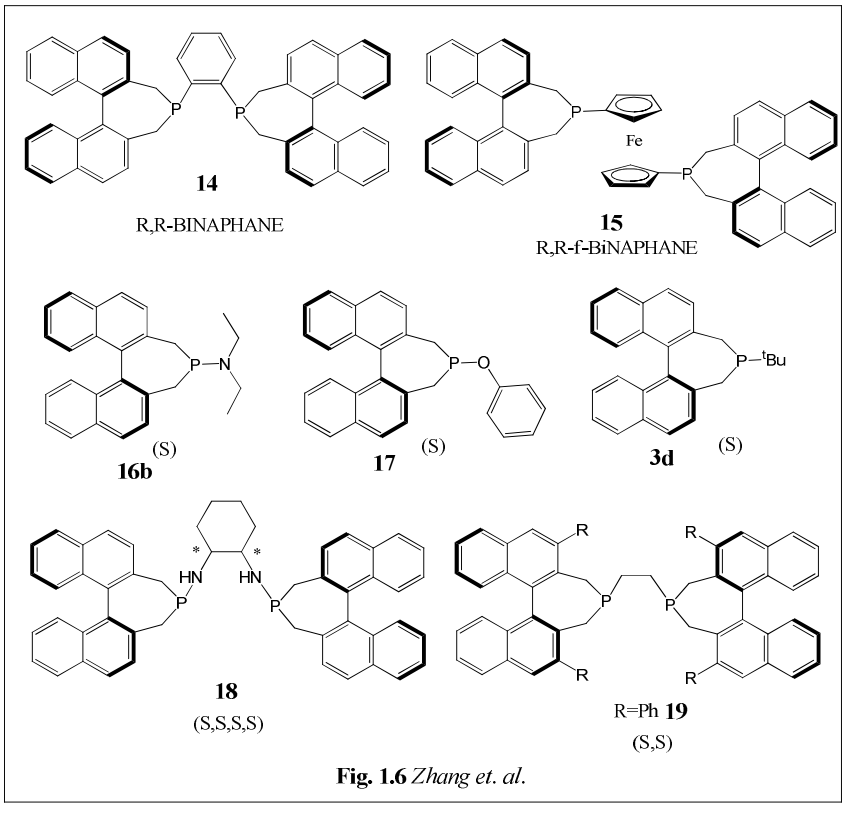


Fig. 1.6 *Zhang et. al.*

Fig. 1.6, shows the first developed bidentate phosphine ligands derived from Binepines. Bidentate phosphepines are beyond the scope of our research and thesis and hence will not be discussed in here.

These publications described the first appealing results of phosphepine ligands in the Rh-catalyzed asymmetric hydrogenation of α-dehydro amino acids, enol acetates, itaconates, and enamides.

In the following years Beller and co-workers expanded the structural diversity of the Binepine ligand family **3** into a library of ligands that were screened with remarkable success in the asymmetric catalysis. In 2003, Beller and his group published a set of new chiral monodentate aminophosphinites (**fig. 1.7**) and their use in catalytic asymmetric hydrogenations[12].

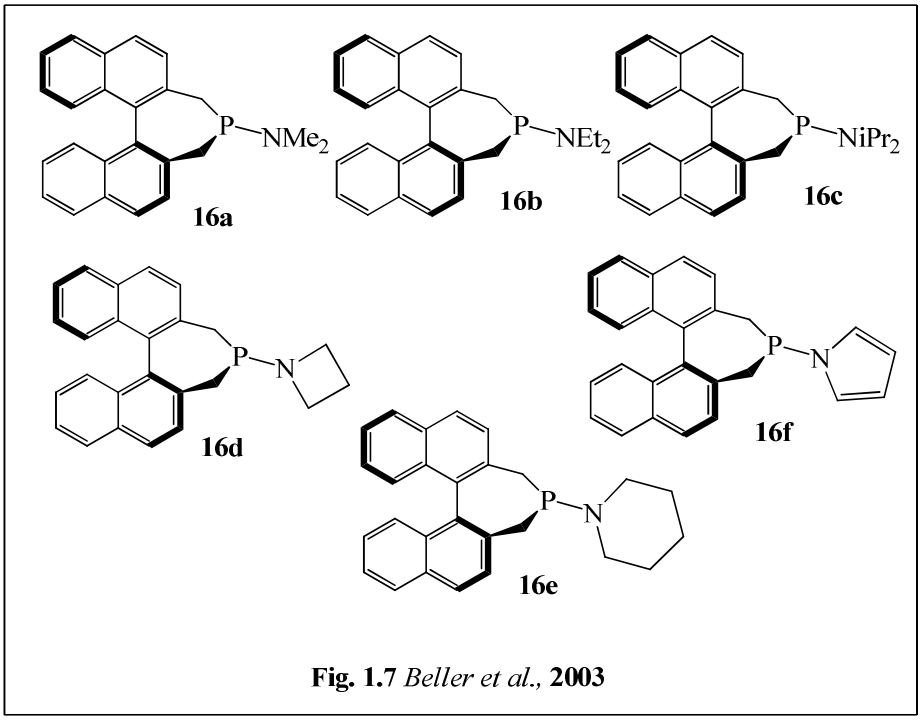


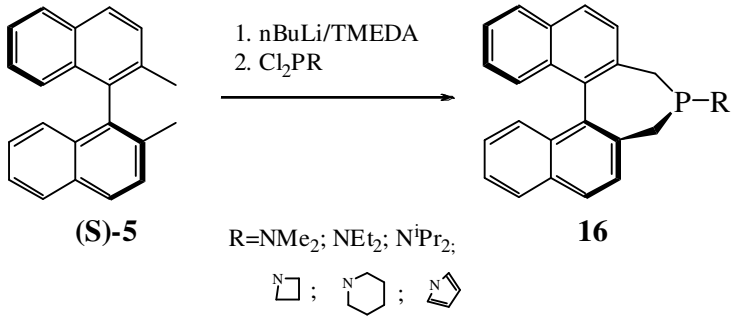
Fig. 1.7 *Beller et al.,* **2003**

Synthesis of these new chiral monodentate aminophosphinites were carried out using same synthetic route as shown in **scheme 1.3**.

Prepararation of the unavailable aminodichlorophosphines

$$PCl_3 + RNH \xrightarrow{[13]} Cl_2PR$$

Preparation of new chiral monodentate aminophosphinites



Scheme 1.5: Synthesis of monodentate aminophosphonites

Commercially available aminodichlorophosphines were directly reacted with the dimetalated species of **(S)-5** to obtain the ligands **16a-b**, respectively (**scheme 1.5**). For unavailable aminodichlorophosphines, **(S)-11** was prepared and then reacted with excess of corresponding amines to obtain **16c-f**. Because of formation of various by-products and inseparable impurities while reacting **(S)-11** with corresponding amines, it was preferred to prepare unavailable aminodichlorophosphines by a published method[13] and then reacting with the dimetalated species of **(S)-5** to obtain the ligands **16c-f**. These resulting monodentate chiral aminophosphinites **16a-f** were tested in the rhodium-catalyzed asymmetric hydrogenation of methyl α-acetamidocinnamate and methyl α-acetamidoacrylate. Enantioselectivities up to 96% e.e. were obtained in the presence of **16a** and sodium dodecylsulfonate in toluene. This was one of the highest reported enantioselectivities for monodentate ligands for the above selected benchmark reactions, at that time.

In 2004, Beller and his group showed for the first time that monodentate phosphine ligands could be used efficiently for the ruthenium-catalyzed hydrogenation of β-ketoesters (**scheme 1.6**)[14]. The catalysts were remarkably temperature-tolerant: Enantioselectivities of up to 95% e.e. were possible, even at 100–120°C. A comparison of **3a** with structurally related **2a** and **2c** demonstrated the superiority of phosphines over phosphites, phosphonates, and phosphoramidites.

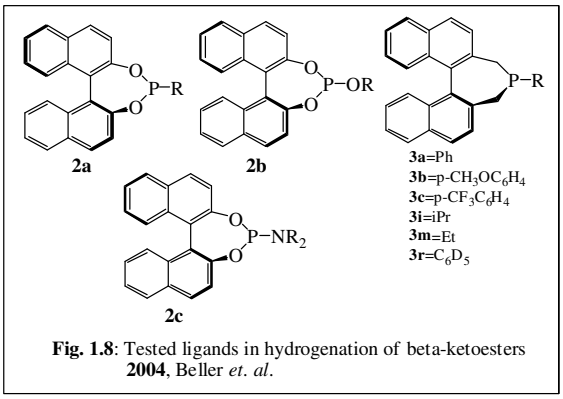
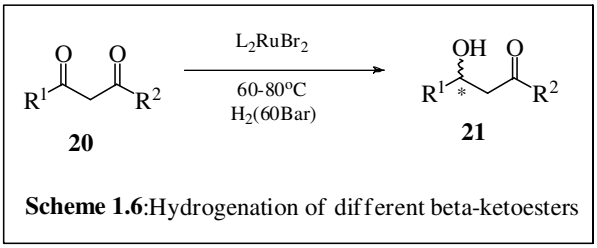
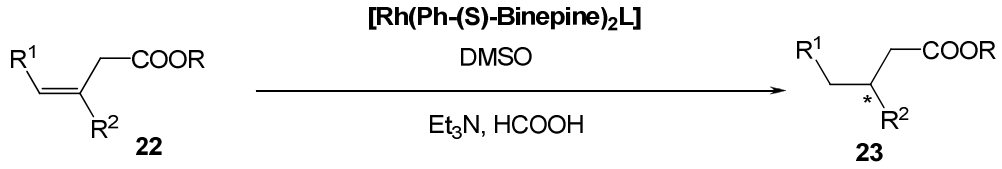


Fig. 1.8: Tested ligands in hydrogenation of beta-ketoesters **2004**, Beller *et. al.*



Scheme 1.6:Hydrogenation of different beta-ketoesters

In 2006, Gladiali and his group expanded the scope of monodentate Ph-Binepine (**3a**) ligand in asymmetric transfer hydrogenation reactions[15]. A range of α,β-unsaturated acids and esters were selectively reduced to the corresponding saturated acid derivatives by hydrogen transfer (**scheme 1.7**). Formic acid was used as the reducing agent in the presence of Rh complexes formed with the chiral Ph-binepine. Very high stereoselectivities (up to 97% ee) were obtained in the case of itaconic acid (**22a**).



a, Itaconic acid, when R^1= H, R^2=COOH, R=H
b, Dimethylitaconate, when R^1=H, R^2=COOMe, R=Me
c, Acetamidocinnamic acid, when R^1=Ph, R^2=$NHCOCH_3$, R=H
d, Acetoamidoacrylic acid, when R^1=H, R^2=$NHCOCH_3$, R=H
e, Methyl Acetamidocinnamate, when R^1=phenyl, R^2=$NHCOCH_3$, R=Me
f, Methyl Acetoamidoacrylate, when R^1=H, R^2=$NHCOCH_3$, R=Me

Scheme 1.7: Rh-catalyzed asymmetric trasfer hydrogenations

To summarize binepine and its family of ligands have showed good to excellent results in asymmetric hydrogenations of various substrates. As well as, it has mostly outperformed the other monodentate phosphine ligands in these asymmetric hydrogenations reactions.

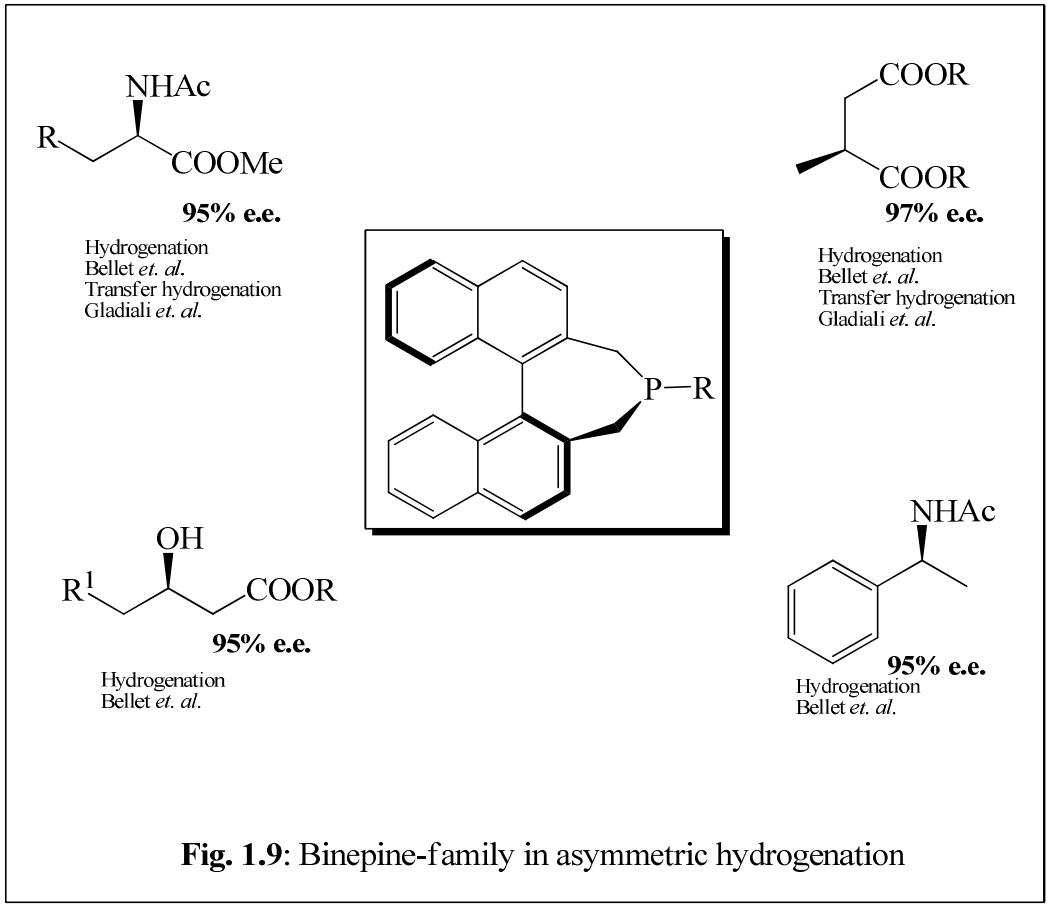
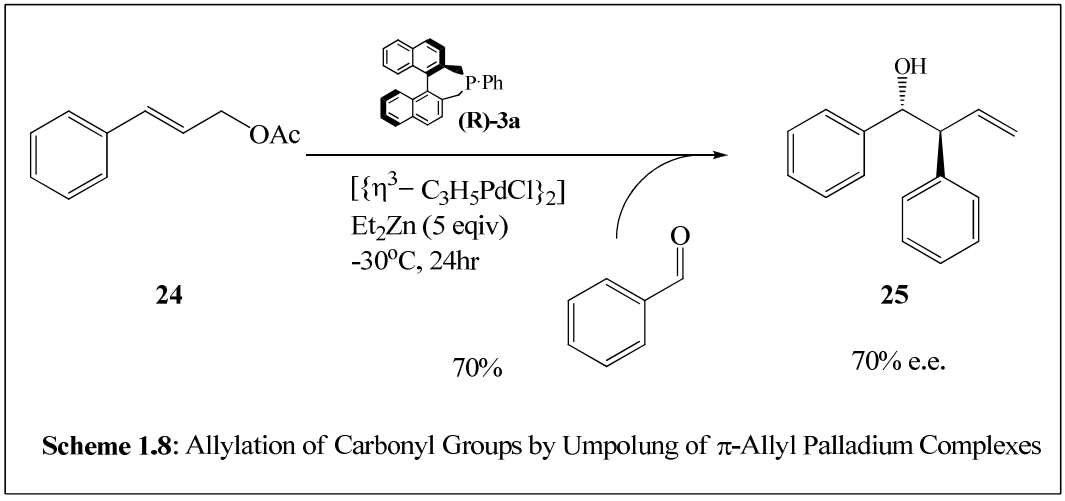


Fig. 1.9: Binepine-family in asymmetric hydrogenation

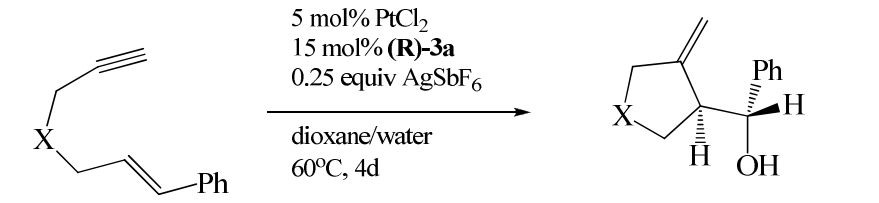
1.4 *Binepine congeners in other applications*

Success of Binepine and its family members in asymmetric catalysis did not exhaust only with asymmetric hydrogenations. In 2004, the first documented asymmetric palladium-catalyzed umpoled allylation of benzaldehyde with cinnamyl acetate[16] (**scheme 1.8**), tested a variety of chiral mono- and bi- phosphane ligands. And, Ph-binepine **3a** performed the best in this reaction to give 70% e.e. in 70% yield.



Scheme 1.8: Allylation of Carbonyl Groups by Umpolung of π-Allyl Palladium Complexes

In the same year; Michelet,Gladiali,Genêt *et. al.* described the asymmetric version of highly atom economical alkoxy- and hydroxy- cyclization of 1,6-enynes, using a combination of silver salts with the Pt(II)/(*R*)-Ph-BINEPINE system[17] (**scheme 1.9**). In order to perform this reaction and drive it in stereoselective manner, various phosphanes were examined under optimized conditions and in combination with silver salts. Silver salts were used as it has a positive effect on reaction rate of this reaction. (R)-Ph-Binepine **3a**, came out to be the best chiral ligand of all the tested ligands, furnishing the desired product upto 85% enantioselectivity.



X = $C(COOMe)_2$ **26a**
X = NTs **26b**

(+)-27a 94% yield 85% e.e.
(+)-27b 86% yield, 84% e.e.

Scheme 1.9: Ph-Binepine/$PtCl_2$ hydroxycyclization of 1,6-eynes

This ideal atom economical reaction leads to the corresponding functionalized five-membered carbo- and heterocycles in good to excellent yields.

In 2005, Fu *et. al.* demonstrated that a chiral phosphepine can catalyze the Kwon [4 + 2] annulation of imines with allenes and that phosphepines are effective nucleophilic catalysts for the synthesis of functionalized piperidine derivatives[18].

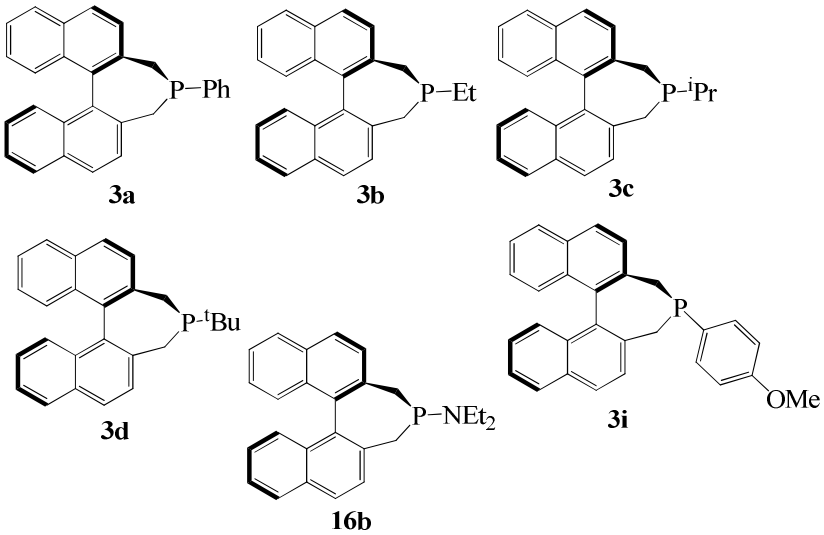
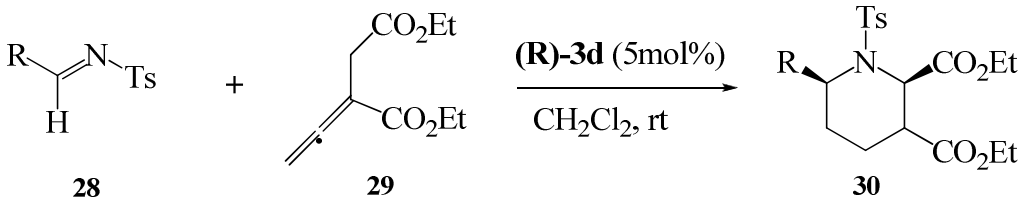


Fig. 1.10: Tested Binepine ligands in [4+2] annulation of imines with allenes **2005**, Fu *et. al.*

Few of Binepine family members as shown in **fig. 1.10** were examined in this reaction. And, **(R)-3d** furnished the desired heterocycles in good yields and excellent enantio- and diastereo- selectivites.

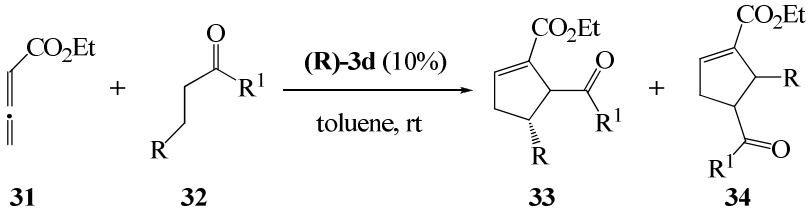


Scheme 1.10: [4+2] annulation of imines with allenes towards the synthesis of piperidines
2005, Fu *et. al.*

The reaction worked well if the allened beared a carbonyl or aryl substituent. Various aryl imines **25** reacted successfully as shown below:

Substrate	R	Yield(%)	Cis : trans	e.e. (%)
28a	Ph	93	91 : 9	98
28b	3-MeC_6H_4	98	93 : 7	98
28c	4-ClC_6H_4	99	91 : 9	96
28d	2-$(NO_2)C_6H_4$	98	96 : 4	68
28d	2-naphthyl	96	93 : 7	99
28e	2-furyl	98	87 :13	97
28f	3-pyridyl	76	91 : 9	97

In the following year, Fu *et. al.* broaden the scope of phosphepine by utilizing **(R)-3d** and carrying out successful nucleophile catalyzed asymmetric [3+2] cycloadditions of allenes with enones to obtain functionalized cyclopentene[19] (**scheme1.11**).



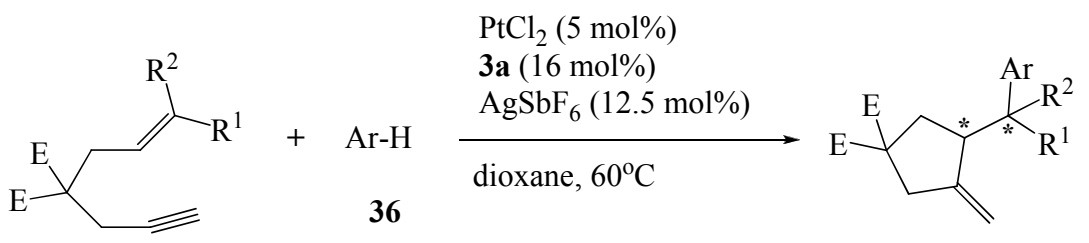
Scheme 1.11: Synthesis of functionalized cyclopentenes through catalytic asymmetric [3+2] cycloadditions
2006, Fu *et.al.*

They established that **3d** catalyzes enantioselective [3+2] cycloadditions of allenes with a variety of β-substituted α,β-unsaturated enones to produce highly functionalized cyclopentenes that contain two contiguous stereocenters. It was noted that these were the first such processes that employ β-substituted α,β-unsaturated carbonyl compounds (other than diethyl maleate) and that the opposite regioisomer **33** was produced preferentially as compared with substrates that lack a β-substituent. A range of substrates **32** were examined with varying degree of success. The results are briefly summarized as shown below:

Substrate	R	R^1	Yield (%)	e.e. (%)	**33 : 34**
32a	Ph	Ph	64	88	13 : 1
32b	Ph	4-ClC_6H_4	76	82	7 : 1
32c	Ph	4-MeC_6H_4	61	87	20 : 1
32d	Ph	4-$MeOC_6H_4$	54	88	>20 : 1
32d	4-ClC_6H_4	Ph	74	87	9 : 1
32e	4-$MeOC_6H_4$	Ph	67	87	10 : 1
32f	2-furyl	Ph	69	88	3 : 1
32g	2-quinolyl	Ph	52	88	20 : 1
32h	4-ClC_6H_4	2-(5-Me-furyl)	54	89	>20 : 1

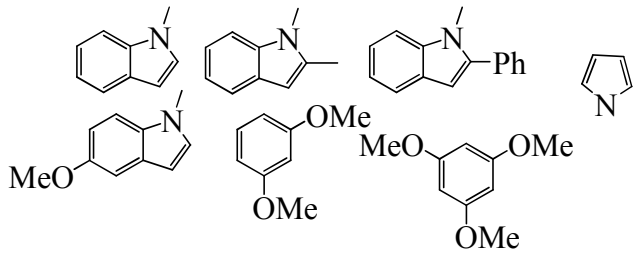
32i	Ph	2-thienyl	74	90	6 : 1

Recently, in 2008, Michelet,GladialiGenêt *et. al.* expanded the scope of platinum(II) chloride/silver hexafluoroantimonate ($PtCl_2/AgSbF_6$) catalytic system associated with Ph-BINEPINE to promote a stereoselective tandem hydroarylation (Friedel–Crafts-type addition) of electron rich aromatic and heteroaromatic derivatives to unactivated alkenes followed by a C-C bond cyclization reaction (e.e. up to 96%)[20] (**scheme 1.12**).



35a E=CO_2Me, R^1=Ph, R^2=H
35b E=$CO_2{}^i$Pr, R^1=Ph, R^2=H
35c E=CO_2Bn, R^1=Ph, R^2=H
35d E=$CO_2{}^t$Bu, R^1=Ph, R^2=H
35e E=CO_2Me, R^1=3,4-(OCH_2O)C_6H_3, R^2=H

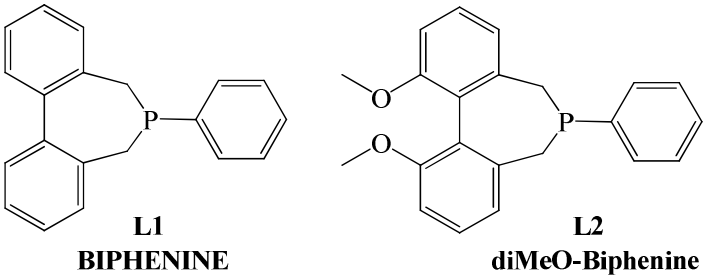
Ar=



Scheme 1.12: Platinum-catalyzed asymmetric tandem hydroarylation/cycloisomerization

1.5 *Aims of the project*

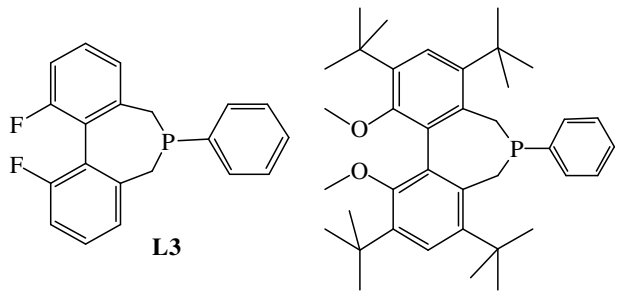
Since the preparation of Ph-Binepine **3a**, many other monodentate phosphepine ligands have been synthesized and tested in asymmetric catalysis. They have exhibited excellent results with high enantioselectivites in many stereoselective reactions. In many instances, Binepine and its congeners have given better enantioselectivites compared to other monodentate phosphine ligands. Most of the known biaryl phosphepine ligands are Binepine derivatives. There is a lack of structurally diverse phosphepines with a different biaryl backbone. Aiming at introducing diversity of ligand scaffold, we decided to explore phosphepine ligands with different biaryl skeleton that can change the reactivity and/or selectivity of the catalyst complexes in asymmetric catalysis.



L1 **L2**
BIPHENINE **diMeO-Biphenine**

Fig. 1.11: First targetted Biphenyl-based phosphepine ligands

Initially we were interested in a biphenyl skeleton in place of binaphthalene; **L1**,and **L2**. **L2**, is ortho substituted biphenyl with locked axial rotation. We aimed at ortho electron donating functional group i.e. methoxy substituted biphenyls for the ligand skeleton. We expected that such a group could possibly increase the electron density on the phosphorus atom, hence favouring a good activity towards Rh-catalyzed hydrogenation of enamides.



L3 **L4**

Fig. 1.12: Other substituted biphenines

While working on **L2**, we developed an interest in preparing other possible substituted biphenine **L3** & **L4**. This was due to the fact that

we had prepared good precursors which could be processed into these possible ligands.

Another diversity in ligand scaffold that we were interested to synthesize involved phosphepines with biaryls having either one or both heteroaromatic ring from the biaryl skeleton i.e. C_2 or C_1 symmetry i.e. **L5**, and **L6** respectively.

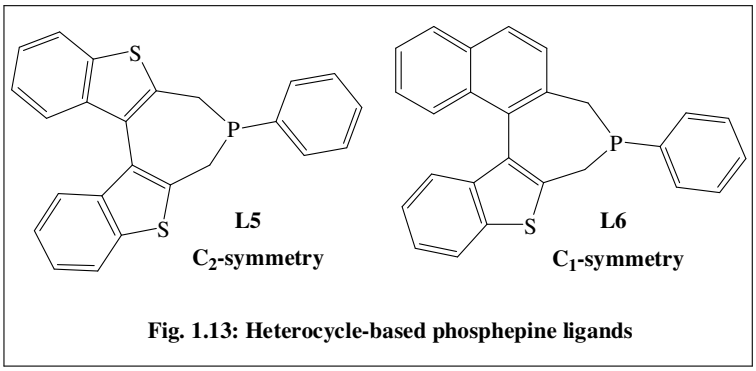


Fig. 1.13: Heterocycle-based phosphepine ligands

Lastly, we were also interested in phosphepine with a C_1 symmetry as opposed to the known C_2 symmetry phosphepines, **L7**.

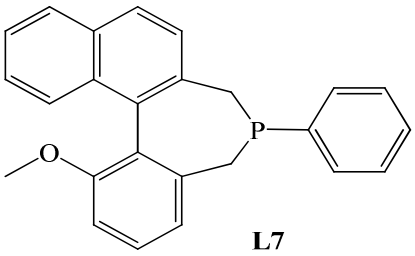


Fig. 1.14: C_1-symmetry phosphepine

Results and discussion

Chapter – 2

2.1 Synthesis of Ligands

2.1.1 *Synthesis of BIPHENINE (L1)*

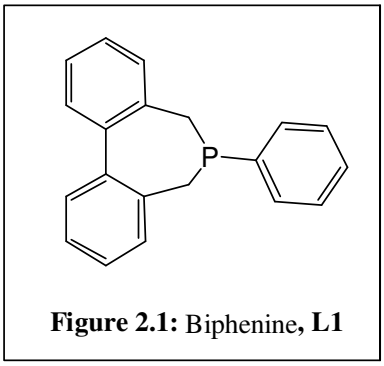
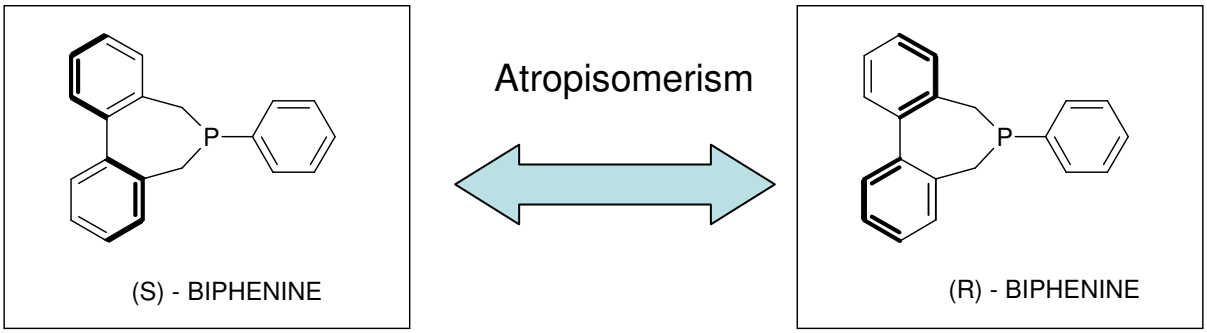


Figure 2.1: Biphenine**, L1**

Biphenyl with no ortho-substitution has a low interconversion barrier between the two atropisomers. They are stereochemically labile and thus readily interconvertible at low temperatures, unlike binaphthalene (in case of BINEPINE) where the interconversion is not facile and are stereochemically fixed. Hence, Biphenyls are more stereochemically flexible. Such flexibility was thought to be exploitable in some enantioselective reactions.



The two different dynamic processes for interconversion that can be anticipated for Biphenine are pyramidal inversion at the phosphorus atom and flipping of the phenyl rings as illustrated in **Figure 2.2**. Because. the phosphorus center is not a stereogenic center, pyramidal inversion does not change the chirality of the molecules.

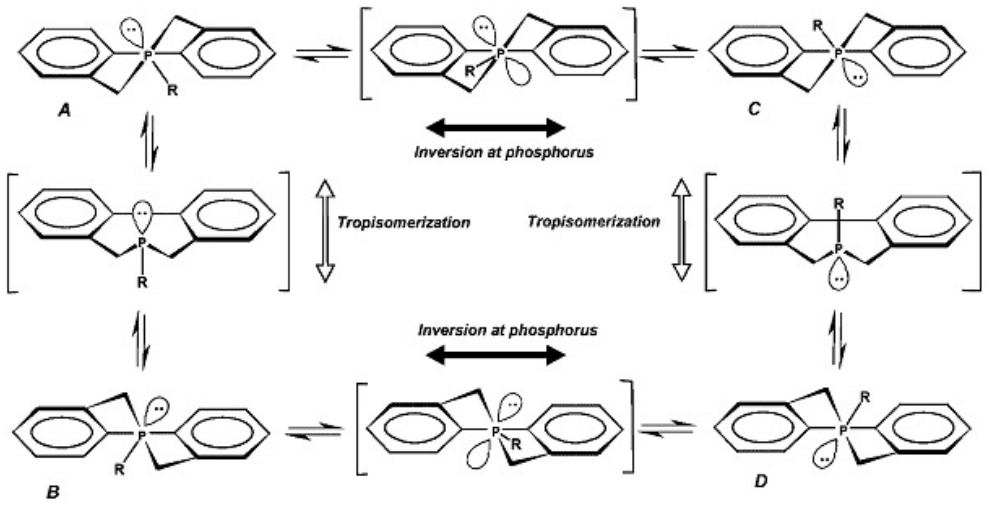


Fig. 2.2 Possible inversions in Biphenine
2007, Christina Moberg *et. al.*

Christina Moberg and group[21] determined and reported the barriers to interconversion of 6-methoxy-6,7-dihydro-5H-dibenzo[c,e]phosphepine and that of the diasteriomeric forms of 6-(-)-menthoxy-6,7-dihydro-3H-dibenzo[c,e]phosphepine (**fig. 2.3**).

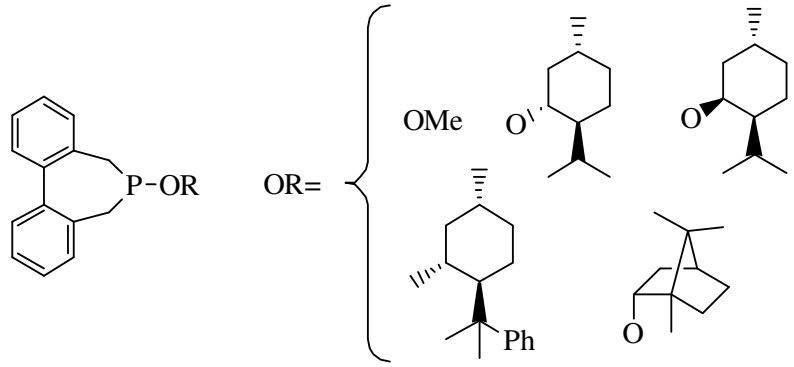
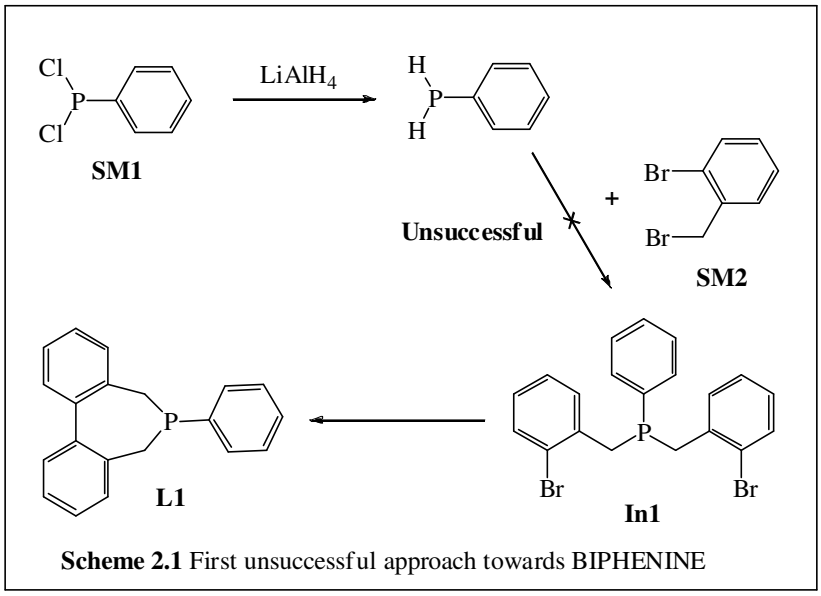


Figure 2.3 Prepared compounds
2007, Christina Moberg *et. al.*

In our synthesis of Biphenine **L1**, various synthetic routes were explored in order to prepare BIPHENINE in the shortest possible way.

One different approach in order to synthesize BIPHENINE was starting from relatively cheap and commercially available dichlorophenylphoshine. After reduction to phenylphosphine, 2-Bromobenzyl bromide (**SM2**) was allowed to react with phenylphosphine in the presence of a base (as shown in the **scheme 2.1**). But this step was unsuccessful and multiple products were observed to form that were too complex to be separated and analyzed. This compelled us to cease all further work with this synthetic approach.



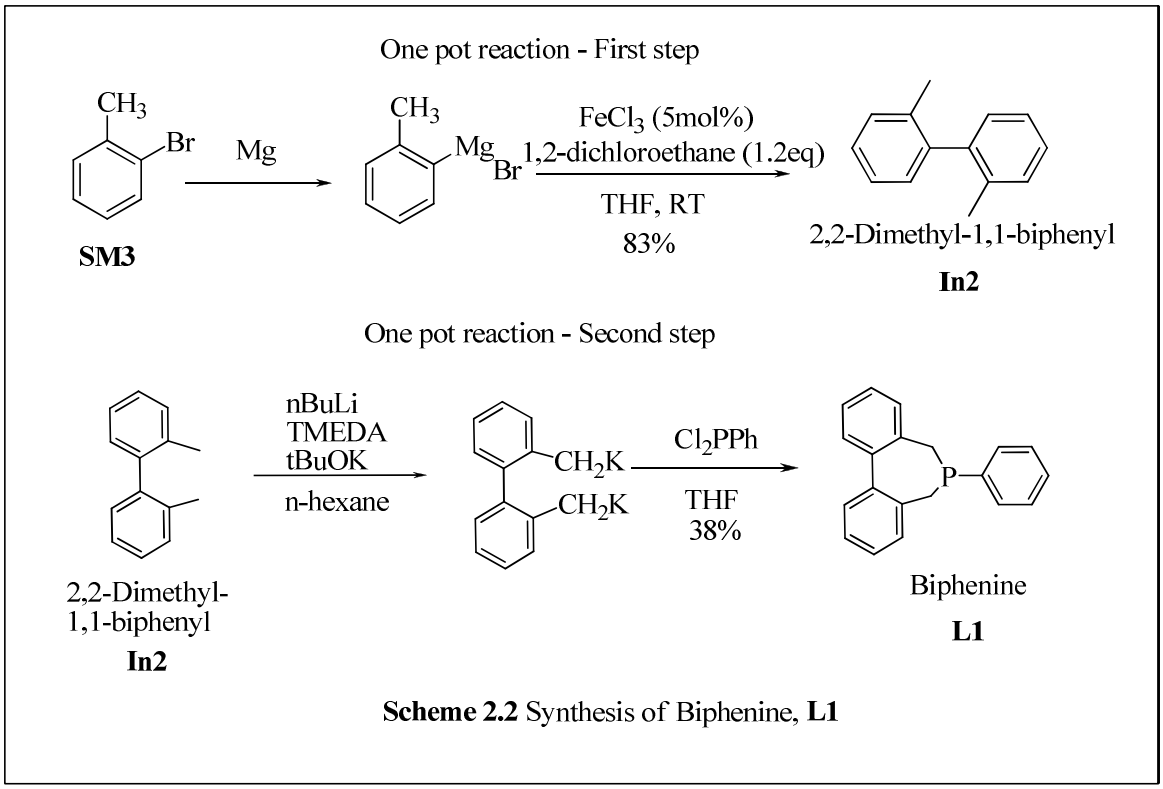
Scheme 2.1 First unsuccessful approach towards BIPHENINE

Best synthetic access to symmetrical biaryls, is the well known homo-coupling of suitable aryl derivative. Oxidative homo-coupling of aryl-metal reagents is one of the most efficient synthetic methods for the construction of a symmetrical biaryl backbone. A wide variety of transition metal halides such as $TiCl_4$[22], TiCl[23], $FeCl_3$[24], $CoCl_2$[25], and $CuCl_2$[26] have been employed as oxidants in stoichiometric amounts in these coupling reactions. Use of re-oxidants like oxygen and dibromoalkanes has also assisted in employing the catalytic use of these metals in the homo-coupling reactions[27-29].

After screening of various classical aryl-aryl homo-coupling methods, we chose iron catalyzed homo-coupling of aryl grignard reagents as published by Hayashi and his group[30]. His work was quiet pleasing and involved cheap

iron(III)chloride in catalytic amount as catalyst along with 1,2-dichloroethane as an oxidant.

Hence, the above C_2-symmetry Phosphorus monodentate ligand, Biphenine **L1**; was prepared as shown in the **scheme 2.2**.



Scheme 2.2 Synthesis of Biphenine, **L1**

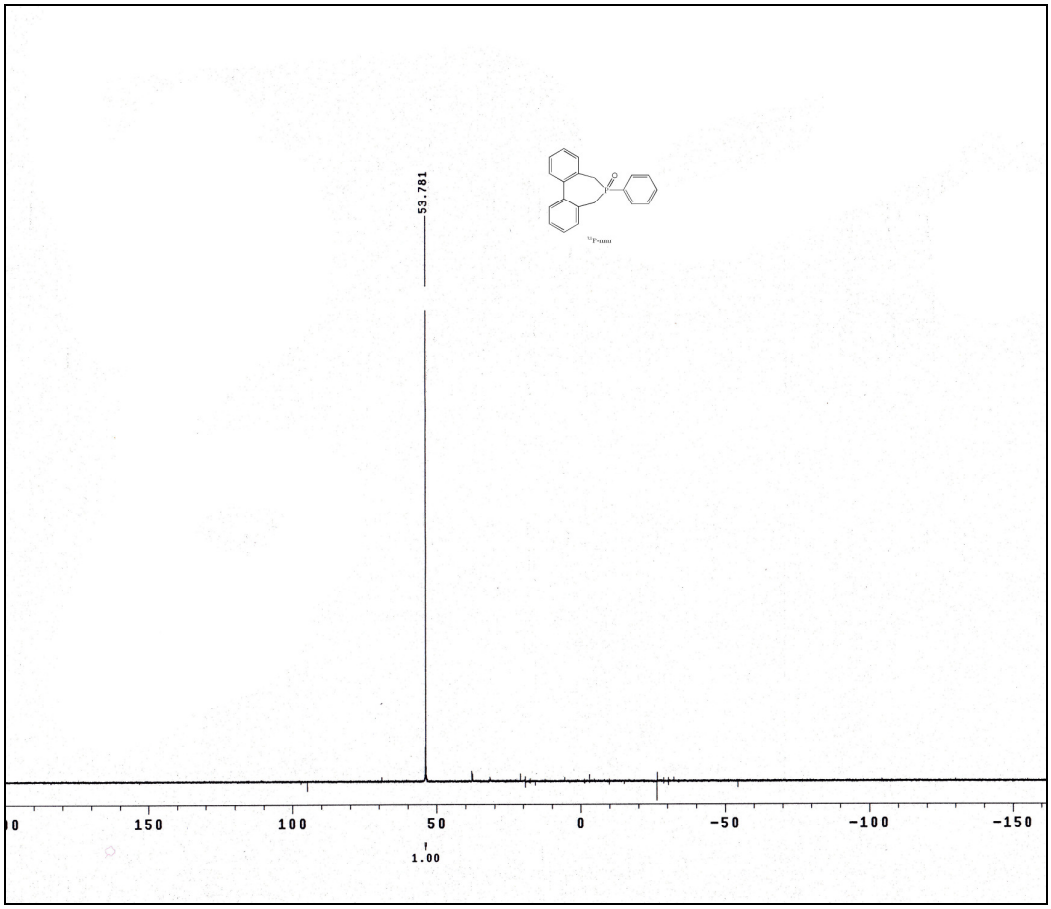
Firstly, 2,2'-Dimethyl-1,1'-biphenyl (**In2**), was prepared using oxidative homo-coupling of 2-Bromotoluene via formation of grignard reagent. The grignard reagent was coupled using catalytic amount of anhydrous $FeCl_3$ and 1,2-Dichloroethane as oxidant. The synthesis was simply carried out at room temperature and was successful with a good yield of about 83% to obtain a clean product **In2**, as published by Hayashi and his group.

2,2'-Dimethyl-1,1'-biphenyl (**In2**) was then used to synthesize the desirable first ligand, Biphenine **L1**. The synthesis was carried out as per the synthetic

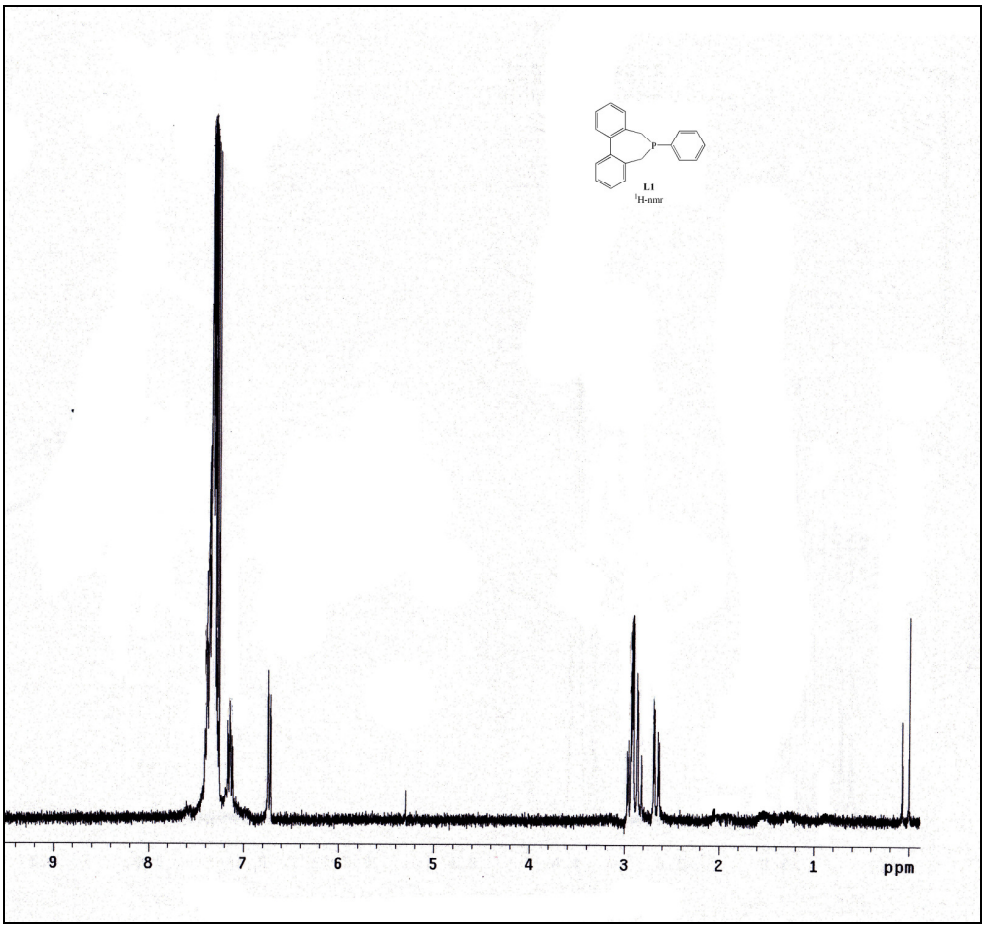
procedure for Ph-Binepine [31] with some modification that was required in selecting the reagents for lithiation.

Biphenine was successfully synthesized, optimised and prepared in 10g scale in order to carry out further examinations and reactions. ^{1}H-nmr and ^{31}P-nmr for Biphenine are as shown in **spectra 1** & **2**.

Spectra 1: ^{31}P-nmr of Biphenine, L1

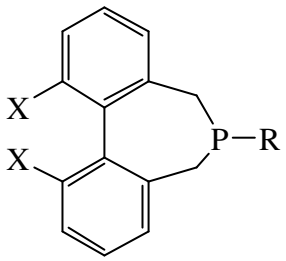


Spectra 2: ^{1}H-nmr of Biphenine, L1



Chapter-2

2.1.2 *Synthesis of diMeO-Biphenine(L2)*



X = OMe, X
C2-symmetry

Figure 2.4 Ortho- substituted Biphenine

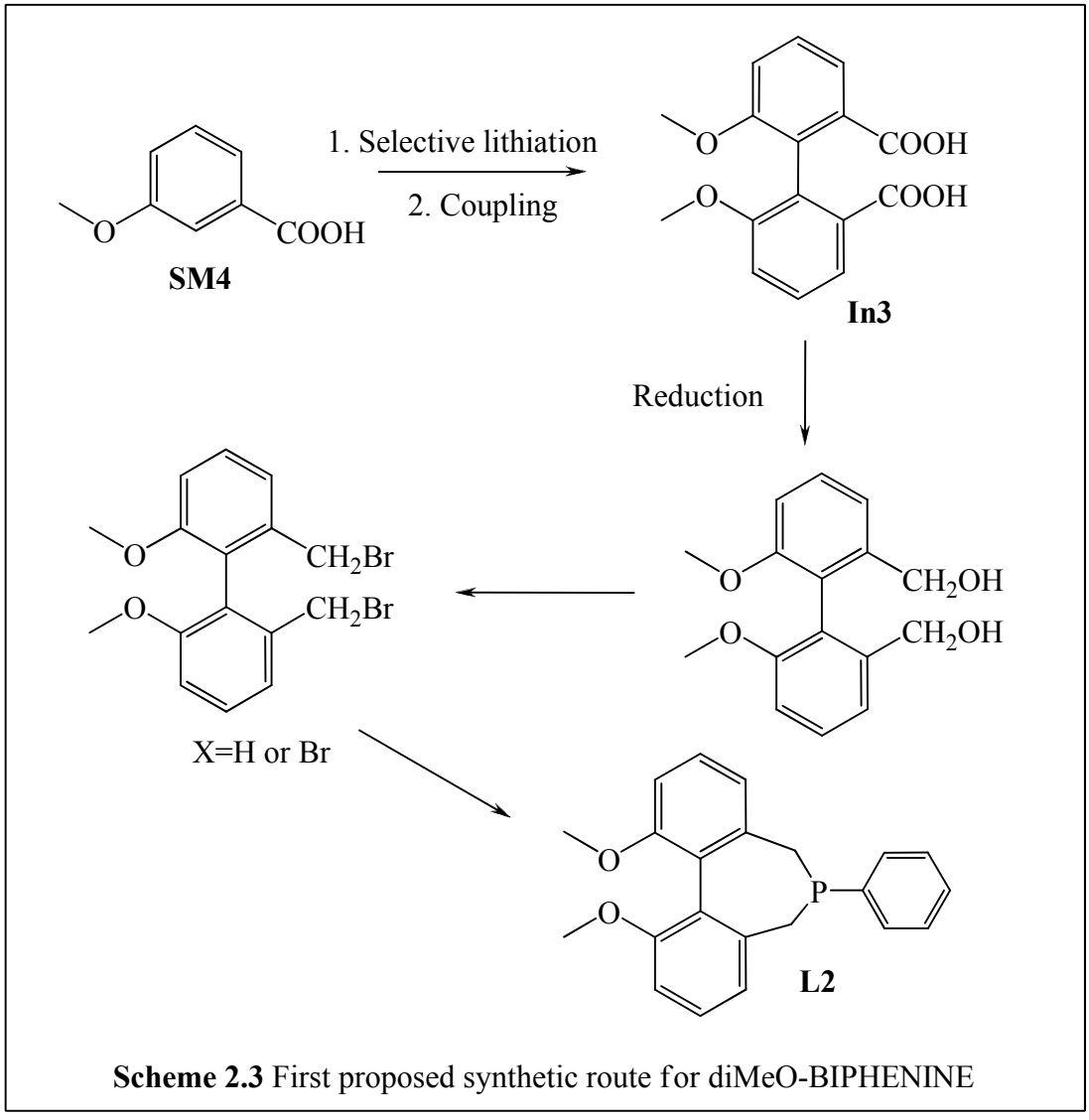
Next ligand of our interest was the ortho- substituted biphenyl-core phosphepine ligand as shown in the **fig. 2.4**.

Being ortho- substituted, these biphenyls are sterically hindered and axially locked. Our aim was to first synthesize a racemic ligand and then explore methods to prepare enantiopure isomer, as required to apply in asymmetric catalysis. With limitations on the required substituents and the position, extensive literature survey had to be undertaken in order to decide for possible routes to synthesize the diX-Biphenine. We decided to initiate work towards synthesis of diMeO-Biphenine **L2**, as our ligand of high interest.

Our synthetic approach was based on the selection of the right starting material with 1,3-substituted phenyls. Substituents that could later be easily transformed to the desired functional group, along with the requirement of possible homo-coupling at 2- position that was necessary to synthesize the targeted ligand. We chose to start from m-anisic acid, since the carboxylic acid could later be easily transformed to the methyl as required for the last step. As well as the presence of carboxylic acid group was advantageous to explore the possible resolution or asymmetric chiral synthesis of the targeted ligand.

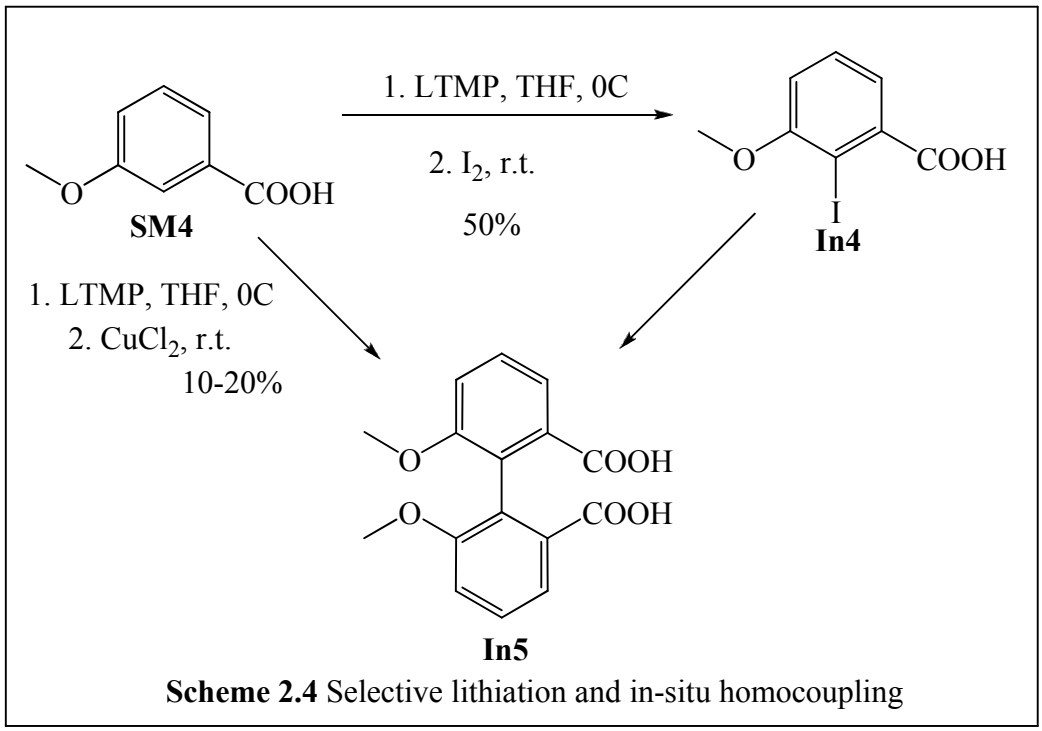
Aryl-aryl bond formation is one of the most important tools of modern organic synthesis. Aryl-aryl bond formation chemistry has been progressing for more than a century with numerous advances and constant improvements in the old methodologies. Marc Lemaire and group have excellently reviewed this topic summarizing the centuries work in this field[32]. Aryl-aryl homo-coupling was our obvious approach to prepare our targeted biphenyl skeleton of our ligand.

Our first approach to synthesize diMeO-Biphenine is as shown in the **Scheme 2.3**.



Scheme 2.3 First proposed synthetic route for diMeO-BIPHENINE

Detailed selective lithiating reagents and reaction conditions that direct the lithiation on m-anisic acid at different positions was first discussed in 2005 [33]. As discussed in the article, lithiation of m-anisic acid selectively at 2- position by use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) was successful, as shown in **scheme 2.4**. After reacting the dilithiated anion of m-anisic acid with the suitable electrophile like iodine as per the article, furnished 2-iodo-m-anisic acid in about 50% yield. In order to have the biphenyl skeleton, the next step was the required homo-coupling of the iodide derivative like Ullmann coupling.



Scheme 2.4 Selective lithiation and in-situ homocoupling

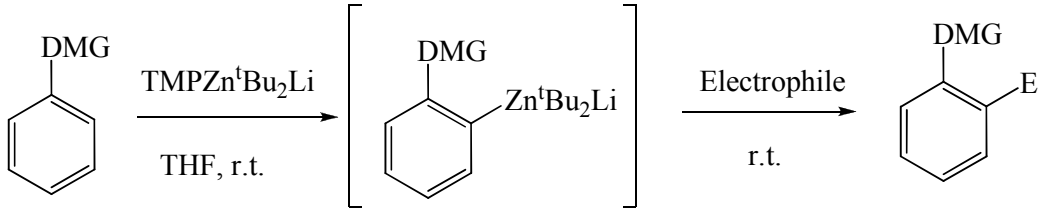
The use of large excess of expensive 2,2,6,6-tetramethylpiperidine and obtaining only 50% yield of iodide derivative, right in the first step was unfavourable. Hence, we were interested in exploring possible *in-situ* and direct homo-coupling of lithiated m-anisic acid. We carried out several trials of in-situ homo-coupling of lithiated m-anisic acid with catalyst like CuI, CuCl and using different reaction conditions. We also carried out in-situ trasmetalation of lithiated m-anisic acid to

grignard using $MgBr_2$ and then homo-coupling with $FeCl_3$ as catalyst. But all the above trials failed to give the desired product. Finally we tried to in-situ homo-couple the lithiated m-anisic acid with $CuCl_2$ as catalyst and obtained the desired product, but only in about 10-20% yield. It was also difficult to separate the product from the reactant.

Due to the unacceptable low yields in the initial stage of the ligand synthesis compelled us to drop this synthetic approach and stop any further research in this synthetic route.

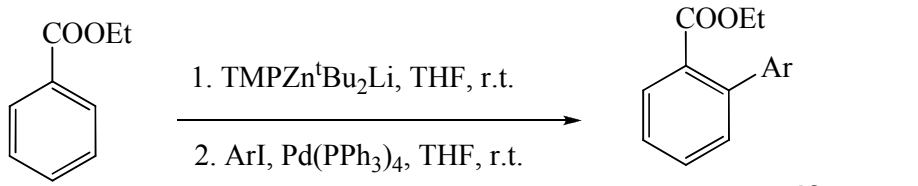
Another approach surfaced from the first synthetic route. Directed ortho metalation has been a topic of big research with many advances that employs various directing groups for this purpose. Ester group has also been regarded as an important and attractive directing group; however, use has been limited because the deprotonation requires strictly controlled reaction conditions due to instability of intermediary aryllithium species with the ester functionality. Chemoselective formation of arylzincates using newly developed di-tert-butyltetramethylpiperidinozincate (TMP-zincate) as a base was published by Yoshinori Kondo and his group[34]. And, they were also successful in performing Pd-catalyzed cross coupling of one of the obtained arylzincate with aryl iodide to give the aryl-aryl bond, as shown in **scheme 2.5**. Since then, there are several other mechanistic studies as well as applications with regards to formation of arylzincates[35].

ArylZincate formation using TMP-zincate



DMG=COOMe
COOEt
COO^{i}Pr
COO^{t}Bu
CON^{i}Pr$_2$
CN

***In-situ* Pd-catalyzed cross coupling**

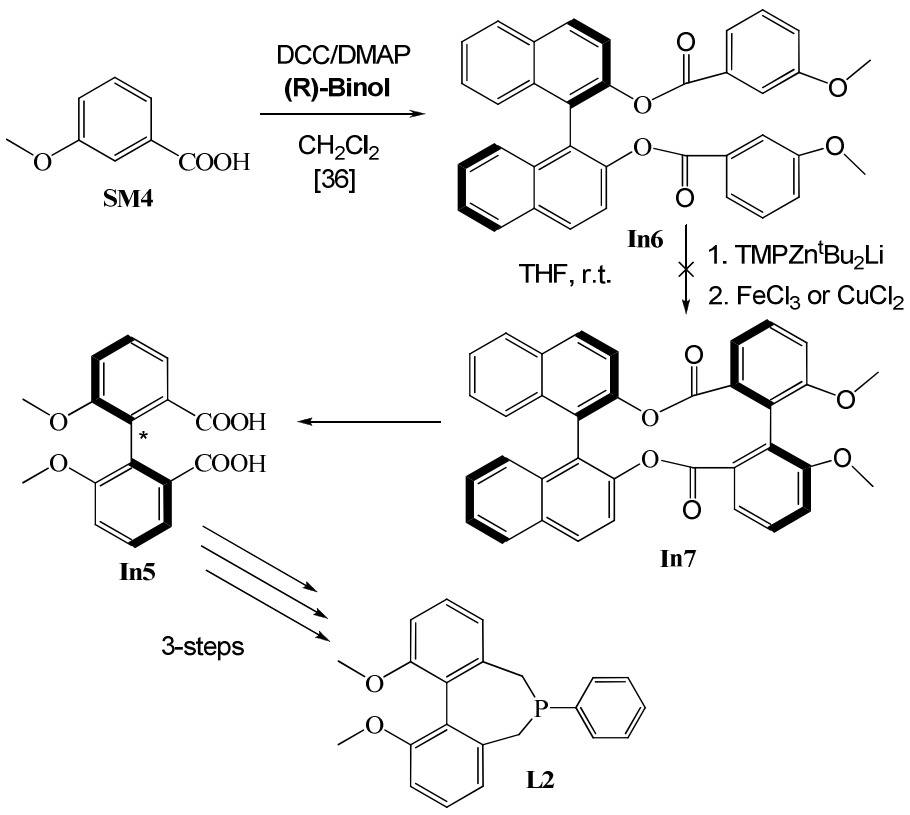


39

Ar=Ph 58% **40a**
3-pyridyl 43% **40b**

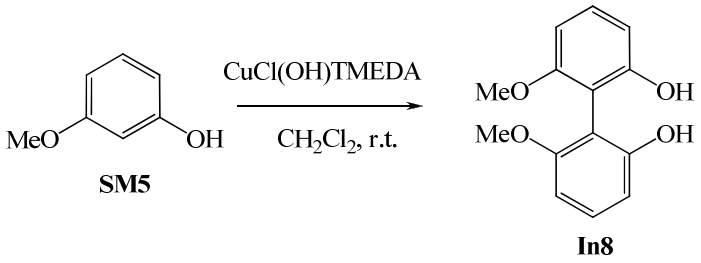
Scheme 2.5 Aryl-zincate formation, **1999** Yoshinori Kondo *et. al*.

Based on this, we decided to try arylzincate formation on **In6** as shown in **scheme 2.6**, where we predicted possible zincate formation at 2-position due to the double DOM effect of methoxy as well as ester group. If possible, we were interested in *in-situ* homo-coupling of the formed zincate derivative to give the desired product, **In6**. And the presence of chiral binol ester as shown in the **scheme 2.6**, it would provide us with a chiral homo-coupled product of interest after reduction, **In5**.



Scheme 2.6 Second approach to synthesize diMeO-Biphenine

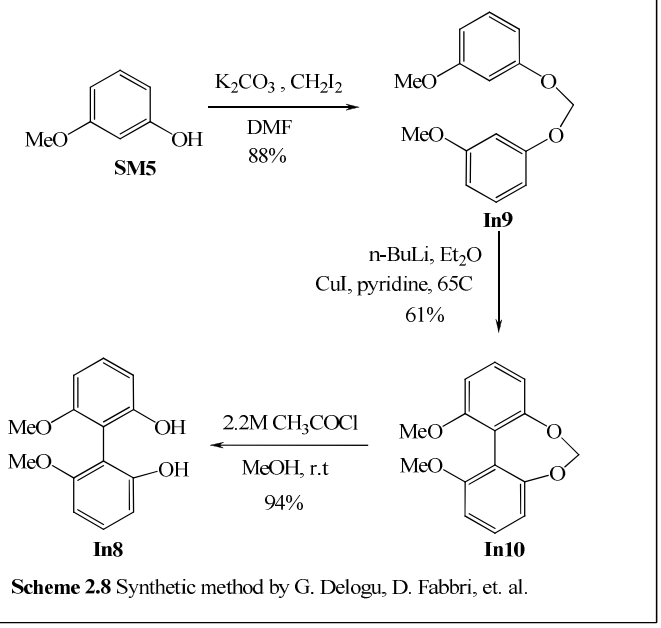
Unfortunately, this methodology failed to give the desired *in*-situ homo-coupled product. And we had to think of another possible starting material and adopt a different approach to synthesize the targeted ligand. Efficient phenolic oxidative coupling of 2-naphthols to binols using copper-amine complexes are known since very long[37]. And the first successful enantioselective oxidative coupling of 2-naphthols catalyzed by chiral amine-copper complexes[38] are also published and described. This method was specially very attractive to us, due to the possible ability of synthesizing our targeted chiral ligand by enantioselective oxidative coupling. We were interested to apply this method in order to oxidatively couple 3-methoxyphenol. We were curious if we could obtain a product coupled at 2-position as shown in the **scheme 2.7**.



Scheme 2.7 Phenolic oxidative coupling of 3-Methoxyphenol

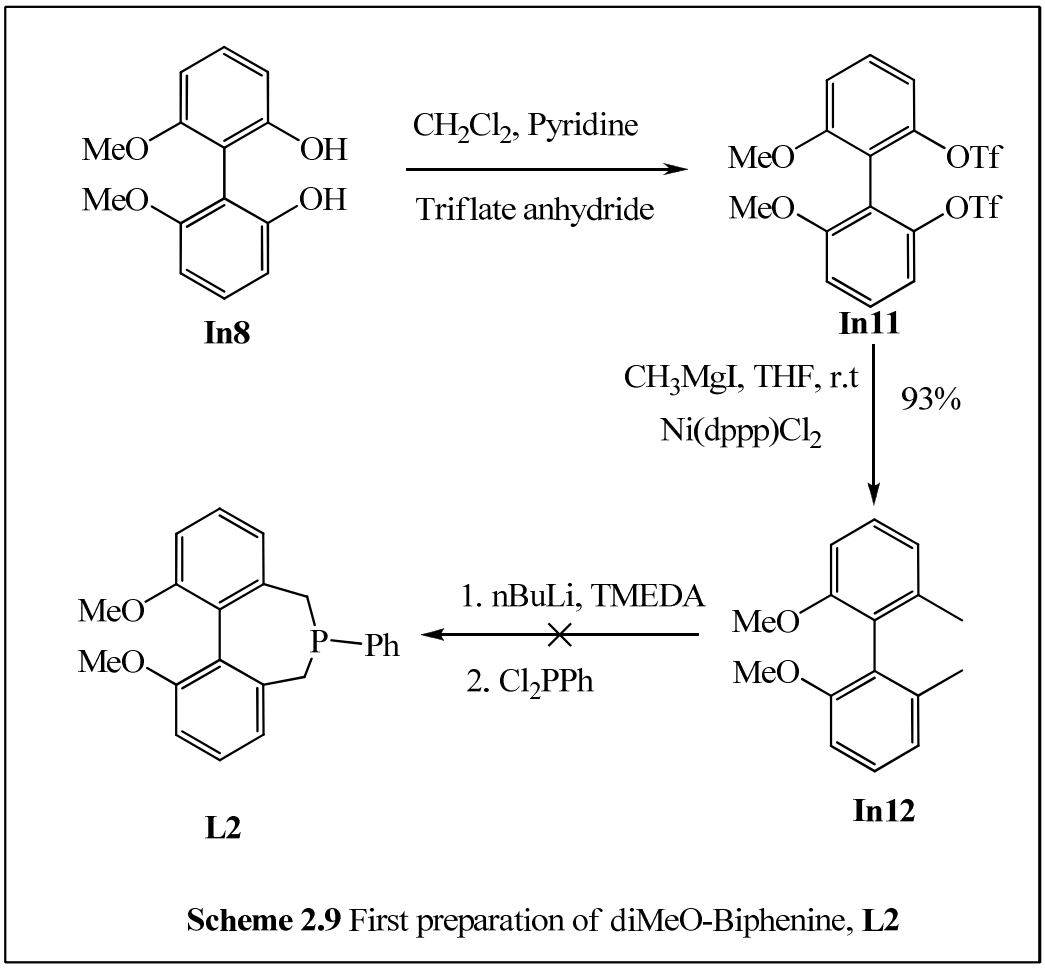
In8, could then be processed further to the required starting material of the last step; for the targeted ligand. Unfortunately, the oxidative coupling yielded multiple polyphenolic products which were not possible to be separated and identified.

Failed attempts in the initially proposed routes and direct oxidative coupling of **SM5** to **In8;** we decided to adopt a known synthetic route from the literature to prepare the intermediate, **In8**. In the literature, G. Delogu, et al. in 1998 prepared 2,2'-Dimethoxy-6,6'-dihydroxy-1,1'-biphenyl [39] (**In8**) in three steps, as shown in **Scheme 2.8**.



Scheme 2.8 Synthetic method by G. Delogu, D. Fabbri, et. al.

The literature synthesis involved a linker like a methylene group to hold the two molecules of **SM5** in the first step. Second step involved lithiation with nBuLi, that easily metalates the doubly directed and most acidic 2-position, followed by *in-situ* homo-coupling of the lithiated species by stochiometric CuI in pyridine to give **In10**. Last step was five day reaction step, involving selective deprotection of methylene group to give the desired intermediate **In8** in 50% overall yield.

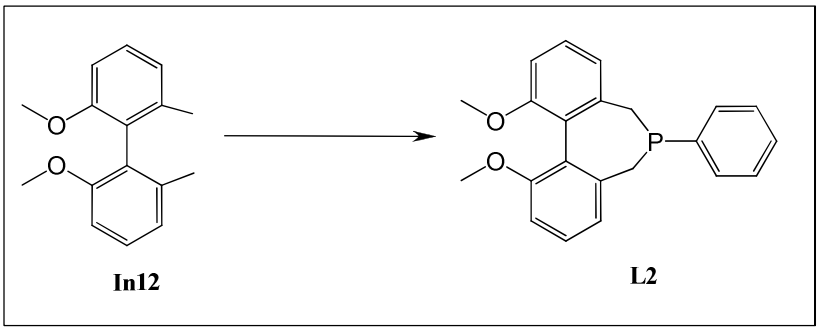


Scheme 2.9 First preparation of diMeO-Biphenine, **L2**

Proceeding further with **In8**, as in case of Ph-BINEPINE; following synthesis of ditriflate derivative **In11**, methyl Kumada cross-coupling to **In12** and finally lithiation and reaction with dichlorophenylphosphine as shown in **Scheme 2.9** was expected to give the targeted ligand. Hence, the 3-steps were carried out in order to prepare

substantial amount of 2,2'-Dimethoxy-6,6'-dihydroxy-1,1'-biphenyl, **In8**. **In8** was obtained but the overall yield of these synthetic steps was not found to be as good as reported in the article and moreover it was contaminated with impurities even after purification by flash chromatography. These impurities did not interfere in the next step and were completely eliminated in the next step, while purifying the ditriflate product (**In11**) by crystallisation in ethanol but in turn giving a lower yield.

Pure **In12**, was prepared in 93% yield of Kumada coupling. Surprisingly, the last step to prepare the targeted ligand failed to give the desired product and only starting material was recovered at the end of the reaction. Several unsuccessful attempts were made to carry out the reaction in varying reagent and solvent as shown in **Table 1**.



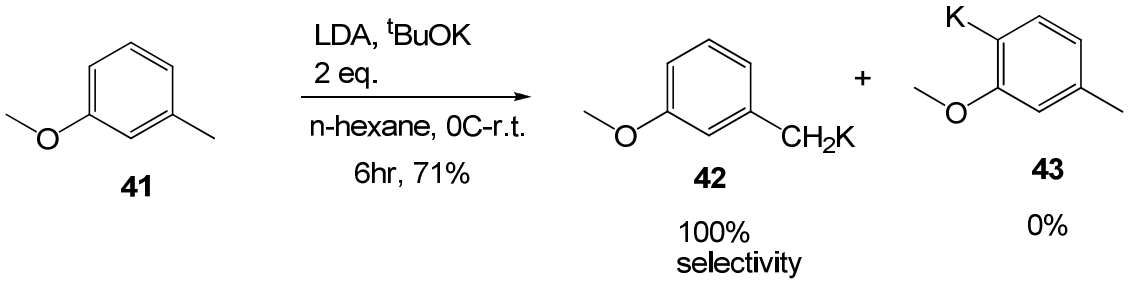
In12 **L2**

Table 1

Reaction conditions	Observation	Conclusion
1. ***nBuLi/TMEDA/Et_2O, 0℃ - r.t*** 2***. n-hexane, Cl_2PPh, -70℃ - r.t*** (Binepine conditions)	Lithiation seemed to occur but gummy intermediate failed the stirring and 2nd step	✗

1.***tBuOK/nBuLi/TMEDA, n-hexane, -40℃ - r.t.*** 2. ***THF, Cl_2PPh, -70℃ - r.t***	Light yellow precipitate in yellow-orange solution SM recovered	✗
1. ***nBuLi/TMEDA, hexane-THF, -50℃ - r.t.*** 2. ***THF, Cl_2PPh, -70℃ - r.t***	Light yellow precipitate in yellow-orange solution SM recovered	✗
1. ***nBuLi/TMEDA/Et_2O, 0℃ - r.t***	Light yellow precipitate in yellow-orange solution SM recovered	✗

It was observed that possibly the lithiation was occurring at ortho position to methoxy group on benzene and not on the benzylic position; as MeO is an ortho directing group. The superbase approach of a mixed-metal reagent for chemoselective lithiations was introduced by Schlosser, and the reagent shows enormous reactivity toward deprotonative metalation. One such selective lithiation studies was carried out by Schlosser and group on m-methoxytoluene[40] (**scheme 2.10**). This confirmed that the conditions that we have been using i.e. BuLi/TMEDA or BuLi/TMEDA/t-BuOK leads to lithiation at ortho position to MeO group as in case of 3-methoxy toluene (resemblance to our case). And, the correct superbase was mentioned in the article that is required to selectively lithiate the benzylic methyl.



Scheme 2.10 Selective benzylic lithiation **1998**, Manfred Schlosser, *et. al.*

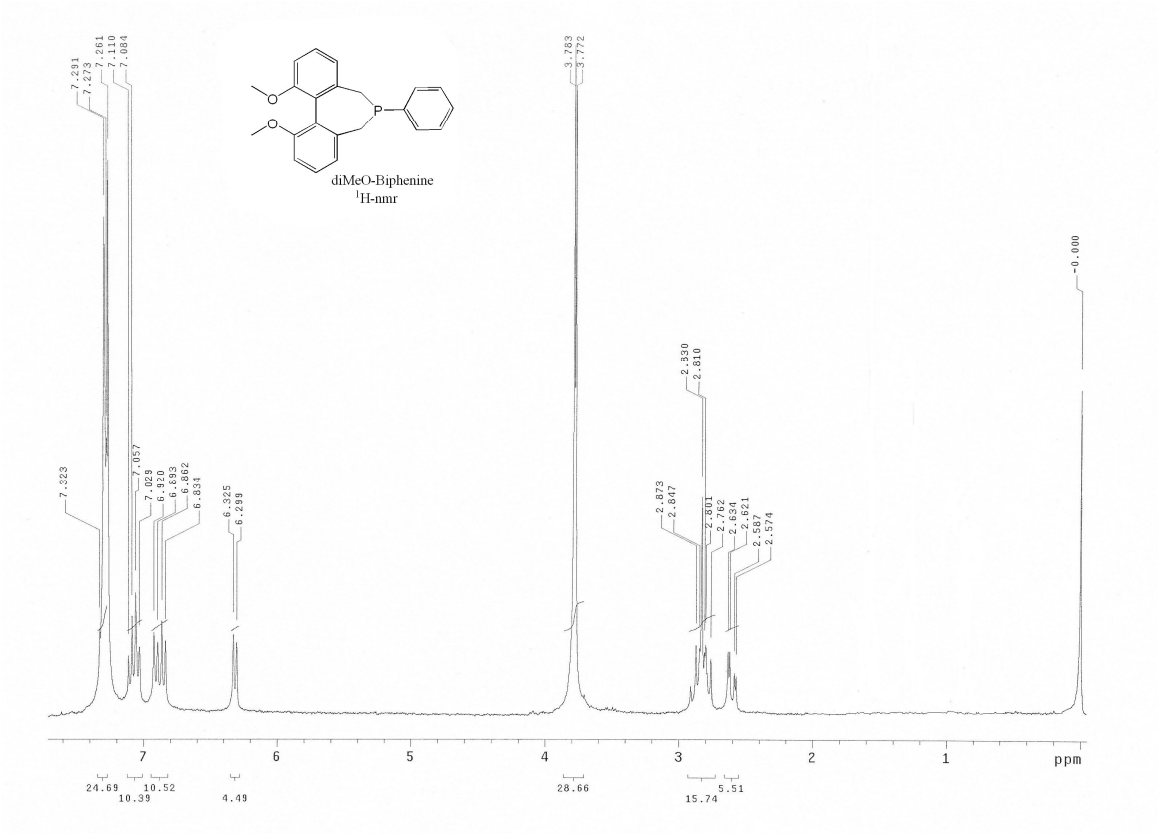
Lithiation, when carried out by LiTMP-KOR or LiDA-KOR; an exclusive benzylic lithation is reported to form. Hence, the lithiation of the **In12** was carried out using LiDA-KOR, and was found to lithiate the benzylic methyl with lithiated species being brown-red in colour. Inspite, of appropriate lithiating conditions the reaction after quenching with dichlorophenylphosphine did not go ahead to give the desired product, **L2**.

Reaction conditions	Observation	Conclusion
1. ***LDA/ ^{t}BuOK 0℃ - r.t*** 2. ***Cl_2PPh, -70℃ - r.t***	Dark red colour precipitate SM recovered	☑Lithiation at benzylic methyl position **No desired product** obtained after quenching

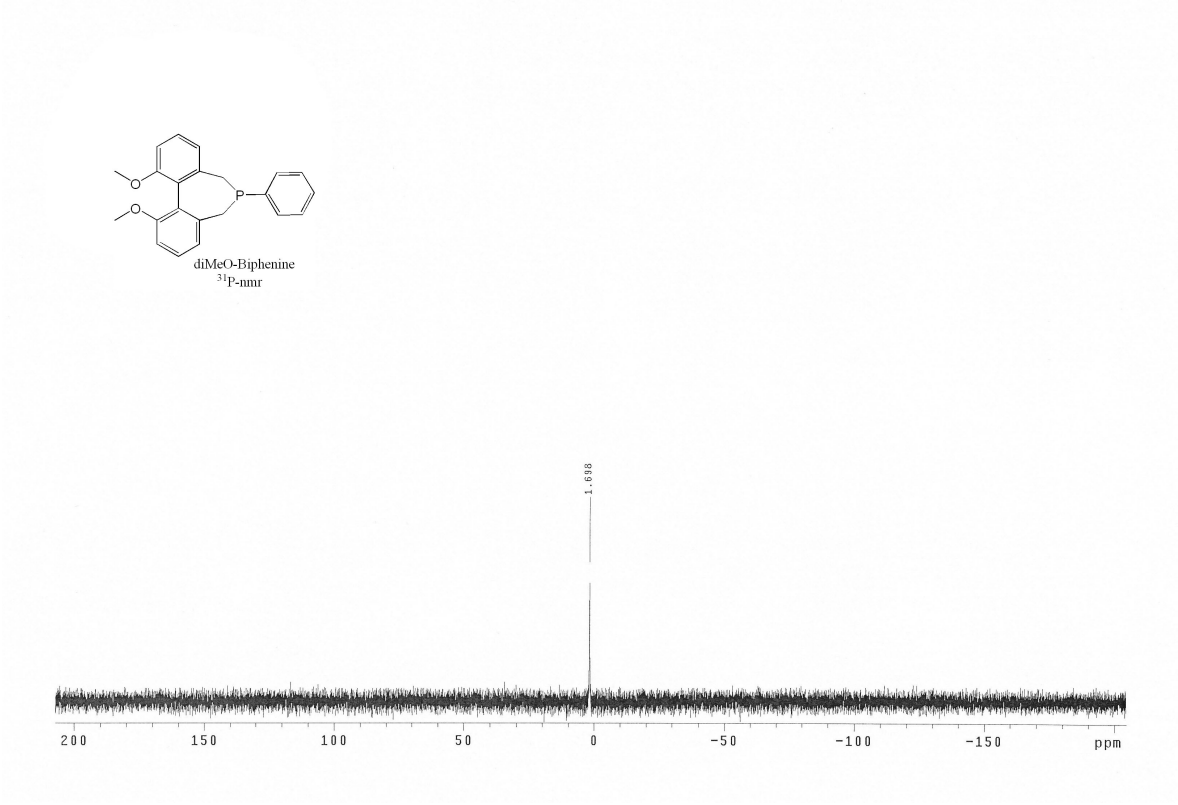
This was possibly due to low yield of dimetalated species and the side reactions of excess lithiating reagents with dichlorophenylphosphine. After understanding the possible problem, metalation of the substrate was carried out

using LiDA-KOR and the metalated species was filtered under argon using schlenk technique. This red-brown precipitate was then transferred back into a schlenk tube and quenched with dichlorophenylphosphine at ***0 ℃*** and stirred at room temperature. This procedure successfully gave the desired product i.e. rac-MeO-Biphenine, **L2** in 28% yield after flash chromatography (^{1}H-nmr **spectra 3**, ^{31}P-nmr **spectra 4**, and ^{13}C-nmr **spectra 5** for **L2**).

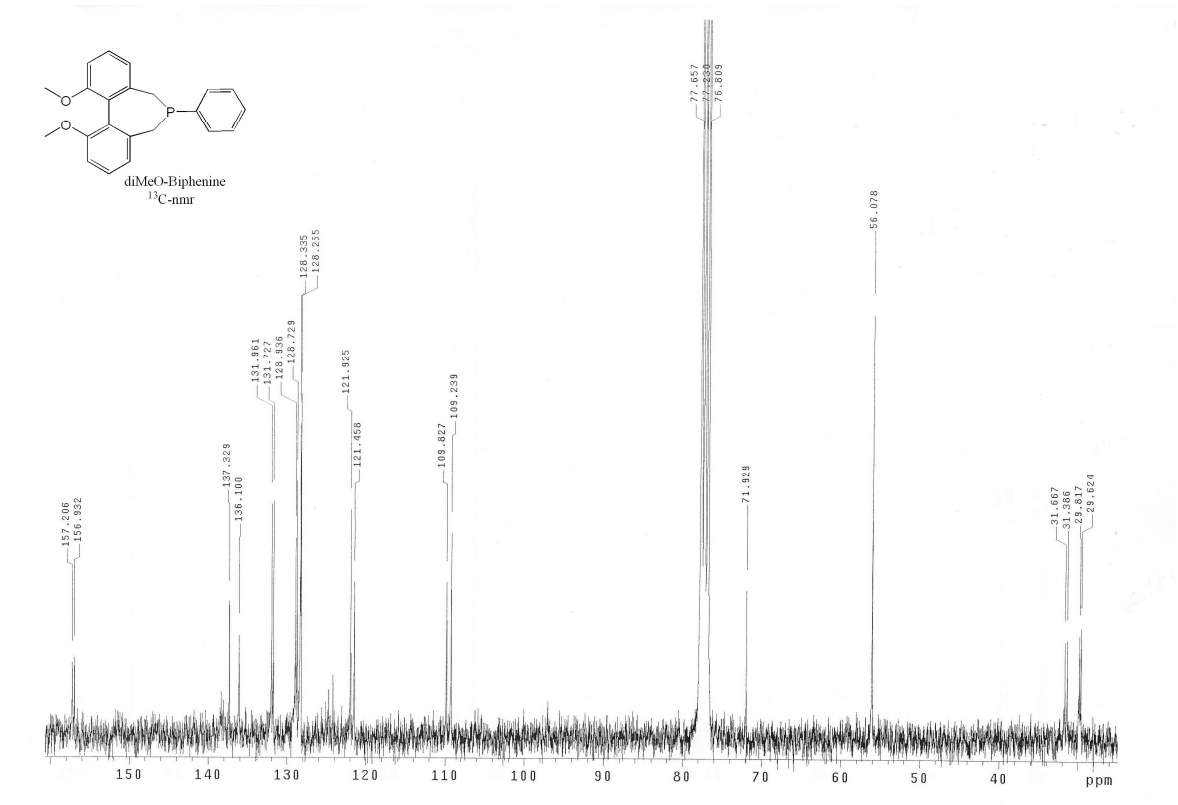
Spectra 3: ^{1}H-nmr of diMeOBiphenine



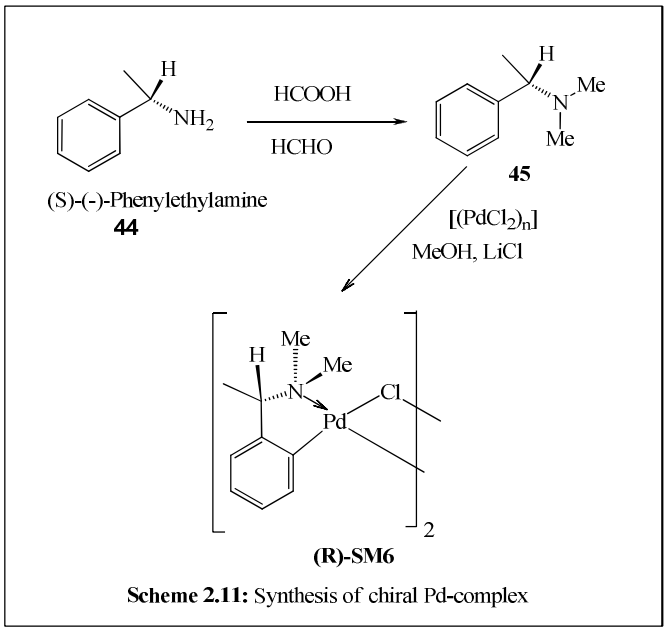
Spectra 4: ^{31}P-nmr of diMeO-Biphenine



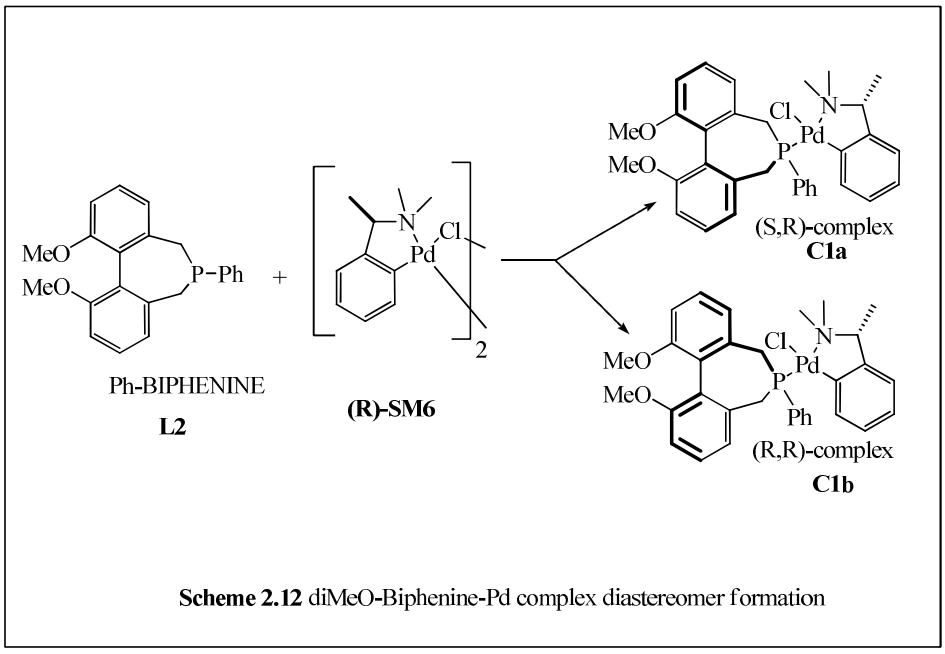
Spectra 5: ^{13}C-nmr of diMeO-Biphenine



Above synthetic route needed additional resolution steps to be undertaken at some stage in order to obtain enantiopure ligand. rac-diMeOBiphenine was reacted with chiral Pd-complex (**scheme 2.12**) ((**R)-SM6** was prepared according to the literature as shown in **scheme 2.11**). And, we tried to resolve the diastereomers by crystallization using various solvents, respectively. But, the diastereomers **C1a** and **C1b** were not resolved in this way.



Scheme 2.11: Synthesis of chiral Pd-complex



Scheme 2.12 diMeO-Biphenine-Pd complex diastereomer formation

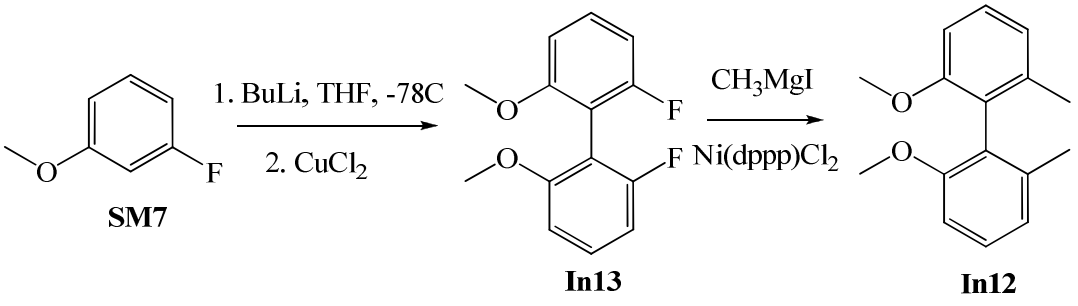
First synthesis of diMeOBiphenine was successfully accomplished to obtain racemic diMeO-Biphenine, but it was necessary to continue exploring other synthetic route for the following reasons:-

1. The obtained ligand was racemic and since the attempts to resolve the prepared rac-diMeOBiphenine by chiral Pd-complex failed; another resolution method was required either for the prepared ligand or for one of the intermediates.

2. It is a 6-step synthesis with only 10% overall yield to the racemic ligand, with future need of extra steps for resolution.

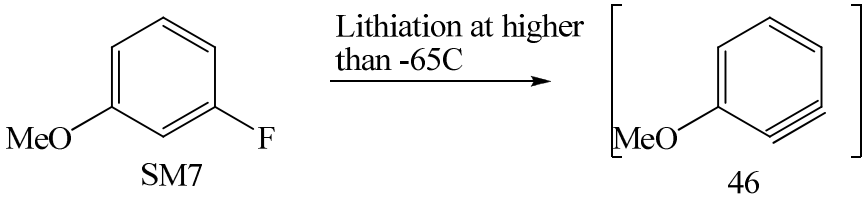
3. **In8** had issues with yield and purity. And, moreover inspite of only 3 steps, it was very time consuming with regards to its preparation, as the third step required five days.

Owing to the issues of yield, purity and time of preparation for **In8**, it was needed to investigate for another possible and shorter synthetic route in order to reach the diMeO-Biphenine, **L2** faster. A new synthetic approach was designed and executed with initial success as shown in the **Scheme 2.13**.



Scheme 2.13 Two-step preparation of **In12**

The first step was performed as per an article [41] that completely failed, with no traces of the desired product, **In13**. Several attempts were made for *in-situ* coupling of lithiated m-fluoroanisole using various catalyst like CuI, $FeCl_3$, and CuCl respectively, without any success. The reaction was successful with the same reagents as mentioned in the article i.e. $CuCl_2$, but at completely different temperature i.e. (-78°C) and different reaction time. Lithiation at -78°C is at most important because over -65°C a side reaction via benzyne formation occurs (as shown in **scheme 2.14**) as also reported in literature.



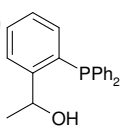
Scheme 2.14 Side reaction via benzyne formation

It was important to check the success of the second step to prepare **In12**, as it is a well known fact that Aryl fluorides (due to the strong C-F bond) are difficult to undergo coupling reactions and only few successful examples are reported in literature[42]. In this case, we were initially successful and complete methylation was achieved with only traces of mono-substituted product except that about 10-20 mol% of Ni(dppp)Cl_2 complex was required to be used and the reaction was slow. Thus, **In12** was obtained in just two-steps with good overall yield and purified by flash chromatography as compared to low yielding five-steps in the initial case.

After repeating the new two-step synthesis to **In12** and while scaling up the reactions; it was observed that the second step i.e. methylation of diFluoro dimethoxy biphenyl intermediate (**In13**) was not reproducible and was extremely

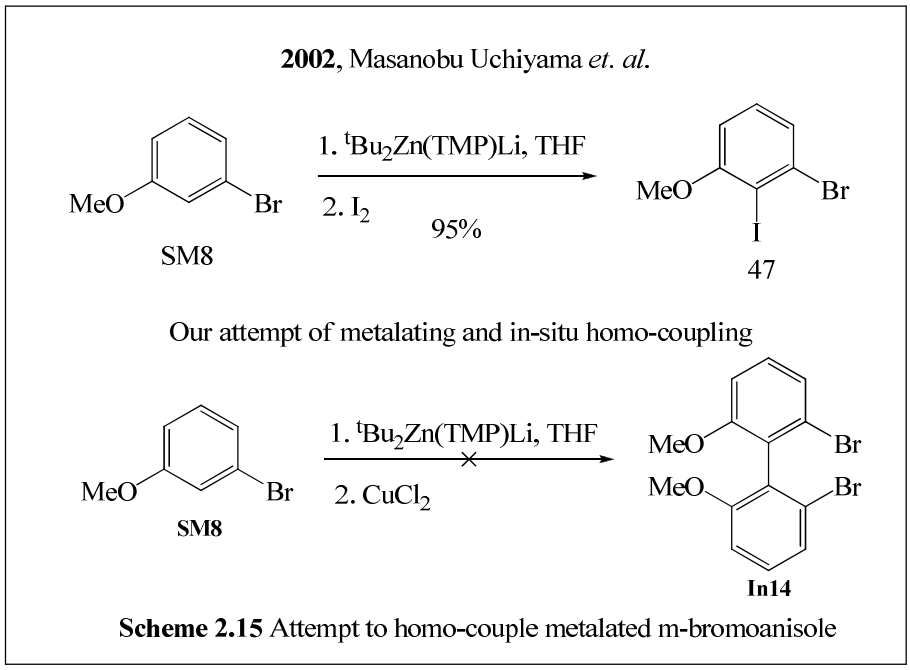
slow. It became challenging to obtain completely converted product, **In12**. This issue was addressed by trying different Nickel and Palladium complexes and trying different solvents like THF, Toluene, etc. as shown in Table 2, with no success in improving the rate of reaction or the conversion. Ni(dppp)Cl_2 complex was still the best of all the used complexes and diethyl ether the only solvent suitable for this conversion.

Table 2

Reagent: CH_3MgI			
Ligand	Solvent	Temperature	Result
Ni(dppp)Cl_2	Et_2O	Reflux	Incomplete conversion, and extremely slow
	THF	r.t. to reflux	No Product
	Toluene	r.t. to reflux	No Product
Ni(acac)$_2$, P(OAr)$_3$, Ar: 2,4-Di-tert-butylphenyl	Et_2O	Reflux	Satisfactory, but extremely slow
	THF	r.t. To reflux	No Product
Ni(acac)$_2$, [43] 	Et_2O	r.t. to reflux	No product
	THF	r.t. To reflux	No product

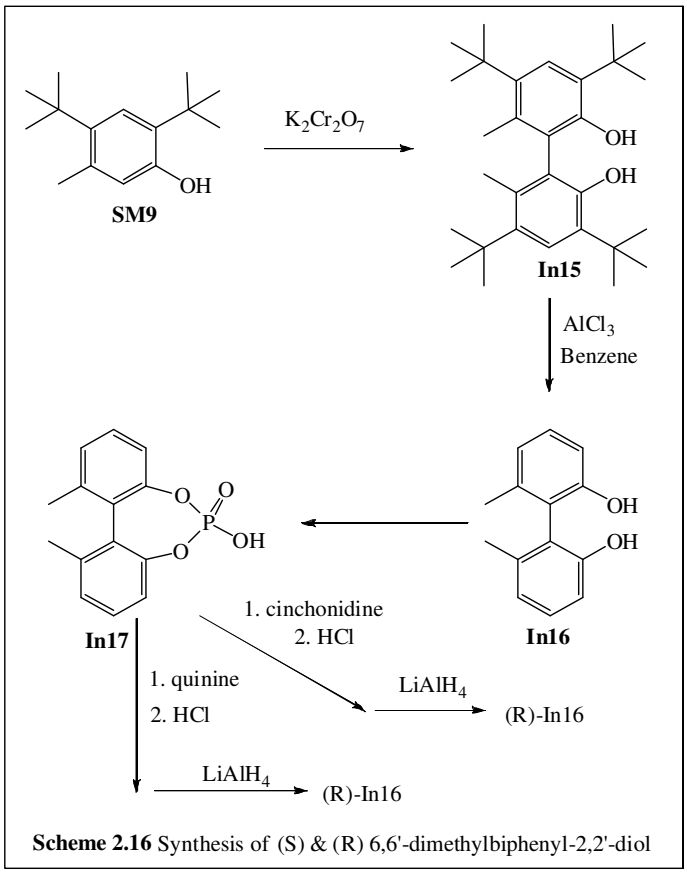
The above mentioned method starting from m-fluroanisole was irreproducible and unreliable and so we tried to start from m-bromoanisole (**SM8**) instead of m-fluoroanisole(**SM7**). Unlike strong C-F bond, C-Br bond would easily undergo cross

coupling reaction to give **In12**, provided that m-bromoanisole could be homo-coupled at 2-position with ease to furnish **In14**, in the first step. Direct lithiation of m-bromoanisole is very difficult as bromo is a too sensitive towards lithiating reagent to give side reactions. So, we tried to metalate m-bromoanisole as per other special methods that are reported in the literature. m-bromoanisole was efficiently derivatized at 2-position using zincating reagent like $^{t}Bu_2Zn(TMP)Li$[44] as shown in **scheme 2.15**.



Scheme 2.15 Attempt to homo-couple metalated m-bromoanisole

We were interested in carrying out same metalation for m-Bromoanisole (**SM8**), and proceed with *in-situ* homo-coupling with a suitable catalyst like $CuCl_2$ to obtain **In14**. Again, the above mentioned synthetic step was unsuccessful to give any trace of the desired product.

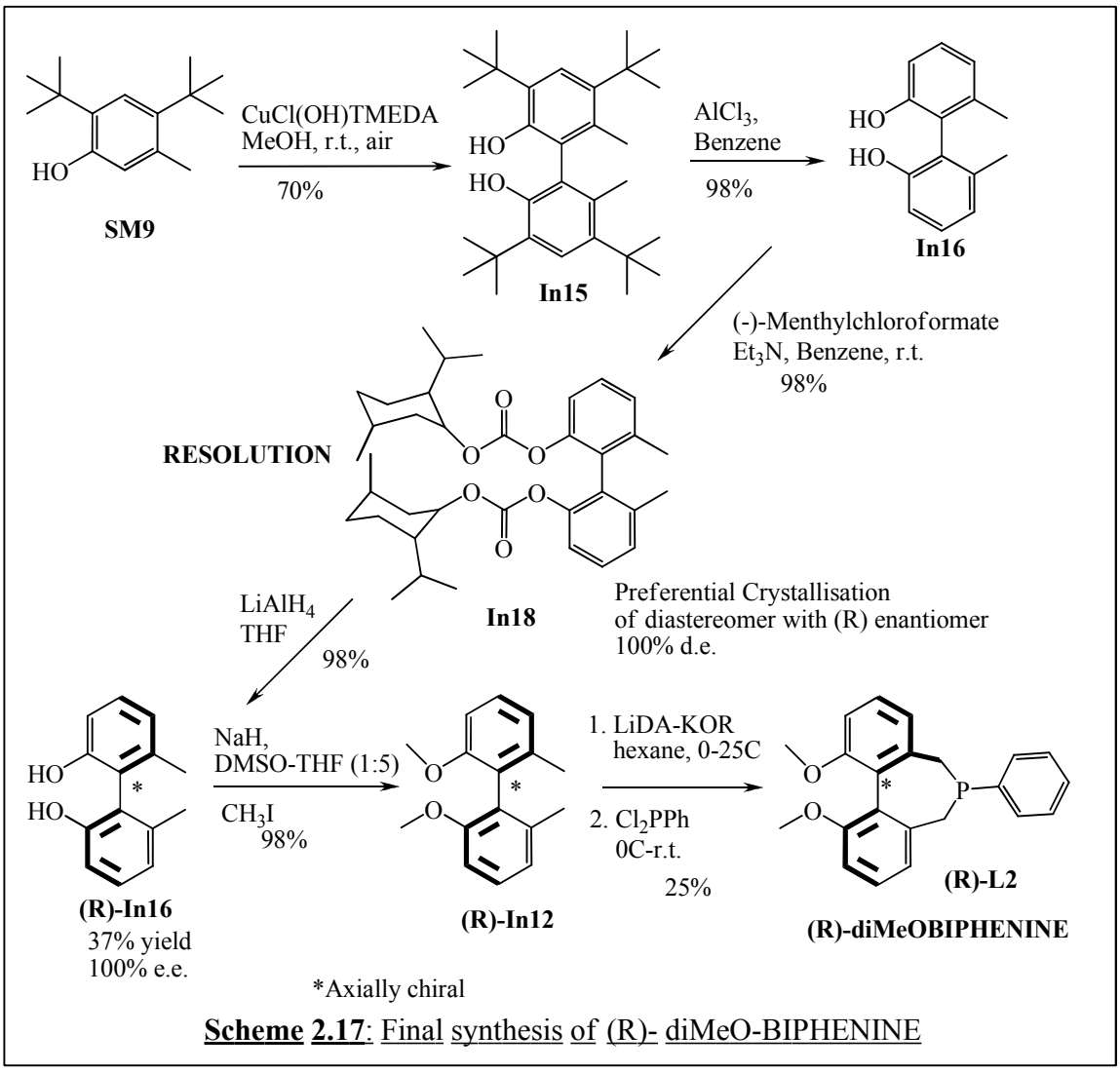


Scheme 2.16 Synthesis of (S) & (R) 6,6'-dimethylbiphenyl-2,2'-diol

We needed to continue exploring another efficient and faster synthetic route, along with enantioselective method to synthesize the targeted chiral ligand, **L2**. We came across an attractive and practical preparation of (S) and (R)-6,6'-dimethylbiphenyl-2,2'-diol, **In17** (>99% ee) respectively, which was conveniently derived from commercially available 4,6-di-tert-butyl-m-cresol (**SM9**) according to the reported procedure[45], as shown in **scheme 2.16**. Though the published resolution gave fairly good yield of respective enantiomers with >99% enantiopurity, it was quiet a tedious experimental procedure with extra steps to be followed. We were interested in exploring a simpler resolution method for the obtained racemic intermediate. We initiated and executed our work towards this synthetic procedure as shown in the **scheme 2.17**. We used pre-prepared CuCl(OH)TMEDA complex for oxidative coupling of 4,6-di-tert-butyl-m-cresol (**SM9**) i.e. the first step.

Initially, when the first step i.e. oxidative coupling was performed in dichloromethane as the solvent, we encountered many impurities that were difficult to be separated by flash. But using methanol as the solvent was very advantageous. The starting material (**SM9**) is soluble in methanol, but the coupled product (**In15**) is insoluble in methanol. And possibly this is the reason why it leads to a much cleaner

reaction and easy separation by simply filtering the product (**In15**) as precipitate to give a pure coupled product **In15** in 70% yield. The coupled product obtained at this stage is very clean and needs no further purification.



Scheme 2.17: Final synthesis of (R)- diMeO-BIPHENINE

In15 was then subjected to Fridel-craft type reaction in order to deprotect the tButyl groups using excess of $AlCl_3$ in benzene to give the desired deprotected product (**In16**), quantitatively. Since, the deprotected product (**In15**) is worked up by extracting in the 10% NaOH aqueous solution from the organic phase, the obtained product is very clean and needs no further purification. At this stage, we needed the racemic **In15** to be resolved in a simpler way.

We used (-)-(R)-menthyl chloroformate for the resolution. One advantage with diastereomers of menthyl chloroformate is that they can possibly be separated by flash chromatography. Diastereomers of **rac-In16** with (-)-(R)-menthyl chloroformate was prepared with ease. Unfortunately, even after trying numerous combinations of solvent systems, thin layered chromatography showed that it was not possible to separate the diasteromers using flash chromatography. But, crystallization in n-hexane gave 38% of diastereomerically pure crystals of (R,R)-diastereomer with >99% d.e. i.e. about 76% yield). The mother liquour contained (S,R)-diastereomer with 60% d.e. The obtained diastereomerically pure compound was then subjected to removal of the chiral auxiliary to give back the enatiomerically pure **(R)-In16**. (R)-**In16** was pure and the stereochemistry was ascertained by measuring the optical rotation. Optical rotation measurement agreed with that published in the literature and confirmed the **In16** to be of (R) configuration and >99% e.e.

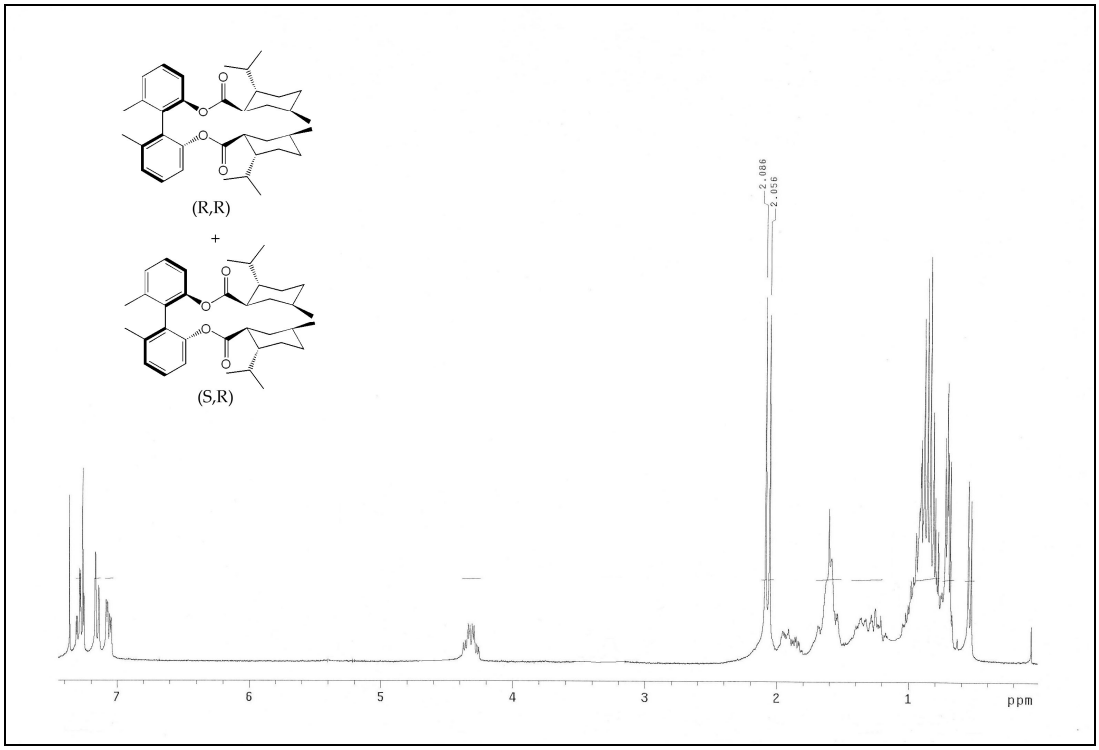
Examining the ^{1}H NMR spectras of the two diastereomers of **In16** with methyl chloroformate; it was noted that the chemical shifts of dimethyl peaks on the biaryl, of the corresponding diastereomers were clearly different and could be used to detect the diastereopurity and inturn the enantiopurity of the **In16 (spectra 6-8)**. This was ascertained by the optical rotation of the obtained chiral **(R)-In16**. Chemical shifts for the dimethyl peaks for (S,R) and (R,R) diastereomers are **2.087** and **2.057**, respectively.

Next step involved simple O-methylation of hydroxyl groups. Initially the reaction was performed in acetone in the presence of excess of K_2CO_3 and iodomethane. These reaction conditions gave the desired methylated product only in about 70% yield. We changed the methylation conditions by using a stronger base

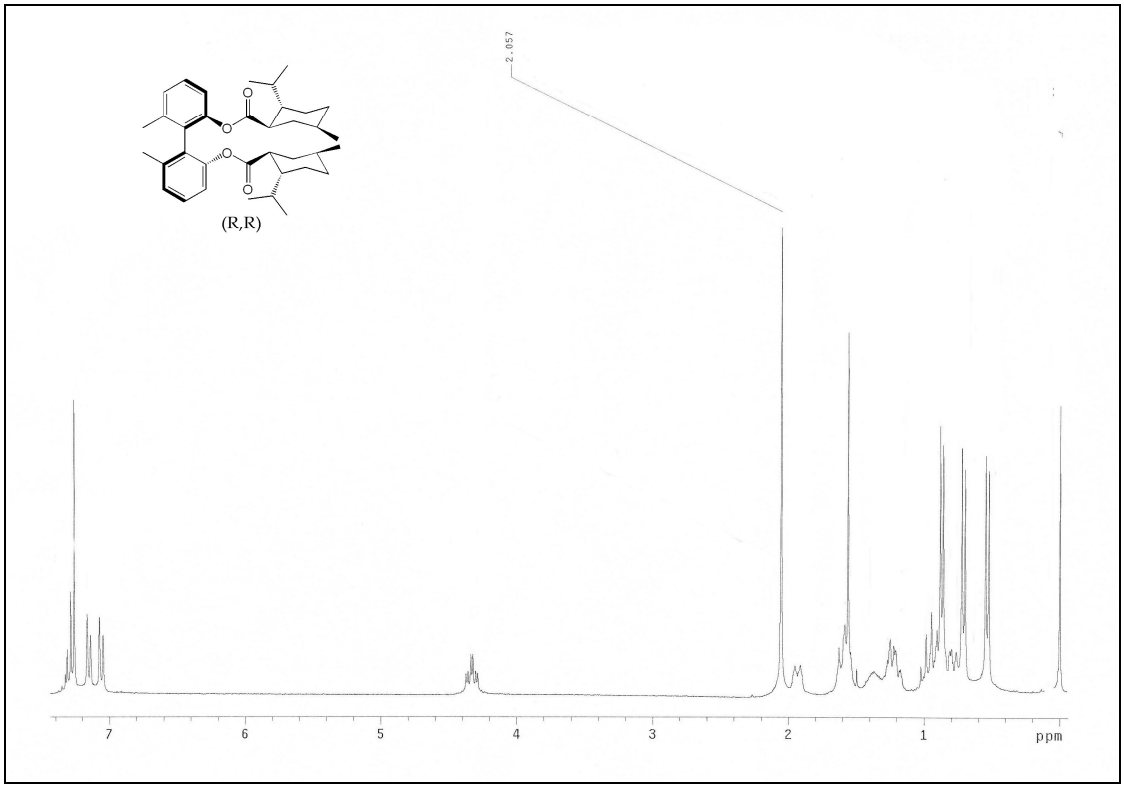
like NaH in THF-DMSO (5:1) solvent system. This change in the reaction condition helped us to achieve complete methylation, quantitatively and hence to avoid any loss of the chiral starting material.

As discussed above, the last step was performed using the optimized conditions to give the desired (R)-diMeO biphenine, **(R)-L2** in 26% yield after flash chromatography. Hence, now we can prepare (R)-2,2'-dimethoxy-6,6'-dimethyl-1,1'-biphenyl in five steps with as high as 65% overall yield. This is a valuable starting material for the last step, which can then processed to give the desired ligand, except only in 28% yield at best.

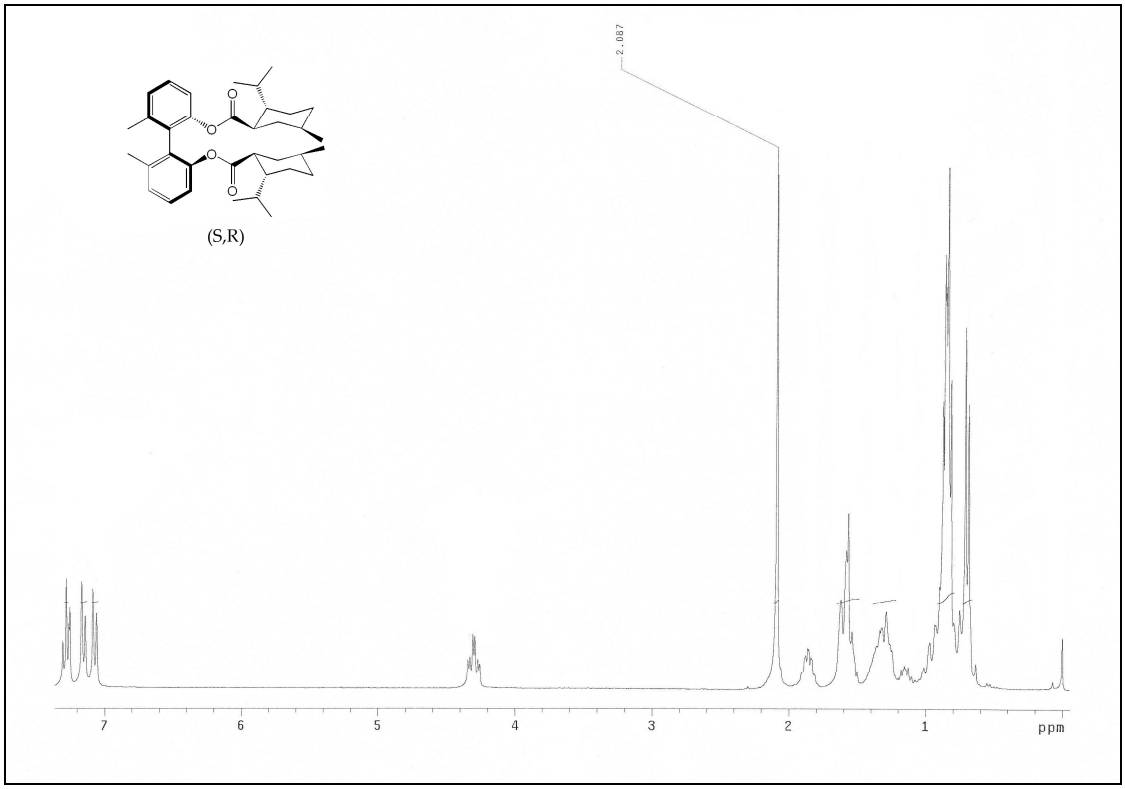
Spectra 6: Racemic mixture of diastereomers of In16 with (-)-(R)-Menthyl chloroformate



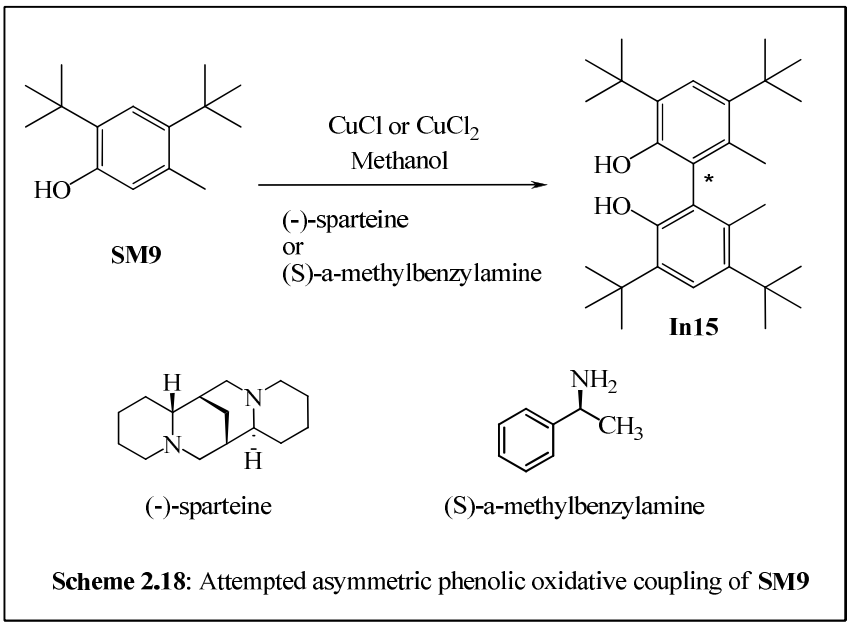
Spectra 7: (R,R)-diastereomer of (R)-In16 with (-)-(R)-Menthyl chloroformate (Crystallized)



Spectra 8: (S,R)-diastereomer of (S)-In16 with (-)-(R)-Menthyl chloroformate



The above synthetic route worked very well to obtain (R)-diMeO-Biphenine. We tried to perform the first step (i.e. Phenolic oxidative coupling) in an asymmetric manner that would possibly reduce the two steps involving resolution of **In16**. There are some methods reported that employ Copper-chiral amine complexes for asymmetric oxidative coupling of phenolic compounds[46]. We applied Copper-chiral amine complex (prepared in-house) in order to check the ability to induce enantioselectivity and prepare chiral **In15**. We investigated this asymmetric oxidative coupling with *in-situ* prepared $CuCl_2$-(-)sparteine complex and $CuCl_2$-(S)-α-methylbenzylamine complex (**scheme 2.18**). We also tried using pre-prepared and separated complexes of each. And, we tried with CuCl as the precursor in place of $CuCl_2$.

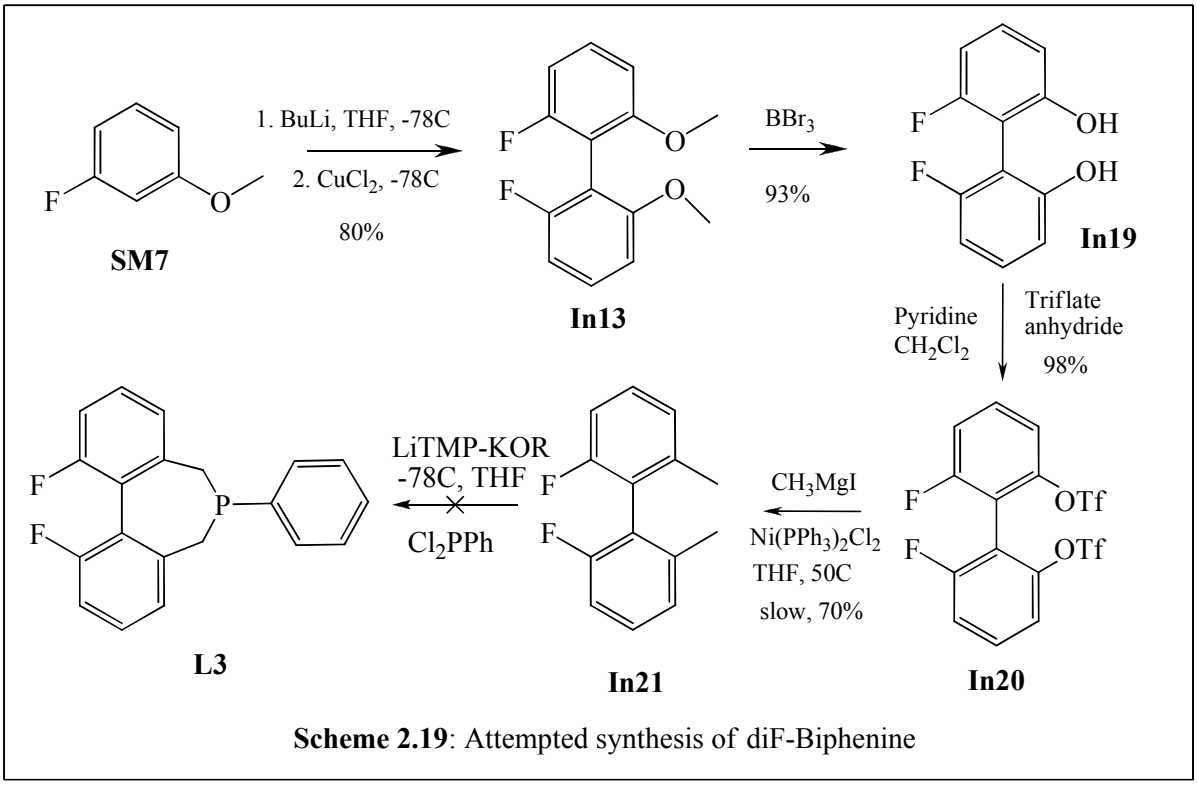


Scheme 2.18: Attempted asymmetric phenolic oxidative coupling of **SM9**

These Copper-chiral amine catalyst systems worked to give the **In15**, in the same yield as in case with CuCl(OH)TMEDA; but unfortunately no enantioselectivity was observed. **In15**, that was obtained was completely racemic without any trace of enantiomeric excess.

2.1.3 *Attempted synthesis of diF-Biphenine (L3)*

While exploring synthetic route to diMeO-Biphenine, we decided to proceed with one of the intermediate in order to make another possible ligand as diF-Biphenine. The synthetic scheme is as shown below.



Scheme 2.19: Attempted synthesis of diF-Biphenine

As we prepared diFdiMeObiphenyl intermediate (**In13**) for the preparation of diMeO-Biphenine (**L2**); we decided to divert and explore the synthesis of diF-Biphenine (**L3**). This was initiated by demethylation of diMeO in **In13** to give diFdiOHbiphenyl (**In19**). The reaction proceeded successfully in 93% yield to give **In19**. Then, we proceeded with two steps further as shown in the **scheme 2.19**; forming a ditriflate derivative and methylation using Kumada cross coupling of ditriflate derivate with methyl magnesium iodide, without any difficulty to obtain **In21**. The case of **In21** was same as in the case of **In12** in the preparation of diMeO-

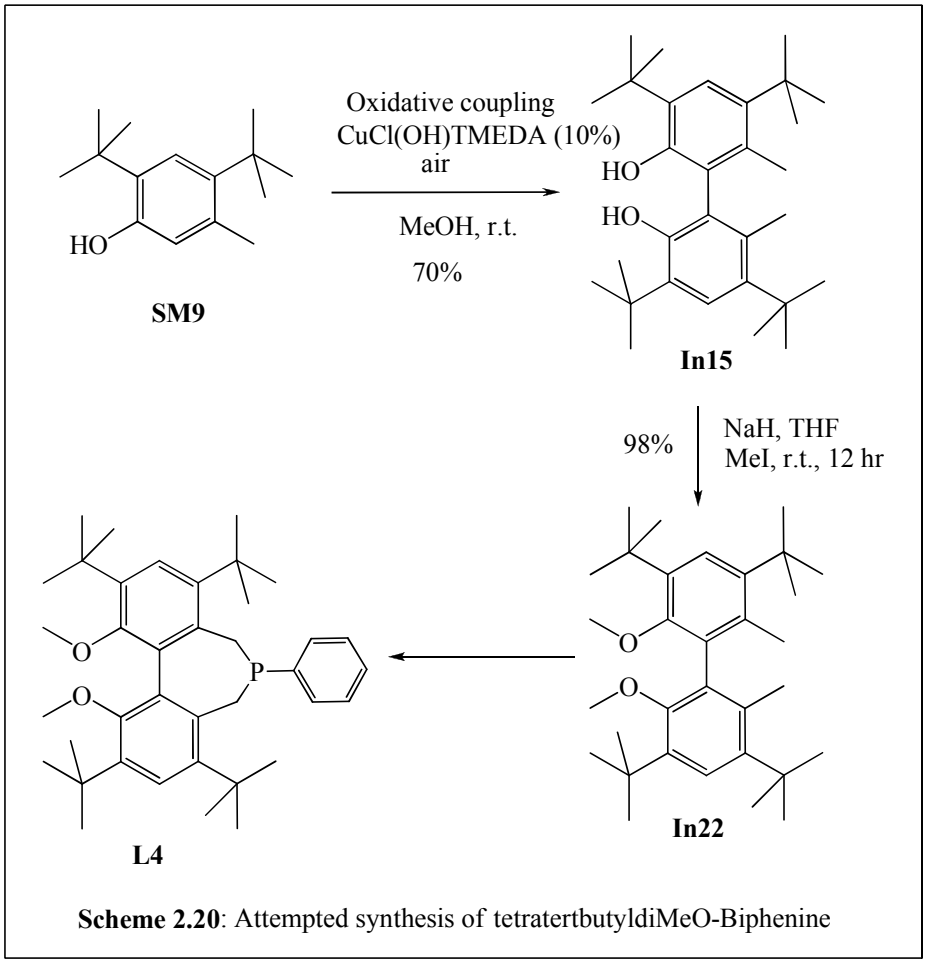
Biphenine. Fluoro is also ortho directing group and care must be taken in order to avoid lithiation on the benzene in order to perform the last step to synthesize diF-Biphenine.

We used the same lithiating reagents as described for diMeO-Biphenine, except that the reaction was carried out at -78C, due to the presence of Fluoro functional group[47]. The lithiation seemed to give red colouration in the reaction as expected, but failed to give the product after quenching with dichlorophenylphosphine. We carried out several attempts but we were unsuccessful to obtain the desired ligand diF-Biphenine.

Due to the presence of the difluoro substituents on the biphenyl in **In21**, the dimetalated derivative of **In21** was either extremely sensitive or not at all formed, thus failing to be quenched by dichlorophenylphosphine, appropriately and as desired

2.1.4 *Attempted synthesis of tetratertButyl-diMeOBiphenine (L4)*

While exploring chiral synthetic route to diMeO-Biphenine, we decided to proceed with one of the intermediate i.e. **In15** in order to make another possible ligand as terta^{t}BudiMeO-Biphenine.



Scheme 2.20: Attempted synthesis of tetratertbutyldiMeO-Biphenine

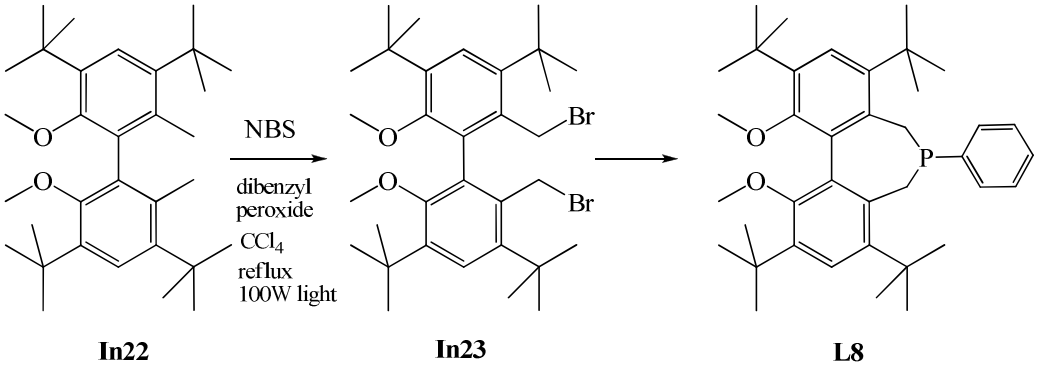
As we prepared intermediate **In15** for the preparation of diMeO-Biphenine (**L2**); we decided to divert by avoiding deprotection of tert-butyl groups from **In15** and proceeding as shown in the **scheme 2.20** to synthesize a new ligand, ttBudiMeO-Biphenine (**L4**). **In22** was prepared quantitively by O-methylation of **In15**. And **In22** was ready to be subjected to the last step in order to prepare ttBudiMeO-Biphenine.

It was necessary to lithiate the benzylic methyl of **In22** and then quench with dichlorophenylphosphine to obtain the desired ligand. We tried several lithiating reagents as shown in **table 3**.

Table 3: Lithiation of In22

Reaction conditions	Observation	Conclusion
nBuLi-TMEDA-Et_2O, 0℃ - r.t	No change in colour. SM recovered	No lithiation X
nBuLi-TMEDA-tBuOK	No change in colour SM recovered	No lithation X
tBuLI	No change in colour SM recovered	No lithation X
LDA-tBuOK	No change in colour SM recovered	No lithation X
LiTMP-tBuOK	No change in colour SM recovered	No lithation X

All possible strong lithiating reagents were tried but it was not possible to lithiate the benzylic methyl of **In22**. To address this problem, we brominated **In22**, as shown in the **scheme 2.21** and then we tried to perform the last step with different reacting conditions to give the desired phosphepine.



Scheme 2.21 Attempted last step via **In23** in different reaction conditions for **L8** synthesis

Table 4: Last step reaction conditions with In23

Reaction conditions	Observation	Conclusion
NaH, H_2PPh, THF, r.t.-reflux	No SM recovered.	No desired product **X**
$NiCl_2$(dppe), Cl_2PPh, Zn, DMF, 110°C	No SM recovered.	No desired product **X**

Also, **In23** failed to give the desired product (**L4**) in the above performed reaction conditions as shown in **table 4**. Hence, a detailed investigation in this last step is required to be undertaken.

2.1.5 *Attempted synthesis of Heterocyclic phospheines (L5 & L6)*

Next ligand of our interest was heterocyclic phosphepine. There has always been an interest in heterocyclic ligands but there are no known heterocyclic phosphepines. So we decided to explore two kinds of heterocyclic ligands as shown in **fig. 2.5**. **L5**, having C_2-symmetry, while **L6** having C_1-symmetry. C_2-symmetry of **L5** consisted homo-coupled benzo[b]thiophene and C_1-symmetry of **L6** consisted of naphthalene coupled with benzo[b]thiophene as the backbone, respectively.

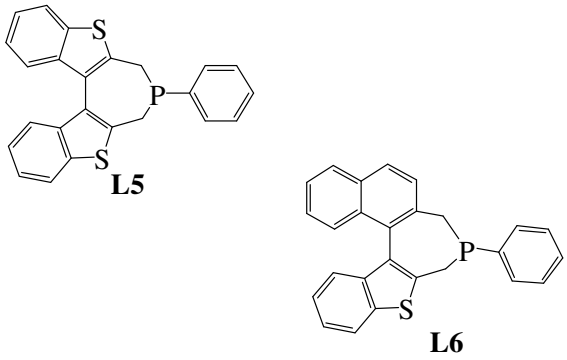
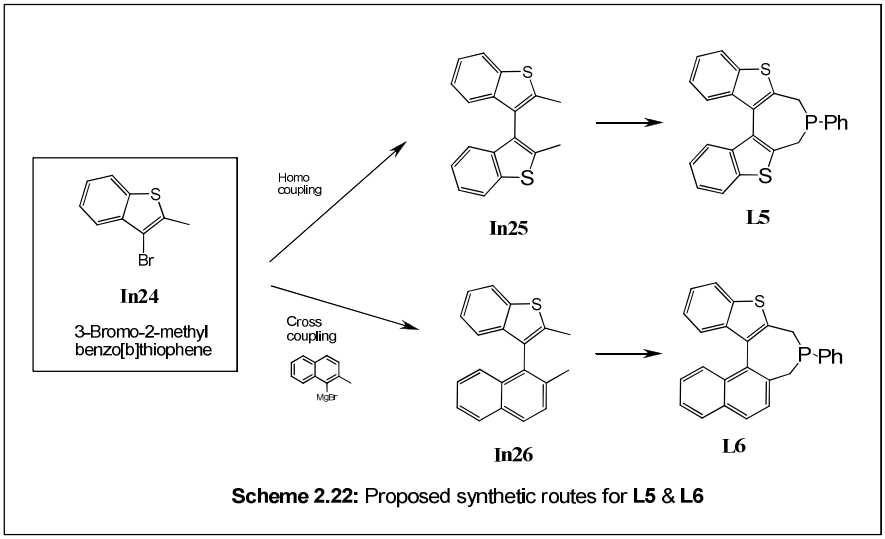


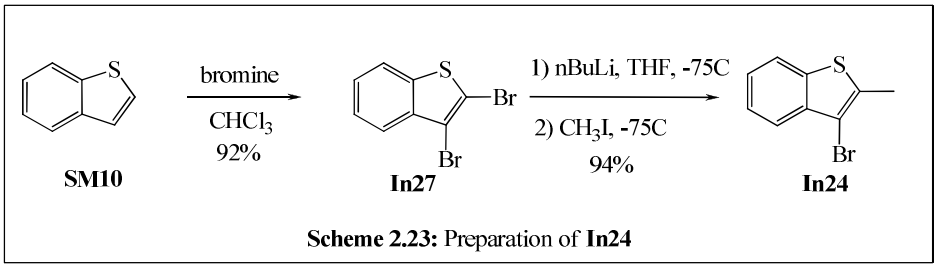
Figure 2.5 Heterocyclic Phosphepine ligands

Using retrosynthetic approach, the best starting material in order to prepare ligands **L5** & **L6** was determined as **In24**. **In24**, seemed to be a good intermediate in order to efficiently and practically prepare both the targeted ligand (**scheme 2.22**). Moreover, **In24** could be easily prepared from the literature procedures. Widely used homo and cross coupling reactions with a suitable aryl derivative would then provide **In25** and **In26** that are required as starting materials in the last step to prepare **L5** and **L6**, respectively. So the key was to find a good coupling reaction that works well for hindered aryls.



Scheme 2.22: Proposed synthetic routes for **L5** & **L6**

In24, was prepared in two steps with excellent overall yield as shown in the **scheme 2.23**:



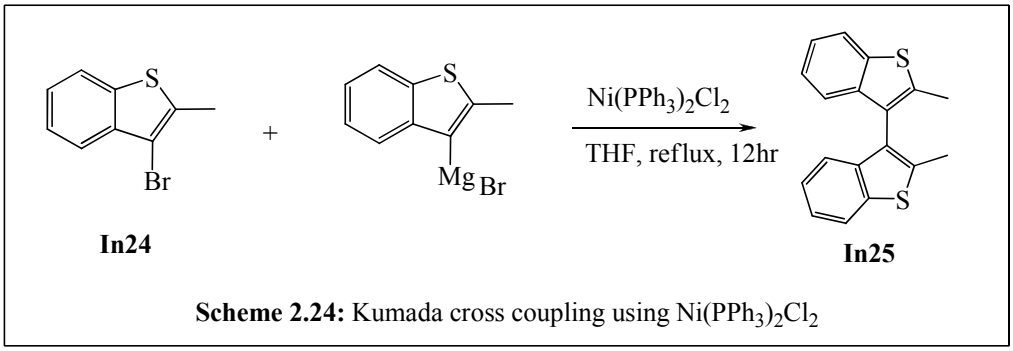
Scheme 2.23: Preparation of **In24**

Benzo[b]thiophene (**SM10**) was brominated in the first step to obtain dibromo-derivative, **In27**[48]. Dibromo benzo[b]thiophene (**In27**) was selectively lithiated and methylated on the 2- position to give the required **In24**[49], in excellent overall yield.

In24, was used for the next step to prepare **In25**, which further is proposed to prepare the targeted ligand **L5** as shown in the **scheme 2.20**. **In25**, was not prepared by homo-coupling but by Kumada cross coupling, firstly in order to test the success of the Kumada cross coupling using $Ni(PPh_3)_2Cl_2$ as it would be the first choice of cross coupling reaction to be undertaken in order to prepare **In26** and secondly, to check the success of the cross coupling reaction in order to later employ

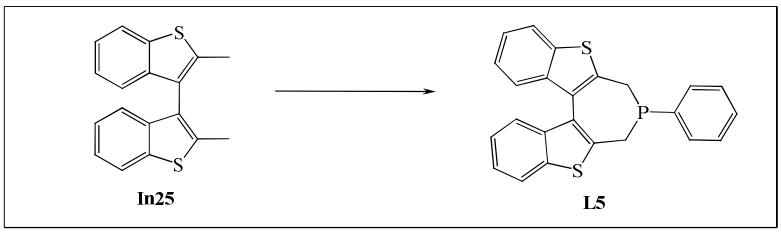
and attempt to perform an asymmetric aryl-aryl cross coupling to prepare the targeted chiral ligand.

Kumada coupling to prepare **In25** was successful with 55% yield as shown in **Scheme 2.24**.



Scheme 2.24: Kumada cross coupling using $Ni(PPh_3)_2Cl_2$

In25 was ready to go through the last step to obtain the desired ligand. But, the last step failed in the attempts as shown below:



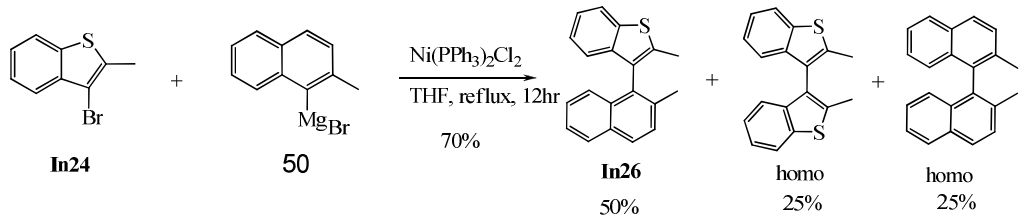
Last step tried 2 times to prepare **L5** as follows:-

Reaction conditions	Observation	Conclusion
1. ***nBuLi/TMEDA/Et_2O*** 2***. n-hexane, Cl_2PPh, -70°C – r.t***	Lithiation seemed to occur but gummy intermediate failed the stirring and 2nd step	✗

1. ***nBuLi/TMEDA/Et_2O*** (twice amount of Et_2O) 2. ***n-hexane, Cl_2PPh, -70°C – r.t***	Dark red precipitate Mono-substituted phosphine product obtained	✗ Possible failure due to large angle bite

The failure was thought to be due to the larger angle bite between the two metalated methyls in **In25**, to form a seven membered ring phosphepine. We obtained only mono-methyl substituted product that was confirmed from NMR. Hence, a different approach would be needed in order to prepare the ligand **L5**.

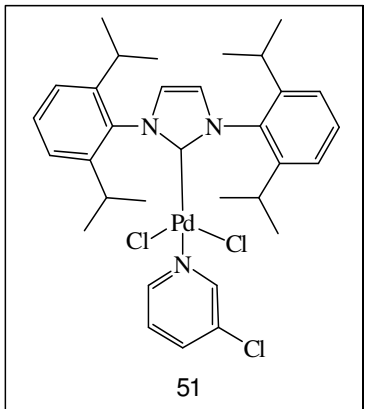
After the success in preparing **In25**, **In24** was used to carry out the preparation of **In26**, by Kumada cross coupling reaction with 2-methylnaphtalene magnesium bromide using the same catalyst system, but a mixture of cross and homo coupled products were obtained as shown in **scheme 2.25**.



Scheme 2.25: Kumada cross coupling using $Ni(PPh_3)_2Cl_2$ for **In26**

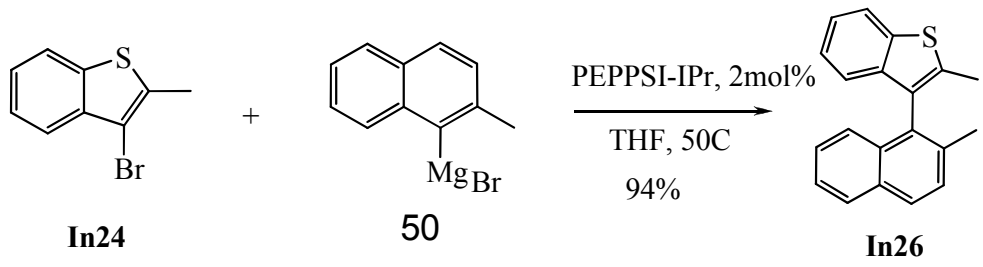
After Kumada cross coupling with $Ni(PPh_3)_2Cl_2$ catalyst system failed to give a clean product, **In26**; Kumada cross couplings was carried out using various Ni-catalyst system using dppp, dppe, and dppb ligands respectively, but only mixture of products were obtained due to the need of high temperature in the reaction.

After some literature survey, we found that commercially available PEPPSI-IPr (**51**) performed very well in a wide range of cross coupling reactions including Kumada[50], Negishi[51], and Suzuki. It was also mentioned in the literature that PEPPSI-IPr worked very well with aryl-aryl couplings involving hindered aryls. We decided to try PEPSI-IPr catalyst system for our cross coupling reaction. Reaction carried out using PEPPSI-IPr gave excellent results obtaining pure **In26** in a excellent yield and purity as shown in **Scheme 2.26**.



51

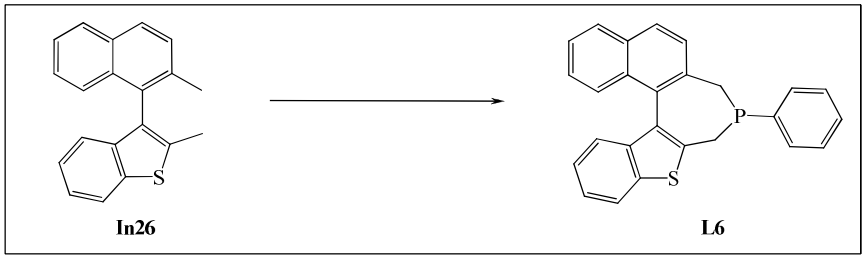
Fig. 2.6 PEPPSI-IPr



In24 50 **In26**

Scheme 2.26: Kumada cross coupling for preparation of **In26**

In26 was also tested in the last step to prepare ligand **L6**. Though, In the case of **In26**, the angle bite between two methyls is larger than in Ph-Binepine and Biphenine; but it is smaller than in case of **In25**. The last step was attempted in following ways with no success.



In26 L6

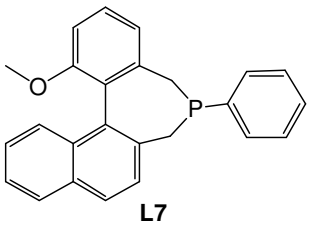
Last step to prepare ligand **L6** tried 2 times as follows:-

Reaction conditions	Observation	Conclusion
1. ***nBuLi/TMEDA/Et_2O*** 2***. n-hexane, Cl_2PPh, -70°C – r.t***	Lithiation seemed to occur but gummy intermediate failed the stirring and 2nd step	✗
1. ***nBuLi/TMEDA/Et_2O*** (twice amount of Et_2O) 2***. n-hexane, Cl_2PPh, -70°C – r.t***	Dark red precipitate SM recovered	✗ Possible failure to be investigated

Lithiation in the last step was observed to go well with red precipitate as expected, but the quenching with dichlorophenylphosphine did not work. Use of organozinc compounds to efficiently prepare tertiary phosphines, are also known in the literature[52]. Hence, we tried to transmetalate the lithiated species of **In21** with $ZnCl_2$ and then quench it with dichlorophenylphosphine. But, this attempt of the last step via transmetalation to Zinc compound also failed to give any trace of desired product (**L6**).

2.1.6 *Attempted synthesis of C_1-symmetry phosphepine ligand (L7)*

Next task of our interest was to have a C_1-symmetry biaryl phosphepine ligand as shown below:

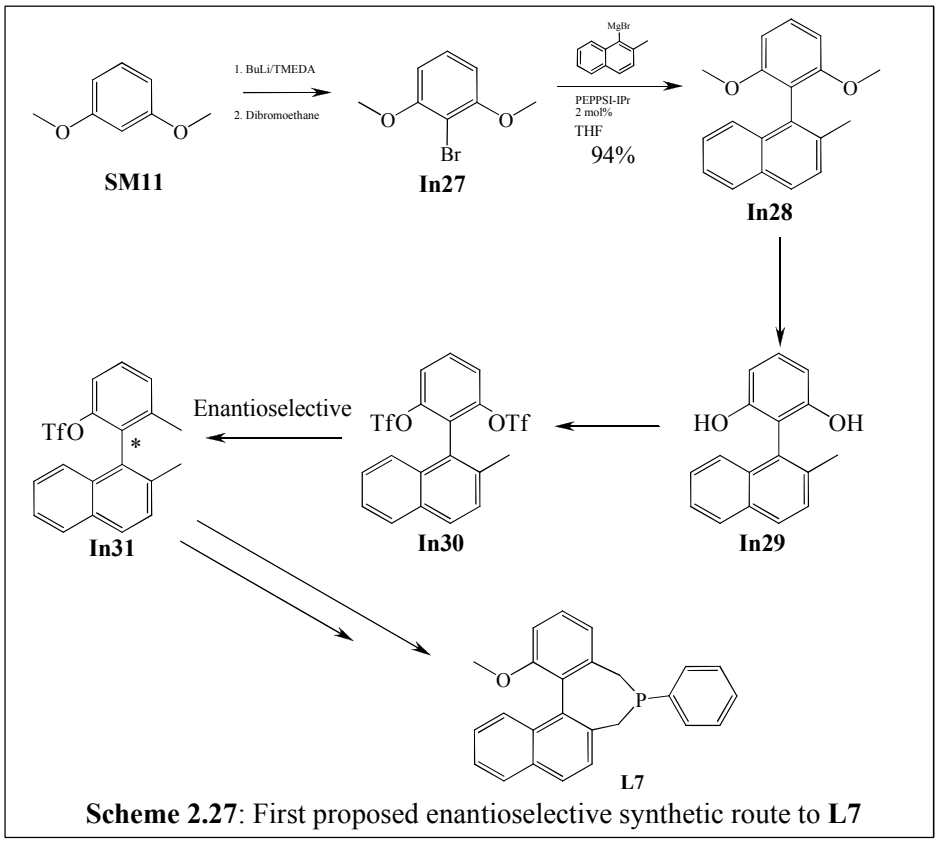


L7

C_1-symmetry Phosphepine ligand

Figure 2.7

Synthetic route in order to prepare **L7**, was proposed as shown in the **scheme 2.27**. Experimental work was initiated to check the crucial step of cross coupling of hindered biaryls i.e. Step-2. Kumada coupling was of first choice owing to the ease in experimental work and preparation. PEPSI-IPr catalyst system was chosen to be the preferred choice after obtaining excellent result in previously prepared **In26**.

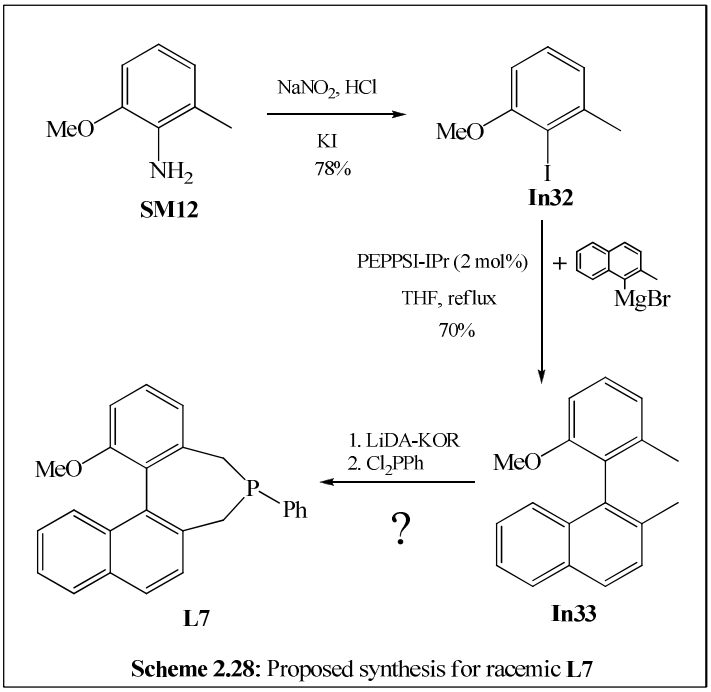


Scheme 2.27: First proposed enantioselective synthetic route to **L7**

In28, was prepared in a very good yield. Especially the Kumada cross coupling to give the hindered biaryl i.e. **In28**, was achieved in 94% yield with milder conditions and by use of just 2 mol% of PEPSI-IPr. The next steps were to be followed as per the **scheme 2.27**.

This longer synthetic route was designed in order to obtain the enantiopure ligand, **L7**. Anticipated enantioselective synthetic step was the desymmtrization of ditriflate[53] of **In30**, to enantioselectively prepare **In-31**. But, due to failures and difficulties in the last step of phosphepine synthesis for other targeted ligands, we decided to primarily test the last step for preparing **L7**, before undertaking this enantioselective synthesis. Hence, our task was to prepare the starting material for the last step as quick as possible in order to test the last step.

Recently, we synthesized intermediate **In33** in merely two steps with ease and reasonably good yield (**scheme 2.28**).



Scheme 2.28: Proposed synthesis for racemic **L7**

Starting from **SM12**, **In32** was prepared in 78% yield as per the literature[54]. **In32** was then subjected to Kumada cross coupling with 2-methylnaphthylmagnesiumbromide in the presence of PEPPSI-IPr (2 mol%) in THF at reflux temperature to give the desired hindered biaryl **In33** (70% yield).

And, we anticipate that **In33** will go through the last step to give racemic **L7**, by following the reactions conditions as discussed above in order to carry out the last step for synthesis of diMeO-Biphenine, **L2**.

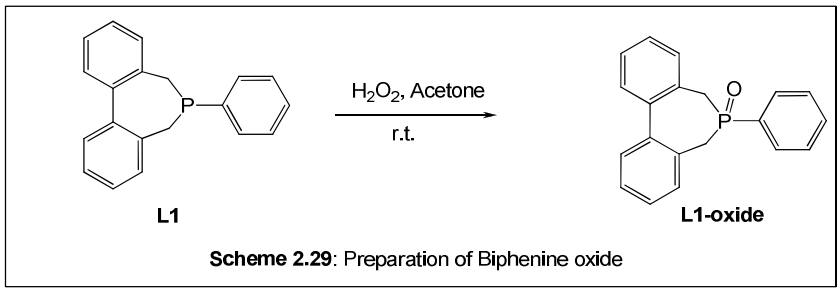
2.2 Examination & characterization of synthesized ligands

2.2.1 *Examination of Biphenine*

❖ **Biphenine oxide** (characterization)

It is necessary to characterize the oxide of the obtained phosphine compound in order to detect any traces of oxide in the prepared phosphine material. And, to detect any formation of oxides after storing the phosphine material, before its usage.

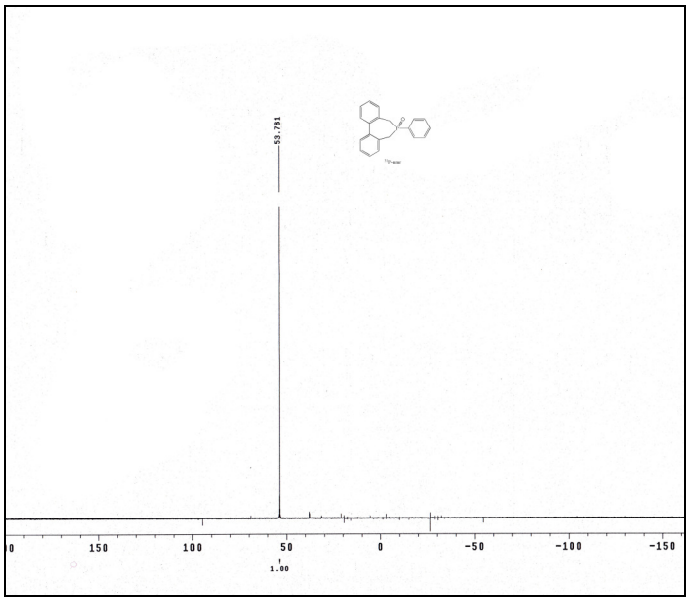
Biphenine oxide was prepared as shown in the **scheme 2.29**.



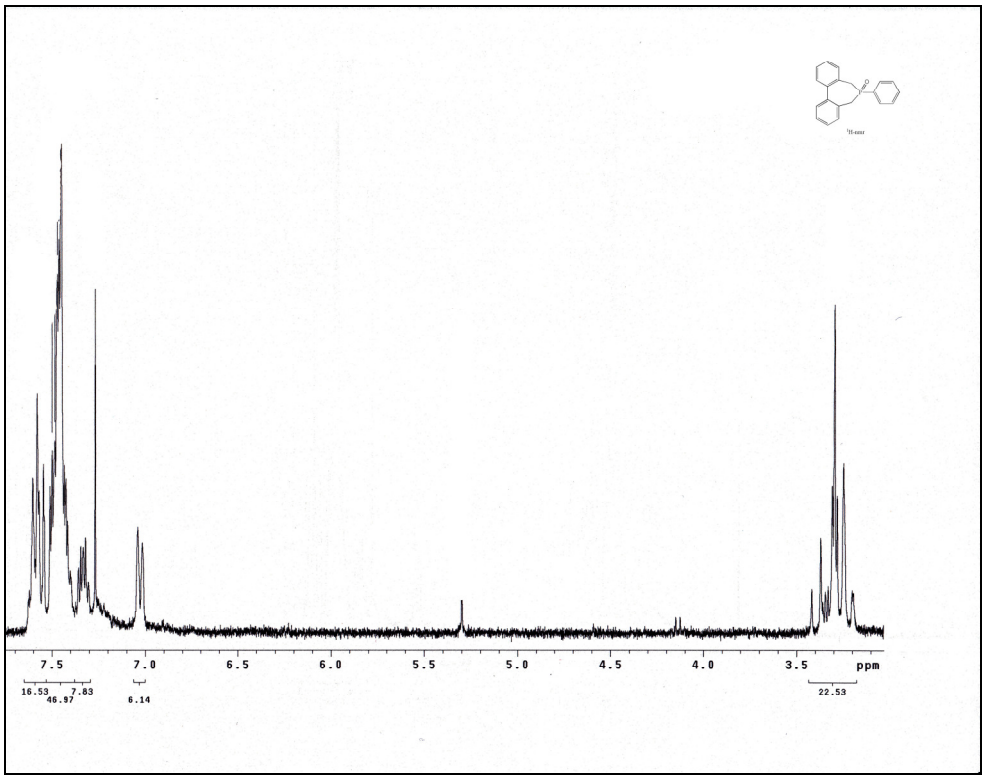
Scheme 2.29: Preparation of Biphenine oxide

^{31}P-nmr and ^{1}H-nmr were recorded (**spectra 9** & **10**)

Spectra 9: ^{31}P-nmr of Biphenine-oxide (L1-oxide)



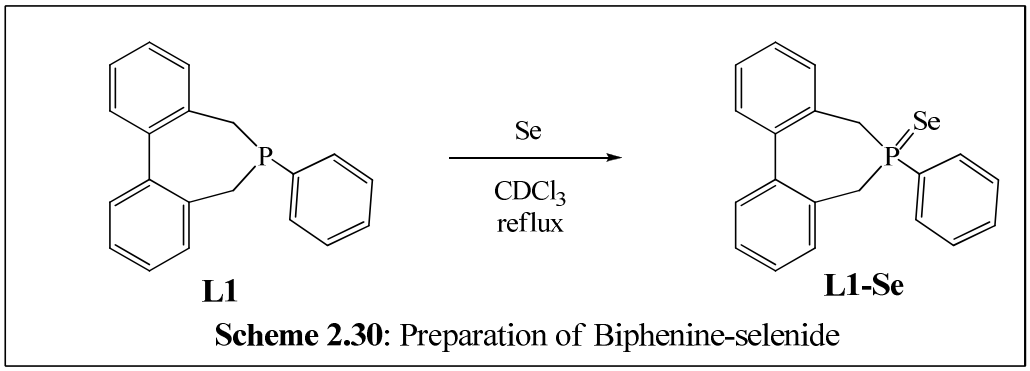
Spectra 10: ^{1}H-nmr of Biphenine-oxide (L1-oxide)



❖ Biphenine-Selenium adduct

The electronic properties of the phosphorus ligands could be examined in detail by measuring the amplitude of the first order coupling between P and Se of the corresponding selenides. This method has been already affirmed and regarded as very reliable for assessing the donating ability of the phosphorus lonepair orbital (smaller coupling constant corresponding to a more basic phosphine and *vice versa*)[55]. Hence, it gives a good idea of the electron density on the phosphorus in the ligand and thus its basicity.

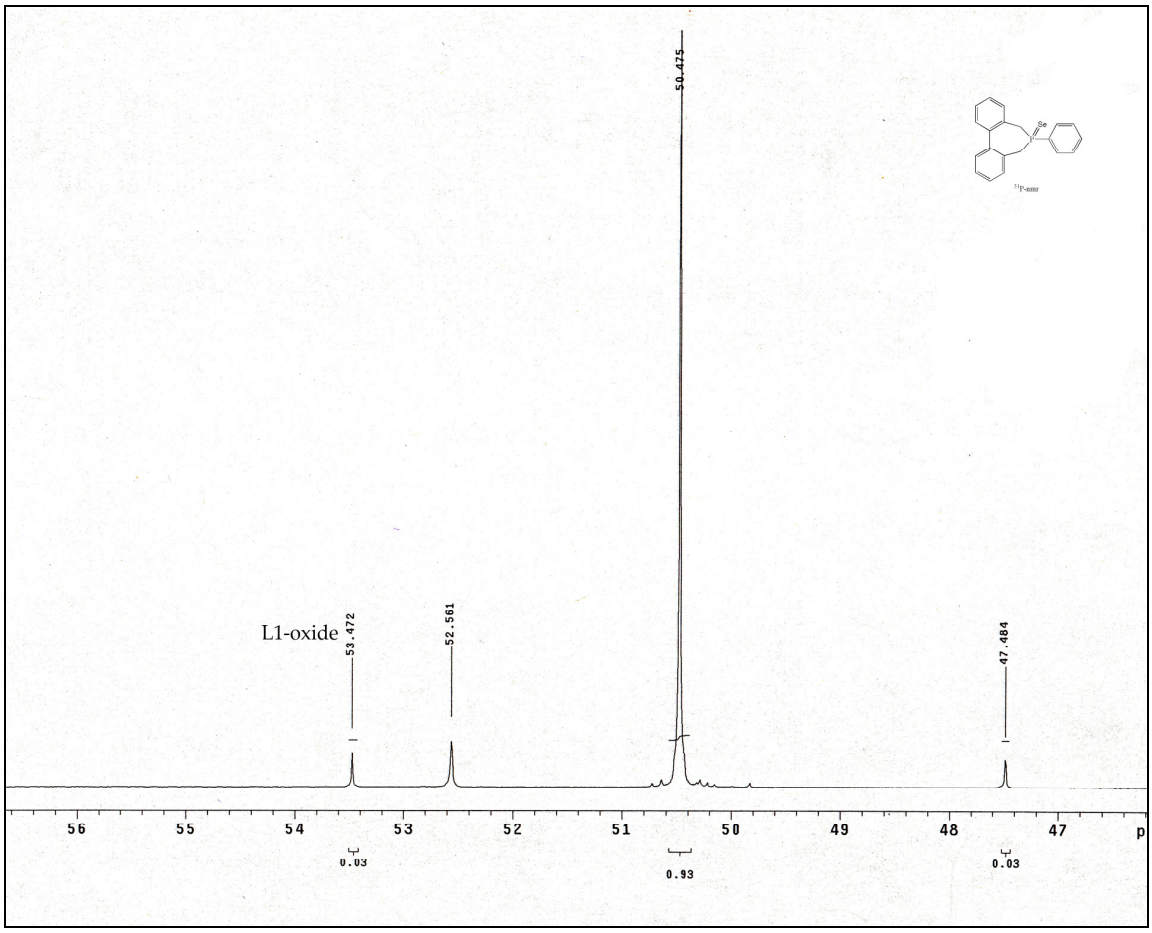
Biphenine selenide was readily prepared by mixing the phosphine and elemental selenium in refluxing deuterated chloroform, and the coupling constant $^{1}J_{P-Se}$ was measured without isolation of the product.



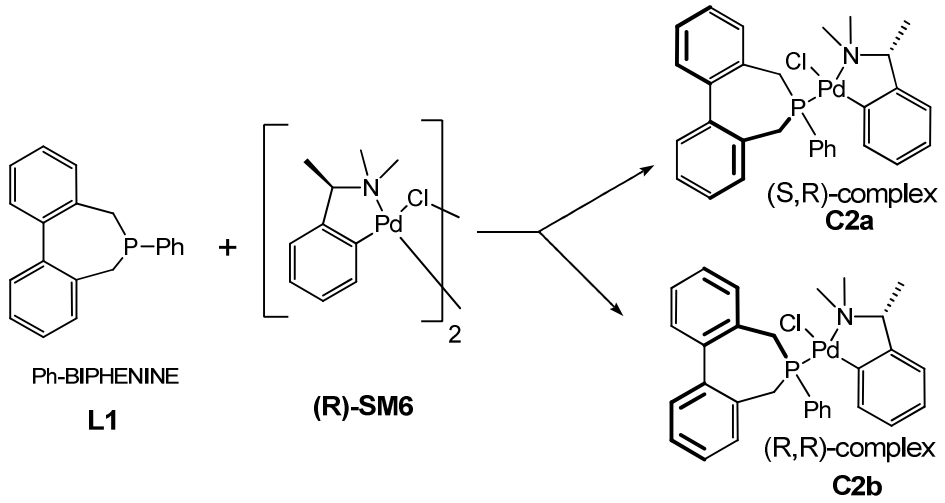
Scheme 2.30: Preparation of Biphenine-selenide

$^{1}J_{P-Se}$ for Biphenine-selenide was determined as ***727 Hz*** as compared to ***728*** **Hz** for Ph-Binepine (**3a**) (**spectra 11**). Hence, it shows that the electron density on phosphorus of Biphenine was little higher or almost the same as in the case Ph-Binepine.

Spectra 11: ^{31}P-nmr of Biphenine-selenide (L1-Se)



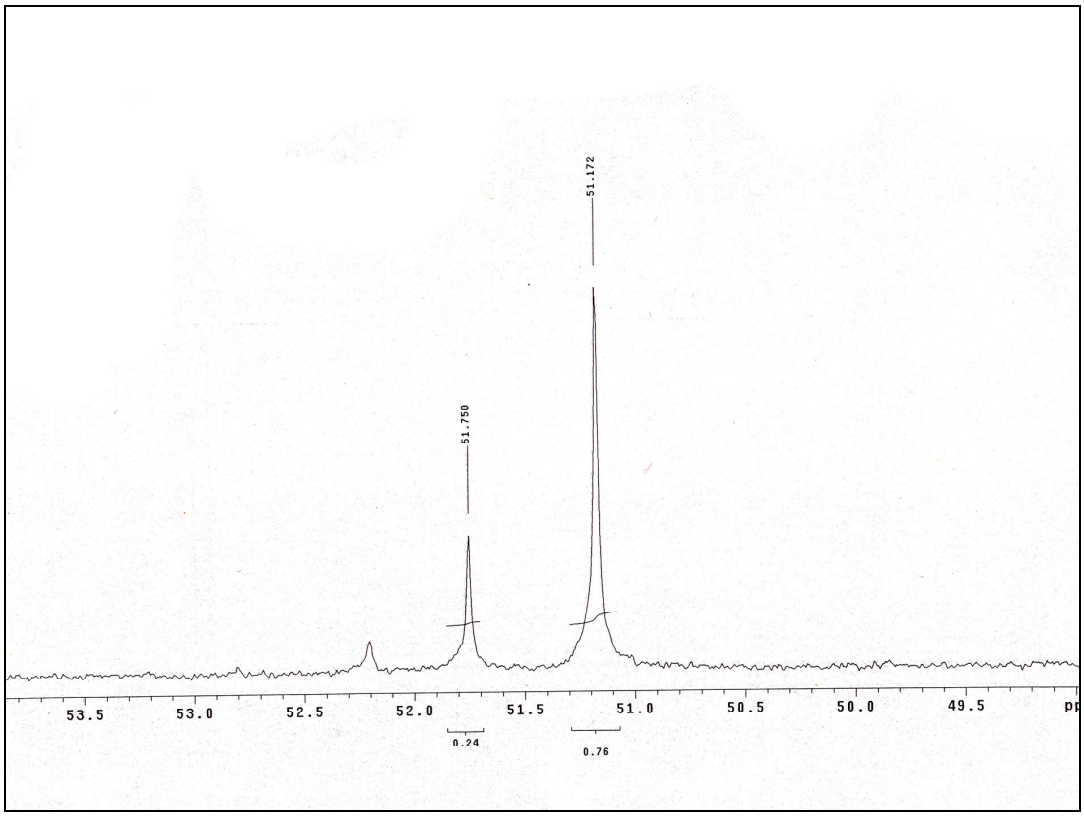
❖ **Diastereomers of Biphenine with chiral Pd-complex {(R)-SM6}**



Scheme 2.31: Preparation of Biphenine-chiral Pd complex

Diastereomers of racemic Biphenine with chiral (R)-Pd-complex (**SM6**) was prepared as shown in the **scheme 2.31** at 20℃. Inspite of racemic **L1**, the ^{31}P-nmr of the prepared diastereomers showed two peaks as expected at **51.172** and **51.75** but in the ratio of 75:25; instead of 50:50. This clearly shows that Biphenine (**L1**), being stereochemically flexible could easily interconvert, even at 20℃ forming a mixture of 75:25 ratio of respective diastereomers. It was not determined, which of the two configuration (S,R or R,R) of diastereomers was favoured and was in excess. (**Spectra 12**)

Spectra 12: ^{31}Pnmr of diastereomers of rac-Biphenine with (R)-SM6 in ratio 75:25

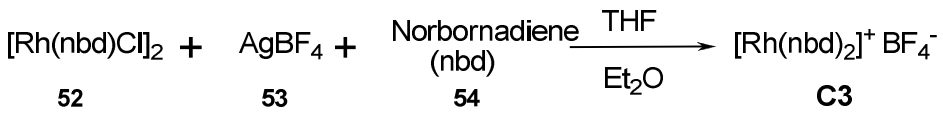


As anticipated, this phenomenon opens up the applicability of this ligand (**L1**) in some enantioselective reactions as a tropos ligand (where it can be enantioselectively evolved into an active catalyst by association with chiral activators)[56].

- **Preparation of [Rh(nbd)2]Biphenine$_2$]$^+$ BF_4^- complex**

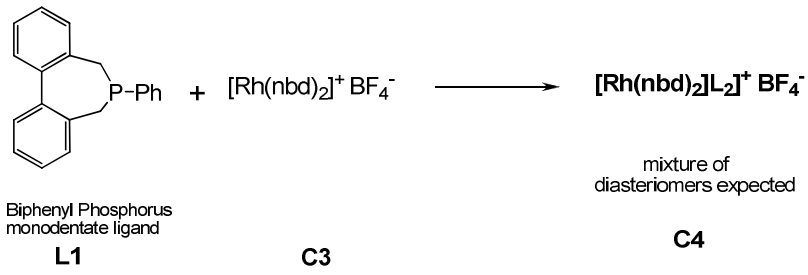
  After observing Biphenine's tropos ability from diastereomers of Biphenine with chiral Pd-complex, we were curious to study the behaviour of Biphenine in forming a complex with non-chiral Rh precursor. And later, study the behaviour of the complex formation in presence of a chiral ligand like (S)-Binepine.

Rhodium cationic complex used for coordination with Biphenine was prepared as shown in the **scheme 2.32**:



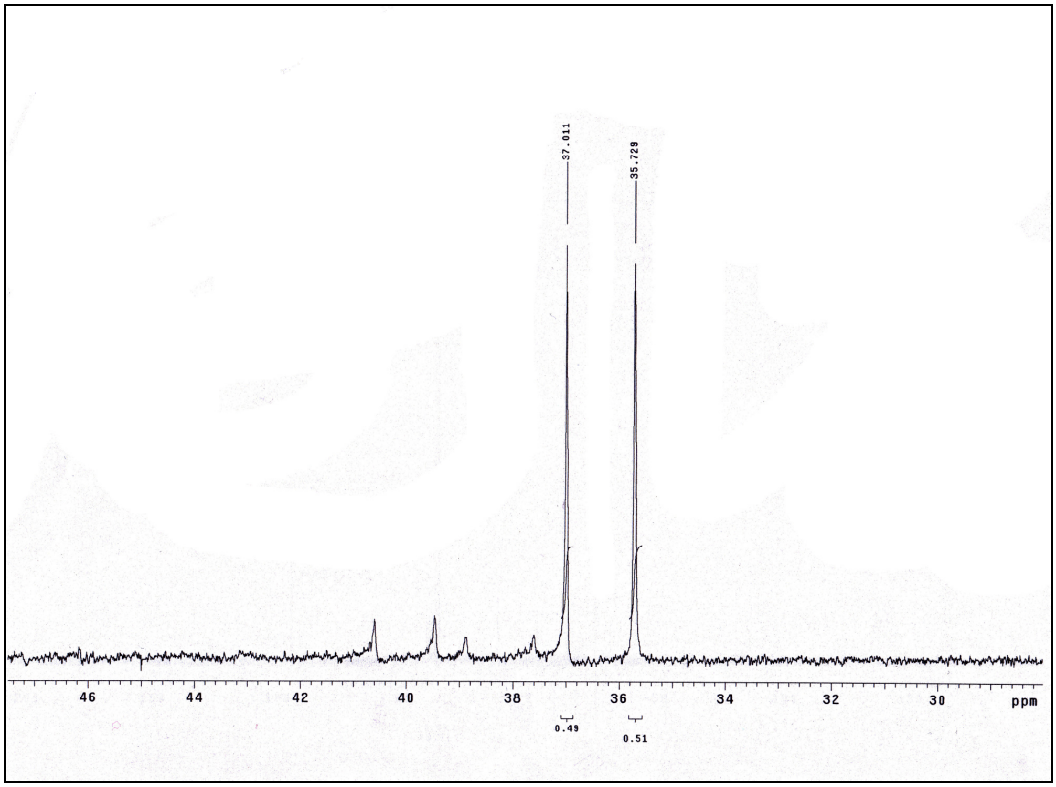
Scheme 2.32: Preparation of Cationic Rh-complex

Biphenine was reacted with Rh-complex(**C3**) as shown in the **scheme 2.33**.



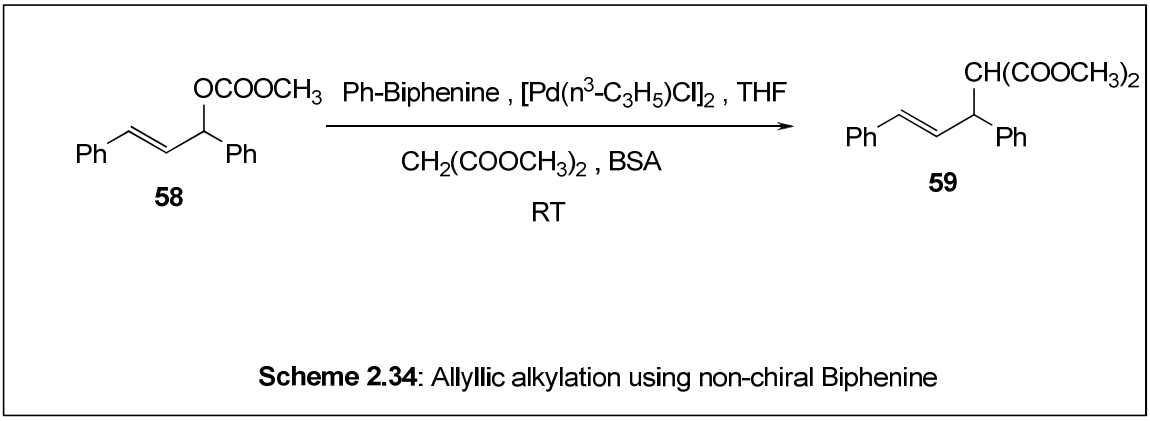
Scheme 2.33: Biphenine-Rh complex diasteriomer formation

The complex obtained was examined by ^{31}P-nmr and was observed to have primarily a huge doublet with respect to the other peaks. Hence, it was largely in favour of homochiral complexes. This means that Biphenine favoured to form a complex with this Rh-precursor in order to have same configured Biphenine in one molecule of **[Rh(nbd)2]Biphenine$_2$]$^+$ BF$_4^{-+}$** complex. Two molecules of Ph-Biphenine must coordinate with the Rh-complex. This confirms that the coordination of two homochiral ligands with Rh are predominantly observed, with only traces of possible heterochiral complexes.



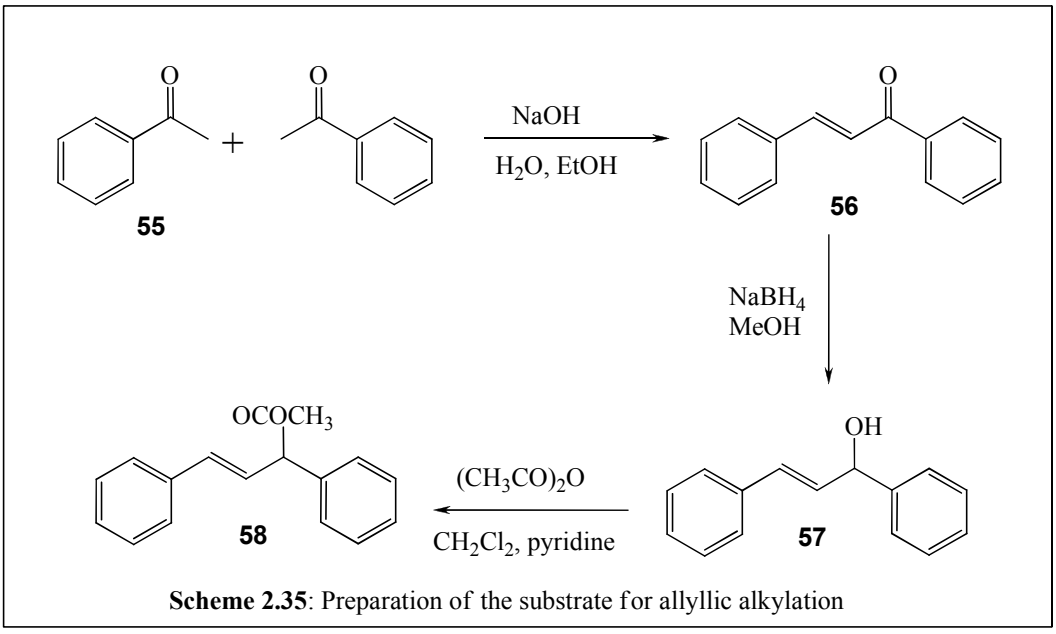
❖ Biphenine in Allyllic alkylation

Biphenine was applied in Pd-catalyzed allyllic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate anion. It was only to check if it works in the reaction to give the racemic product (**scheme 2.34**), and the time for conversion; giving an idea about the catalytic activity of this new monodentate phosphepine ligand.



Scheme 2.34: Allyllic alkylation using non-chiral Biphenine

1,3-diphenyl-2-propenyl acetate (**58**) was prepared in 3 steps as per the literature[57] (**scheme 2.35)**.



Scheme 2.35: Preparation of the substrate for allyllic alkylation

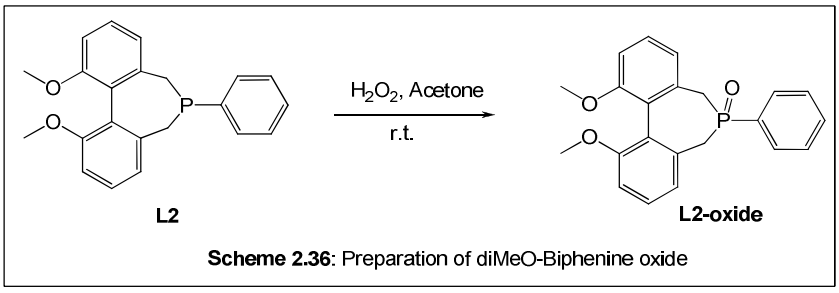
The reaction was performed and observed to have 100% conversion in few minutes. Thus, Biphenine has the same catalytic activity as Ph-Binepine (only with respect to conversion).

2.2.2 *Examination of diMeO-Biphenine*

❖ **diMeO-Biphenine oxide** (characterization)

It is necessary to characterize the oxide of the obtained phosphine compound in order to detect any traces of oxide in the prepared phosphine material. And, to detect any formation of oxides after storing the phosphine material, which is important to be analyzed before its usage.

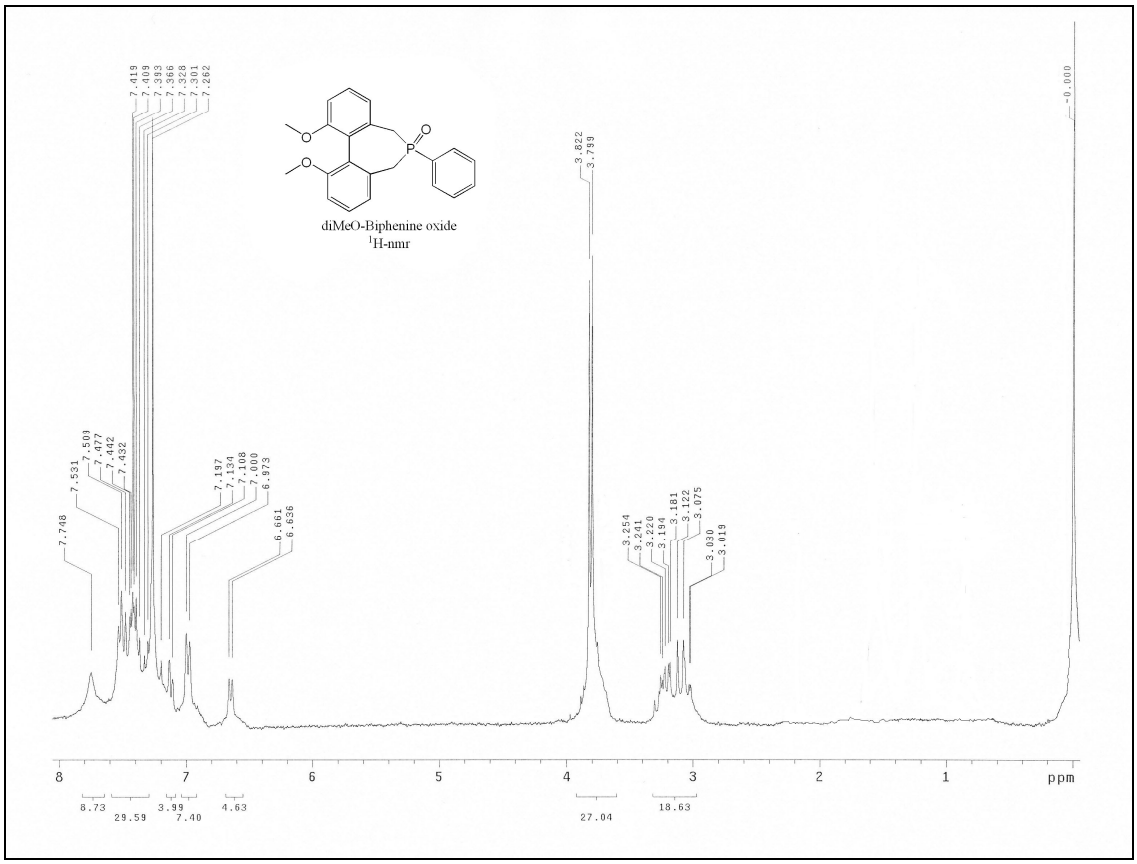
diMeO-Biphenine oxide was prepared as shown in the **scheme 2.36**.



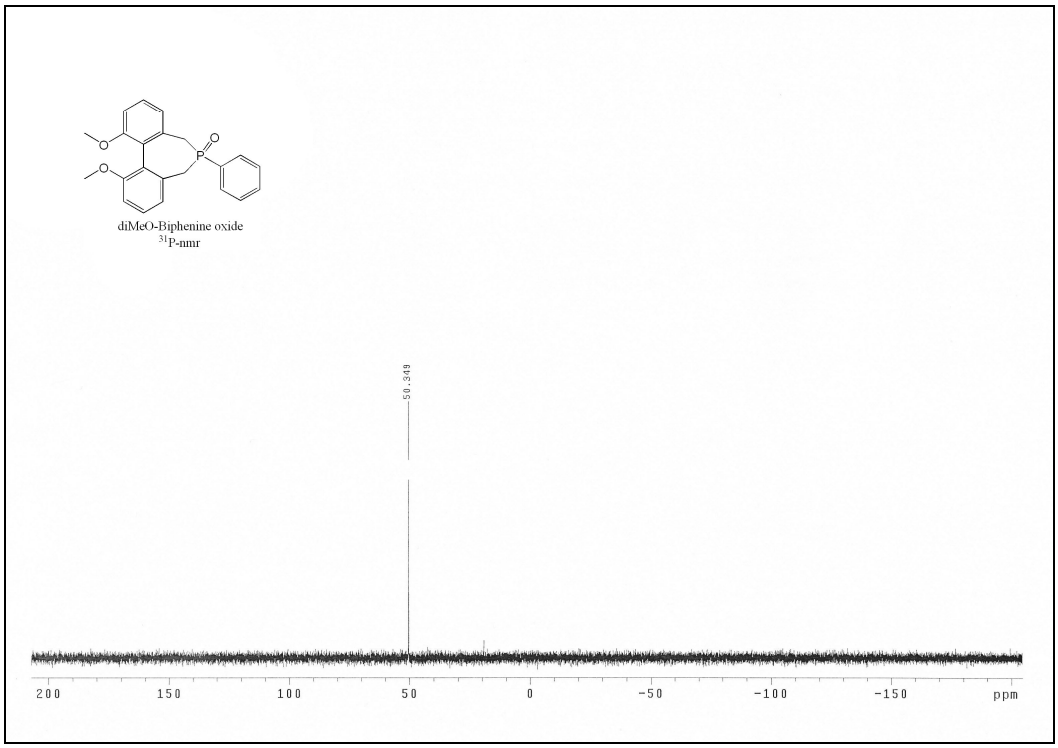
Scheme 2.36: Preparation of diMeO-Biphenine oxide

^{1}H-nmr and ^{31}P-nmr were recored (**spectra 13** & **14** on next page)

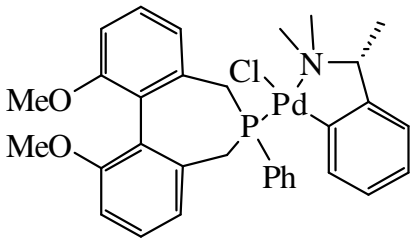
Spectra 13: ^{1}H-nmr of diMeOBiphenine-oxide (L2-oxide)



Spectra 14: ^{31}P-nmr of diMeO-Biphenine oxide



❖ **Diastereomers of diMeO-Biphenie with chiral Pd-complex {(R)-SM6}**



(S,R)-complex **C1a**
(R,R)-complex **C1b**

Fig. 2.8

^{31}P-nmr of the prepared diastereomers of diMeO-Biphenine (**L2**) with chiral Pd-complex (which has R configuration) were recorded. As expected, the racemic diMeO-Biphenine gives two peaks each correlating to (S,R) and (R,R) diastereomers (**spectra 15**).

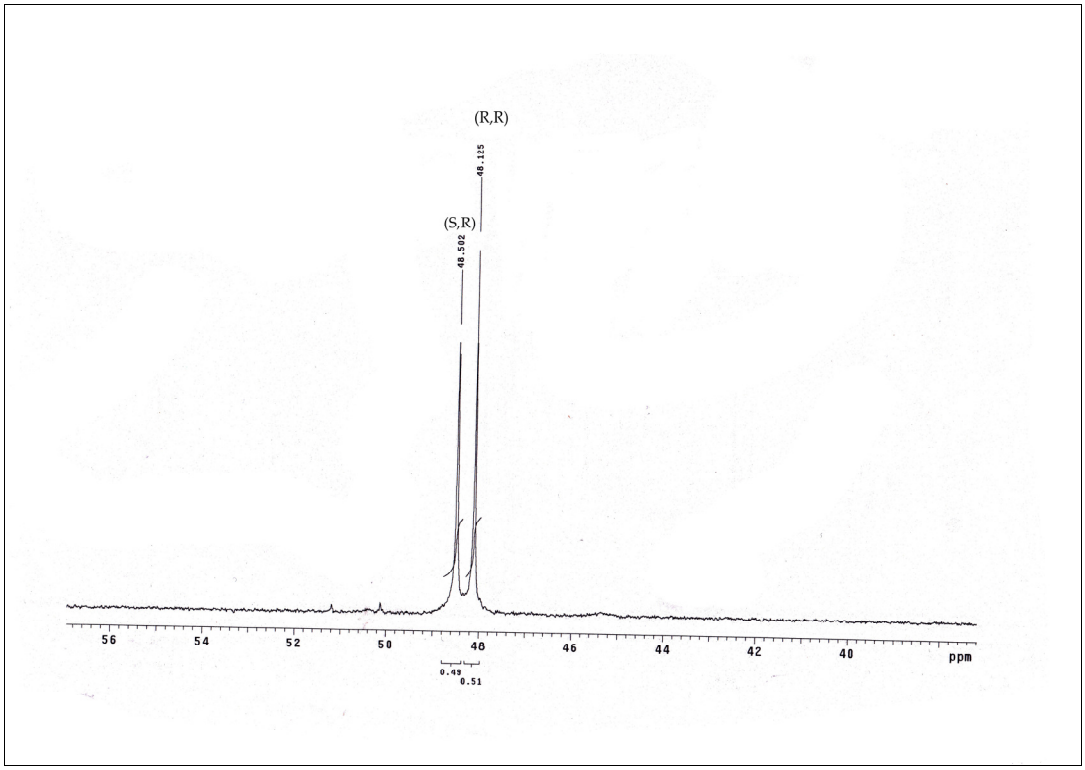
(S,R) diasteriomer (**C1a**) = **48.502** [with (S)-diMeOBiphenine]

(R,R) diasteriomer (**C1b**) = **48.125** [with (R)-diMeOBiphenine] (**spectra 16**)

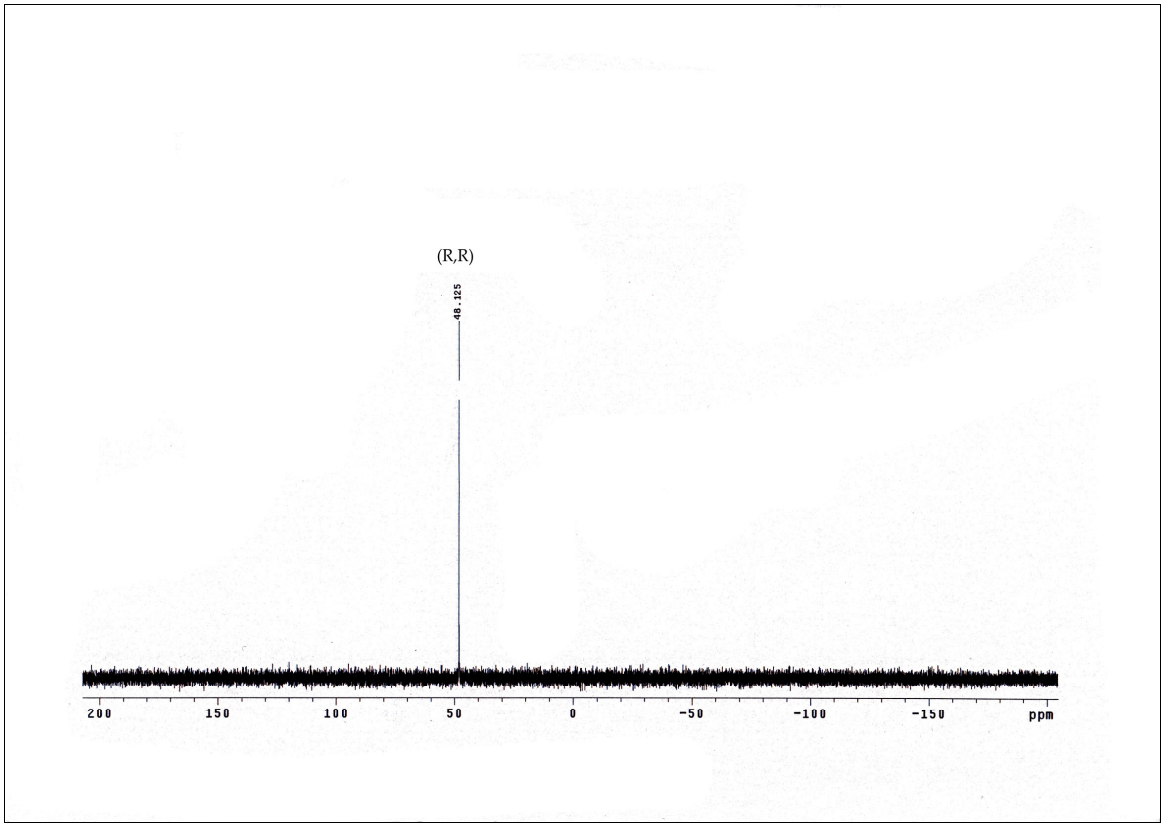
As expected, diastereomer of pure (R)-diMeO-Biphenine with this chiral Pd-complex showed a single peak at **48.125**. Thus, confirming that the ligand was 100% enantiomerically pure, and characterizing or labelling which ^{31}P peak corresponds to the respective diastereomeric configuration.

This can now, be used in the future to check and confirm the configuration and enanitopurity of the obtained diMeO-Biphenine.

Spectra 15: 31Pnmr of diastereomers of diMeO-Biphenine with chiral (R) Pd-amine



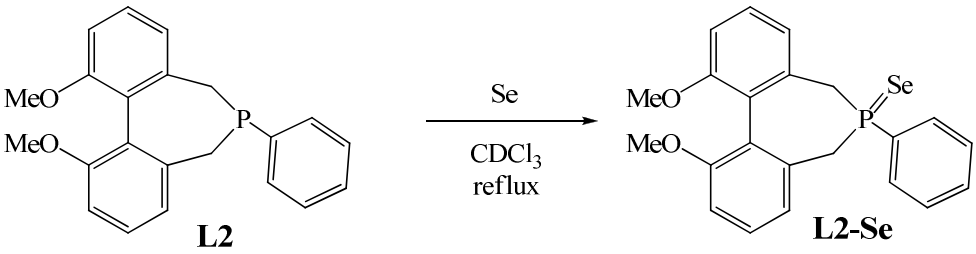
Spectra 16: 31Pnmr of R-diMeOBiphenine with chiral (R) Pd-amine



❖ **diMeOBiphenine-Selenide** compound

As explained earlier, phosphine-selenide gives a good idea of the electron density on the phosphorus in the ligand and thus its basicity.

diMeO-Biphenine selenide was readily prepared by mixing the phosphine and elemental selenium in refluxing deuterated chloroform, and the coupling constant $^1J_{P-Se}$ was measured without isolation of the product.

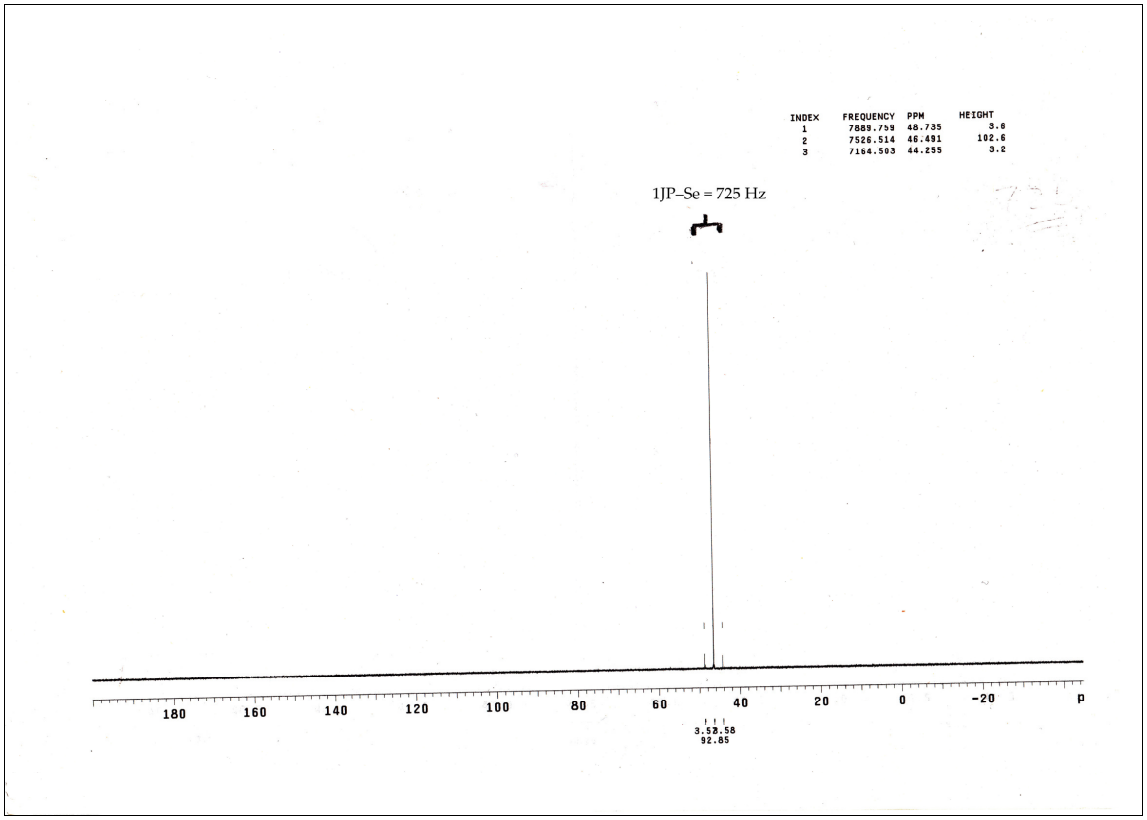


Scheme 2.37: Preparation of diMeOBiphenine-selenide

$^1J_{P-Se}$ for diMeO-Biphenine was determined as ***725 Hz*** (**spectra 17**) as compared to ***728*** **Hz** for Ph-Binepine (**3a**). Hence, it was confirmed that the electron density was slightly higher than in the case Ph-Binepine.

We then anticipated that diMeO-Biphenine might work slightly better than Ph-Binepine in Rh-catalyzed hydrogenations.

Spectra 17: ^{31}Pnmr of diMeOBiphenine-selenide

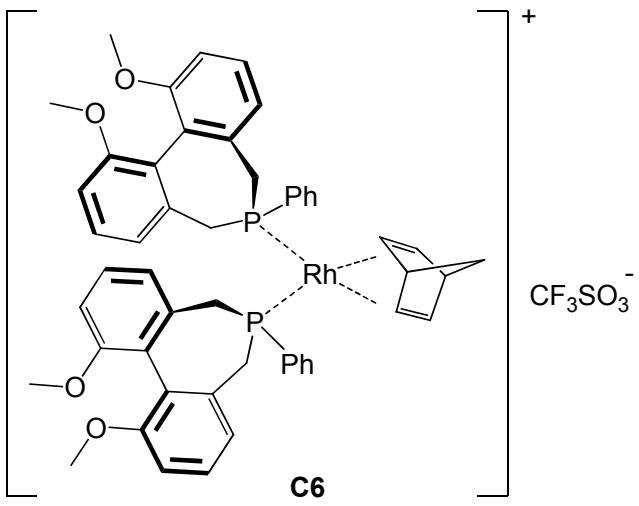


2.3 Asymmetric catalysis with (R)-diMeO-Biphenine

In order to initiate with the applications of our new ligand, diMeO-Biphenine (**L2**); we decided to carry out preliminary studies in similar manner as carried out for Ph-Binepine in this group. We were interested in comparing the performance of diMeO-Biphenine with Ph-Binepine in the same reactions. Hence, we primarily examined diMeO-Biphenine in Rh-catalyzed asymmetric hydrogenations including classical as well as transfer hydrogenation. And, we tested diMeO-Biphenine in other benchmark reactions like Pd-catalyzed allylic alkylation and Rh-catalyzed asymmetric hydroformylation.

2.3.1 diMeO-Biphenine in Rh-catalyzed classical hydrogenations

Primarily, we were interested in carrying out Rh-catalyzed asymmetric classical hydrogenations of C-C double bonds. We chose to perform the reaction with the pre-prepared complex of Rhodium with diMeO-Biphenine than *in-situ* preparation. We prepared [Rh(nbd)(R-diMeOBIPHENINE)$_2$]$^+$CF$_3$SO3$^-$ (**C6**) complex for our reactions as shown in **fig. 2.9**.

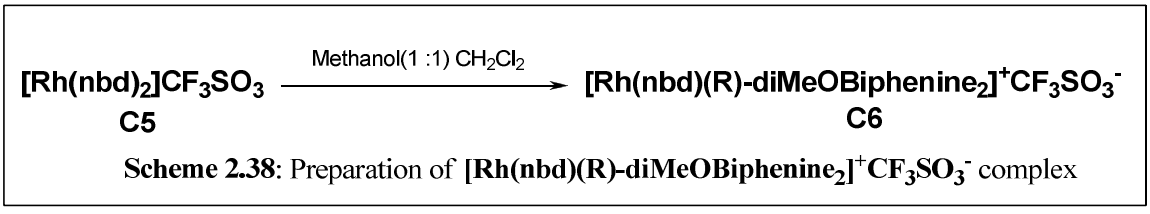


C6

[Rh(nbd)(R-diMeOBIPHENINE)2]$^+$CF3SO3$^-$
complex

Fig. 2.9

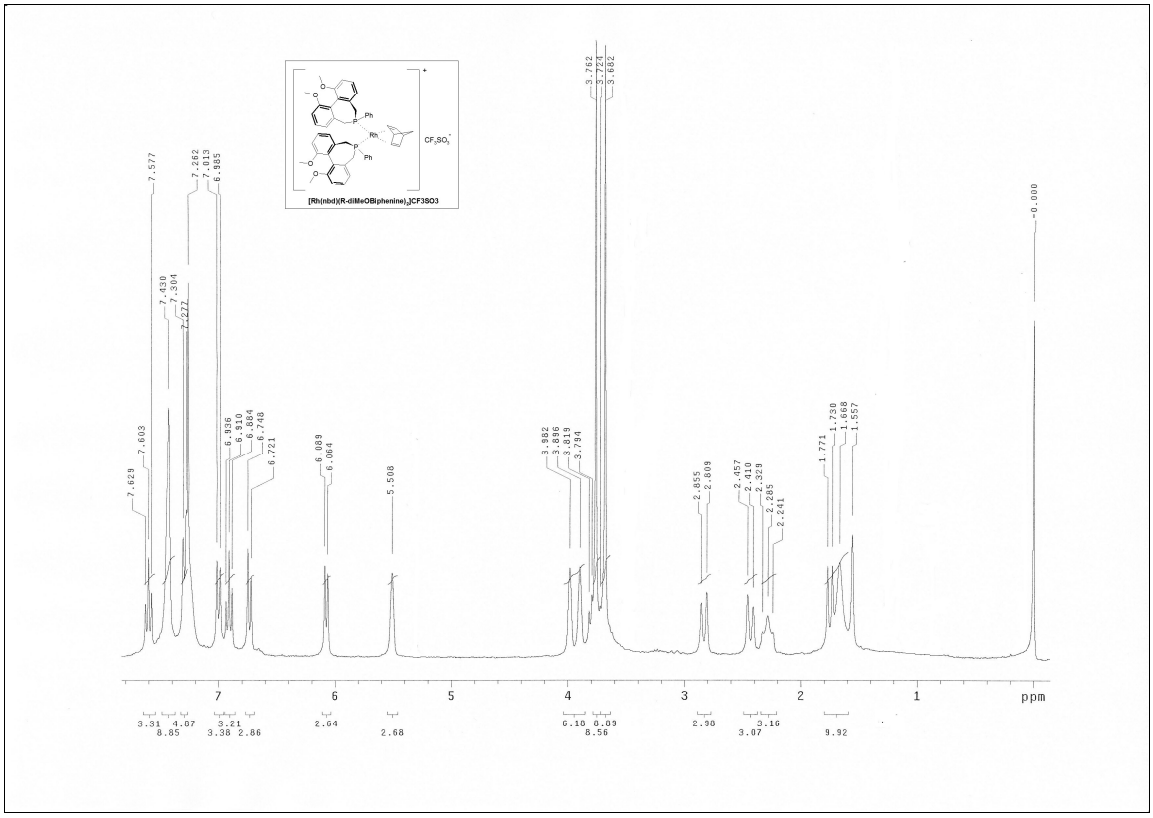
We prepared the complex as shown in the **scheme 2.38 (spectra)**.



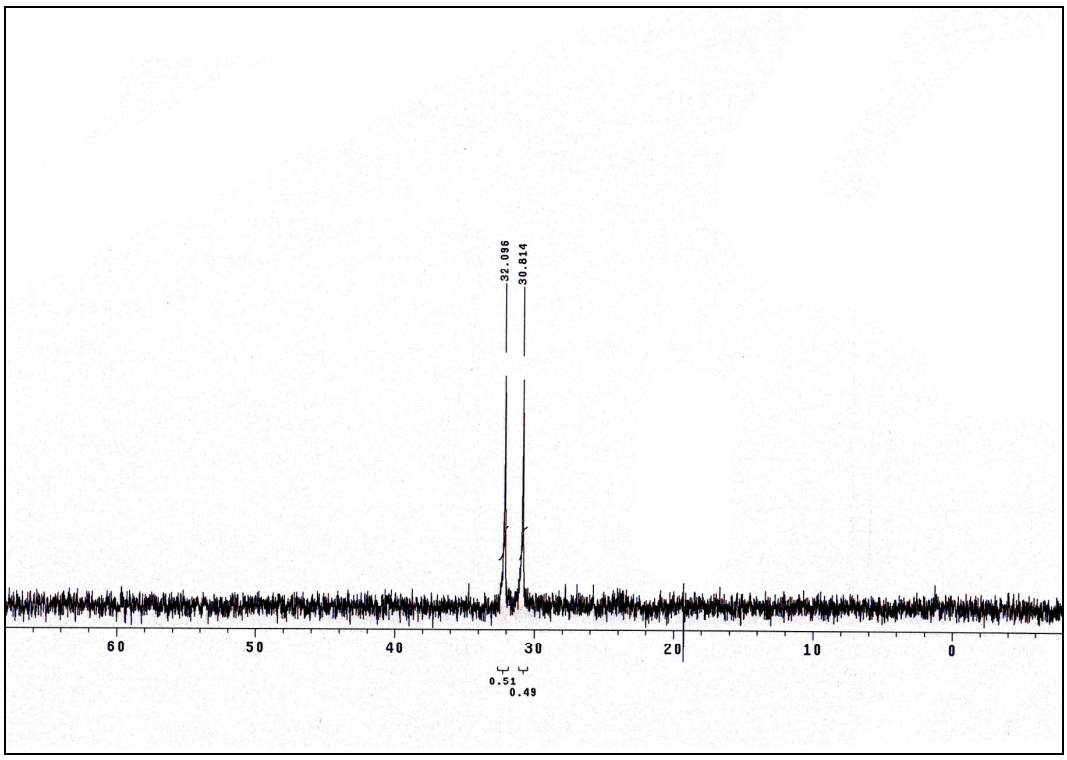
Scheme 2.38: Preparation of **[Rh(nbd)(R)-diMeOBiphenine$_2$]$^+$CF$_3$SO$_3^-$** complex

^{1}H-nmr and ^{31}P-nmr for **C6** were recorde. (**spectra 18** & **19**)

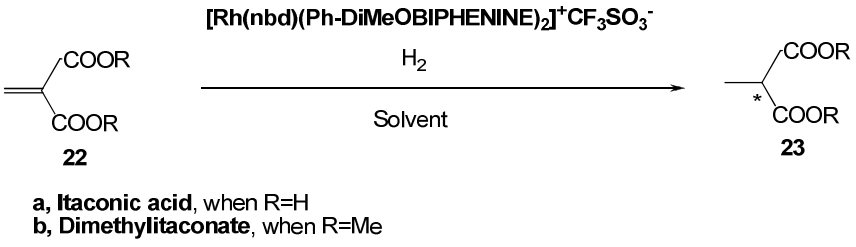
Spectra 18: ^{1}Hnmr of [Rh(nbd)(R-diMeOBIPHENINE)$_2$]$^{+}$CF$_3$SO3^{-}



Spectra 19: ^{31}P-nmr of [Rh(nbd)(R-diMeOBIPHENINE)$_2$]$^{+}$CF$_3$SO3^{-}



After preparing the complex, we performed the Rh-catalyzed hydrogenation on one of the most popular benchmark substrates like Itaconic acid and dimethyl itaconate as shown in the **scheme 2.39**. Hydrogenations were carried at atmospheric pressure.



a, Itaconic acid, when R=H
b, Dimethylitaconate, when R=Me

Scheme 2.39: Reduction of Itaconic acid and dimethyl itaconate

Results of these performed reactions are as shown in the **table 5**.

Table 5

Entry	Ligand	Substrate	Catalyst Loading[#]	Solvent	Time	Temp °C	Conv. %	e.e. %
1)	**(R)-L2**	Itaconic acid	1.0 mol%	1 : 1 MeOH : CH_2Cl_2	1 hr	25	92	**94** (R)
2)	**(R)-L2**	Itaconic acid	0.1 mol%	1 : 1 MeOH : CH_2Cl_2	1 hr	25	92	**94** (R)
3)	**(S)-PhBinepine**	DiMethyl Itaconate	1.0 mol%	CH_2Cl_2	56 min	25	>99	86 (S)
4)	**(R)-L2**	DiMethyl Itaconate	1.0 mol%	CH_2Cl_2	1 hr	25	87	**92** (R)

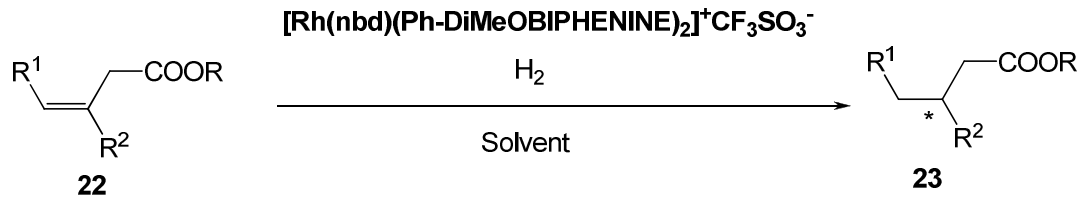
[#]Catalyst: **$[Rh(nbd)(R\text{-}diMeOBIPHENINE)_2]^+CF_3SO3^-$** complex prepared separately.

Itaconic acid (entry 1, table 5) was reduced with a conversion of 92% and and 94% e.e. It was noted that, when the same reaction was performed at reduced catalyst loading (from 1 mol% to 0.1 mol%); the conversion of the reaction as well as enantioselectivity was not affected. Hence, even at lower catalyst loading (0.1

mol%), the catalytic activity was the same. This suggests that Rhodium-diMeOBiphenine catalyst system has a high catalytic activity in this kind of reaction.

Second substrate i.e. dimethyl itaconate was also reduced in 87% conversion and 92% e.e (entry 4, table 5). And in comparison with Ph-Binepine, diMeO-Biphenine performed slightly better by giving a little higher e.e. (entry 3 & 4, table 5). It was also observed that the handedness of the reaction is 'opposite;. This trend was the same as in the case of Ph-Binepine.

After this good start, we tested some more of benchmark substrates to cover a class of α-amino acids and its derivatives.



c, Acetamidocinnamic acid, when R^1=Ph, R^2=$NHCOCH_3$, **R**=H

d, Acetoamidoacrylic acid, when R^1=H, R^2=$NHCOCH_3$, **R**=H

e, Methyl Acetamidocinnamate, when R^1=phenyl, R^2=$NHCOCH_3$, **R**=Me

f, Methyl Acetoamidoacrylate, when R^1=H, R^2=$NHCOCH_3$, **R**=Me

Scheme 2.40: Reduction of α-amino acids and its derivatives

Results are as shown in the **table 6**.

Table 6

Entry	Ligand	Substrate	Catalyst Loading[#]	Solvent	Time	Temp °C	Conv. %	e.e. %
1)	**(R)-L2**	Acetamido cinnamic acid	0.1 mol%	1:1 MeOH : toluene	24 hr	25	33	87 (S)
2)	**(R)-L2**	2-Acetamido acrylic acid	1 mol%	1:1 MeOH: CH_2Cl_2		25	69	87 (S)
3)	**(S)-PhBinepine**	Methyl Acetamido cinnamate	1.0 mol%	toluene	50 min	25	>99	90 (R)
4)	**(R)-L2**	Methyl Acetamido cinnamate	1.0 mol%	toluene	30 min	25	>99	96 (S)
5)	**(S)-PhBinepine**	Methyl acetamido acylate	1.0 mol%	CH_2Cl_2	18 min	25	>99	67 (R)
6)	**(R)-L2**	Methyl Acetamido acrylate	1.0 mol%	CH_2Cl_2	2 hr	25	82	70 (S)

Reductions of α-acetoamido cinnamic acid and α-acetoamido acrylic acid using Rhodium-PhBinepine catalyst system is not reported in the literature. We performed reductions of these acids using our new ligand i.e. Rhodium-diMeObiphenine catalyst and recorded 87% e.e. for both the substrates (entry 1 & 2, table 6).

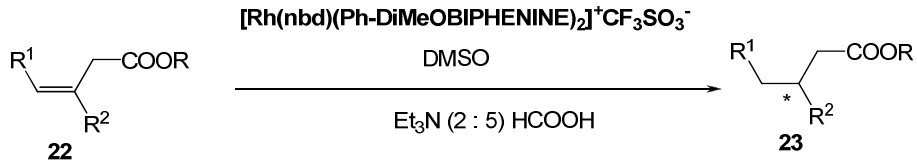
We also carried out reductions of methyl esters of α-acetoamido cinnamic acid and α-acetoamido acrylic acid, respectively. We recorded 96% and 70% e.e. results for these substrates, respectively (entry 4 & 6, table 6). In both the cases we found that diMeO-Biphenine provides slightly higher e.e.'s than that reported for Ph-Binepine for the same substrates.

Hence, as well as in this case, diMeO-Biphenine gives slightly higher enantioselectivity than Ph-Binepine.

2.3.2 diMeO-Biphenine in Catalytic Transfer hydrogenation (CTH)

Next, we decided to test Rhodium-diMeObiphenine catalyst system in asymmetric transfer hydrogenations. Transfer hydrogenations are preferred for its simple operations and possibility to avoid handling of highly inflammable hydrogen gas. Ph-Binepine was tested and reported in the literature[X], where upto 96% e.e. was obtained for itaconic acid. We examined diMeO-biphenine for the benchmark substrates as selected for the classical hydrogenations.

Transfer hydrogenation was carried out with formic acid as the hydrogen source and $[Rh(nbd)(R\text{-}diMeOBIPHENINE)_2]^+CF_3SO3^-$ as the catalyst (as prepared for classical hydrogenations). The reactions were carried out as shown in the **scheme 2.41**.



a, Itaconic acid, when R^1= H, R^2=COOH, R=H
b, Dimethylitaconate, when R^1=H, R^2=COOMe, R=Me
c, Acetamidocinnamic acid, when R^1=Ph, R^2=$NHCOCH_3$, R=H
d, Acetoamidoacrylic acid, when R^1=H, R^2=$NHCOCH_3$, R=H
e, Methyl Acetamidocinnamate, when R^1=phenyl, R^2=$NHCOCH_3$, R=Me
f, Methyl Acetoamidoacrylate, when R^1=H, R^2=$NHCOCH_3$, R=Me

Scheme 2.41: Rh-catalyzed asymmetric trasfer hydrogenations

Results obtained are as shown in the **table 7**.

Table 7

Entry	Ligand	Substrate	Catalyst Loading #	Solvent	Time	Temp °C	Conv. %	e.e. %
1)	**(S)-PhBinepine**	Itaconic acid	1.5 mol%	DMSO	2 hr	25	>99	97 (S)
2)	**(R)-L2**	Itaconic acid	1.5 mol%	DMSO	2 hr	25	>99	96 (R)
3)	**(S)-PhBinepine**	DiMethyl Itaconate	1.5 mol%	DMSO	2 hr	25	57	13 (R)
4)	**(R)-L2**	DiMethyl Itaconate	1.5 mol%	DMSO	2 hr	25	>99	16 (S)
5)	**(S)-PhBinepine**	Acetoamido cinnamic acid	1.5 mol%	DMSO	4 hr	22	40	58 (S)
6)	**(R)-L2**	Acetoamido cinnamic acid	1.0 mol%	DMSO	4 hr	25	52	8 (R)
7)	**(S)-PhBinepine**	Methyl Acetamido cinnamate	1.5 mol%	DMSO	4 hr	22	57	46 (S)
8)	**(R)-L2**	Methyl Acetamido cinnamate	1.0 mol%	DMSO	4 hr	25	20	31 (R)
9)	**(S)-PhBinepine**	2-Acetamido acrylic acid	1.5 mol%	DMSO	4 hr	22	n.r.	-
10)	**(R)-L2**	2-Acetamido acrylic acid	1.5 mol%	DMSO	4 hr	25	72	40 (S)
11)	**(S)-PhBinepine**	Methyl acetamido acrylate	1.5 mol%	DMSO	4 hr	22	35	33 (R)
12)	**(R)-L2**	Methyl acetamido acrylate	1.5 mol%	DMSO	4 hr	25	51	50 (S)

#Catalyst: **$[Rh(nbd)(R\text{-}diMeOBIPHENINE)_2]^+CF_3SO3^-$** complex prepared separately.

Itaconic acid was reduced efficiently with 96% e.e. (entry 2, table 7), while for the rest of examined substrates low to moderate e.e.'s were obtained using Rhodium-diMeOBiphenine catalyst system.

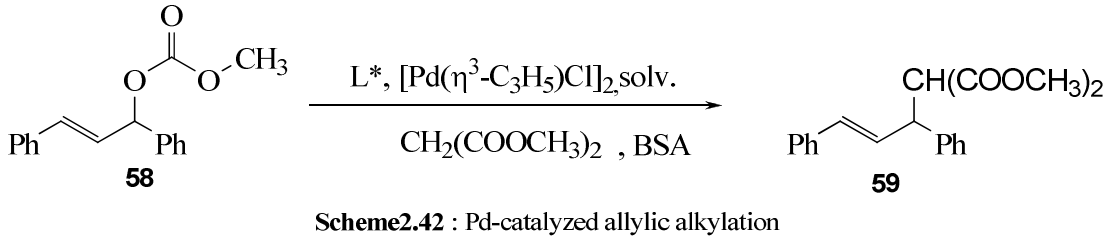
When compared to the reported results for Ph-Binepine; in general the trend of the reactivity was quiet similar. In most cases, the conversions were higher for diMeO-Biphenine than Ph-Binepine. Enantioselectivites with diMeO-Biphenine were either similar or higher in some cases (entry 2,4 &12, table 7), while lower in other (entry 6 & 8, table 7). It was reported that no reaction was observed for 2-Acetamidoacrylic acid with Ph-Binepine, but we obtained 72% conversion (4hr) and 40% e.e. for reduction of 2-acetamidoacrylic acid with diMeO-biphenine (entry 10, table 7).

The handedness of the reaction was found to exactly behave as reported for Ph-Binepine.

2.3.3 diMeO-Biphenine in Pd-catalyzed Allylic Alkylation

We tested the ability of (R)-diMeO-Biphenine to induce stereoselectivity in palladium-catalyzed allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate anion.

Allylic alkylation was carried out as shown in **scheme 2.42**.



Scheme2.42 : Pd-catalyzed allylic alkylation

Results displayed by diMeO-Biphenine are as follows:-

Table 8

Entry	Ligand	Pd/L	Solvent	Salt	Time	Temp°C	Conv. %	e.e. %
1)	**(S)-PhBinepine**	1:2	THF	KOAc	10 min	25	>99	74 (R)
2)	**(R)-L2**	1:2	THF	KOAc	2 hr	25	>99	59 (S)
3)	**(S)-PhBinepine**	1:2	CH_2Cl_2	KOAc			>99	18 (R)
4)	**(R)-L2**	1:2	CH_2Cl_2	KOAc	1 hr	28	>99	8 (S)
5)	**(S)-PhBinepine**	1:2	THF	KOAc	10 min	0	>99	86 (R)
6)	**(R)-L2**	1:2	THF	KOAc	3 hr	0-5	>99	**70 (S)**

Initially, the reaction was performed as per the conditions known in our group for Ph-Binepine. Using THF as the choice of solvent, and KOAc as the salt; reaction was carried out using Pd/(R)-DiMeOBiphenine (1:2) at 25°C. Only 59% e.e. was obtained with complete conversion after 2 hours, in this reaction (entry 2, table 8).

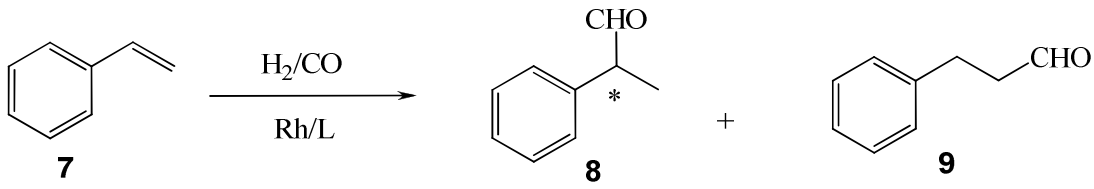
Changing the solvent from THF to CH_2Cl_2 complete conversion was obtained within 1 hour, but drastic decrease in the enantioselectivity to 8% e.e. (entry 4, table 8). This was also observed in the case of Ph-Binepine.

Hence, by performing the reaction in the best known conditions for Ph-Binepine; we obtained 70% e.e. with complete conversion after 3 hours (entry 6, table 8) with (R)-diMeOBiphenine.

In comparison with Ph-Binepine, diMeO-Biphenine performed poor in this Pd-catalyzed allylic alkylation and much more time was required for completion of reaction. Only upto 70% e.e. was achieved by performing the reaction at 0℃ with complete conversion (entry 6, table 8). It was noticed that the trend of change in the enantioselectivity induced by diMeO-Biphenine against the reaction conditions was as observed for Ph-Binepine.

2.3.4 diMeO-Biphenine in Hydroformylation

Rhodium-catalyzed hydroformylation of styrene was the first reaction in which Ph-Binepine was examined for its chiral inducing property. We decided to test diMeO-Biphenine in this same reaction.



Scheme2.44: Rh-catalyzed hydroformylation of styrene

$Rh(CO)_2(acac)$ was used as the catalyst precursor and (R)-diMeOBiphenine as the ligand. Ratio of substrate : P : Rh used was 2000 : 8 : 1.

Table 9

Entry	Solvent	T (°C)	pH_2/CO (bar)	Rh/L	Time (hr)	Conv. (%)	*Iso/n*	e.e. (%)
1)	Toluene	60	40	1/8	24	63	83/17	Racemic

The reaction was performed as per the conditions mentioned in the **table 9**. Unfortunately no e.e. was obtained for the branched aldehyde (**8**). But, the reaction did undergo chemoselectively towards branched aldhehyde (**8**) with 83% of branched aldhehyde vs. 17% of linear aldhehyde (**9**). While Ph-Binepine was reported to give chemoselective **8,** in excellent yields along with 29% e.e[58].

Conclusions

and

future recommendations

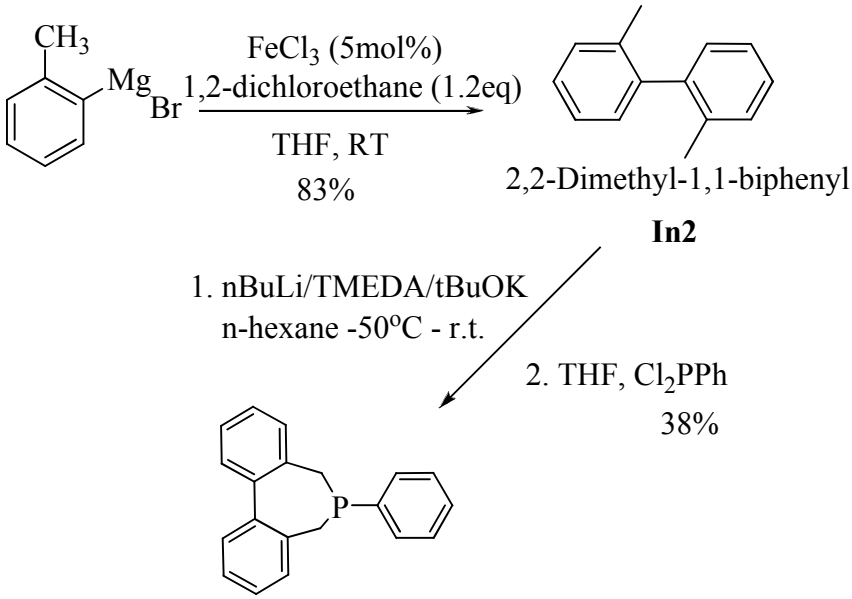
Chapter – 3

Conclusions and future recommendations

Research work reported here was aimed at the synthesis of structurally diverse biaryl-based new phosphepine ligands for asymmetric catalysis. We aimed to prepare phosphepines with a different biaryl backbone that are not synthesized or known until now.

- **Biphenine (L1)**

  Racemic Biphenine was synthesized in two steps in 32% overall yield as shown in the **scheme 3.1**.



Scheme 3.1 Synthesis of Biphenine, **L1**

An attempt was undertaken to resolve the racemic **L1** via diastereomer with Pd-chiral complex, but it was unsuccessful. This was a consequence of the low

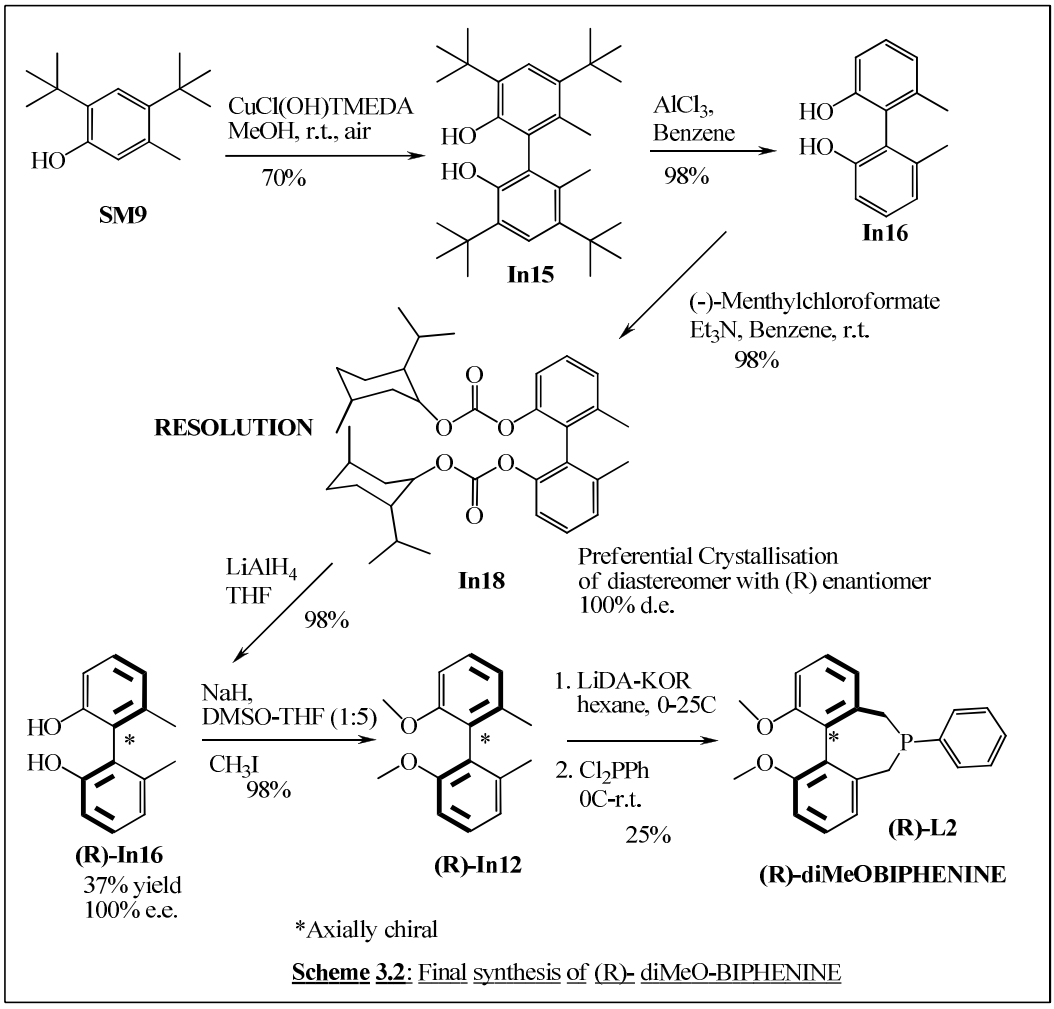
energy barrier of **L1** associated to the interconversion between its two enantiomers at room temperature.

But this phenomenon opens up the applicability of this ligand (**L1**) in some enantioselective reactions as a tropos ligand (where it can be enantioselectively evolved into an active catalyst by association with chiral activators).

- **diMeO-Biphenine (L2)**

diMeO-Biphenine (**L2**) was our prime targeted ligand. Extensive work was undertaken in order to explore various synthetic routes including asymmetric synthetic path to prepare **L2**. We worked thoroughly to synthesize **L2** in shortest possible way, considering and aiming to design practically simple experimental procedure.

Our goal was accomplished and we hereby present the first synthesis of (R)-diMeO-Biphenine (**(R)-L2**), in six steps with 18% overall yield (**scheme 3.2**). Starting material (**In12**) for the last step was prepared with a great ease in 5-steps and as high as 65% overall yield.



Scheme 3.2: Final synthesis of (R)- diMeO-BIPHENINE

Resolution was carried out for **In16** via diastereomers of **L2** with (-)-(R)-Menthyl chloroformate. The separation of pure (R,R)-diastereomer was achieved by single crystallization from n-hexane in 38% yield and >99% d.e. **(R)-In16** was obtained quantitatively from the crystallized (R,R)-diastereomer. The right reaction conditions and experimental procedure for the last step was established; leading to pure (R)-diMeO-Biphenine, **(R)-L2**.

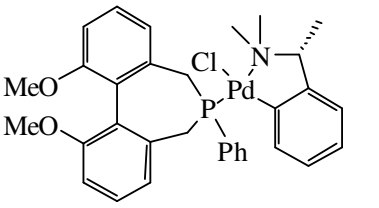
Synthetic route to **L2** initiates from phenolic oxidative coupling of **SM9**. In future, an appropriate asymmetric oxidative coupling of **SM9** can improve the

usefulness of this synthetic route to prepare **L2**, by reducing two steps that are needed to resolve **In16**.

In summary, a practical synthesis of (R)-diMeO-Biphenine is presented, to obtain **L2** in >99% e.e.

diMeO-Biphenine and its corresponding oxide were characterized by ^{1}H-nmr, and ^{31}P-nmr.

Diastereomer of diMeO-Biphenine (**L2**) with chiral Pd-complex was prepared and characterized by ^{31}P-nmr, which can be used to detect and confirm the enantiopurity and configuration of the obtained **L2** in future.



(R,R)-complex **C1a** ^{31}P = **48.125**
(S,R)-complex **C1b** ^{31}P = **48.502**

Fig. 3.1

diMeOBiphenine-selenide was prepared to examine the electron density over the phosphorus i.e. the basicity of phosphorus. $^{1}J_{P\text{-}Se}$ was found to be 725 Hz, suggesting slightly higher electron density on phosphorus of **L2** than compared to the well known Ph-Binepine (**3a**). This makes **L2** attractive in Rhodium-catalyzed asymmetric hydrogenations.

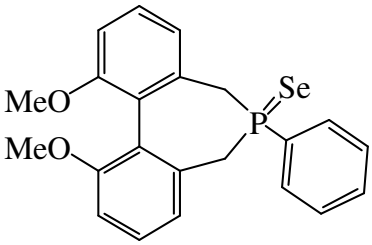
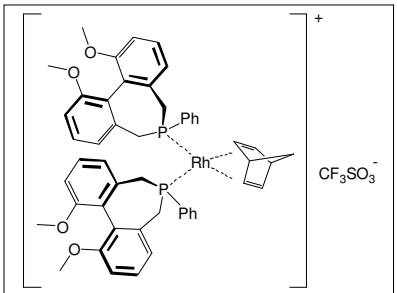


Fig. 3.2

(R)-diMeO-Biphenine was used to prepare **[Rh(nbd)(R-diMeOBIPHENINE)$_2$]$^{+}$CF$_3$SO3^{-}** complex. The complex was characterized and checked for its ability to induce

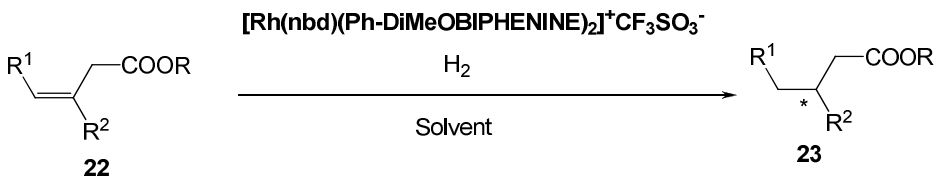


[Rh(nbd)(R-diMeOBIPHENINE)2]$^{+}$CF3SO3^{-} complex

Fig. 3.3

enantioselectivity in asymmetric hydrogenations.

Classical asymmetric hydrogenations were carried out using this complex on benchmark substrates like itaconic acid, dimethyl itaconate and α-amino acids & esters. Rhodium-diMeOBiphenine catalyst system provided excellent e.e.'s in these hydrogenations with most recordings over 90% e.e. and upto 96% e.e. for Methyl acetamido cinnamate.



Itaconic acid, when R^1= H, R^2=COOH, R=H .....**94% e.e.**
Dimethylitaconate, when R^1=H, R^2=COOMe, R=Me .....**92% e.e.**
Acetamidocinnamic acid, when R^1=phenyl, R^2=$NHCOCH_3$, R=H .....**87% e.e.**
Acetoamidoacrylic acid, when R^1=H, R^2=$NHCOCH_3$, R=H .....**87% e.e.**
Methyl Acetamidocinnamate, when R^1=phenyl, R^2=$NHCOCH_3$, R=Me .....**96% e.e.**
Methyl Acetoamidoacrylate, when R^1=H, R^2=$NHCOCH_3$, R=Me .....**70% e.e.**

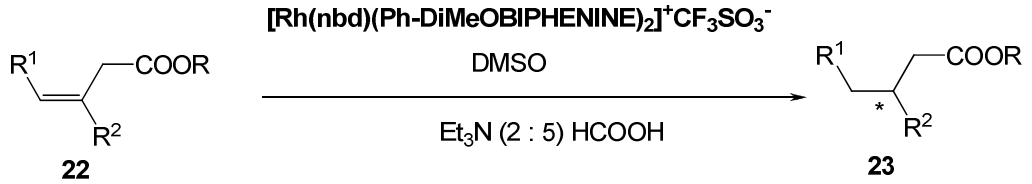
Scheme 3.3: Rh-catalyzed Classical asymmetric hydrogenations

It was also noted that Rh-diMeOBiphenine catalyst system was highly active in these asymmetric hydrogenations. Reducing the catalyst loading from 1 mol% to 0.1 mol% in case of itaconic acid did not lower the conversion or the enantioselectivity of the reaction.

Moreover, in comparison to Ph-Binepine (**3a**); diMeO-Biphenine has ***marginally outperformed*** Ph-Binepine in this type of classical asymmetric hydrogenations for each tested substrates.

This same Rhodium-diMeOBiphenine complex was used in asymmetric transfer hydrogenations. Only low to moderate e.e.'s were obtained in these

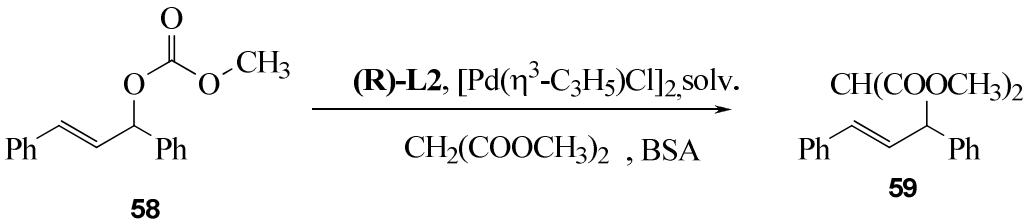
reactions. But, in case of Itaconic acid 96% e.e. with complete conversion was obtained using this catalyst system.



Itaconic acid, when R^1= H, R^2=COOH, R=H .....**96% e.e.**
Dimethylitaconate, when R^1=H, R^2=COOMe, R=Me .....**16% e.e.**
Acetamidocinnamic acid, when R^1=Ph, R^2=$NHCOCH_3$, R=H .....**8% e.e.**
Acetamidoacrylic acid, when R^1=H, R^2=$NHCOCH_3$, R=H .....**40% e.e.**
Methyl Acetamidocinnamate, when R^1=phenyl, R^2=$NHCOCH_3$, R=Me .....**31% e.e.**
Methyl Acetoamidoacrylate, when R^1=H, R^2=$NHCOCH_3$, R=Me .....**50% e.e.**

Scheme 3.4: Rh-catalyzed asymmetric trasfer hydrogenations

diMeO-Biphenine was examined in Pd-catalyzed asymmetric allylic alkylations of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate anion. We were able to achieve upto 70% e.e. in this catalysis by optimizing the reaction conditions.

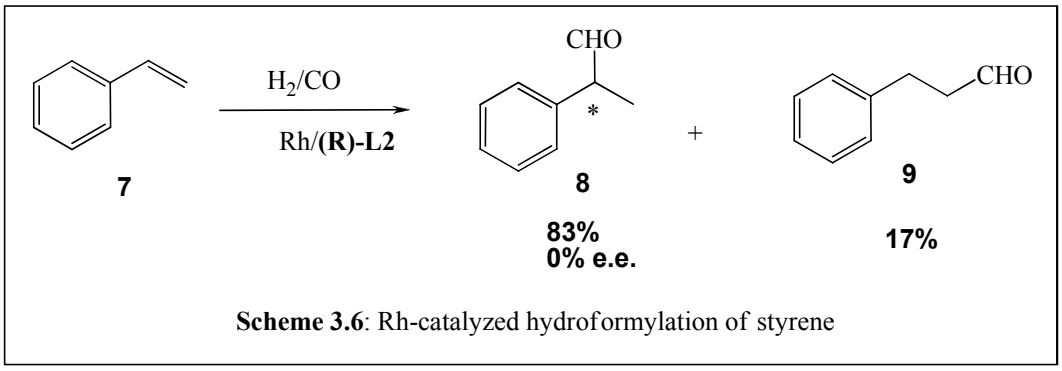


Scheme 3.5: Pd-catalyzed allylic alkylation

In comparison to Ph-Binepine, diMeO-Biphenine exhibited reduced enantioselectivites and slower conversions in this Pd-catalyzed asymmetric allylic alkylation. It was as well noted that in the hydrogenation processes the

trend in the change of enantioselectivities induced by diMeO-Biphenine against the reaction conditions matched with that observed for Ph-Binepine.

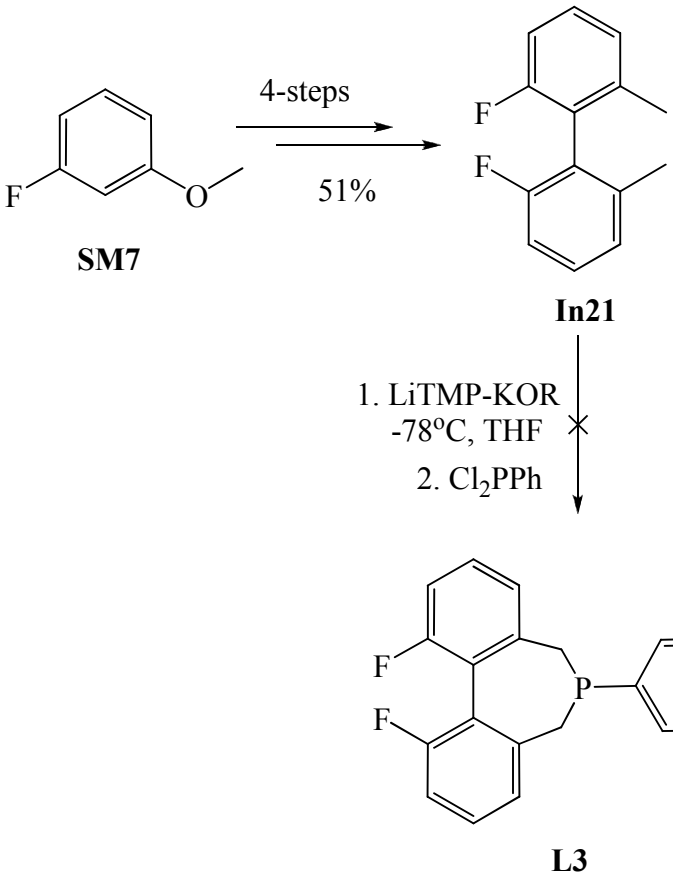
Lastly, diMeO-Biphenine was tested in Rh-catalyzed asymmetric hydroformylation of styrene. Unfortunately, diMeO-Biphenine induced no enantioselectivity in this reaction resulting in a racemic product. But, the reaction did undergo chemoselectively affording a quantitative conversion towards branched aldhehyde with 83% of branched aldehyde vs. 17% of linear aldehyde.



Scheme 3.6: Rh-catalyzed hydroformylation of styrene

❖ **diF-Biphenine (L3)**

Starting from 3-Fluoroanisole (**SM7**), **In21** was prepared in 4 steps with 51% overall yield, with ease. But, unfortunately the last step failed to give the desired product (**L3**).

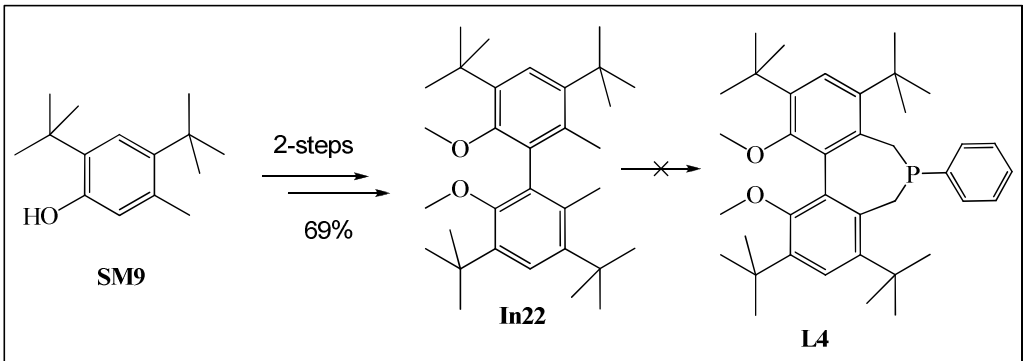


Scheme 3.7: Attempted synthesis of diF-Biphenine

Attributed to the nature of the difluoro substituents on the biphenyl in **In21**, the dimetalated species of **In21** was thought to be extremely sensitive and thus failing to be quenched by dichlorophenylphosphine, appropriately and as desired. A more precise control and a deeper understanding over the reaction is needed for its success.

❖ ***tetratertButyl-diMeOBiphenine(L4)***

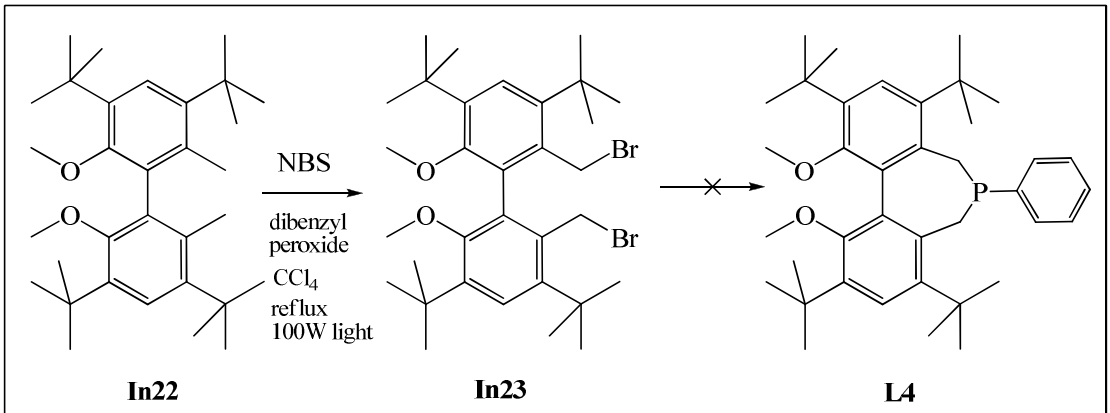
Starting from **SM9**, **In22** was prepared in just 2 steps with 69% overall yield. But, the last step to give the desired ligand (**L4**) was unsuccessful.



Scheme 3.8: Attempted synthesis of tetratertbutyldiMeO-Biphenine

In the last step, it was observed that lithiation failed to give the dimetalated species of **In22**, and this in-turn failed to give the desired product. Lithiation of **In22** was examined using various metalating reagents including strong reagents like tBuLi; but it was not possible to lithiate **In22**.

Steps were taken to address this problem, by brominating **In22**, and investigating other reaction conditions in order to prepare **L4**.



Scheme 3.9 Attempted last step via **In23** in different reaction conditions for **L4** synthesis

In23, was prepared without any problem. But, we were unable to accomplish **L4** from **In23**, inspite of trying different reagents and conditions in this reaction. It was observed that in the last step involving **In23**, the reaction failed to give the desired product and still we did not recover the starting material i.e. **In23** at the end of reaction. This meant that **In23**, was possibly a too reactive species loosing on its bromine without forming the bond with phosphorus.

Hence, possibly carrying out this reaction at lower temperature or converting dibromo in **In23** into dichloro compound, would give the control on the reaction resulting the desired product.

❖ Hetereocyclic phosphepines

Syntheses of heterocyclic phosphepines were one of our profuse interests throughout our quest to prepare structurally diverse phosphepines. We were successful in synthesizing our desired starting materials for the last step (**In25** & **In26**) in good overall yields.

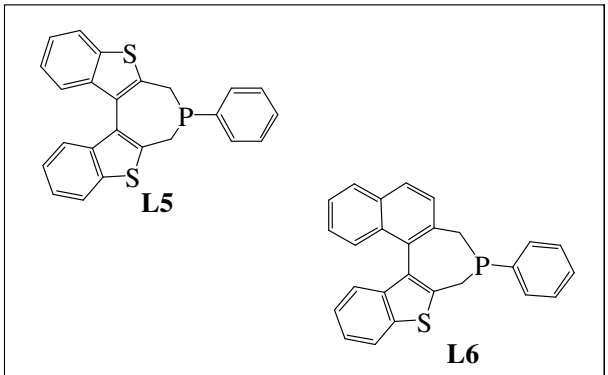
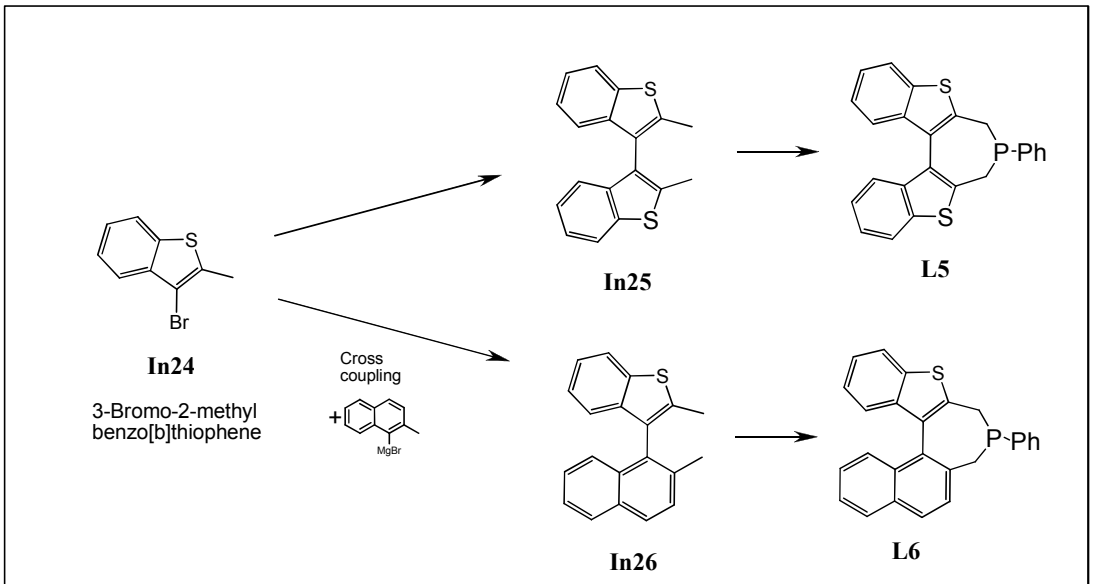


Figure 3.4 Heterocyclic Phosphepine ligands



Scheme 3.10: Undertaken synthetic routes to prepare **L5** & **L6**

In25 was prepared without any problem. And to obtain **In26**, we optimized and carried out efficient hetero aryl-aryl Kumada cross coupling of hindered biaryls using PEPSI-IPr to give **In26** in excellent yield and purity.

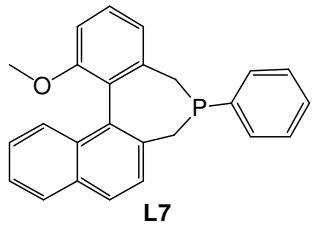
Unfortunately, the last step to prepare the desired ligands **L5** and **L6** was unsuccessful. Regardless of examining various reaction reagents and conditions, we failed to prepare the desired ligands.

Failed synthesis for **L5** was possibly due to the large angle bite angle between the two methyls of **In25**, inhibiting the closure of seven-membered ring with dichlorophenylphosphine that is desired.

In case of **In26**, the angle bite between the two metalated methyls is thought to be smaller than that for **In25**. But, still the last step failed to give the desired product. The reasons of this failure were not clear, and there is a need to investigate this reaction in detail following each stage of the reaction under scrutiny.

❖ C_1-symmetry phosphepine ligand, (L5)

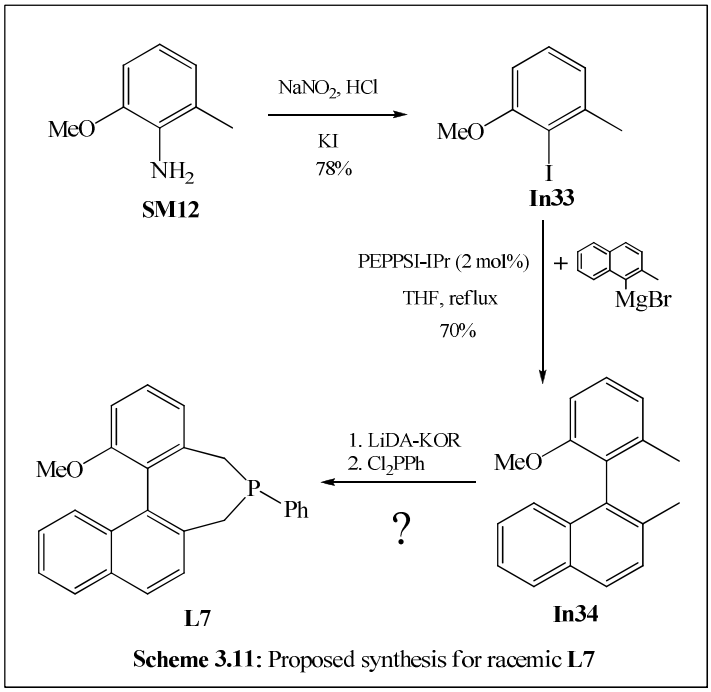
We accomplished a fast preparation of **In34** in just 2 steps. It was possible, due to the success of PEPPSI-IPr mediated hetero aryl-aryl cross coupling of hindered aryls to give **In34**, in reasonable yield and good purity. Once again, PEPPSI-IPr proved to be an excellent catalyst system to carry out such hindered aryl couplings.



L7

C_1-symmetry Phosphepine ligand

Figure 3.5



Scheme 3.11: Proposed synthesis for racemic **L7**

In34 was prepared recently and has not yet been tested for its last step to give the desired ligand, **L7**. We anticipate that the use of exactly same reaction conditions as employed for the preparation of diMeO-Biphenine (**L2**), should provide us the targeted **L7**.

Experimental section

4. Experimental section

1. General

All reactions were carried out under argon atmosphere, unless specified. Nuclear magnetic resonance spectra were obtained on a Varian VXR-5000 spectrometer at 300 MHz for ^{1}H, 121.42 MHz for ^{31}P and 75 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from internal Me_4Si in $CDCl_3$ for ^{1}H- and ^{13}C- and from H_3PO_4 for ^{31}P-NMR. Optical rotations were measured on a Jasco P-1010 polarimeter. For column chromatography was used silica gel (230-400 mesh, Merk 60). All commercially purchased reagents were used without further purification and solvents were distilled after refluxing under nitrogen and stored under inert atmosphere until used.

2. Asymmetric hydrogenation product analysis

Acids obtained from transfer and classical hydrogenation of the corresponding unsaturated substrates were converted to the corresponding esters with (trimethylsilyl)diazomethane before analysis by chiral GC. The enantiomeric excess (ee) was determined by chiral GC (see below).

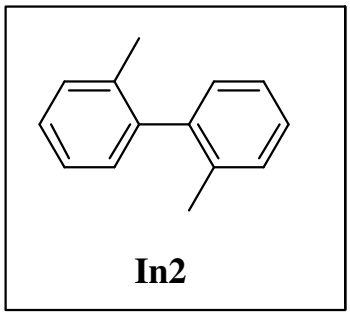
Determination of Enantiomeric Excess. The ee values of the following products were determined by chiral GC or optical rotation. GC Retention times (t_R) are given in min.

2.1. *2-Methylsuccinic Acid Dimethyl Ester* (=*Dimethyl 2-Methylbutanedioate)*. Column, *DACTBSGAMMA-OV 1701* (25 m, i.d. 0.25 mm, ft 0.25 mm); temp. 50°C, 2°C/min, 170°C, 20 min; *PTV* injector (0–400°), detection at 250°, N_2 carrier gas (15 psi, 2 ml/min); t_R 24.29 (*S*), 25.03 (*R*).

2.2. N-*Acetylalanine Methyl Ester* (=*Methyl 2-(Acetamido)propanoate*). Column, *Chirasil-Val-L* (50m, i.d. 0.32 mm, ft 0.25 mm); temp. 80°C, 10 min, 1°C/min, 110°C, 20 min, 2°C/min, 200°C, 30 min; *PTV* injector (0–400°C), detection at 250°C, N_2 carrier gas (20 psi, 2 ml/min); t_R 7.12 (*R*), 7.54 (*S*).

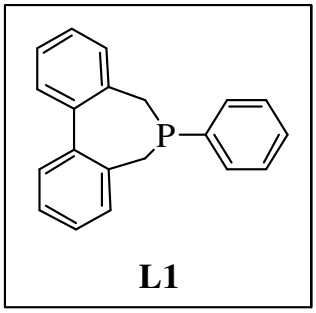
2.3. N-*Acetylphenylalanine Methyl Ester* (=*Methyl 2-(Acetamido)-3-phenylpropanoate*). Column, *Chirasil-Val-L* (50 m, i.d. 0.32 mm, ft 0.25 mm); temp. 110°, 5 min, 1.5°/min, 180°, 1 min, 2°/min, 200°, 30 min; *PTV* injector (0–400°), detection at 250°, N_2 carrier gas (20 psi, 2 ml/min); t_R 40.41 (*R*), 41.19 (*S*).

4.1 Synthesis of Biphenine (L1)


In2

2,2'-Dimethyl-1,1'-biphenyl, In2. Under argon, Mg turnings (1.96 g, 80.74 mmol) and a crystal of iodine to activate the Mg was taken. Anhydrous THF was added just enough to cover the Mg. 2-Bromotoluene (8.66ml, 71.91 mmol) was taken in a dropping funnel and few drops without any dilution was added to the Mg in order to initiate the reaction, all under inert atmosphere. About 77ml of anhydrous THF was added in the dropping funnel to dissolve 2-Bromotoluene, and the solution of 2-Bromotoluene was added to Mg dropwise. The reaction mixture was kept stirring at room temperature for next 2 ½ hours. About 230 ml of anhydrous THF was taken in another dry flask. Anhydrous $FeCl_3$ (0.59g, 3.6 mmol) and 1,2-Dichloromethane (6.82 ml, 86.51 mmol) was added to the THF in this second flask and kept stirring. The grignard reagent prepared above was slowly transferred to the second flask using cannular, under argon. The reaction mixture is kept stirring at room temperature overnight. 10% HCl (about 50 ml) was slowly added to the reaction mixture. The solvent is reduced to minimum on rotary evaporator. The crude product was extracted in diethyl ether; organic phase was dried over Na_2SO_4 and evaporated on rotary evaporator. The crude product was purified on Silica [Dichloromethane (1 : 1) Petroleum ether] to give the product as colourless oil (5.44 g, 83% yield).

^{1}H NMR ($CDCl_3$, 300MHz) δ = **2.05** (s, 6H, -CH_3), **7.09** (d, 2H, ArH), **7.18-7.27** (m, 6H, ArH)



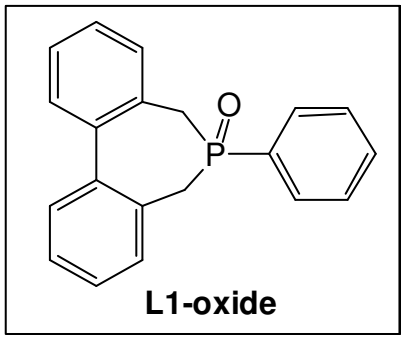
L1

6-phenyl-6,7-dihydro-5H-dibenzo[c,e]phosphepine, Biphenine (L1). To a mixture of ^{t}BuOK (7.40 g, 65.95 mmol), TMEDA (9.80 ml, 65.88 mmol) and anhydrous n-hexane (72 ml), cooled to -50°C, n-BuLi (30.0 ml [1.6M solution], 48.0 mmol) was added and after 30 minutes 2,2'-Dimethyl-1,1'-biphenyl (4.0 g, 21.95 mmol) was added with sirring and cooling. The reaction mixture was kept stirring for 5hours at about -40°C to -30°C. The mixture was then stirred for 30 minutes at room temperature. The temperature was lowered to -30°C, anhydrous THF (40 ml) and dichlorophenylphosphine (3.6 ml, 23.36 mmol) were added. The reaction mixture was then kept stirring at room temperature for 12 hours. Reaction was quenched with 40 ml of distilled water and neutralised with conc. HCl. The organic phase was separated using a syringe, in a filtering flask under argon and the aqueous phase was washed with Dichloromethane twice and collected in the filtering flask. Organic phase was dried over Na_2SO_4 and the solvent evaporated. The crude was purified on silica [n-hexane (70 : 30) Dichloromethane] to obtain the product as white solids (2.40 g, 38% yield)

^{31}P-nmr ($CDCl_3$): **5.83** (s)

^{1}H NMR ($CDCl_3$, 300MHz) δ = **2.63-2.96** (m, -CH_2, 4H), **6.71** (d, Ar, 1H), **7.12-7.17** (m, Ar, 1H), **7.25-7.40** (m, Ar, 11H)

Biphenine oxide, L1-oxide. To a solution of **L1** (0.084 g, 0.29 mmol) in acetone (2 ml) was added H_2O_2 (0.2 ml, 1.74 mmol, 30% solution in water). The reaction mixture was kept stirring for 2 hours at room temperature. Solvent was reduced under vacuum and the product was extracted in dichloromethane. The organic phase was separated, dried over Na_2SO_4, and solvent removed under vacuum to give white solids as the product (quantitative).

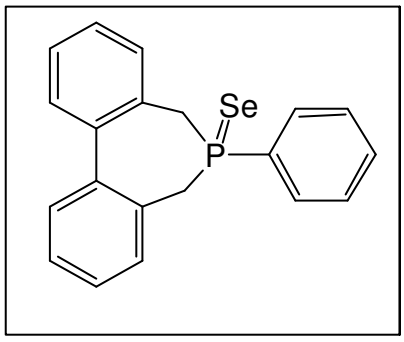


L1-oxide

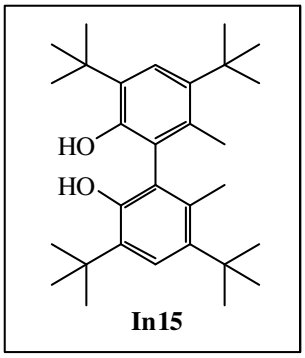
^{31}P-nmr ($CDCl_3$): **53.78** (s)

^{1}H NMR δ: **3.15-3.5** (m, 4H), **7.05** (d, 1H), **7.25-7.70** (m, 12H)

Biphenine-selenium adduct, L2-Se. CDCl3 (1 ml) was added to schlenk tube containing 1,11-dimethoxy-6-phenyl-6,7-dihydro-5H-dibenzo[c,e] phosphepine (0.01 g, 0.029 mmol) and Selenium powder (0.0023 g, 0.029 mmol), under argon. The mixture was refluxed for 2 hours. Sample was directly subjected to NMR analysis. ^{31}P-NMR ($CDCl_3$): **50.475** (s). Small amount of coupling isotope of Selenium gave a duplet with J=727 Hz



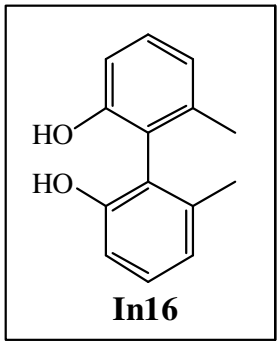
4.2 Synthesis of (R)-diMeO-Biphenine (L2)



In15

3,3',5,5'-tetra-tert-butyl-6,6'-dimethylbiphenyl-2,2'diol, In15. To a solution of 4,6-di-tert-butyl-m-cresol (10.0 g, 45.38 mmol) in methanol (100 ml) was added CuCl(OH)TMEDA (0.53 g, 2.27 mmol, 5 mol%). And the reaction mixture was kept stirring in air for 24 hr. The reaction mixture was filtered to give white precipitate as the product. The precipitate was washed with methanol (1 x 20 ml) and then dissolved in dichloromethane. The dichloromethane solution was washed with 10% HCl solution and the organic phase was separated, dried over Na_2SO_4 and the solvent evaporated under vacuum to give yellow-white solid as the clean product (7.0 g, 70%).

^{1}H NMR δ: **1.42** (d, 36H, four tBu), **2.006** (s, 6H, two -Me), **4.809** (s, 2H, two -OH), **7.384** (s, 2H)

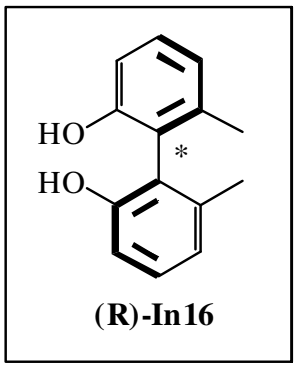


In16

6,6'-dimethylbiphenyl-2,2'-diol, In16. To a solution of 3,3',5,5'-tetra-tert-butyl-6,6'-dimethylbiphenyl-2,2'diol (5.68 g, 12.95 mmol) in benzene (200 ml) was slowly added anhydrous $AlCl_3$ (10.36 g, 77.70 mmol) at 0℃, under argon. The reaction mixture was kept stirring at about 50℃ for 3 hours. At 0℃, distilled water (25 ml) was slowly added, followed by 10% HCl solution (100 ml). Diethyl ether (20 ml) was added to the quenched reaction, and the organic phase was separated, followed by (2 x 20 ml) diethyl ether washings of aqueous phase. The product was extracted in 10% NaOH solution (3

x 30 ml), from the combined organic phase. Combined NaOH solution containing the product was then slowly neutralized with conc. HCl to acidic pH, until pale yellow precipitate was persistent. The precipitate was extracted in diethyl ether (3 x 30 ml), separated, dried over Na_2SO_4, and the solvent was removed under vacuum to give pale yellow colour solids as the pure product (2.86 g, 97%). ^{1}H NMR ($CDCl_3$) δ: **2.011** (s, 6H, 2 –CH_3), **4.677** (s, 2H, 2 -OH), **6.919** (t, 4H, ArH), **7.26** (t, 2H, ArH)

(R)-6,6'-dimethylbiphenyl-2,2'-diol, (R)-In16. To a solution of 6,6'-dimethylbiphenyl-2,2'-diol (3.06 g, 14.28 mmol) in benzene (83 ml) and triethylamine (28 ml), was added (-)-(1R)-Menthyl chloroformate (6.12 ml, 28.56 mmol) dropwise, at 0℃, under argon. The reaction mixture was kept stirring at room temperature for 3 hours. The reaction was quenched with distilled water (30 ml), followed by 10% HCl solution (30 ml). The organic phase was separated and aqueous phase was washed with diethyl ether (2 x 25 ml). Solvent was evaporated from the combined organic phase under vacuum, to give gummy oil as the crude product (8.26 g, quantitative). The crude product was dissolved in solvent mixture (Petroleum ether 9:1 Ethyl acetate) and filtered through silica pad with several washings of the same solvent mixture. Solvent was evaporated under vacuum, and the residue was crystallized from n-hexane. The obtained white crystals were pure diastereomer of (R)-6,6'-dimethylbiphenyl-2,2'-diol (2.97 g, 37%, >99% d.e).



(R)-In16

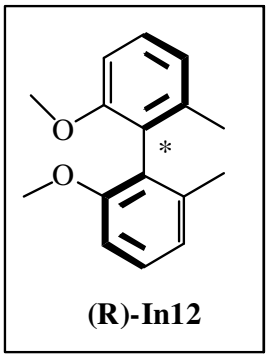
^{1}H NMR (Diastereomer of (R)-6,6'-dimethylbiphenyl-2,2'-diol i.e. **R,R**) (CDCl3) δ: 0.54 (d, J=6.9 Hz, 6H), 0.71 (d, J=6.9 Hz, 6H), 0.75-1.6 (series of m, 22H), **1.90-**

1.96 (m, 2H), **2.057** (s, 6H, -$ArCH_3$), **4.33** (m, 2H), **7.06** (d, 2H, ArH), **7.15** (d, 2H, ArH), **7.313** (t, 2H, ArH)

^{1}H NMR (Diastereomer of (S)-6,6'-dimethylbiphenyl-2,2'-diol i.e. **S,R**) (CDCl3) δ: **0.70** (d, J=6.9 Hz, 6H), **0.71-1.0** (series of m, 18H), **1.1-1.6** (series of m, 10H), **1.8-1.9** (m, 2H), **2.087** (s, 6H, $ArCH_3$), **4.30** (m, 2H), **7.07** (d, 2H, ArH), **7.15** (d, 2H, ArH), **7.28** (t, 2H, ArH)

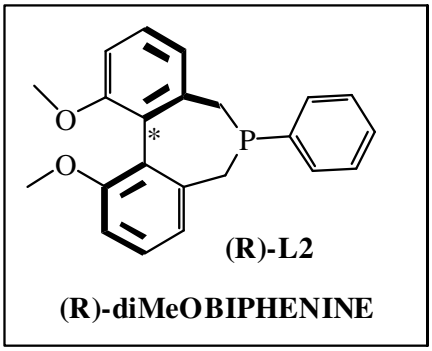
To a solution of above obtained pure diastereomer of (R)-6,6'-dimethylbiphenyl-2,2'-diol (2.97 g, 5.13 mmol) in anhydrous THF (45 ml) was added $LiAlH_4$ (2.60 g) very slowly, at 0°C, under argon. The reaction mixture was kept stirring at room temperature for 15 hours. The reaction mixture was slowly poured into a beaker containing ice, followed by 10% HCl solution (100 ml) and the crude was extracted with washing of aqueous phase with diethyl ether (3 x 40 ml). The combined organic phase was then washed with 10% NaOH solution (3 x 30 ml), in order to extract the desired pure product in NaOH solution from the crude. The combined NaOH solution was slowly neutralized using conc. HCl to acidic pH until the pale yellow precipitate was persistent. The precipitate was extracted in diethyl ether (3 x 30 ml), separated, dried over Na_2SO_4, and the solvent was removed under vacuum to give pale yellow colour solids as the pure product (1.04 g, 34%, >99% e.e.). $[\alpha]_D^{25}$= +85.5° (c=1.0, ethanol). ^{1}H NMR ($CDCl_3$) δ: **2.011** (s, 6H, 2 –CH_3), **4.677** (s, 2H, 2 -OH), **6.919** (t, 4H, ArH), **7.26** (t, 2H, ArH)

(R)-2,2'-dimethoxy-6,6'-dimethylbiphenyl, (R)-12. To a solution of (R)-6-6'-dimethylbiphenyl-2,2'-diol (1.04 g, 4.85 mmol) in anhydrous acetone (50 ml) was added K_2CO_3 (6.70 g, 48.50 mmol), followed by Iodomethane (6.0 ml, 97 mmol), under argon. The reaction mixture kept stirring at room temperature for 15 hours. The reaction mixture was filtered through celite pad, with several acetone washings. Solvent was evaporated from the filtrate under vacuum, and the residue was dissolved in diethyl ether. The organic phase was washed with 10% HCl solution (2 x 40 ml), separated, dried over Na_2SO_4, and solvent evaporated under vacuum to give the crude as white solids. The crude was purified by chromatography [Petroleum ether 9:1 Ethyl acetate] to give the pure product as white solids (0.88 g, 75%). $[\alpha]_D^{25}$= **+51°** (c=0.625, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: **1.939** (s, 6H, 2 $-CH_3$), **3.697** (s, 6H, 2 $-OCH_3$), **6.821** (d, 2H, ArH), **6.918** (d, 2H, ArH), **7.237** (t, 2H, ArH).



(R)-In12

(R)-diMeOBiphenine ***((R)-1,11-dimethoxy-6-phenyl-6,7-dihydro-5H-dibenzo[c,e]phosphepine), (R)-L2.*** Under argon, to a solution of nBuLi (9.10 ml, 14.56 mmol, 1.6M solution in n-hexane) in anhydrous n-hexane (3 ml) was added diisopropylamine (2.06 ml, 14.60 mmol) at 0°C, and kept stirring for 5 minutes at the same temperature. tBuOK (1.638 g, 14.60 mmol) was then added to the reaction mixture at 0°C, and kept stirring for 15 minutes. (R)-2,2'-dimethoxy-6,6'-dimethylbiphenyl (0.88 g, 3.63 mmol) was added as solids directly to the above prepared LiDA-KOR mixture, followed by anhydrous



(R)-L2

(R)-diMeOBIPHENINE

n-hexane (12 ml). The reaction mixture was kept stirring at 28℃ for 20 hours, to obtain a red-brown dimetallated species. Dark red-brown precipitate of dimetallated salt of (R)-2,2'-dimethoxy-6,6'-dimethylbiphenyl was filtered using a Schlenk filter, and transferred to a schlenk tube under argon, followed by addition of anhydrous n-hexane (15 ml). At 0℃, dichlorophenylphosphine (0.495 ml, 3.65 mmol) was slowly added. The reaction mixture was kept stirring at room temperature for further 5 hours. Degassed distill water was added to the reaction mixture, under argon and kept stirring for 5 minutes. Dichloromethane (20ml) was added to the reaction mixture and the organic phase was separated. Aqueous layer was washed with dichloromethane (2 x 10 ml). The combined organic phase was collected, dried over Na_2SO_4, and the solvent was removed under vacuo. The crude obtained was purified by chromatography [n-hexane 7:3 Dichloromethane] to give white solids as the pure product (0.32 g, 25%).

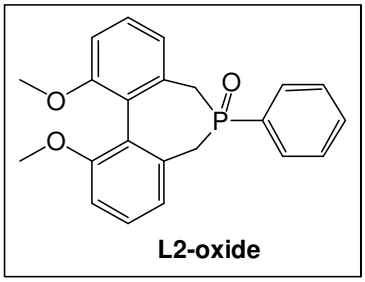
$[\alpha]_D^{25}$= **+142.50°** (c=0.5, $CHCl_3$).

^{31}P-NMR ($CDCl_3$): **1.698** (s).

^{1}H NMR ($CDCl_3$) δ: **2.56- 2.88** (m, 4H, 2 –CH_2), **3.778** (d, 6H, two -OMe), **6.312** (d, 1H, ArH), **6.83-6.93** (m, 2H, ArH), **7.0-7.33** (m, 8H, ArH).

^{13}C-NMR ($CDCl_3$) δ: (aliphatic carbons only) **29.72** (d, $^1J_{C-P}$=14.56 Hz), **31.53** (d, $^1J_{C-P}$=21.20 Hz), **56.08** (s, -OMe)

4.3 Characterization of diMeO-Biphenine

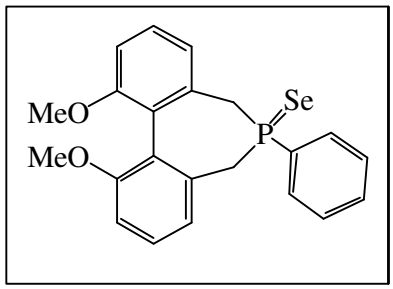


L2-oxide

diMeOBiphenine oxide (1,11-dimethoxy-6-phenyl-6,7-dihydro-5H-dibenzo[c,e] phosphepine oxide, L2-oxide. To a solution of 1,11-dimethoxy-6-phenyl-6,7-dihydro-5H-dibenzo[c,e] phosphepine (0.10 g, 0.29 mmol) in acetone (2 ml) was added H_2O_2 (0.2 ml, 1.74 mmol, 30% solution in water). The reaction mixture was kept stirring for 2 hours at room temperature. Solvent was reduced under vacuum and the product was extracted in dichloromethane. The organic phase was separated, dried over Na_2SO_4, and solvent removed under vacuum to give white solids as the product.

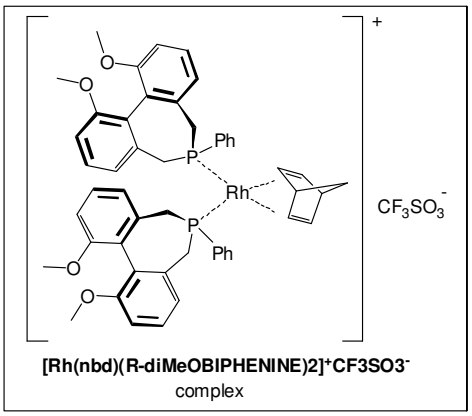
^{31}P-NMR ($CDCl_3$): **50.35** (s).

^{1}H NMR ($CDCl_3$) δ: **3.0-3.30** (m, 4H, 2 –CH_2), **3.799** (s, 3H, -OMe), **3.822** (s, 3H, -OMe), **6.65** (d, 1H, ArH), **6.985** (d, 2H, ArH), **6.90-7.8** (m, 8H, ArH).



diMeOBiphenine-selenium adduct, L2-Se. CDCl3 (1 ml) was added to schlenk tube containing 1,11-dimethoxy-6-phenyl-6,7-dihydro-5H-dibenzo[c,e] phosphepine (0.01 g, 0.029 mmol) and Selenium powder (0.0023 g, 0.029 mmol), under argon. The mixture was refluxed for 2 hours. Sample was directly subjected to NMR analysis. ^{31}P-NMR ($CDCl_3$): 46.49 (s). Small amount of coupling isotope of Selenium gave a duplet with J=725 Hz

[Rh(nbd)(R-diMeOBiphenine)$_2$]$^+$CF$_3$SO$_3^-$,

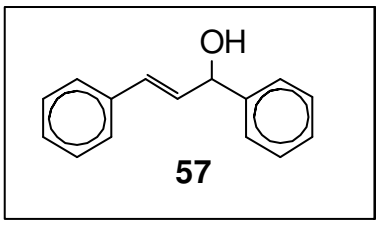


[Rh(nbd)(R-diMeOBIPHENINE)2]$^+$CF3SO3$^-$ complex

C6. [Rh(nbd)2]CF_3SO_3 (60 mg, 0.1375 mmol) was dissolved in 1:1 mixture of anhydrous methanol and anhydrous dichloromethane (10 ml). (R)-diMeOBiphenine (96 mg, 0.2755 mmol) was added and the solution stirred at room temperature for one hour. The solvent was removed at reduced pressure and residue dissolved in dichloromethane (2 ml). Addition of diethyl ether brought about precipitation of the complex which was filtered off, washed with diethyl ether and dried in vacuo. ^{31}P-NMR ($CDCl_3$): 31.46 (d, J_{PRh} = 155.16 Hz). ^{1}H NMR ($CDCl_3$) δ: 1.66 (bs, 2H, nbd), 1.75 (d, 2H, J=12.0 Hz, CH_2), 2.29 (m, 2H, CH_2), 2.43 (d, 2H, J=14.40, CH_2), 2.83 (d, 2H, J=14.10 Hz, CH_2), 3.68 (s, 6H, -OCH_3), 3.76 (s, 6H, -OCH_3), 3.90 (bs, 2H, nbd), 3.98 (bs, 2H, nbd), 5.51 (bs, 2H, nbd), 6.08 (d, 2H, 7.5 Hz, ArH, 6.74 (d, 2H, 8.1 Hz, ArH), 6.91 (t, 2H, ArH), 7.0 (d, 2H, J=8.4 Hz, ArH), 7.26-7.50 (m, 12H, ArH), 7.603 (t, 2H, ArH)

4.4 Asymmetric catalysis with (R)-diMeO-Biphenine

1,3-Diphenylprop-2-enol, 57:

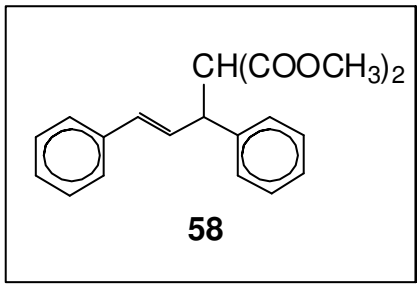


57

Sodium borohydride (1.2g, 31.7 mmol) was added in small portions to a stirred solution of 1,3-diphenylprop-2-en-3-one **56** (6g, 28.81 mmol) in dry methanol (350 ml). After 1 hour the solvent was evaporated and the residue was taken up in ethyl acetate. The organic solution was washed with water (3 x 50 ml), dried and the solvent was evaporated to afford the product as a white solid (5g, 82%).

^{1}H-NMR ($CDCl_3$): δ **8.74** (d, 1H, J=6Hz), **8.6** (s, 1H), **8.23** (d, 1H, J=12Hz), **8.11-8.07** (t, 2H), **7.89-7.77** (m, 2H), **7.63-7.57** (t, 1H), **7.41** (d, 1H, J=11.8Hz), **5.47** (s, 1H), **4.91** (s, 1H), **4.24** (s, 1H), **3.91** (s, 5H).

Methyl-1,3-Diphenyl-2-propenyl carbonate, 58:



58

To a solution of 1,3-diphenylpropen-2-enol **58** (5g, 23.8 mmol) and 7.5 ml (91.8 mmol) of pyridine and a catalytic amount of 4-(dimethylamino)pyridine in 24 ml of dry THF was added methyl chloroformate (6.2 ml, 80 mmol) at 0 □C under argon. The solution was stirred at room temperature for 8h, then quenched with water and extracted three times with diethyl ether. The ether extracts were washed three times with 10% hydrochloric acid, once with saturated sodium bicarbonate solution, and once with water. The combined organic layers were dried over sodium sulphate, filtered and the

solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate=3/1) to give the pure product (75%).

^{1}H-NMR ($CDCl_3$): δ **7.45-7.23** (m, 10H), **6.68** (d, 1H, J=15.6), **6.40-6.32** (m, 1H), **6.26** (d, 1H, J=7.2Hz), **3.78** (s, 3H).

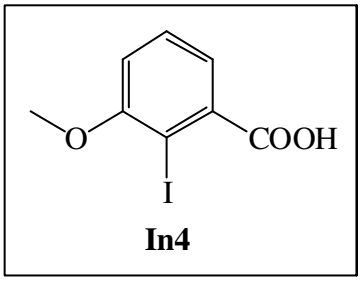
General procedure for Allylic alkylation. A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) and (R)-diMeOBiphenine (5 mol%) in anhydrous solvent (1 ml) was stirred at room temperature for half an hour. At an appropriate temperature, 1,3-diphenylprop-2-enylacetate (0.4 mmol) in solvent (1 ml), dimethylmalonate (0.12 mmol), N,O-bis(trimethylsilyl)acetate (BSA) (0.12 mmol) and potassium acetate (3 mol%) were added in sequence. The reaction mixture was stirred for the appropriate time until conversion was complete. The reaction mixture was diluted with diethyl ether and washed with saturated ammonium chloride. The organic phase was dried and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum ether 3:1 diethyl ether) to afford dimethyl 1,3-diphenylprop-2-enylmalonate. The enantiomeric excess of the reaction were determined through ^{1}H-NMR spectrum in the presence of the enantiomerically pure shift reagent tris[3-(heptafluoropropylhydroxymethylene-(+)-camphorate]. Splitting for one of the two methoxy groups were observed.

General procedure for Asymmetric transfer hydrogenation. The substrate (2 mmol) and the pre-formed Rh complex (0.030 mmol) were dissolved in DMSO (4

ml) under argon. Then, HCOOH :Et_3N (5 : 2) (10 mmol HCOOH, 4 mmol Et_3N) was added, whereupon the color of the soln. changed from orange to yellow under evolution of gas. After stirring the mixture at the given temp. for the required time, the mixture was quenched with saturated $NaHCO_3$ solution (10 ml). The aqueous layer was washed with diethyl ether (4 x 15 ml) The combined org. layers were dried (Na_2SO_4), and the solvent was removed *in vacuo*. The identity of the crude product was checked by NMR. Conversions and e.e. values were determined by GC, as reported above.

General procedure for Asymmetric classical hydrogenation. The substrate (0.50 mmol) and the pre-formed Rh complex (0.005 mmol) were dissolved in the appropriate solvent (7.5 ml), under argon. Then, argon was removed under vacuum and the reaction flask was purged with hydrogen. Hydrogenation was proceeded at atmospheric pressure using hydrogen balloon. The identity of the crude product was checked by NMR. Conversions and ee values were determined by GC, as reported above.

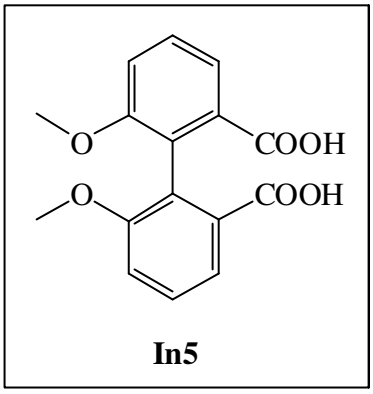
4.5 Experimental procedures for other attempted synthetic route for diMeO-Biphenine



In4

2-Iodo-3-methoxybenzoic acid, In4. To a stirred solution of n-BuLi (9.4 ml, 15 mmol, 1.6M sol. in hexane) was added 2,2,6,6,-tetramethylpiperidine (2.12 g, 15 mmol) in THF (20 mL) at 0℃. 3-methoxybenzoic acid (**6**) (0.46 g, 3 mmol) in THF (5 mL) was added dropwise to the prepared LTMP solution. After 2 h stirring at this temperature, the solution was quenched with the iodine (4.57 g, 18 mmol). After being stirred for 30 min at 0℃, the mixture was heated at 65℃ for 2 h. After water (30 ml) was added, the aqueous phase was washed with diethyl ether (20 mL), acidified with aqueous (2M) HCl, and extracted with diethyl ether. The organic layer phase dried over MgSO4, filtrated and concentrated in vacuo to give the crude benzoic which after purification by chromatography (cyclohexane/ethyl acetate 80:20) gave yellow solid (53% yield) as the pure product.

^{1}H NMR (CDCl3) δ: **3.94** (s, 3H), **6.99** (dd, 1H, J = 7.9 Hz and J = 1.5 Hz), **7.38** (t, 1H, J = 7.9 Hz), **7.49** (dd, 1H, J = 7.9 Hz and J = 1.5 Hz).



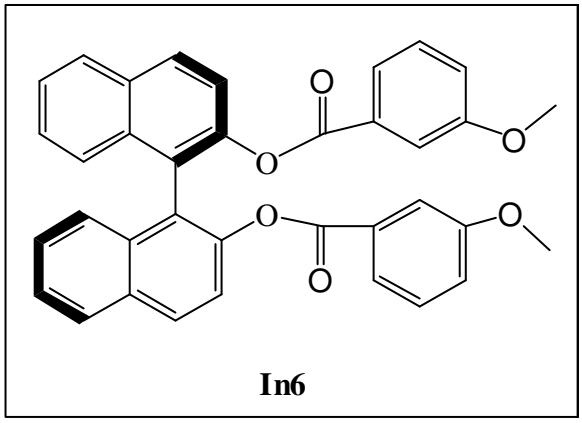
In5

6,6'-dimethoxybiphenyl-2,2'-dicarboxylic acid, In5. To a stirred solution of n-BuLi (9.4 ml, 15 mmol, 1.6M sol. in hexane) was added 2,2,6,6,-tetramethylpiperidine (2.12 g, 15 mmol) in THF (20 mL) at 0℃. 3-methoxybenzoic acid (**6**) (0.46 g, 3 mmol) in THF (5 mL) was added dropwise to the prepared LTMP solution. After 2 h stirring at this temperature, anhydrous $CuCl_2$

(0.444 g, 3.30 mmol) was slowly added to the reaction mixture at 0℃. The reaction mixture was then stirred for 1 hour at 0℃. 10% HCl solution was used to quench the reaction and the product was extracted in Diethyl ether. The organic phase was separated, dried over Na2SO4 and solvent evaporated under pressure to give the crude (10-20% from NMR).

The crude obtained was unable to be purified by flash chromatography and contained 80% of starting material.

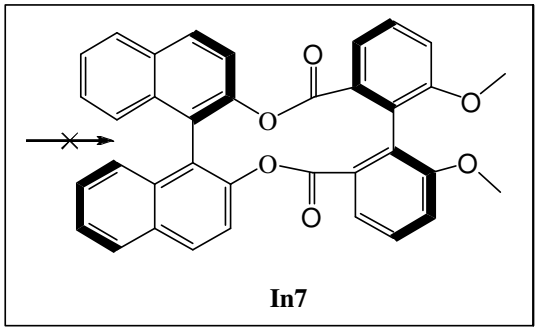
(R)-1,1'-binaphthyl-2,2'-diyl bis(3-methoxybenzoate), In6. A solution of DCC (0.867 g, 4.2 mmol) and DMAP (0.029 g, 0.24 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of (R_a)-(+)-1,1'-bi-2-naphthol (0.573 g, 2.0 mmol) and m-anisic acid (0.609 g, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0℃. The mixture was allowed to react at 25℃ for 3–5 h. Addition of Et_2O, filtration of the precipitate formed and evaporation of the solvent under reduced pressure yielded an oil which was purified by flash chromatography (hexane/diethyl ether 5:1) to give the product (95%).



In6

^{1}H NMR (CDCl3) **δ**: **3.593** (s, 6H), **6.975** (d, 2H, ArH), **7.064** (s, 2H, ArH), **7.152** (t, 2H, ArH), **7.26-7.48** (m, 8H, ArH), **7.575** (d, 2H, ArH), **7.91** (d, 2H, ArH), **7.99** (d, 2H, ArH).

16,17-dimethoxydibenzo[h,j]dinaphtho [2,1-b:1',2'-d][1,6]dioxacyclododecine-12,21-dione, In7. Under argon atmosphere, 2,2,6,6-tetramethylpiperidine (1.1 mmol) was added to dry THF (5 ml) and the mixture was cooled to -78C. n-BuLi (1.0 mmol) was added to the mixture at -78C and the mixture was stirred at 0C for 30 min. To a mixture, di-t-butylzinc (1.2 mmol) prepared from $ZnCl_2$ (1.2 mmol) and t-BuLi (2.4 mmol) was added at -78Cand the mixture was stirred at room temperature for 30 min.



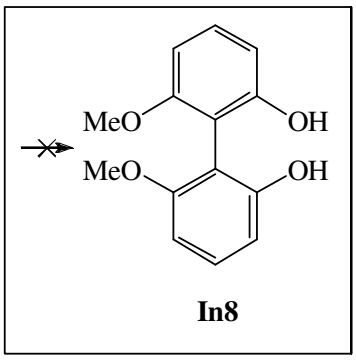
In7

To TMPZn^{t}Bu$_2$Li solution (1.0 mmol or 2 mmol) prepared as described above, **In6** was added at room temperature and the mixture was stirred for 3 h. Then the respective catalyst was added to the reaction mixture and the reaction was stirred for further 5 hours at room temperature.

The reaction was unsuccessful and the starting material was recovered.

6,6'-dimethoxybiphenyl-2,2'-diol, In8.

(Direct oxidative coupling)

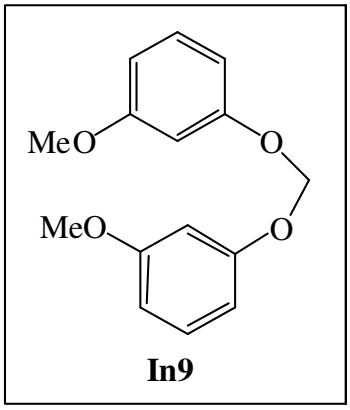


In8

3-Methoxyphenol (1.018 g, 8.20 mmol) was dissolved in MeOH (10 ml) and the previously prepared catalyst [Cu(OH)TMEDA]Cl (0.19 g, 0.82 mmol) was added to the reaction. The reaction mixture was kept stirring in air at room temperature for 24 hr.

The reaction was unsuccessful and gave multiple poly-phenolic products at the end of the reaction.

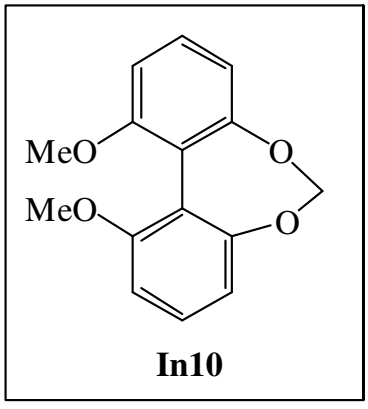
bis(3-methoxyphenoxy)methane, In9. In a dry flask, 3-Methoxyphenol (8.77 ml, 80.55 mmol) was taken in dry DMF (160 ml) and kept stirring. K_2CO_3 (22.23 g) was added to this stirred solution. The reaction mixture was kept stirring at room temperature for 1 hour. Diiodomethane (21.58) solution in dry DMF (90 ml) was added to the above reaction mixture dropwise. The reaction mixture was kept stirring for 48hr. The reaction mixture was quenched with distilled water. 10% HCl solution was added until neutral pH. The organic phase was extracted with Diethyl ether, dried over Na_2SO_4 and evaporated to give the crude. The crude was purified on Silica [Dichloromethane (1 : 1) Petroleum ether] to give product as colourless oil (88%).



In9

^{1}H NMR (CDCl3) **δ**: **3.755** (s, 6H, two -OMe), **5.676** (s, 2H, -CH_2), **6.55** (dd,2H, ArH), **6.64** (dd, 2H, ArH), **6.65** (dd, 2H, ArH), **7.154** (t, 2H, ArH)

1,11-dimethoxydibenzo[d,f][1,3]dioxepine, In10. To a stirred solution of **In9** (1.5 g, 5.76 mmol) in 20 ml of anhydrous Diethyl ether, n-BuLi (1.6M solution in hexane; 14.40 ml, 23.04 mmol) was added dropwise under inert atmosphere. The reaction mixture was

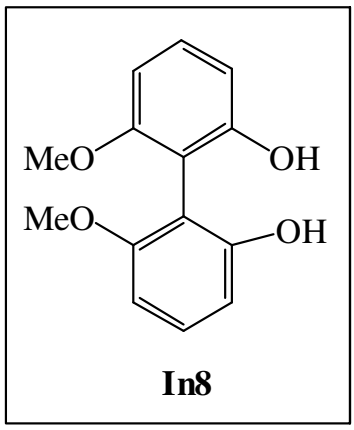


In10

kept stirring for 24 hours. CuI (4.39 g, 23.04 mmol) and pyridine (24 ml) was added at 0℃. The reaction was heated at 65℃ for 24hr under inert atmosphere. Some ice pieces were introduced in the reaction mixture, and the reaction mixture was then acidified using conc. HCl. The organic phase was extracted in Diethyl ether, dried over Na_2SO_4 and evaporated to give brownish solid as the crude (61%).

^{1}H NMR (CDCl3) **δ**: **3.86** (s, 6H, two -OMe), **5.53** (s, 2H, -CH_2), **6.83** (dd, 2H, ArH), **6.89** (dd, 2H, ArH), **7.35** (t, 2H, ArH).

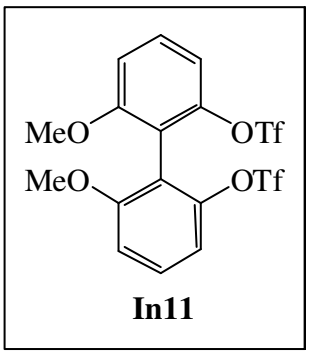
6,6'-dimethoxybiphenyl-2,2'-diol, In8. To an ice cooled solution of **In10** (1.49 g, 5.76 mmol) in Methanol (310 ml), Acetyl chloride (48.90 ml, 691.20 mmol) was slowly added. After stirring at room temperature for 96 h, the reaction mixture was poured in 700 ml of water and extracted with ether (5 x 100 ml). The organic extracts were collected, dried over Na_2SO_4 and solvent evaporated. Purification by flash chromatography (PE 1:1 CH_2Cl_2) afforded product (94%). (There were some purity issues which did not interfere in the next steps)



In8

^{1}H NMR (CDCl3) **δ**: **3.77** (s, 6H, two -OMe), **5.105** (s, 2H, two -OH), **6.615** (d, 2H, ArH), **6.72** (d, 2H, ArH), **7.31** (t, 2H, ArH).

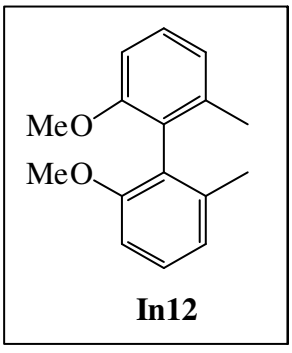
6,6'-dimethoxybiphenyl-2,2'-diyl bis(trifluoromethanesulfonate), In11. In a dry flask at 0℃, 2,2'-Dihydroxy-6,6'-Dimethoxy-1,1'-biphenyl (1.03 g, 4.18 mmol) was introduced in dry Dichloromethane (9 ml) and distilled pyridine (1.2 ml), under Argon. A drying tube having $CaCl_2$ was fitted to the flask. Triflate anhydride (1.79 ml, 10.65 mmol) was added to the reaction mixture dropwise. The ice bath is removed and reaction kept stirring. The reaction is monitored by TLC and was completed in about 1 ½ hours. The flask is subjected to an ice bath (at 0℃), 10% HCl solution was added to the reaction mixture A precipitate was seen to form. Addition is continued until the precipitate is completely redissolved. The organic phase was separated and the aqueous phase extracted with Dichloromethane. The organic phase was dried on Na_2SO_4 and the solvent evaporated to give maroon oil as the crude product. Crystallisation of the crude in hot n-hexane gave the purified product.



In11

^{1}H NMR (CDCl3) **δ**: **3.793** (s, 6H, two -OMe), **7.0** (dd, 4H, ArH), **7.472** (d, 2H, ArH).

2,2'-dimethoxy-6,6'-dimethylbiphenyl, In12. In a 50ml dry 2-neck flask under argon, Mg-turnings (0.40 g, 16.45 mmol), two drops of 1,2-Dibromoethane and anhydrous Et_2O just enough to cover the Mg- turnings were added and warmed in order to activate Mg. Iodomethane (1.02 ml, 16.38 mmol) in Diethyl ether (5 ml) was added to the reaction flask containing

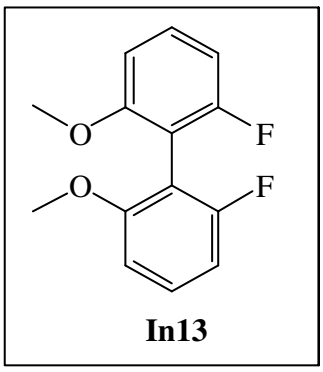


In12

Mg. The reaction mixture was stirred until complete formation of grignard reagent. Ni(dppp)Cl_2 complex (0.29 g, 0.533 mmol) was added to the grignard reagent mixture. **In11** Dimethoxy biphenyl ditriflate (1.4 g, 2.744 mmol) in anhydrous Et_2O (10 ml) was added dropwise to the reaction mixture. The reaction mixture was kept stirring for 24 hours at room temperature. The reaction was very slowly quenched with 10% HCl solution and extracted in Diethyl ether. The organic phase was dried over Na_2SO_4 and the solvent evaporated. The crude obtained was purified by flash chromatography [Petroleum ether 9:1 ethyl acetate] to give white crystals (93% yield)

^{1}H NMR ($CDCl_3$) **δ**: **1.93** (s, 6H, two -Me), **3.69** (s, 6H, two -OMe), **6.82** (d, 2H, ArH), **6.91** (d, 2H, ArH), **7.24** (t, 2H, ArH)

2,2'-difluoro-6,6'-dimethoxybiphenyl, In13. To a dry Schlenk tube, 3-Fluoroanisole (1.0 g, 7.93 mmol) in anhydrous THF (8 ml) was added and kept stirring at -78°C to attain the temperature. n-BuLi (5.0 ml, 1.6M solution in hexane, 8.0 mmol) was added slowly over 5-10 minutes to the reactant solution at -78°C. The reaction mixture was kept stirring at the same temperature for further 30 minutes. Anhydrous $CuCl_2$ (1.365 g, 10.15 mmol) was added to the lithiated reactant at -78°C and the reaction mixture kept stirring at this same temperature for further 20 minutes. The reaction mixture is then allowed to warm to room temperature and kept stirring at r.t. for further 20 minutes. 10% HCl solution was used to quench the reaction and the

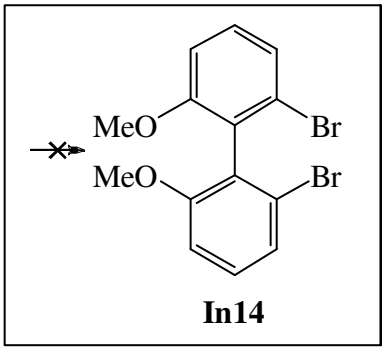


In13

product was extracted in Diethyl ether. The crude obtained was purified by chromatography [Petroleum ether 4:1 Acetone] to obtain white solids (0.76 g, 77% yield)

^{1}H NMR ($CDCl_3$) δ: **3.78** (s, 6H, two -OMe), **6.76-6.82** (dd, 4H, ArH), **7.28-7.362** (m, 2H, ArH)

2,2'-dibromo-6,6'-dimethoxybiphenyl, In14.



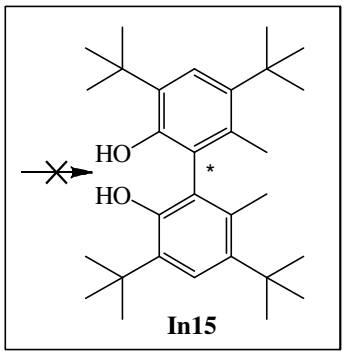
In14

Under argon atmosphere, 2,2,6,6-tetramethylpiperidine (1.1 mmol) was added to dry THF (5 ml) and the mixture was cooled to -78C. n-BuLi (1.0 mmol) was added to the mixture at -78C and the mixture was stirred at 0C for 30 min. To a mixture, di-t-butylzinc (1.2 mmol) prepared from $ZnCl_2$ (1.2 mmol) and t-BuLi (2.4 mmol) was added at -78Cand the mixture was stirred at room temperature for 30 min.

To TMPZn^tBu_2Li solution (1.0 mmol or 2 mmol) prepared as described above, m-Bromoanisole (**SM8**) was added at -30℃ and the mixture was stirred for 12 h. Then $CuCl_2$ was added to the reaction mixture at -30℃ and the reaction was stirred for further 5 hours at -30℃.

The reaction was unsuccessful giving a mixture of products that were difficult to be separated and identified. Starting material was not observed at the end of the reaction.

3,3',5,5'-tetra-tert-butyl-6,6'-dimethylbiphenyl-2,2'diol, In15.



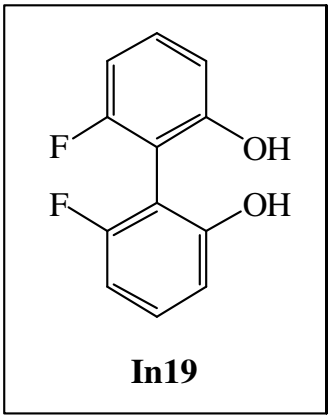
In15

(Attempted asymmetric oxidative coupling with (-)-sparteine or S)-α-methylbenzylamine)

To a solution of anhydrous copper(II) chloride (0.06 g, 0.4538 mmol) in degassed methanol (5 mL) was added (-)-sparteine (0.213 g; 0.91 mmol) in degassed methanol (5 mL), and after purging with argon for 10 min, a solution of 4,6-ditertbutyl-m-cresol (**SM9**) (1.0 g; 4.54 mmol) in degassed methanol (20 mL) was added. The mixture was stirred for 24 hr under argon atmosphere. The reaction mixture was filtered to give white precipitate as the product. The precipitate was washed with methanol (1 x 20 ml) and then dissolved in dichloromethane. The dichloromethane solution was washed with 10% HCl solution and the organic phase was separated, dried over Na_2SO_4 and the solvent evaporated under vacuum to give yellow-white solid as the clean product (70%).

Optical rotation (0°) measurement showed no enantiopure **In15**, which was confirmed to be racemic after deprotection of tert-butyl groups on **In15** to prepare **In16**; and then checking the optical rotation. (as optical rotation for **In16** is a known in the literature)

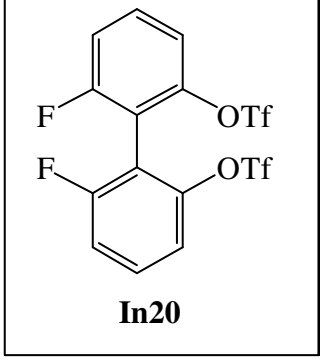
4.6 *Synthesis towards diF-Biphenine*



In19

6,6'-difluorobiphenyl-2,2'-diol, In19. To a solution of **In13** (2.0 g, 7.99 mmol) in dry CH_2Cl_2 (90 mL) was slowly added a solution of BBr_3 (1.87 mL, 19.41 mmol) at -78 ℃ under argon atmosphere. The mixture was allowed to stir at room temperature for 5 h, and quenched carefully with 10% HCl at 0℃. It was then extracted with diethyl ether and the organic layer was dried over anhydrous Na_2SO_4. After evaporation under reduced pressure, silica gel column chromatography [hexane (1 : 1) ethyl acetate] gave colourless oil (93% yield).

^{1}H NMR (CDCl3) δ: **5.70** (bs, 2H, two -OH), **6.70-6.90** (m, 4H, ArH), **6.27-7.35** (m, 2H, ArH).



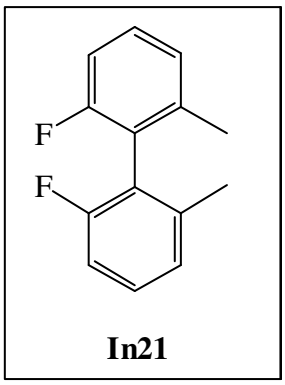
In20

6,6'-difluorobiphenyl-2,2'-diyl bis(trifluoromethanesulfonate), In20. In a dry flask at 0℃, **In19** (1.78 g, 8.01 mmol) was introduced in dry dichloromethane (18 ml) and distilled pyridine (2.6 ml), under Argon. A drying tube having $CaCl_2$ was fitted to the flask. Triflate anhydride (3.51 ml, 20.83 mmol) was added to the reaction mixture dropwise. The ice bath is removed and reaction kept stirring. The reaction is monitored by TLC. After the reaction was completed. The flask is subjected to an ice bath (at 0℃), 10% HCl solution was added to the reaction mixture A precipitate was seen to form. Addition is continued until the precipitate is completely redissolved. The organic phase was separated and the

aqueous phase extracted with Dichloromethane. The organic phase was dried on Na_2SO_4 and the solvent evaporated to give maroon oil as the crude product. The crude was purified by chromatography (Petroleum ether 8 : 2 Ethyl acetate] to give product (98%).

^{1}H NMR (CDCl3) **δ**: **7.26-7.33** (m, 4H, ArH), **7.55-7.65** (m, 2H, ArH).

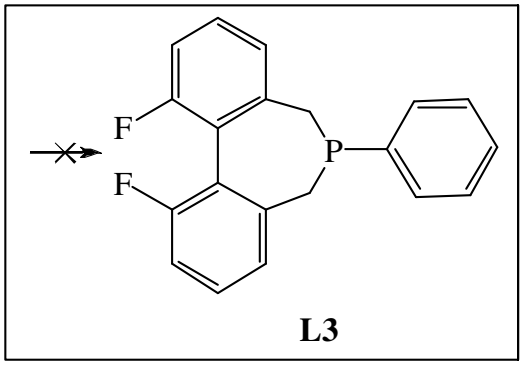
2,2'-difluoro-6,6'-dimethylbiphenyl, In21. In a 50ml dry 2-neck flask under argon, Mg-turnings (0.15 g, 6.17 mmol), two drops of 1,2-dibromoethane and anhydrous Et_2O just enough to cover the Mg- turnings were added and warmed in order to activate Mg. Iodomethane (0.39 ml, 6.18 mmol) in anhydrous diethyl ether (15 ml) was added to the reaction flask containing Mg. The reaction mixture was stirred until complete formation of grignard reagent. $Ni(PPh_3)_2Cl_2$ complex (0.07 g, 0.107 mmol) was added to the grignard reagent mixture. **In20** (1.0 g, 2.06 mmol) in anhydrous Et_2O (10 ml) was added dropwise to the reaction mixture. The reaction mixture was kept stirring for 24 hours at 50°C. The reaction was very slowly quenched with 10% HCl solution and extracted in Diethyl ether. The organic phase was dried over Na_2SO_4 and the solvent evaporated. The crude obtained was purified by flash chromatography [Petroleum ether 9:1 ethyl acetate] to give white crystals (70% yield).



In21

^{1}H NMR ($CDCl_3$) **δ**: **2.07** (s, 6H, two -Me), **6.992** (t, 2H, ArH), **7.10** (d, 2H, ArH), **7.24-7.32** (m, 2H, ArH).

1,11-difluoro-6-phenyl-6,7-dihydro-5H-dibenzo[c,e]phosphepine,

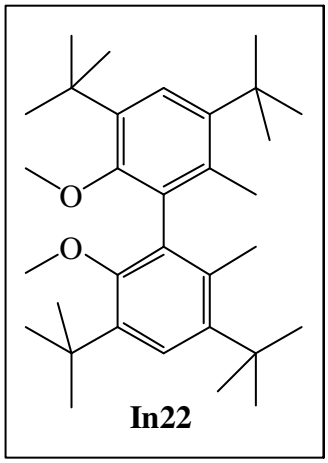


L3

diF-Biphenine, L3. In a dry Schlenk tube, n-BuLi (1.25 ml, 2.0 mmol) and anhydrous THF (2ml) was taken and kept stirring at -78℃. 2,2,6,6-Tetramethylpiperidine (0.34 ml, 2.0 mmol) was added to BuLi solution and kept stirring for 15 minutes. t-BuOK (0.224 g, 2.0 mmol) was added to the above LiTMP solution and kept stirring for another 15 minutes. A solution of 2,2'-Difluoro-6,6'-dimethyl-1,1'-biphenyl (**In21**) (0.25 g, 1.15 mmol) in anhydrous THF (4ml) was added slowly to the above prepared LiTMP-KOR solution at -78℃. The reaction is kept stirring at -78℃ overnight for complete dimetalation. Dichlorophenylphosphine (0.17 ml, 1.25 mmol) was added to the above reaction at -78℃ and kept stirring at this same temperature for about 1 hour. The cryostat was put off and the temperature of the reaction was allowed to rise very slowly in the cryostat to about -30℃.

The reaction was unsuccessful to give the desired product. And starting material was recovered.

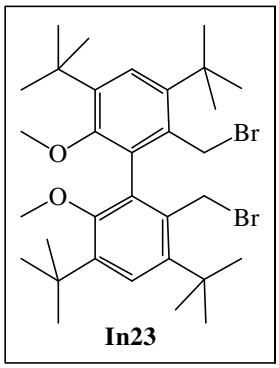
4.7 *Synthesis towards Tetratertbutyl-diMeOBiphenine*



In22

3,3',5,5'-tetra-tert-butyl-2,2'-dimethoxy-6,6'-dimethylbiphenyl, In22. In a dry 2-neck 100ml flask, NaH (0.36g, 9.0 mmol, 60% in oil) was taken, under argon. NaH was washed twice with dry n-hexane in inert atmosphere. Dihydroxyditert-butylbiphenyl (1.0 g, 2.28 mmol) in 30 ml of anhydrous THF was added to NaH in the flask, followed by Iodomethane (6.47g, 45.58mmol). The reaction mixture was kept stirring at room temperature, overnight. Water was slowly added to the reaction mixture followed by 10% HCl. The crude was extracted in Diethyl ether, separated from aqueous phase, dried over Na_2SO_4 and filtered through a silica pad. The solvent was evaporated on rotary evaporator to give white solids as the product (98% yield).

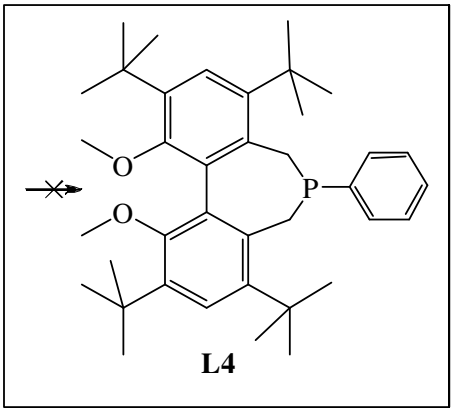
^{1}H NMR δ: **1.41** (d, 36H, four tBu), **2.122** (s, 6H, two -Me), **3.083** (s, 6H, two -OMe), **7.374** (s, 2H, ArH)



In23

2,2'-bis(bromomethyl)-3,3',5,5'-tetra-tert-butyl-6,6'-dimethoxybiphenyl, In23. In a dry 2-neck flask, DiMeO diMe ditBu Biphenyl [1SK236] (1.05 g, 2.25 mmol) in 10 ml CCl4 was taken under argon. N-BromoSuccinimide (0.783 g, 4.50 mmol) and Dibenzoyl peroxide (0.01 g, 0.041 mmol) were added to the above solution. The reaction was kept refluxing and exposed to 100W light overnight. The reaction mixture was filtered over filter paper to remove the solids with washings of CCl_4. The solvent was evaporated from the filtrate to give the product.

^{1}H NMR δ: **1.407** (s, 18H, two tBu), **1.535** (s, 18H, two tBu), **3.286** (s, 6H, two -OMe), **4.57** (s, 4H, two –CH_2), **7.532** (s, 2H, ArH)

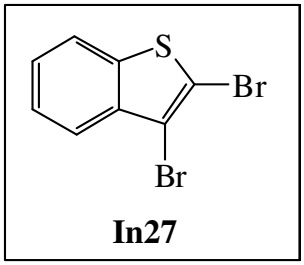


L4

2,4,8,10-tetra-tert-butyl-1,11-dimethoxy-6-phenyl-6,7-dihydro-5H-dibenzo[c,e]phosphepine, L4. To a suspension of **In23** (0.25 g, 0.40 mmol) and NaH (0.05 g, 1.25 mmol) in THF (5 ml) was added phenylphosphine (0.44 ml ml, 0.40 mmol, 10% wt in hexane) at 0℃ under argon. The mixture was stirred at ambient temperature for 24 hours. The reaction was quenched with water, and the crude extracted in dichloromethane.

The reaction failed to give any desired product and starting material was not detected by NMR. Hence, the reaction had given some undesired products that were not identified.

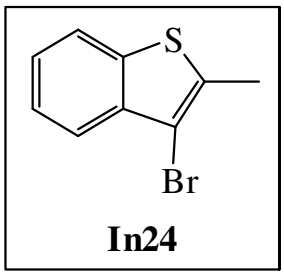
4.8 Synthesis towards Heterocyclic phosphepines



In27

Dibromo Benzo[b]thiophene. In a dry flask fitted with a reflux condenser and drying tube ($CaCl_2$), Benzo[b]thiophene (8.9 g, 66.32 mmol) is taken in Chloroform (45 ml). Bromine (7.10 ml, 138.84 mmol) is taken in a dropping funnel having Chloroform (22 ml). The bromine solution is added to the Benzo[b]thiophene solution at 0°C and kept stirring overnight. The reaction was allowed to attain the room temperature over the night. Aqueous Sodium hydroxide solution was added to the reaction mixture and the organic phase was separated. The organic phase was twice washed with 3N NaOH solution and once with water. The organic phase was dried over Na_2SO_4 and evaporated under rotary evaporator. The crude as pale yellow solid was purified on Silica [100% Petroleum ether] to give product as solid (10.0 g, 92%).

^{1}H NMR ($CDCl_3$) **δ**: **7.35-7.46** (m, 2H, ArH), **7.70-7.76** (m, 2H, ArH)



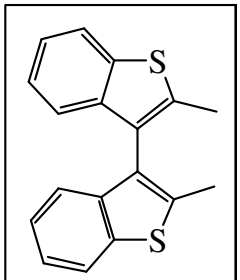
In24

3-Bromo-2-methylbenzo[b]thiophene. In a dry Schlenk tube, 2,3-Dibromobenzo[b]thiophene (5.0 g, 17.12 mmol) was dissolved in anhydrous THF (130 ml) and kept stirring at -75°C. n-BuLi (10.75 ml, 1.6M solution in hexane, 17.20 mmol) was added to the reaction mixture and the reaction was kept stirring at -75°C for 45 minutes. Iodomethane (5.48 ml, 88.01 mmol) was added to the reaction mixture and the reaction mixture was further kept stirring at -75°C for 1 hour. The reaction mixture was then allowed to warm to room temperature.

Distilled water (100 ml) was added to the reaction mixture. THF was evaporated to minimum on rotary evaporator and the product extracted in Dichloromethane (2 x 70ml). The organic phase was washed twice with water (90 ml), dried over Na_2SO_4, evaporated to give the product as brown oil. Crystals are obtained as the product is dried on high vacuum (3.66 g, 94%).

^{1}H NMR ($CDCl_3$) δ: **2.53** (s, 3H, -CH_3), **7.27-7.42** (m, 2H, ArH), **7.695** (dd, 2H, ArH)

2,2'-Dimethyl-3,3'-bibenzo[b]thiophene. In a 25ml dry 2-neck flask under argon, Mg-turnings (0.097 g, 3.99 mmol), two drops of 1,2-Dibromoethane and anhydrous THF just enough to cover the Mg- turnings were added and warmed in order to activate Mg. 3-Bromo-2-methylbenzo[b]thiophene (0.90 g, 3.963 mmol) in anhydrous THF (10 ml) was added to the reaction. The reaction mixture was refluxed until complete formation of grignard reagent.



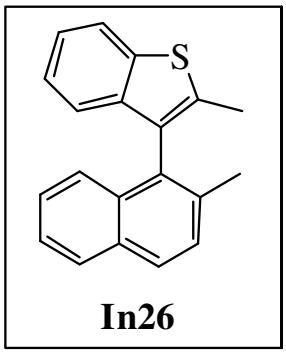
In25

$Ni(PPh_3)_2Cl_2$ complex (0.130 g, 0.199 mmol, 4.2 mol%) was added to the grignard reagent mixture. 3-Bromo-2-methylbenzo[b]thiophene (0.90 g, 3.963 mmol) in anhydrous THF (5 ml) was added dropwise at reflux to the reaction mixture. The reaction mixture was kept refluxing for next 24 hours.

10% HCL was added slowly to quench the reaction and the product extracted in Diethyl ether from aqueous phase in 3 washes. The organic phase is separated, dried over Sodium sulfate and evaporated on rotary evaporator. The crude is purified by chromatography [100% Petroleum ether] to give the desired coupled product (0.60 g, 50%).

^{1}H NMR ($CDCl_3$) **δ**: **2.362** (s, 6H, two –Me), **7.16-7.32** (m, 6H, ArH), **7.83** (d, 2H, ArH)

2-Methyl-3-(2-methyl-1-naphthyl)benzo[b]thiophene. In a 25ml dry 2-neck flask under argon, Mg-turnings (0.155 g, 6.38 mmol), two drops of 1,2-Dibromoethane and anhydrous THF (5 ml) were added and warmed in order to activate Mg. 1-Bromo-2-methylnaphthalene (0.98 ml, 6.34 mmol) was added to the reaction. The reaction mixture was refluxed until complete formation of grignard reagent. At room temperature under argon, PEPPSI catalyst (0.054g, 0.079 mmol, 2 mol%) was added to the above prepared grignard in the same flask, followed by 2-Bromo-1,3-Dimethoxybenzene (0.90 g, 3.963 mmol). The reaction mixture was kept stirring at about 60℃ overnight.

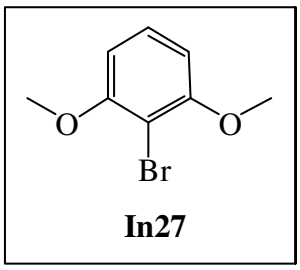


In26

10% HCl was added slowly to quench the reaction and the product extracted in Dichloromethane from aqueous phase in 3 washes. The organic phase was separated, dried over Sodium sulfate and evaporated under vacuum. The crude obtained was purified by chromatography [100% Petroleum ether, Product R_f = 0.12) to give colourless gum-like product (1.05 g, 92%).

^{1}H NMR ($CDCl_3$) **δ**: **2.17** (s, 3H, -Me), **2.23** (s, 3H, –Me), **6.95** (d, 1H, ArH), **7.12-7.50** (m, 6H, ArH), **7.87** (t, 3H, ArH)

4.9 *Synthesis towards C1-symmetry phosphepine*

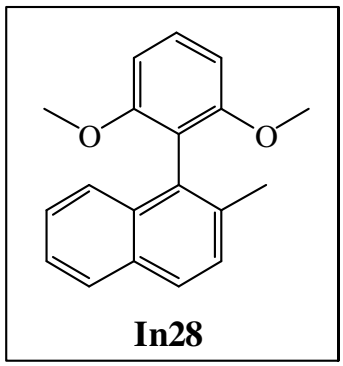


In27

1-Bromo-2,6-Dimethoxybenzene, In27. Under Argon, 70 mL of dry diethylether and 0.14 mL of TMEDA were taken in a 1 L three-necked flask and cooled to 0 ºC. *n*-Butyllithium (43.1 mL of a 1.6 M solution in hexane, 68.96 mmol) was added to this solution over a period of 10 min. After stirring for an additional 10 min at 0 ºC, 1,3-dimethoxybenzene (**SM11**) (9.0 mL, 68.73 mmol) was added slowly and the mixture stirred for 1.5 h at 0 ºC. 1,2-Dibromoethane (23.69 ml, 274.90 mmol) was added dropwise over a period of 3 h. The reaction mixture was slowly warmed to RT and stirred overnight.

To the resulting suspension a mixture of 70 mL H2O and 0.14 mL H2SO4 was added and the layers were separated. The organic layer was washed with H2O (2 x 35 mL), dried over MgSO4, filtered and concentrated by rotary evaporation to about 7 mL. After addition of 140 mL EtOH, the orange liquid was placed in a freezer (-10 ºC) affording **pure product** as colorless needles (10.02 g, 67%).

^{1}H NMR (CDCl3) δ: **3.88** (s, 6H, two –OMe), **6.57** (d, 2H, ArH), **7.22** (t, 1H, ArH)



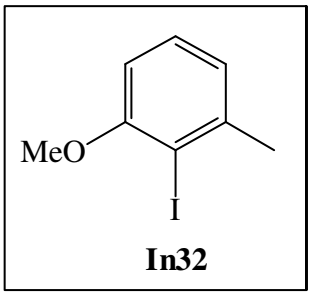
In28

2,6-Dimethoxy-1-(2-methyl-1-naphthyl)benzene, In28. In a 25ml dry 2-neck flask under argon, Mg-turnings (0.114 g, 4.70 mmol), two drops of 1,2-Dibromoethane and anhydrous THF (5 ml) were added and warmed in order to activate Mg. 1-Bromo-2-methylnaphthalene (0.71 ml, 4.59 mmol) was added to the reaction. The reaction

mixture was refluxed until complete formation of grignard reagent. At room temperature under argon, PEPPSI catalyst (0.032g, 0.046 mmol, 2 mol%) was added to the above prepared grignard in the same flask, followed by 2-Bromo-1,3-Dimethoxybenzene (**In27**) (0.50 g, 2.304 mmol). The reaction mixture was kept stirring at about 60℃ overnight. 10% HCL was added slowly to quench the reaction and the product extracted in Dichloromethane from aqueous phase in 3 washes. The organic phase was separated, dried over Sodium sulfate, and evaporated under vacuum. The crude was purified by chromatography [100% Petroleum ether] to give white solid as the desired product (0.60 g, 94%).

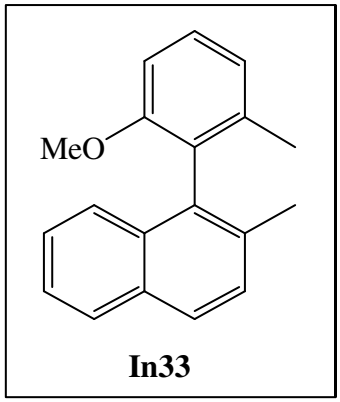
^{1}H NMR (CDCl3) δ: **2. 19** (s, 3H, -Me), **3.61** (s, 6H, 2 –OMe), **6.71** (d, 2H, ArH), **7.28-7.44** (m, 5H, ArH), **7.74-7.79** (m, 2H, ArH)

2-iodo-1-methoxy-3-methylbenzene, In32. A solution of the 2-Methoxy-6-methylaniline (**SM12**) (2.50 g, 18.22 mmol) in concentrated HCl (9.5 mL) was cooled to 0℃. A solution of $NaNO_2$ (1.296 g, 18.78) in H_2O (19 mL) was added and the mixture was stirred at 0℃ for 1 h. This mixture was added dropwise over 30 min to a solution of KI (3.93 g, 23.68 mmol) in H_2O (19 mL) at 0℃. The reaction mixture was allowed to warm to 25℃ and was stirred at this temperature for 12 h. The mixture was extracted with Et_2O (3 x 15 mL). The combined extracts were washed with saturated aqueous NaCl (1 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a clear oil. Purification by flash chromatography (silica, hexane) gave iodoanisole **In32** (78%) as a colorless oil: ^{1}H NMR (CDCl3) δ: **2.47** (s, 3H, -Me), **3.88** (s, 3H, -OMe), **6.635** (d, 1H, ArH), **6.88** (d, 1H, ArH), **7.185** (dd, 1H, ArH).



In32

2-methoxy-6-methylphenyl)-2-methylnaphthalene, In33. Under argon, Mg-turnings (0.16 g, 6.60 mmol), two drops of 1,2-dibromoethane and anhydrous THF (20 ml) were added and warmed in order to activate Mg. 1-Bromo-2-methylnaphthalene (1.0 ml, 6.41 mmol) was added to the reaction. The reaction mixture was refluxed until complete formation of grignard reagent.



In33

At room temperature under argon, PEPPSI catalyst (0.056g, 0.08 mmol, 2 mol%) was added to the above prepared grignard in the same flask, followed by **In32** (1.0 g, 4.032 mmol). The reaction mixture was kept stirring at about 50°C overnight.

10% HCL was added slowly to quench the reaction and the product extracted in Dichloromethane from aqueous phase in 3 washes. The organic phase was separated, dried over Sodium sulfate, and evaporated under vacuum. The crude was purified by chromatography [Petroleum ether 9:1 dichloromethane] to give white solid as the desired product (70%).

^{1}H NMR (CDCl3) **δ**: **1.812** (s, 3H, -Me), **2.144** (s, 3H, -Me), **3.618** (s, 6H, -OMe), **6.89** (d, 1H, ArH), **6.98** (d, 1H, ArH), **7.25-7.45** (m, 5H, ArH), **7.76-7.85** (m, 2H, ArH).

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