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Squelettes chiraux originaux porteurs d'un centre P-stéréogénique

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2.1 Introduction

Les composés organiques ayant une chiralité sur un atome de phosphore sont appelés composés P-stéréogènes, P-chirogènes ou P-chiraux.[1] Ces composés sont largement utilisés en agrochimie en tant que pesticides[2–5] en pharmacie en tant que molécules biologiquement actives[6–9], en chimie de coordination où ils aident à la détermination de la structure tridimensionnelle du complexe métallique[10,11], en catalyse organométallique asymétrique, comme en témoigne la conception de l'une des classes les plus importantes de ligands chiraux (prix Nobel 2001; WS Knowles)[12–14] Cependant, malgré leur immense importance dans plusieurs domaines susmentionnés, l'accès à ces composés P-stéréogènes est plutôt difficile étant donné la complexité des méthodes de synthèse existantes, qui reposent souvent sur des procédures fastidieuses et multi-étapes. Nous rapportons ici le développement d'une nouvelle méthodologie d'accès aux composés P-stéréogéniques basée sur l'utilisation d'un auxiliaire chiral de type sulfoxyde. La réaction correspond à un couplage O-P entre un substrat organophosphoré racémique, le H-phosphinate **41**, et un phénol énantiopur portant un auxiliaire chiral sulfoxyde en position *ortho* **370** (**370-373**) (schéma 1). La réaction se déroule via une résolution cinétique dynamique (DKR) avec un bon rendement et une diastéréosélectivité élevée. De plus, les composés P-stéréogéniques nouvellement obtenus **400** peuvent être post-fonctionnalisés en utilisant des réactifs tels qu'organolithiens ou magnésiens, afin d'obtenir divers squelettes P-stéréogéniques originaux. En conséquence, les composés P-chiraux obtenus ici **400** peuvent être considérés comme des précurseurs standard pour obtenir une variété de molécules P-stéréogéniques originales.
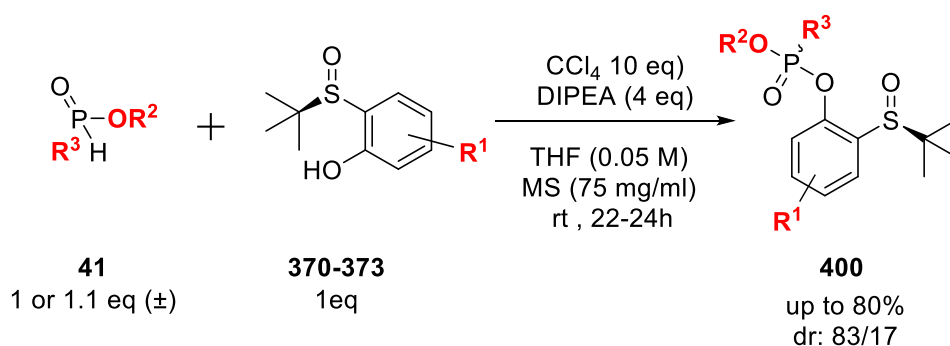
Schéma 1. Example représentatif de couplage O-P.

2.2   Résultats et discussions

Ce projet de recherche doctoral a débuté dans le cadre d'un contrat Franco-Indien Cefipra (Centre indo-français pour la promotion de la recherche scientifique) en 2015, avec comme collaborateur indien, le Dr Rajender Reddy de l'IICT-Hyderabad.

Notre objectif initial était de concevoir de nouvelles voies de synthèse pour accéder à des composés à chiralité axiale, combinant une activation C-H stéréosélective, basée sur l'utilisation d'un groupement sulfoxyde à la fois comme groupe directeur et comme auxiliaire chiral et la génération de radicaux comme partenaires de couplage. Pour atteindre cet objectif, compte tenu des progrès extraordinaires accomplis récemment dans la chimie de l'iode hypervalent, nous avons porté notre attention sur l'arylation atropo-sélective sans métal, en utilisant des composés iodés hypervalents comme partenaires de couplage.[15–19] Nous avons alors essayé plusieurs conditions réactionnelles en utilisant des biaryls porteurs d'un sulfoxyde chiral **361/312** et des composés iodés hypervalents **379**, mais les produits de couplage n'ont pas pu être obtenus (schéma 2).[15,20,21]
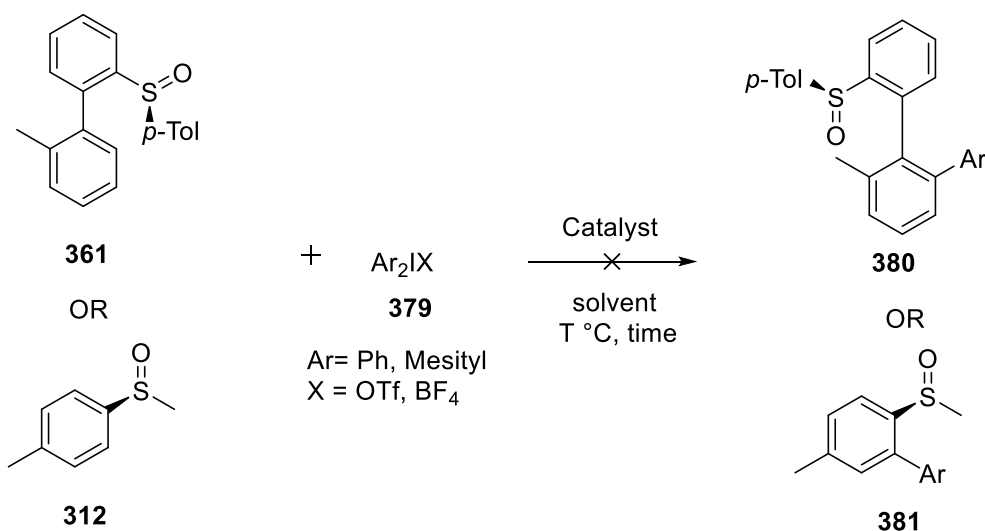
Schéma 1. Essai d'arylation de biaryls/monoaryls par utilisation d'iodes hypervalents.

Ensuite, nous avons décidé de changer notre approche. Nous avons supposé que les espèces d'iode hypervalentes portant un fragment sulfoxyde chiral en position ortho pourraient être des réactifs très attractifs pour les réactions d'arylation asymétriques. Bien qu'un travail expérimental intensif ait été effectué, ni le transfert de l'arylsulfoxyde ni du fragment aryle simple n'a été observé (schéma 3).[22,23]
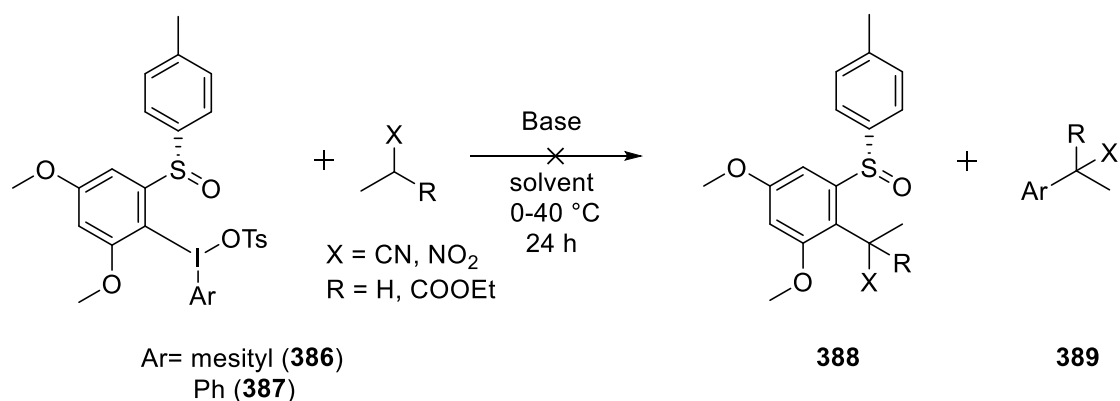
Scheme 3. Essai d'arylation utilisant des iodes hypervalents chiraux

En 2016, le Dr Rajender Reddy, notre collaborateur dans le cadre du contrat CEFIPRA, a visité notre laboratoire à Strasbourg. Cette réunion scientifique nous a donné l'occasion de partager les travaux les plus récents des deux groupes de recherche. Nous nous sommes particulièrement intéressés aux réactions de couplage O-P développées à ce moment-là, dans le groupe du Professeur Reddy. Inspirés par ce projet et tournés vers un travail collaboratif, nous avons décidé d'étudier le potentiel des phénols portant un groupe sulfoxyde chiral dans de telles réactions de couplage O-P. Nous avons spécialement ciblé le potentiel d'accès aux composés organophosphorés P-stéréogènes via de telles transformations, ce qui a ajouté une nouvelle dimension à ce projet, avec des perspectives très attrayantes pour les applications industrielles.

Initialement, nous avons sélectionné les H-phosphinates **41a** comme substrat modèle organophosphoré et un biarylsulfoxyde phénol **363** (schéma 4). Dans les conditions de réaction de couplage O-P développées par M. Reddy, un mélange réactionnel complexe a été obtenu (schéma 4).
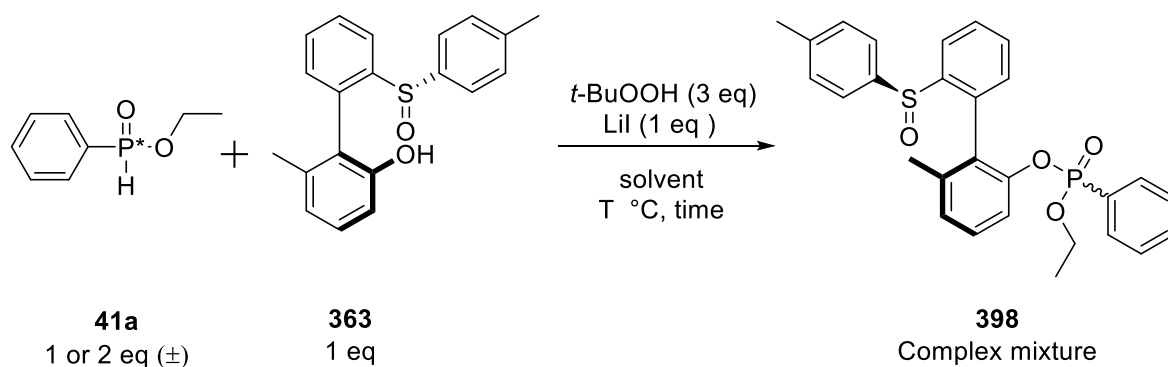
Schéma 4. Essai de couplage O-P entre un H-phosphinate **41a** et un sulfoxyde biarylique **363**.

Plus tard, nous avons porté notre attention sur d'autres méthodologies pour les réactions de couplage O-P. Nous avons essayé deux approches, avec ou sans métal, pour cette réaction.

Heureusement, il s'est avéré que dans les conditions de réaction d'Atherton-Todd à savoir dans le tétrachlorure de carbone en présence de triéthylamine à température ambiante, la réaction de couplage O-P est réalisée (schéma 5).[24–26] Cependant, en ce qui concerne le stéréocentre P, nous avons obtenu les deux diastéréomères du produit correspondant **398** (schéma 5) dans un rapport 50/50.
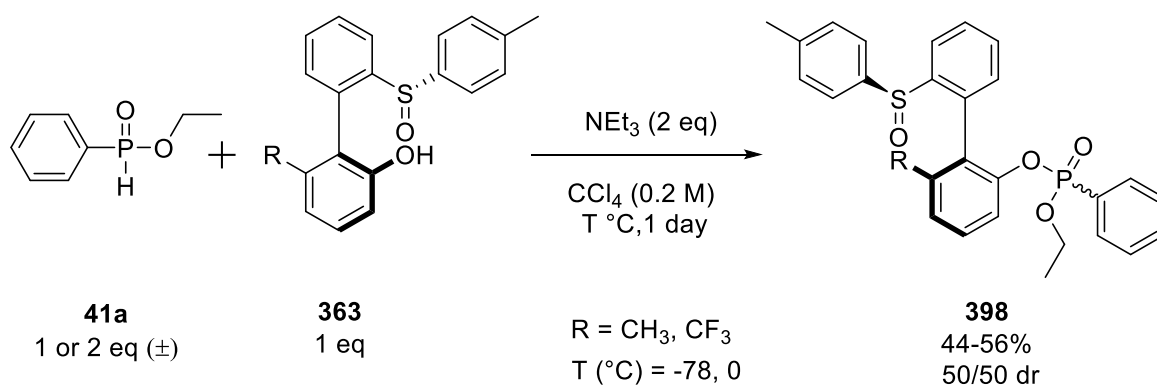
Schéma 5. Réaction d'Atherton-Todd pour le couplage O-P entre **41a** et **363**.

Nous avons alors émis l'hypothèse que l'auxiliaire chiral sulfoxyde devrait se trouver à proximité du groupe phénolique afin d'apporter l'induction chirale attendue au niveau de l'atome de phosphore au cours de la réaction de couplage O-P. Et pour se faire, dans notre prochaine série d'expériences, nous avons installé un groupe sulfoxyde chiral sur la position *ortho* du noyau phénol pour obtenir **366** (schéma 6).
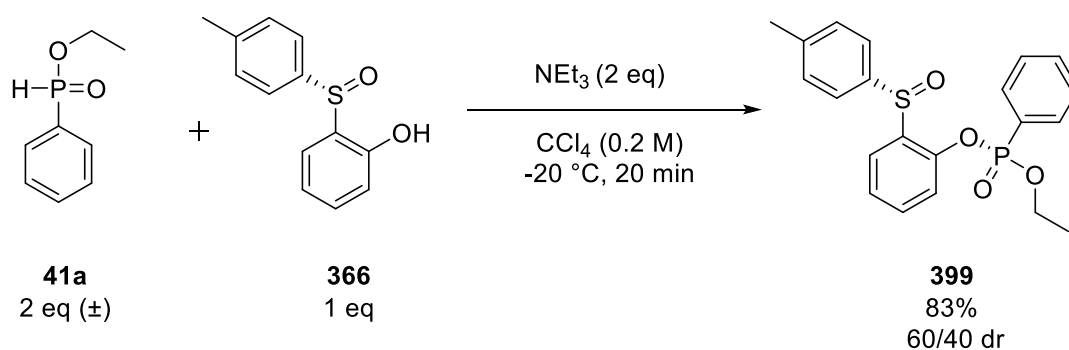
Schéma 6. Atherton-Todd réaction pour couplage O-P entre **41a** et **366**.

La réaction de couplage O-P entre ce substrat chiral **366** et le H-phénylphosphinate d'éthyle racémique **41a** conduit au produit de couplage correspondant avec un rendement de 83% et une diastéréosélectivité décevante de 60/40.

Par conséquent, afin d'augmenter la stéréoinduction au cours de cette réaction de phosphorylation, nous avons décidé d'utiliser un auxiliaire chiral plus encombré sur le phénol, à savoir le *t*-butylsulfoxyde et toujours dans les conditions réactionnelles similaires d'Atherton-Todd, nous avons réussi à effectuer la phosphorylation diastéréosélective pour obtenir le produit souhaité **400**, avec un rapport diastéréomérique excellent de 90/10 (schéma 7).

Schéma 7. Réaction d'Atherton-Todd pour le couplage O-P entre **41a** et **370**.

Par la suite, les conditions de réaction ont été modifiées, en particulier, le solvant toxique CCl$_4$ a été remplacé par un solvant moins toxique, le THF et CCl$_4$ a donc été utilisé comme réactif d'halogénation. De plus, nous avons constaté un phénomène de résolution cinétique dynamique (DKR): c'est-à-dire qu'à partir d'un équivalent de chacun des substrats racémiques **41a** et énantiopur **370**, le produit de couplage O-P correspondant **400a** a pu être obtenu avec un rendement allant jusqu'à 80% et un rapport diastéréomérique de 83/17 (schéma 8) suggérant sans ambiguïté un phénomène de résolution cinétique dynamique avec équilibre entre les 2 énantiomères **41a** .

Schéma 8. Couplage O-P diastereoselectif / phosphorylation entre **41a** et **370** *via une resolution cinétique dynamique (DKR)*.

Les molécules **400a** P-stéréogéniques nouvellement obtenues sont des précurseurs attrayants pour l'accès à une grande variété de squelettes P-stéréogéniques par addition d'organométallique variés. Ces réactions mettant en jeu une résolution cinétique dynamique (DKR) sont reconnues comme la stratégie économique la plus puissante pour accéder aux composés énantiopurs (diastéréomères).

La réaction d'Atherton-Todd modifiée est efficace avec des substrats de type H-phosphinates ainsi que des oxydes de phosphine secondaire. Les conditions réactionelles optimisées sont : 1 équivalent du composé organophosphoré racémique (H-phosphinate ou oxyde de phosphine secondaire) et 1 équivalent d'un phénol énantiopur portant l'auxiliaire chiral *t*-butylsulfoxyde en présence de 10 équivalents de CCl$_4$, 4 équivalents de base, DIPEA (diisopropyléthylamine), tamis moléculaires à 75 mg /ml dans du THF (0,05 M) à température ambiante pendant environ 22 à 24 heures.

La table 1 représente l'étendue de la réaction. En général, à mesure que l'encombrement stérique du groupe alkoxy lié à l'atome de phosphore dans les H-phosphinates augmente (**400a-400e**, **400i**, tableau 1), le rendement et la diastéréosélectivité de la réaction diminuent. Lorsque nous avons remplacé le noyau phényle lié à l'atome de phosphore dans les H-phosphinates, par exemple, par un groupe naphtyle, mésityle, cyclohexyle ou simplement un groupe méthyle, on observe aucun changement important si ce n'est dans certains cas une diminution du rendement et de la diastéréosélectivité de la réaction (**400i-400o**, tableau 1). Les oxydes de phosphine secondaires racémiques ont également été soumises à la réaction mais les produits correspondants ont été obtenus avec un rapport diastéréomèrique de 50/50.

Dans le cas des substrats **400p-400r** (table 1), portant un substituant méthoxy ou bromo en position *para* ou *ortho* du phénol chiral, les produits de couplage O-P sont obtenus avec de bons rendements et diastéréosélectivités.

Des efforts considérables ont également été déployés pour séparer les diastéréomères des produits de couplage O-P par chromatographie sur colonne / flash ou par recristallisation. Cependant, la séparation des diastéréoisomères n'a pas pu être réalisée dans tous les cas. (table 1).

Table 1.
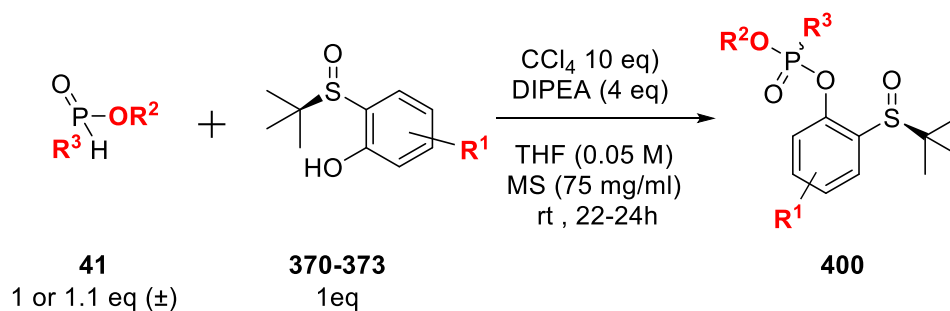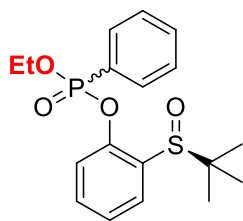
400a

76% (dr: 83/17)
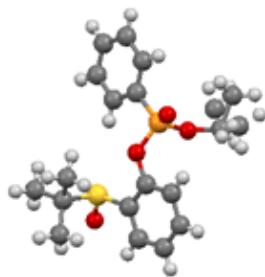
(S_sS_p)
Major diastereomer d1
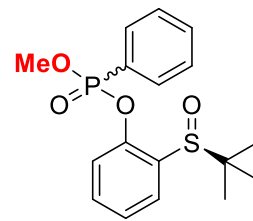
400b

71% (dr: 83/17)
(Recrystallisation:
dr: 94/6, 20%)
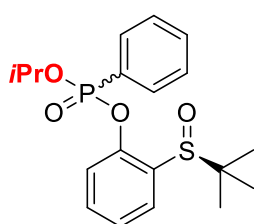
400c

total 64%
(crude dr: 77/23)
d1 (28%) : dr: 98/02
fr2 (24%) : dr: 62/38
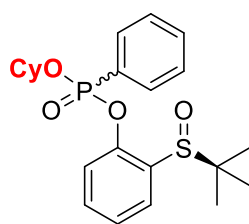
400d

total 67%
(crude dr : 60/40)
d1 (41%): 97/3
d2 (26%): 85/15
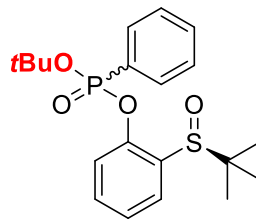
400e

dr: 60/40
d1 (22%): 90/10
d2 : impure
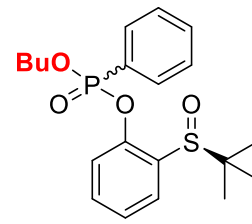
400f

80% (dr: 71/29)
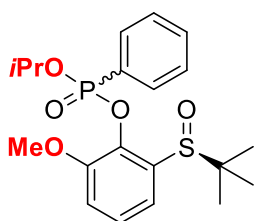
400g

52% (dr: 78/22)
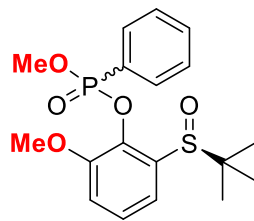
400h

58% (dr: 80/20)
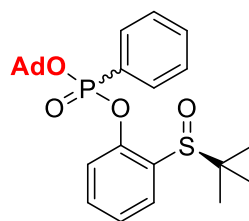
400i

total 64%
(crude dr : 50/50)
d1: 35%
d2: 33%

400j

total 67%
(crude dr: 55/45)
d1: 31%
d2: 26%

400k
total 75%
(dr crude: 51/49)
d1: 34%
d: 41%

400l
72%
(dr; 83/17)

400m
34%(dr: 78/22)

400n
34%(dr: 72/28)
inseparable from sm
(sm = ethyl mesitylphosphinate)

400o
80%(dr: 70/30)

400p
64% (dr: 77/23)

400q
68% (dr: 66/34)

400r
78% (dr: 83/17)
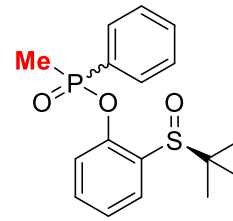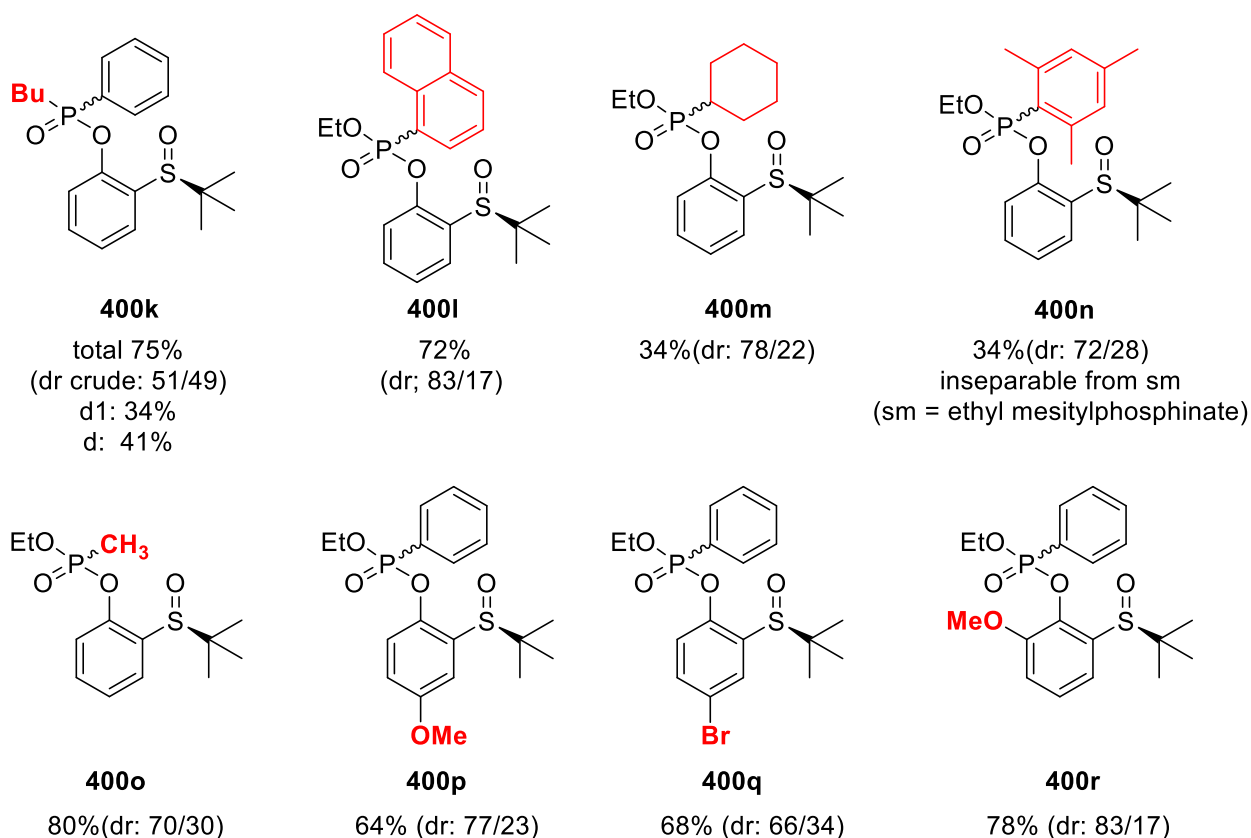
Par la suite nous avons étudié la post-fonctionnalisation des produits de couplage O-P pour accéder à divers squelettes P-stéréogènes, en utilisant des réactifs de Grignard adaptés. De plus, au cours de l'étape de post-fonctionnalisation, l'auxiliaire chiral **370** a été récupéré avec un très haut rendement et une rétention complète de la chiralité sur le sulfoxyde ce qui démontre son caractère recyclable dans cette réaction.

Ainsi, du (*S*)-PAMPO **40** a été préparé avec un rendement de 84% et un rapport énantiomèrique de 98/2 dans des conditions réactionnelles douces, par addition d'un équivalent de *o*-AnMgBr sur le produit de couplage O-P **400j** énantiopur dans du THF à une température de 0 ° C à 40 ° C en environ 16 heures (schéma 9).

400j (d2)
S_sR_p
dr: 99/1

o-AnMgBr (1 eq)

THF (0.5 M)
0/40 °C, 16h

inversion @ P

40

84%, er > 98/2

(S)-PAMPO
(Precursor for
DiPAMP ligand)

370

94%, er > 99/1

Recyclable
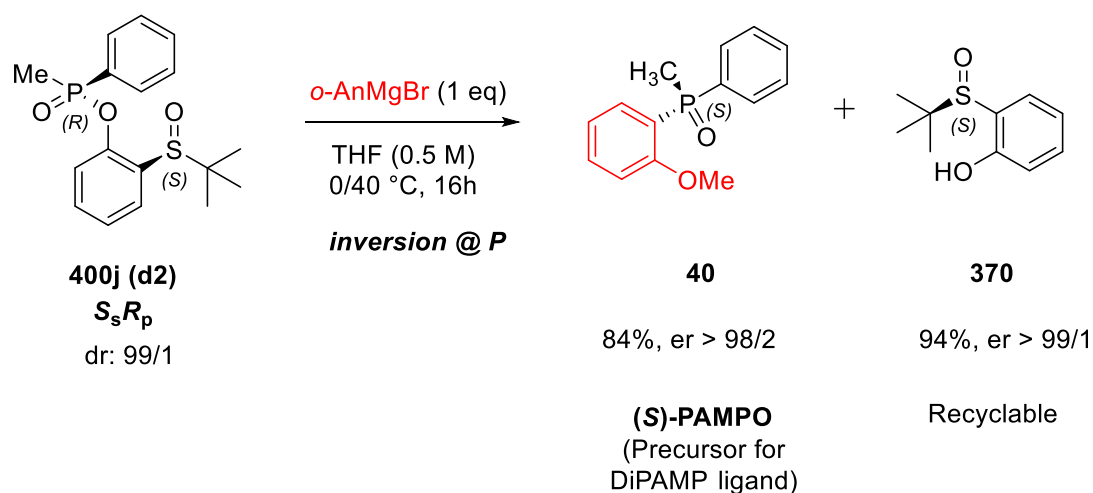
Schéma 9. Synthèse de (*S*)-PAMPO **40** à partir de **400j**.

2.3 Conclusion Générale

Ainsi, nous avons développé une nouvelle méthodologie très efficace pour accéder à des composés P-stéréogéniques en utilisant des conditions réactionnelles d'Atherton-Todd modifiées avec comme substrat organophosphore un H-phosphinate / oxyde de phosphine secondaire et comme partenaire de couplage un phénol énantiopur portant un fragment sulfoxyde chiral. Dans certains cas, la réaction se déroule via une résolution cinétique dynamique (DKR), fournissant le produit de couplage O-P avec un rendement et une diastéréosélectivité élevés. En outre, le produit de couplage O-P peut potentiellement être utlisé dans des conditions douces pour obtenir divers composés P-stéréogéniques originaux, comme illustré par la synthèse de (S) -PAMPO, avec un rendement élevé et un excellent excès énantiomérique. Ainsi, ces produits de couplage O-P peuvent être considérés comme des synyhons electrophiles pour accéder à une variété de molécules P-stéréogéniques.

2.4 Publications:

P-stereogenic phosphonates via dynamic kinetic resolution: a route towards enantiopure tertiary phosphine oxides (*manuscript in preparation*). Aabid Mohd, Rajender Reddy, Joanna Wencel-Delord and Françoise Colobert.

3 Introduction

The *universe* is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequences. **The universe is asymmetric.**

-Louis Pasteur, Works Vol. 1 (1 June 1874) Comptes Rendus de l'Académie des Sciences.

3.1 Chirality

Chirality is a fundamental property of three-dimensional objects and systems. It plays an important role in many fields of science. In terms of chemistry, it's a geometrical property of some molecules and ions. The word chirality is derived from the Greek word (χειρ) *kheir*, which means "hand". Our hands, for examples, are non-superimposable mirror images of each other. We would simply feel the difference if by chance, we place our right hand into a left-handed glove. Indeed, the mirror images of chiral objects/systems are distinguishable in orientation in space from each other and are called *enantiomorphs,* or *enantiomers/optical isomers,* while dealing with molecules. A mixture containing equal amount of two enantiomers, is called a racemic mixture. And, the process of separation of enantiomers from its racemic mixture, is called *resolution.* In general, chirality of a molecule arises from the presence of a stereocenter. However, other elements of chirality, such as axial chirality or planar chirality, also exist.
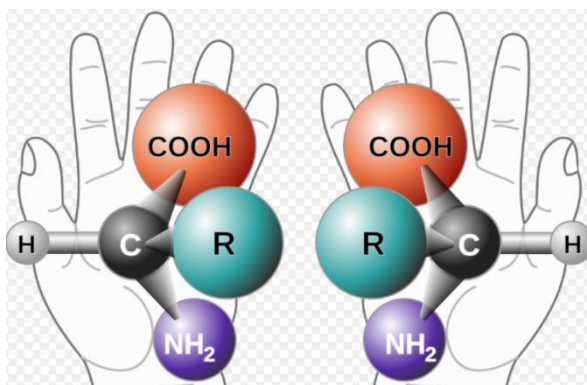
Fig. 1. Two enantiomers of a generic chiral amino acid.[27]

Historically, the ability of the chiral molecules to rotate plane polarised light, was first observed by Jean-Baptiste Biot in 1815.[28] However, Louis Pasteur in 1848, for the first time was able to demonstrate molecular chirality in organic compound by carefully resolving enantiomers of the tartaric salt.[2] Later, in 1894 Lord Kelvin coined the term chirality;[30]

"I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself".

A chiral molecule can possess different types of chiral elements, such as point chirality that is based on stereogenic centre, axial chirality that is based on hindered rotation of atropoisomers, planar chirality that arises due to the hindered rotation of two non-coplanar and dissymmetric rings attached to each other and inherent/intrinsic chirality that arises due to the twisting of the molecules in three dimensions (fig. 2).[31–33]

1
Point chirality

2
Intrinsic chirality

3
Axial chirality

4
Planar chirality
(Ferrocene derivative)
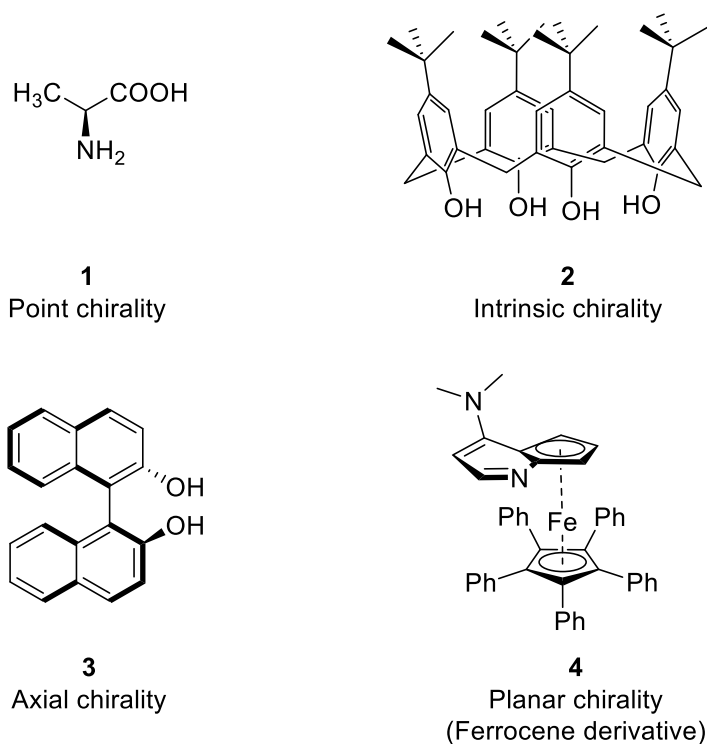
Fig. 2. Different elements of chirality.

But it is the point chirality, that is dominant in nature as well as in synthetic chemistry world. In this case, presence of an asymmetric centre or a stereo centre is one of the main characteristics of a chiral molecule. In most cases, this asymmetric centre of a chiral molecule is based on sp^3 hybridised tetrahedral C atom having four different substituents. However, based on substitution of carbon atom with other heteroatoms, several other asymmetric centres are known, such as P, S, metal-stereocentre etc (fig. 3).[34–36]

5
C-stereocentre

6
Metal stereocentre

7
S-stereocentre

8
P-stereocentre
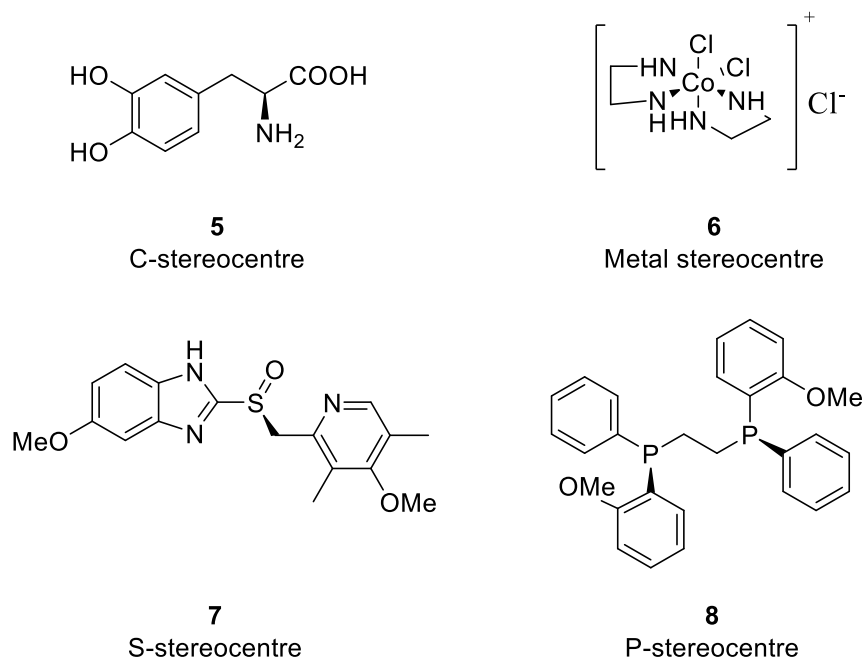
Fig. 3. Different types of stereocentres in chiral molecules.

It is well known that two given enantiomers of a molecule have the same physico-chemical properties but can interact distinctly at biomolecular level with living cells. For example, two enantiomers of limonene differ in their smells; (*R*)-enantiomer smells like an orange while (*S*)-enantiomer smells like a lemon.[37,38] More significantly, chiral compounds are of great importance in life sciences and pharmaceutical industry. Fig. 4 shows some of the representative examples of the chiral drugs, such as L-DOPA, dextroamphetamine, levocetirizine, thalidomide and esomeprazole. About 50% of the currently used drugs are chiral.[39–41] And very often, two enantiomers of a drug have different biological and/or pharmaceutical properties, which can have serious consequences on their respective biological activities. For example, (*R*)-thalidomide **12** helps to cure morning sickness in pregnant women, while its other enantiomer (*S*)-thalidomide **12**, notoriously affects the development of foetus (fig. 4).[42,43]

9
L-DOPA
(Parkinson's disease)

10
Dextroamphetamine
(CNS stimulant))

11
Levocetrizine
(Anti-histamine)

12
(*R*)-thalidomide
(Sedative)

12
(*S*)-thalidomide
(Teratogenic)

13
Esomeprazole
(Proton pump inhibitor)
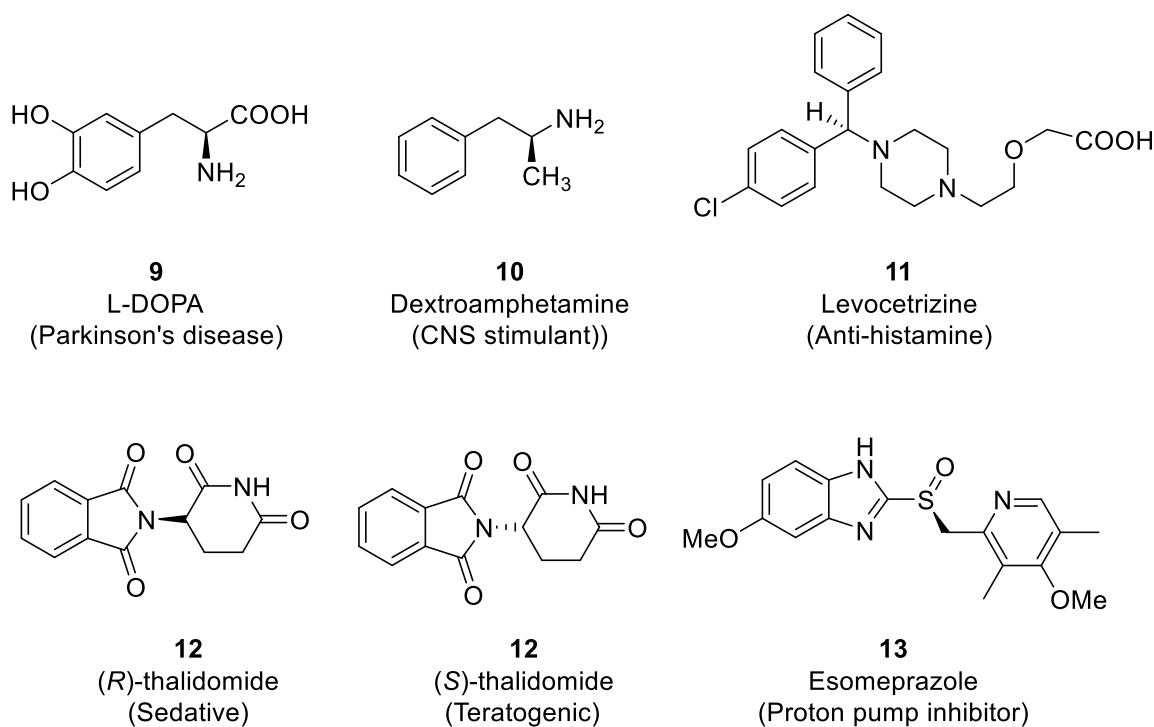
Fig. 4. Representative examples of some chiral drugs.

In 2015, almost all the chiral drugs approved by FDA were enantiopure.[39] Therefore, it is of paramount importance, especially in life sciences and pharmaceutical industry to selectively access a single enantiomer (diastereomer) of a chemical compound. As a result, a number of methods have been developed to access optically active compounds. These methods can be divided mainly into two types; resolution and asymmetric synthesis.

Resolution of a racemic mixture of a compound into its individual enantiomers, is one of the most classical methods to obtain optically active compounds.[29] In a resolution process, both enantiomers of a compound can be obtained with up to 50% yield and, with up to a very high optical purity. This process is still frequently employed in industry, as it is relatively simple and scalable using cheap chiral resolving agents/techniques. Moreover, using dynamic kinetic resolutions, even a single enantiomer can selectively be obtained with up to 100% yield and with up to 100% ee. Resolution of a compound can be achieved by using a suitable resolving agent, a chiral metal complex or by chiral HPLC technique. Resolving agents, such as dibenzoyl tartaric acid (DBTA), cinchonine, BINAP, camphor sulfonic acid form the corresponding pair of diastereomeric salts/complexes. These diastereomeric salts/complexes can then be separated into individual diastereomers, based on the differences in their physical properties, such as solubility, melting point etc. Finally, an acid-base treatment of the resolved diastereomeric salt cleaves the salt/complex into an enantiopure compound and the resolving agent with high optical purities.[44,45] A chiral metal complex, such as chiral orthometallated palladium complexes with a chiral amine (for example 1-phenylethylamine or 1-naphthylethylamine) works on the same principle as that of a resolving agent.[46–48] A chiral HPLC technique utilises a chiral stationary phase, which selectively interacts with the two

enantiomers of an organic compound and thus, directly provides an access to both the enantiomers of the organic compound.[49,50]

The process of selective synthesis of a single enantiomer (or a single diastereomer) of a chemical compound, is called enantio- or diastereoselective synthesis. This is though, a challenging task, but it can be achieved by several strategies, such as by use of a "chiral pool" synthesis, chiral auxiliary or asymmetric catalysis (biocatalysis, organocatalysis and organometallic catalysis). In case of "chiral pool" synthesis, a naturally available chiral starting material is used, which upon chemical transformation is converted into the desired final product.[51] This method is particularly interesting if the target molecule has the same chirality as the naturally available starting material, such as cheap sugars and amino acids.

Usually, a chiral auxiliary is an enantiopure molecule that is readily derived from the chiral pool.[52] It is temporarily installed on a substrate via covalent bonding thus, rendering the substrate chiral and allowing a stereo induction during a desired chemical transformation. At the end of the reaction, the chiral auxiliary is cleaved from the target molecule (or its precursor) and, ideally recycled. Thus, the main advantage of this approach includes the formation of two separable diastereomers of a compound and removal of a chiral auxiliary providing the desired product in a high optical purity. However, stoichiometric use of a chiral auxiliary in this process is considered as a main drawback of this strategy. Biocatalysis utilises enzymes and cells to bring about an asymmetric transformation.[53] In most cases, biocatalytic reactions have high specificity for a narrow range of substrates and also, such reactions generally require low concentration of the reaction to proceed well. In organocatalysis, it is the chiral organic compound which brings about an asymmetric transformation to access a target molecule in absence of a metal.[54] One of the most popular organocatalyst is proline, widely used for aldol reactions.[55]

Of all the above-mentioned methodologies of asymmetric synthesis, asymmetric catalysis is the best choice in terms of its broader scope, very high efficiency, often good atom economy, lower catalyst loading and a high versatility. A chiral complex in general, is composed of a chiral ligand, attached to a transition metal.[56,57] These chiral catalysts bring about enantioselective/asymmetric transformations to access the desired single enantiomers (or diastereomers) of the chemical compounds. Some of these chiral catalysts are suitable for the industrial applications.[57,58]

Amongst the numerous different chiral ligands, chiral phosphorous ligands have attracted much attention of the chemists in transition metal catalysed asymmetric reactions due to their excellent chiral induction ability and tunability in their electronic and steric properties. Indeed, the first man-made artificial enzymatic catalytic activity was achieved by the use of P-stereogenic ligands in catalysed asymmetric hydrogenation reactions, developed by Horner and W. S. Knowles in 1968.[59] Along with Knowles, Horner also contributed independently for the development of P-stereogenic ligands and asymmetric catalysis.[13,60] In 1975, while exploring various novel P-stereogenic ligands for asymmetric hydrogenation reactions, Knowles was inspired by the work of Kagan[61,62] on diphosphine chelating ligand-DIOP (fig. 5)

and thus, he developed a diphosphine chelating P-stereogenic ligand-DiPAMP **17**, which provided the highest enantioselectivity in asymmetric hydrogenation reaction at that time (96% ee).[63] This led to the first ever industrial application of asymmetric hydrogenation reaction in the form of the monsanto synthesis of L-DOPA **16** (scheme 1).[14,57]For the pioneering work done by W. S. Knowles (along with Ryoji Noyori and Barry Sharpless), in the development of asymmetric catalysis, he was awarded Nobel Prize in 2001.[14]
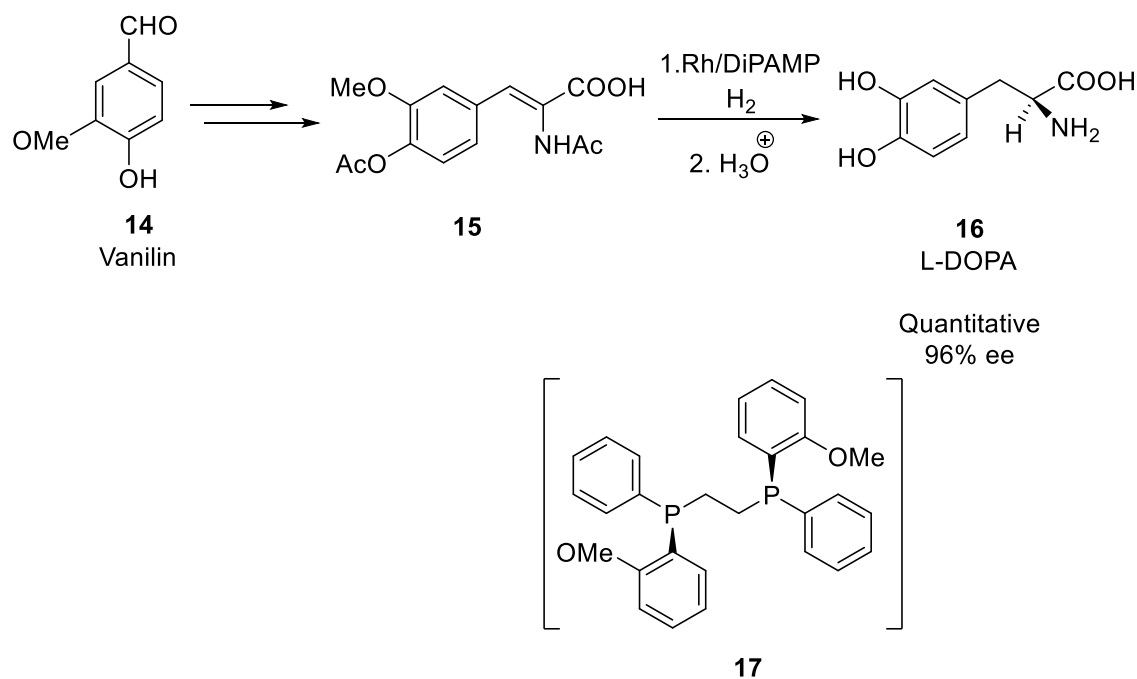
Scheme 1. The Monsanto synthesis of L-DOPA.

Today, innumerable P-stereogenic ligands provides very high to excellent enantioselectivities in various asymmetric organometallic catalytic reactions, more popularly in asymmetric hydrogenation reactions. The chiral phosphorous ligands fall into two categories; one with chirality on the backbone of phosphorous atom (fig. 5) and the other one, where chirality lies on phosphorous atom, called P-chirogenic, P-stereogenic or P-chiral compounds.[1]

In 1970s, along with the development on the synthesis of P-stereogenic compounds, mainly led by Knowles and Horner, several other researchers worked on the development of chiral phosphines having chirality on backbone of P atom. Their work gained an important recognition in asymmetric catalysis.[61,62,64,65,65–68] Indeed, these compounds were found to be configurationally more stable and easier to access, compared to P-stereogenic compounds. Notable work includes; synthesis of BINAP **18** by Noyori,[64] DIOP **19** by Kagan,[61] BPE **20** and DuPHOS **21** by Burk[66,69] Chiraphos **22** by Bosnich,[65] and Josiphos **23** by Togni[67] (fig. 5).
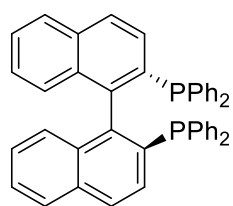
18
BINAP (Noyori 1980)
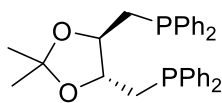
19
DIOP (Kagan 1971)
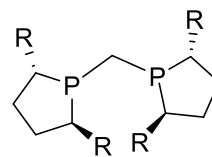
20
BPE (Burk 1991)
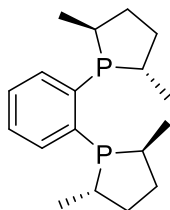
21
DuPhos (Burk 1991)
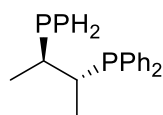
22
Chiraphos (Bosnich 1977)
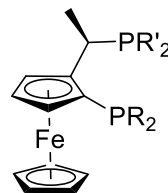
23
Josiphos (Togni 1993)

Fig. 5. Chiral phosphorous ligands with backbone chirality.

3.2 P-Stereogenic Compounds

"The time has come for the P-chiral ligands to merge the stream and to bring in the P-chirality factor into play again".[70]

Organic compounds having chirality on phosphorous atom, are called P-stereogenic, P-chirogenic or P-chiral compounds.[1] These compounds are widely used in agrochemistry as pesticides,[2–5] in pharmacy as biologically active molecules[6–9], in coordination chemistry where these compounds help in determination of three dimensional structure of the metal complex[71] and in organometallic asymmetric catalysis as a very important class of chiral ligands.[12–14] This section would highlight naming and structures of various organophosphorus compounds, natural abundance and configurational stability of the P-stereogenic compounds.

3.2.1 Various Types of Organophosphorous Compounds

Organic compounds having a phosphorous atom are generally called organophosphorous compounds. These compounds are widely used as pesticides, in addition to their uses in other fields of science.[2,6,66,72–74] Based on the oxidation state of phosphorous atom, organophosphorous compounds can be classified as P(III) or P(V) compounds. Following two subsections briefly describe some of the P(III) or P(V) organophosphorous compounds with their corresponding names and structures.

3.2.1.1 P(V) Organophosphorous compounds

Some of the P(V) organophosphorous compounds are represented in fig. 6. Phosphates **24** (general formula, $P(=O)(OR)_3$), phosphonates **25** (general formula, $RP(=O)(OR)_2$) and phosphinates **26** (general formula, $R_2P(=O)(OR)$) are mainly used in agrochemistry as pesticides. [2,75]

H-phosphinates **29** (general formula, $HRP(=O)(OR)$), chlorophosphinates **30** (general formula, $RP(=O)Cl(OR)_2$) and secondary phosphine oxides **28** (general formula, $HR_2P(=O)$), are mainly used as intermediates for the synthesis of tertiary phosphine oxides and other more complex organophosphorous compounds. .[76–81] Secondary phosphine oxides **28** are also being employed as ligands in organometallic catalysis.[82,83] Tertiary phosphine oxides **27** (general formula, $P(=O)R_3$) are one of the most thermally stable forms of organophosphorous compounds and widely used as ligands in organometallic catalysis.[66,68,84–86]

| **24** | **25** | **26** |
| Phosphates | Phosphonates | Phosphinates |

| **27** | **28** | X = H, **29** H-phosphinates |
| Tertiary phosphine oxides | Secondary phosphine oxides | X = Cl, **30** Chlorophosphinates |
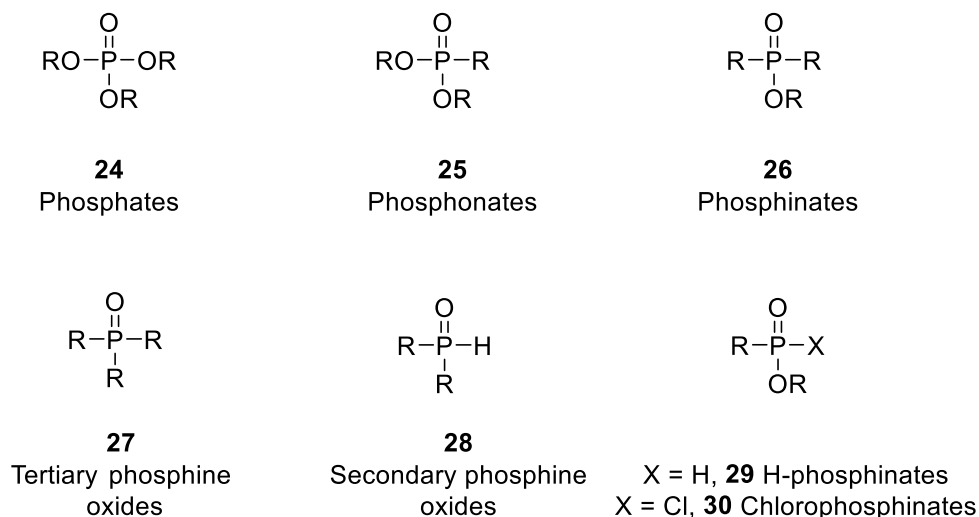
Fig. 6. Some of the representative examples of P(V) Organophosphorous compounds.

3.2.1.2 P(III) Organophosphorous compounds

Some of the P(III) organophosphorous compounds are represented in Fig. 7. Chlorophosphines **31** (general formula, $PClR_2$), and phosphine boranes **32** (general formula, $P(BH_3)R_3$) are mainly used as intermediates and precursors for phosphines. While tertiary phosphines **33** (general formula, PR_3) are widely used in asymmetric catalysis by transition metal complexes. [87]

| **31** | **32** | **33** |
| Chlorophosphines | Tertiary phosphine boranes | Tertiary phosphines |
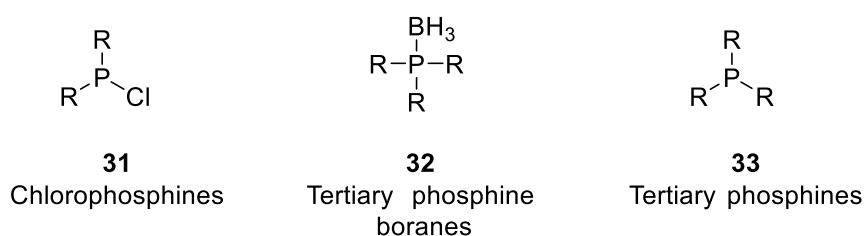
Fig. 7. Some of the representative examples of P(III) Organophosphorous compounds.

3.2.2 Natural Occurrence

Organophosphorus compounds with P-C bond, are not dominant in nature, rather organic compounds with P-O bond as phosphate/phosphonate groups, are widely prevalent in living cells, such as ATP molecule, phospholipids etc.[88,89] In 1959, β-aminoethyl phosphonic acid **34** (fig. 8) was the first organophosphorous compound isolated from rumen protozoa.[90] Moreover, cyclophostin **35** and salinipostin **36** are two recently isolated organophosphorous

compounds from microbes, showing promising anti-microbial and anti-tumoral activities (fig. 8).[3,91,91,92]

34
β-aminoethyl phosphonic acid

35
cyclophostin

36
salinipostin
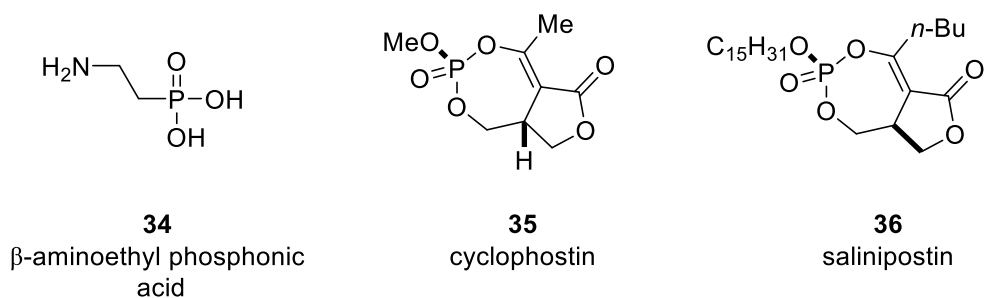
Fig. 8. Some naturally occurring organophosphorous compounds.

Phosphate minerals serve as the natural source for obtention of the phosphorous compounds, and their chemical treatment provides phosphoric acid, PCl_3 and PCl_5 etc. which are often starting materials for the synthesis of various organophosphorous compounds by carrying out their further chemical modifications (scheme 2).[93,94]

$$Ca_5(PO_4)_3 \longrightarrow H_3PO_4, PCl_3, PCl_5$$

Phosphate minerals

A family of organophosphorous compounds
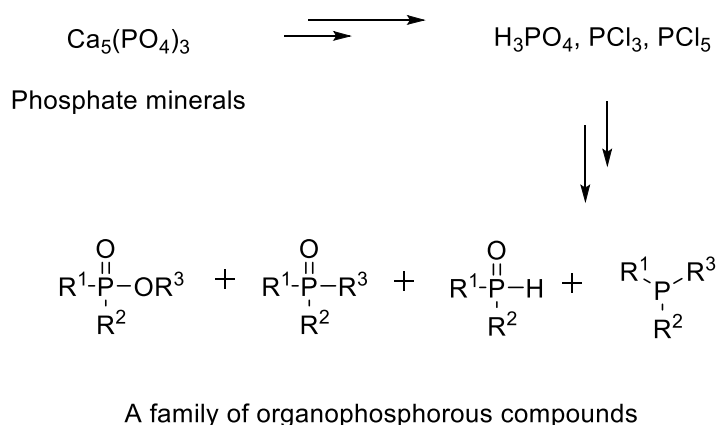
Scheme 2. A General scheme for the synthesis of P-stereogenic compounds from phosphate minerals.

Considering the tremendous importance of these organophosphorous compounds in several fields of science, a number of synthetic methodologies have been developed to access the target organophosphorous compounds.[44,64,70,73,87,95–104] Some general methods to prepare the racemic organophosphorous compounds from the simple phosphorous precursors (scheme 2) are highlighted below.

19

Triphenyl phosphine **37** is one of the most important phosphine and produced industrially on a scale of million kilograms. It is produced by using PCl_3, chlorobenzene and sodium (scheme 3).[105]

$$PCl_3 \; + \; 3\,C_6H_5Cl \; + \; 6Na \longrightarrow P(C_6H_5)_3$$

37
Triphenyl phosphine
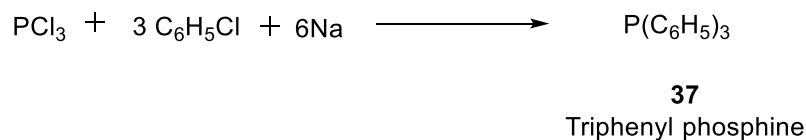
Scheme 3. Industrial production of triphenyl phosphine.

Other general methods to prepare organophosphorous compounds include reaction of phosphorous precursors with Grignard reagents (scheme 4).[105]

$$PCl_3 \quad + \quad 3RMgX \longrightarrow PR_3$$

$$POCl_3 \quad + \quad 3RMgX \longrightarrow R_3P=O$$

$$RO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR}{|}}{P}}-H \; + \; 3RMgX \; + \; R'X \longrightarrow R_2R'P=O$$
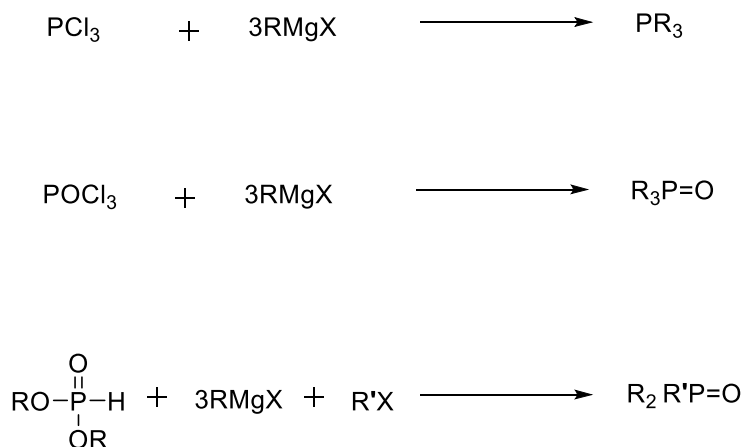
Scheme 4. General synthesis of organophosphorous compounds using Grignard reagents.

Alcoholysis of dihalophosphine in presence of a base, such as pyridine or triethylamine, is another method used for the preparation of phosphinates (scheme 5).[79,106]

$$RPCl_2 \quad + \quad R'OH \xrightarrow{\text{Base}} R_2(OR')P=O$$
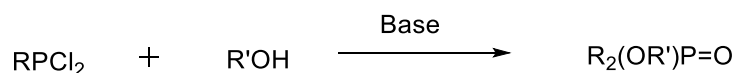
Scheme 5 . Alcoholysis of dihalophosphine.

Atherton-Todd reaction is also employed in many nucleophilic substitution reactions of secondary phosphine oxides and H-phosphinates to form the corresponding phosphinates, aminophosphine oxides and thio-derivatives (scheme 6).[107]

Nu-H: RNH$_2$, ROH, ArOH, ArSH

Intermediate
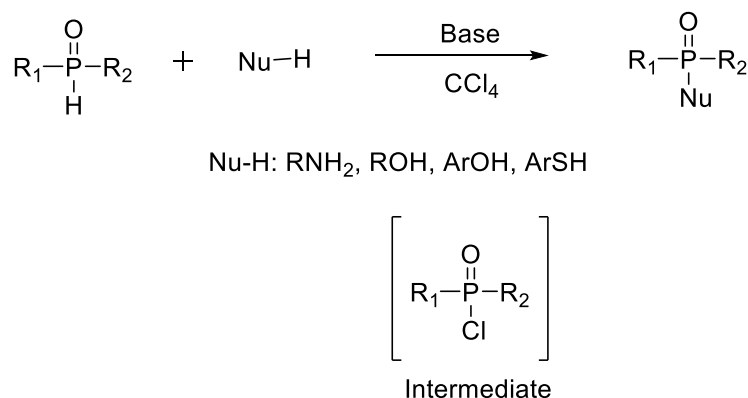
Scheme 6. Nucleophilic substitution reaction of secondary phosphine oxides using Atherton-Todd reaction.

3.2.3 Configurational Stability of P-Stereogenic Compounds

In literature, configurational stability studies are limited, with respect to the P-stereogenic compounds.[108] In general, an atom attached to three different substituents and having an electron lone pair is stereogenic in nature (e.g. P, N, As). Depending on the inversion energy barrier, these compounds can exist as enantiopure molecules or get racemised.[109,110] The racemisation of these compounds can occur via *pyramidal inversion* (scheme 7). The P-stereogenic compounds are configurationally more stable, compared to ammonia and amines, which have about 25 kJ/mol inversion barrier (pyramidal inversion occurs rapidly at room temperature), while the inversion barrier for phosphine is about 125-145 kJ/mol.[110,111]

Pyramidal inversion

A= P, N, As
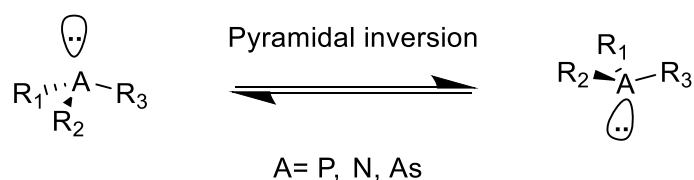
Scheme 7. Pyramidal inversion of a tricoordinated, pyramidal compound.[109,110]

However, the value of inversion barrier of phosphines depends upon steric and electronic properties of the substituents attached to P atom. Scheme 8 demonstrates a general configurational stability trend of P-stereogenic organophosphorous compounds. Generally, P(V) organophosphorous compounds are configurationally more stable than their corresponding P(III) organophosphorous compounds.

Very often, electron-withdrawing groups (EWG) attached to P atom in a P-stereogenic compound decrease the configurational stability. For example, chlorophosphines (**40** scheme

8), where chlorine is an electron-withdrawing group at P atom, are not configurationally stable at room temperature.[84] Tertiary phosphines, such **39** in scheme 8 are relatively stable but, can racemise under thermal conditions of 130 °C within one day.[87] While, secondary phosphine oxides for example are also stable but, prone to racemisation under acid-base or thermal conditions[112]. Tertiary phosphine oxides like, PAMPO **40** in scheme 8, are configurationally most stable among all P-stereogenic compounds.[84,85]

	(a)	(b)	(c)	(d)
	Tertiary Phosphine with EWG	Tertiary Phosphine	Secondary Phosphine oxide	Tertiary Phosphine oxide

EWG = Electron withdrawinng group

Increasing order of configurational stability

	38	**39**	R = alkyl, aryl	**40**
	chloro(2-methoxyphenyl) (phenyl)phosphine	cyclohexyl(methyl)(propyl) phosphine	Phosphine oxide	PAMPO
	Fast racemisation at room temperature	Racemisation in 24h at 130°	Racemisation under acid/base conditions	Configurationally stable

Scheme 8. A general configurational stability trend of P-stereogenic organophosphorous compounds.

Recently, Buono et al. reported that configurational stability of H-phosphinates depended on the steric hindrance of alkoxy group attached to phosphorous atom.[106] For example, ethylphenyl H-phosphinate **41a** and isopropyl H-phosphinate **41b** are prone to racemisation at room temperature in several minutes and hours respectively. While, with the sterically more hindered alkoxy groups, such as *tert*-butyl H-phosphinate **41c** and adamantly H-phosphinate **41d**, it was found that these H-phosphinates were configurationally stable at room temperature for a considerably longer time period (fig. 9).

Fig. 9. Some examples of configurational stability trend of alkylphenyl H-phosphinates.

Overall, it can be said that configurational stability of P-stereogenic compounds depends on the substituents attached to the P atom; their electron richness and steric hindrance. In general, tertiary phosphine oxides are stable P-stereogenic compounds.

3.3 Applications of P-stereogenic compounds

In this section, a brief account of the applications of P-stereogenic compounds in various fields of science will be highlighted. The sub-sections regarding asymmetric organocatalysis and organometallic catalysis with P-stereogenic ligands will be discussed in more details. An excellent review on P-stereogenic compounds has recently been published by Jugé et al.[1]

Applications of P-stereogenic compounds

Biologically active molecules	Coordination complexes	Chiral reagents	Chiral ligands
• Agrochemistry • Pharmaceutical industry	• Mechanistic studies • Anti-tumoral • Materials chemistry	• Asymmetric transformations	• Organocatalysis • Organometallic catalysis
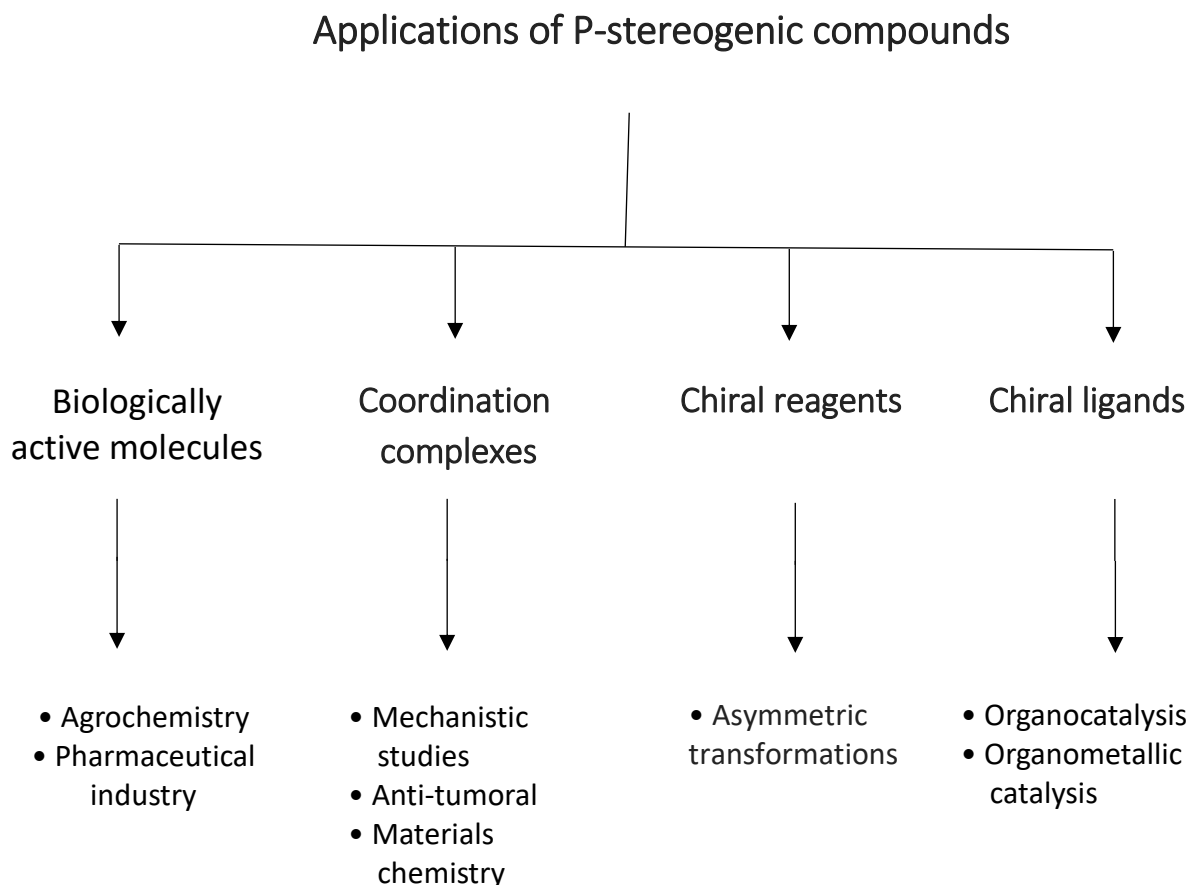
3.3.1 Agrochemistry

P-stereogenic organophosphorous compounds are an important class of insecticides in agrochemistry.[113] A number of insecticides which are currently in the market, such as organophosphorus and pyrethroids, are chiral. Chiral pesticides currently contribute about 25% of all the pesticides used globally, and this trend is expected to increase in future. For example, insecticide (*S*)-salithion **42** (fig. 10) is ten times more potent than its other enantiomer.[3] However, almost all of these chiral pesticides are mostly commercialised as a racemic mixture. Therefore, concerning the environmental issue of effects of pesticides on eco-system, selective access to P-stereogenic pesticides and their application can significantly

reduce the amount of pesticides applied to the crops. Therefore, there is a great need to develop practical and feasible synthetic procedures to access these kinds of P-stereogenic organophosphorous compounds. Also, further studies are needed to evaluate the impact of different enantiomers/diastereomers used as P-stereogenic pesticides.

42
Salithion (insecticide)
(*S* enantiomer is 10 times
more active than *R* enantiomer)

43
(insecticide)

44
Fosetyl-Al
(insecticide)
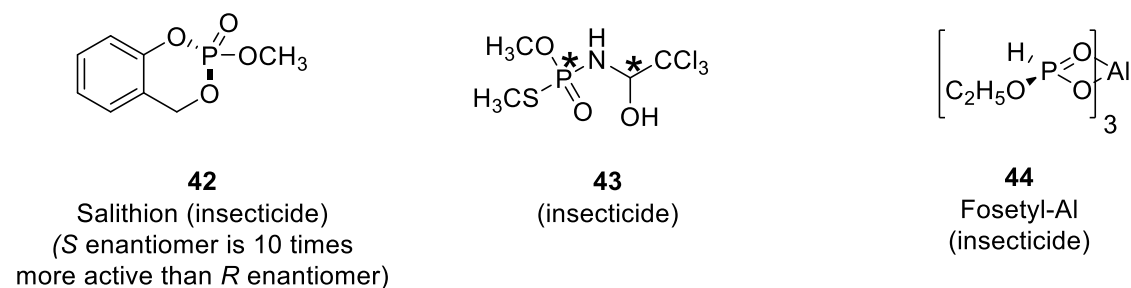
Fig. 10. Some examples of P-stereogenic insecticides.

3.3.2 Pharmaceutical Industry

P-stereogenic compounds find important applications in pharmaceutical industry as biologically active molecules (fig. 11). Cytoxan **45**, a cyclophosphamide is one of the popular anti-neoplastic drugs. It is also used as immunosuppressive agent in blood and bone marrow-

45
cytoxan
(anti-tumoral)

46
Sofosbuvir
(anti-viral drug, Hepatitis C)

47
salinipostin A
(anti-malarial activity)

48
Phostin
(anti-tumoral)
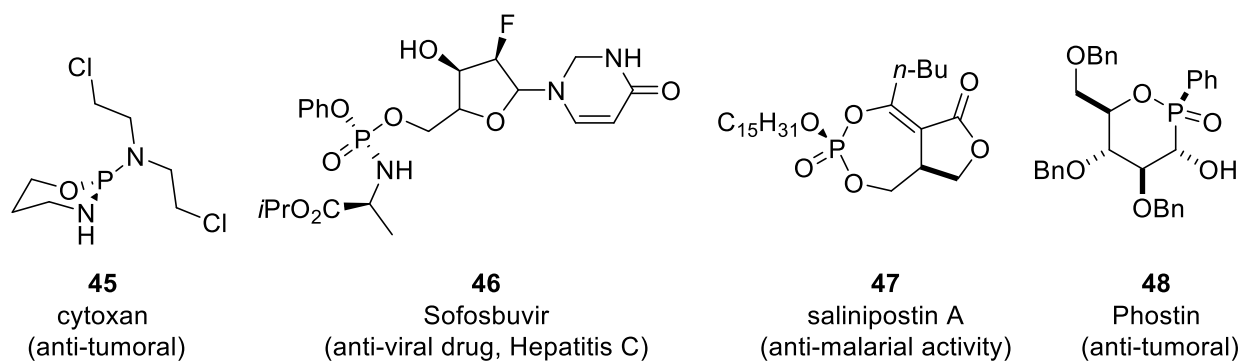
Fig. 11. Some examples of P-stereogenic biologically active molecules in pharmaceutical industry.

transplantation.[6,114] Sofosbuvir **46**, a pronucleotide, is a recent promising drug to treat Hepatitis C. Its popularity among the other drugs is due to its direct mechanism of action on the virus, high potency, low side effects, oral administration and a high barrier to resistance.[6,115] Considering the emerging anti-malarial drug resistance, salinipostins **47** are interesting anti-malarial candidates, recently isolated from a marine-derived *Salinospora* species of bacteria.[92] Another notable example of a drug includes phostin **48**, a mimic of

glycosides. This drug is a promising candidate for its powerful action against tumour cells in human.[102,116]

3.3.3 Coordination Complexes and Material Chemistry

Many P-stereogenic compounds are involved in complexation with transition metals (fig. 12). These complexes help in determination of three-dimensional space around the metal centre.

49
Miniphos-Pd(I) complex

50
DiPAMP-Rh complex

51
QuinoxP*-Au(I) complex

52
Polymetllic lithium complex

53
DiPAMP chiral cluster

54
methylphenyl *n*-propylphosphine chiral cluster
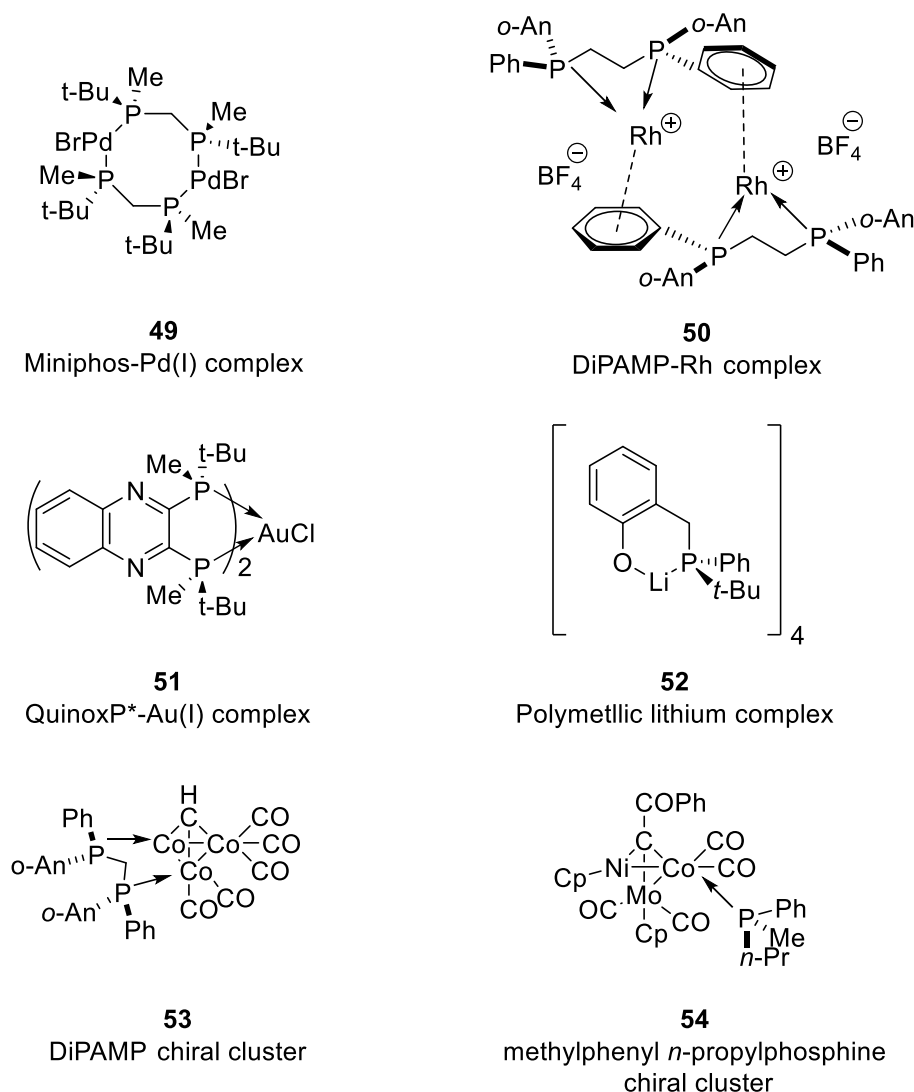
Fig. 12. Some examples of metal coordination complexes with P-stereogenic compounds.

Their detailed study along with NMR analysis, X-ray structure and computational studies can contribute to the determination of mechanism of asymmetric catalytic reaction and thus, it can allow to design more efficient chiral ligands. For example, in case of Rh[117] catalysed

asymmetric hydrogenations and Pd[118] catalysed asymmetric allylations, the enantioselectivities of these asymmetric reactions have been studied using this strategy.

Some Cu(I), Ag(I) and Au(I) complexes have shown promising anti-tumour activities.[119,120] For example, Quinox-P*-Au(I) complex **51** (fig. 12) has been reported for strong anti-tumoral activity and low toxicity.

P-stereogenic compounds have also been used for the synthesis of dendrites as dendritic complexes, polymetallic complexes and coordinating polymers with metals, such as Rh and Li (**50** and **52** fig. 12)[121].

DiPAMP and (S)-(+)-methyl phenyl-*n*-propylphosphine, have also been used in the formation of chiral clusters , which simultaneously carry multiple chiral centres on different atoms (**53** and **54**, fig. 12).[122,123]

3.3.4 Chiral Reagents

P-stereogenic compounds have the potential to transfer chirality from P atom to the C atom during a chemical transformation, where these compounds act as *asymmetric inductors*. However, P-stereogenic compounds have seldomly been exploited as chiral reagents. Indeed, only some asymmetric reactions have been reported in literature, such as alkylation (Wittig-type, Claisen and Michael types) and 1,4-addition reactions.

In 1969, the first example where, P-stereogenic compounds were used as chiral reagents was reported by Bestmann et al in a Wittig-type reaction (scheme 9).[124]
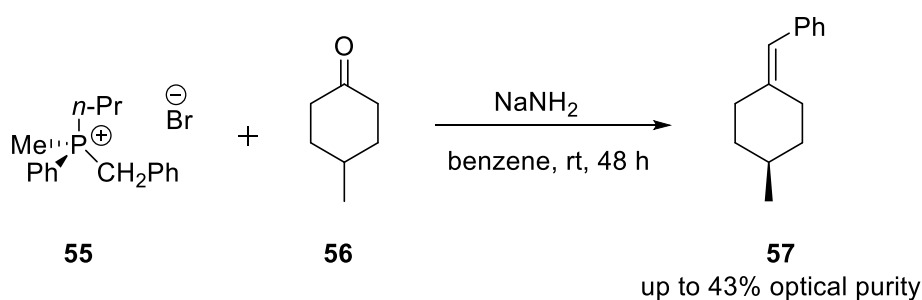
Scheme. 9. First report of asymmetric transformation using P-stereogenic compound as a chiral reagent in a Wittig-type reaction.

Later in 1994, it was reported that by using a P-stereogenic cyclic phosphamide **58**, a Horner-Wadsworth-Emmons (HWE) type reaction provided alkylidene cyclohexane **60** with up to 86% ee (scheme 10).[125]
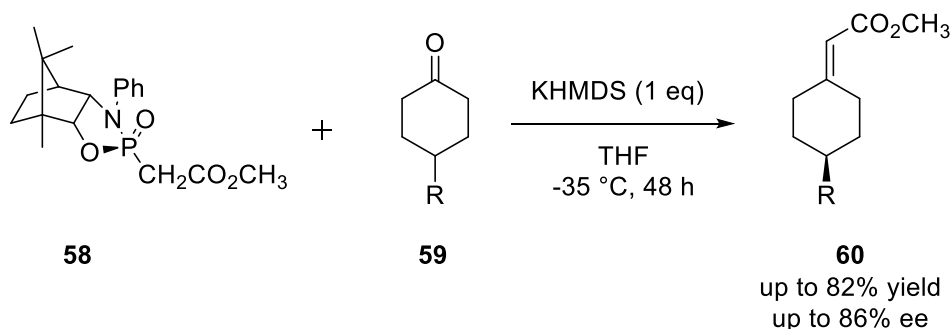
Scheme 10. P-stereogenic cyclophosphamide as a chiral reagent in Horner-Wadsworth-Emmons (HWE) reaction.

Some asymmetric 1,4-additions have also been reported using P-stereogenic compounds and their derivatives.[126–128] For example, a diastereoselective Michael addition reaction has been described between a chirally modified P-allyl anion **61** and cyclic enones **62**. The desired product **64** was obtained with good yields and high enantiomeric excess after ozonolysis of the corresponding 1,4-additions adduct **63** (scheme 11).[126]
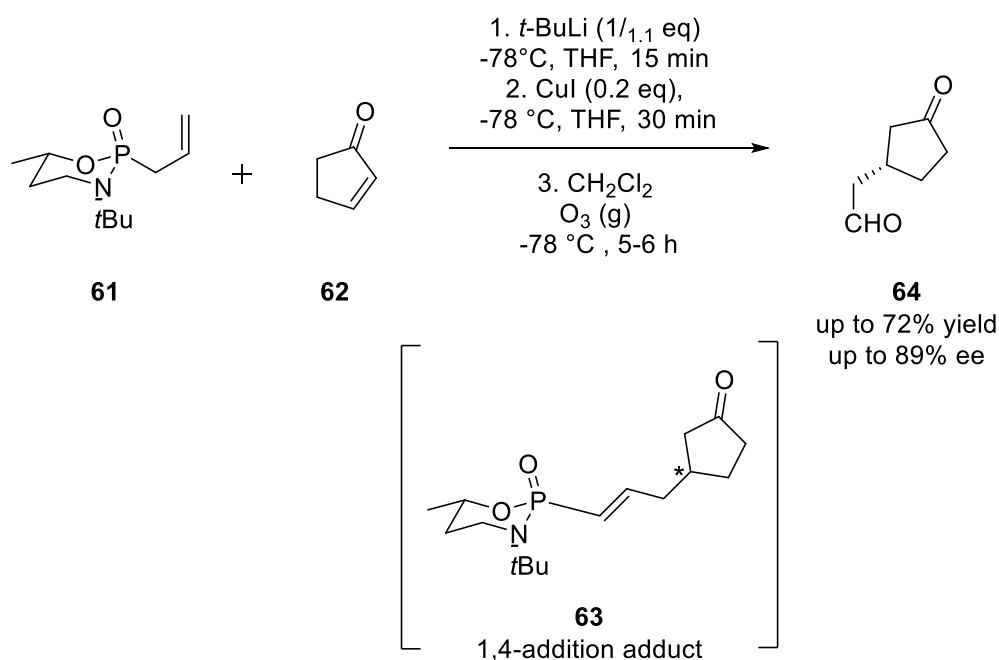
Scheme 11. Asymmetric Michael addition reaction of chirally modified P-allyl anion **61** with cyclic enones **62**.

In 2006, another example has been reported by H. Krawczyk et al. in a highly efficient and diastereoselective asymmetric synthesis of α-methylene-δ-valerolactone **68** using P-stereogenic acrylate **66**. The key step being the Michael addition of racemic **67** with the P-

chirogenic acrylate **66**, which finally gives the desired product **68** after reduction with KBH$_4$ and Horner–Wadsworth–Emmons reaction (scheme 12).[129]
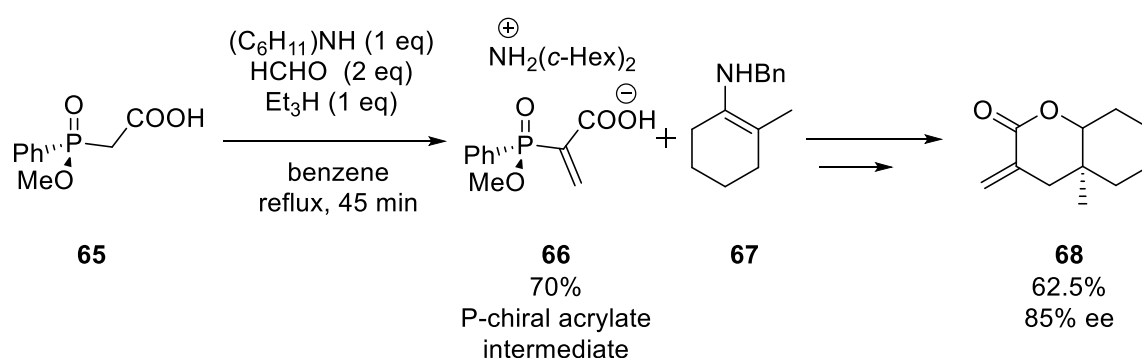
Scheme 12. Asymmetric synthesis of α-methylene-δ-valerolactone using P-stereogenic acrylate.

3.3.5 Asymmetric Organocatalysis

Recent years have witnessed tremendous development in chiral organophosphorous catalysed asymmetric transformations under metal free conditions.[72,74,130–133] Since, the synthetic methods to obtain P-stereogenic compounds have evolved greatly, especially in last decades, applications of these P-stereogenic compounds have been under steady progress in organocatalysis. In particular, the use of sub-stoichiometric amount of P-stereogenic compounds as organocatalysts, and their unique reactivity, make them popular in many asymmetric processes, such as kinetic resolution of alcohols, alkylation, aldolization, acylation, desymmetrisation reactions etc.[72,131,132,134–137]

To give a broad perspective in this section, a number of diverse asymmetric organocatalysed reactions, such as Steglich rearrangement, cycloaddition, 1,4 addition, allylation, amination, reduction of quinolines and deracemisation of amino acids will be presented briefly.

The work done by Vedejs et al. in organocatalysis is worth mentioning. They have studied a number of asymmetric reactions using P-chirogenic phospholanes, such as the formation of azalactone **70** via Steglich rearrangement of the carbonate precursor **69** with good yields and high enantioselectivities (scheme 13).[138]
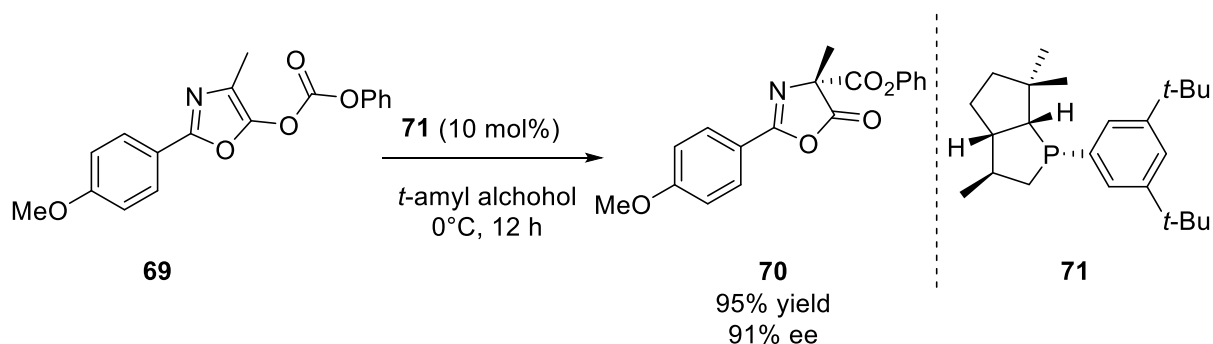
Scheme 13. Synthesis of azalactone by use of P-chirogenic phospholanes.

In 2010, T.-P. Loh reported an outstanding paper on DiPAMP **17** organocatalysed selective one pot (3+2)-cycloaddition via isomerisation of 3-butynoates **73** with electron deficient olefins **72**. They obtained highly functionalised cyclopentenes **74** with up to 95% yield and 99% ee (scheme 14).[139]
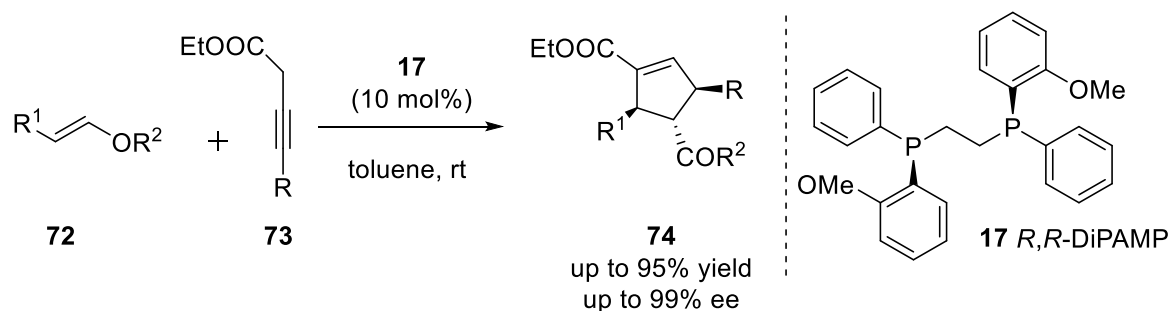
Scheme 14. DiPAMP organocatalysed synthesis of highly functionalised cyclopentenes.

Another notable example includes a highly enantioselective aza-Morita-Baylis-Hilman reactions of ketimines **76,** providing α,α-disubstituted α-amino acid derivatives **77** with up to 97% ee. These α-amino acid derivatives are important intermediates in fine chemistry (scheme 15).[140,141]
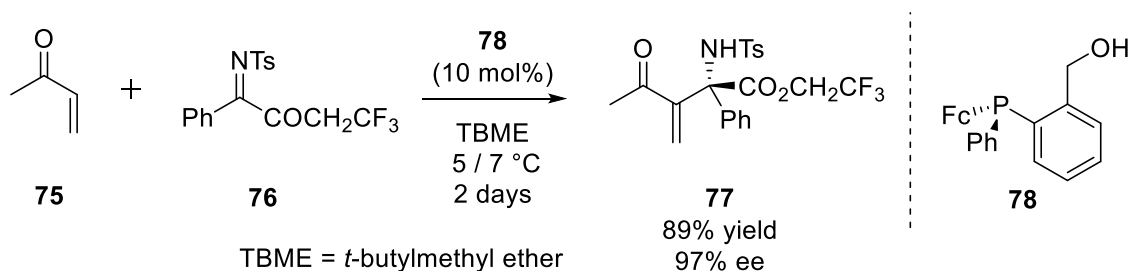
Scheme 15. P-stereogenic phosphine organocatalysed aza-Morita-Baylis-Hilman reactions of ketimines.

Due to the high polarity and stronger Lewis basicity of phosphoryl group attached to the nitrogen atom in phosphoramides, such as hexamethyl phosphoric triamide (HMPA), many asymmetric organocatalysed reactions, based on the use of P-chirogenic phosphoramides have been reported in the literature.[131] For example, the asymmetric allylation of benzaldehyde 79 was reported in the presence of a P-chirogenic phosphoramide 82 based on (S)-proline, affording the homoallylic alcohol 81 with good yield and high enantioselectivities (scheme 16).[142]
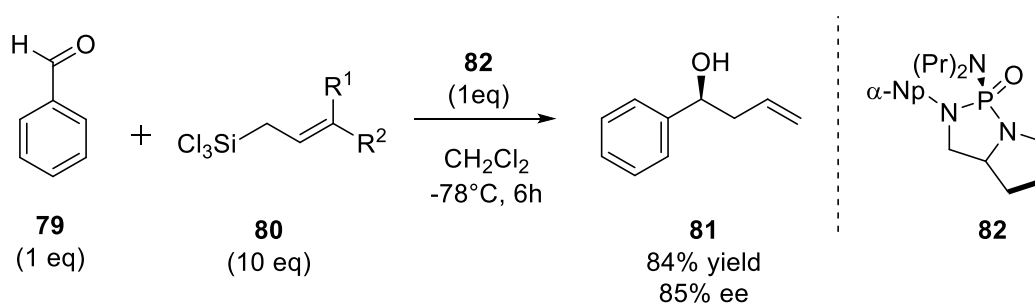
Scheme 16. Asymmetric allylation of benzaldehyde using P-chirogenic phosphoramides.

Currently, designing of bulky P-stereogenic organo-superbase catalysts have evolved significantly, especially due to their high reactivity towards activation of less acidic pro-nucleophiles, such as azodicarboxylates, which are less acidic pro-nucleophile species.[143–147] Terada et al. have reported the synthesis of a highly reactive P-stereogenic organosuperbase catalyst based on bis(guanidino)imino phosphorane 86.[148,149] This P-stereogenic organosuperbase catalyst 86 has been used in asymmetric electrophilic amination of tetralone 83 to generate the corresponding hydrazine derivatives 85 with good yields and high enantioselectivities (scheme 17).
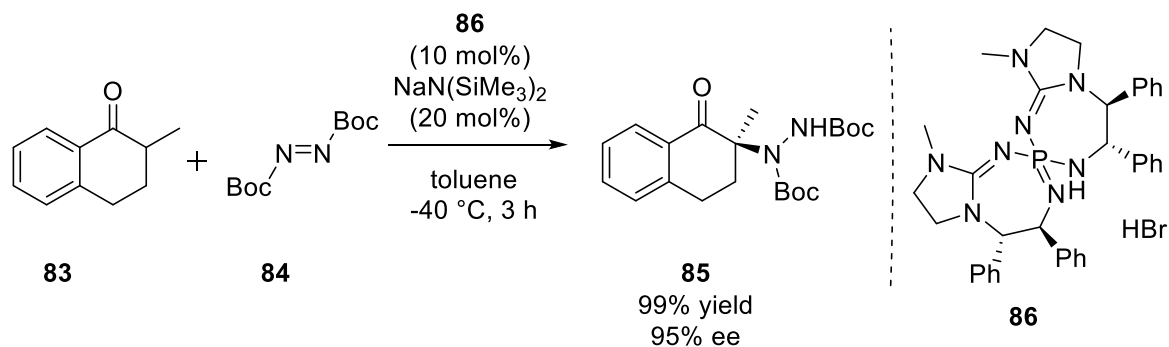
Scheme 17. P-stereogenic iminophosphorane organocatalysed asymmetric amination of tetralone.

A few examples of P-stereogenic Bronsted acid organocatalysed reactions have recently been reported. Notable examples include asymmetric reduction of quinolines **87** using P-stereogenic thiophosphonic organocatalyst **89**, described by X. Guinchard (scheme 18),[150] and asymmetric deracemization of amino acids using P-spiro diaminodioxaphosphonium barfates **92** as chiral proton transfer agents (scheme 19).[151]
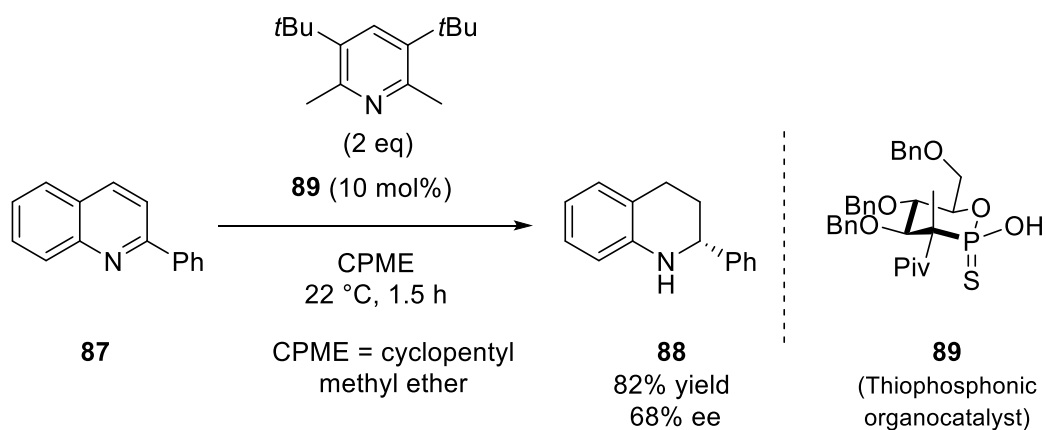
Scheme 18. Asymmetric reduction of quinolines using P-stereogenic thiophosphonic organocatalyst.
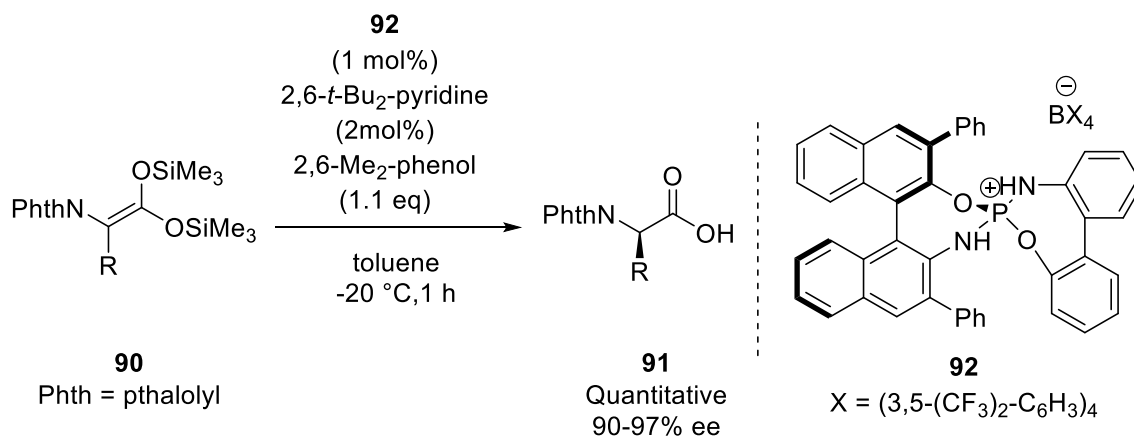
Scheme 19. P-spiro Bronsted acid organocatalysed deracemization of amino acids.

3.3.6 P-stereogenic Ligands in Asymmetric Catalysis by Transition Metal Complexes

Chiral catalysts that are efficient in inducing asymmetry will have their region of maximum stereoinduction spatially congruent with the site of chemistry, but inefficient catalysts will not.

J. N. Stack, *J. Am. Chem. Soc.* **2002**, *124*, 14255-14267.

P-stereogenic compounds are most popularly used in organometallic asymmetric catalysis as one of the most important classes of chiral ligands, due to their strong affinity to coordinate with transition metals and to facilitate the catalytic reactions.

As described previously (pages 6-7), the first man-made artificial catalytic activity was achieved by the use of P-stereogenic ligands in organometallic asymmetric hydrogenation reaction, developed by W. S. Knowles in 1972.[59] Today, innumerable P-stereogenic ligands provides very high to excellent enantioselectivities in various asymmetric organometallic catalytic reactions, more popularly in asymmetric hydrogenation reactions. In particular a number of challenging substrates have been employed for this purpose. Nevertheless, P-stereogenic ligands are also being employed in several other cross-coupling reactions.

This section would describe historical developments in designing some of the most important P-stereogenic ligands and their applications in organometallic catalysed asymmetric hydrogenation reactions along with some other cross-coupling reactions.

3.3.6.1 Asymmetric Hydrogenation/Reduction Reactions

After the development of the pioneering P-stereogenic ligands (fig. 13) including CAMP **93** [59] and DiPAMP **17** [63] by Knowles (fig. 13), it took several years for this class of ligands to emerge freely as highly efficient tools in organometallic asymmetric catalysis.

17	**93**	**94**	**95**
DiPAMP	CAMP	PAMP	

96	**97**	**98**
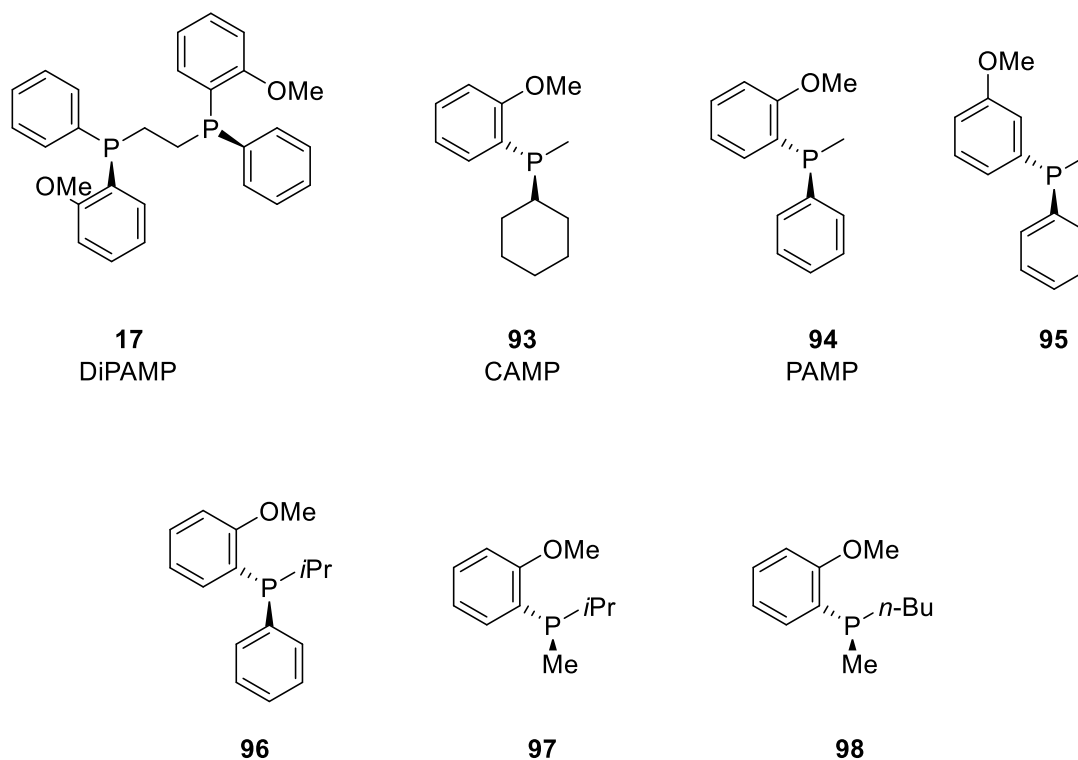
Fig. 13. P-stereogenic ligands prepared by Knowles.

The main interest of the P-stereogenic ligands lies in easy tunability of steric and electronic properties at P-stereogenic centre, which is in a close proximity to the metal i.e. active catalysis site. With time, these ligands have evolved significantly towards more sterically hindered and electron rich on P-stereogenic centre, thereby, improving kinetics of an organometallic catalytic cycle of asymmetric hydrogenation/cross coupling reaction, in particular, during the oxidative addition step of a substrate to the metal centre (fig. 14).[117,152–159]
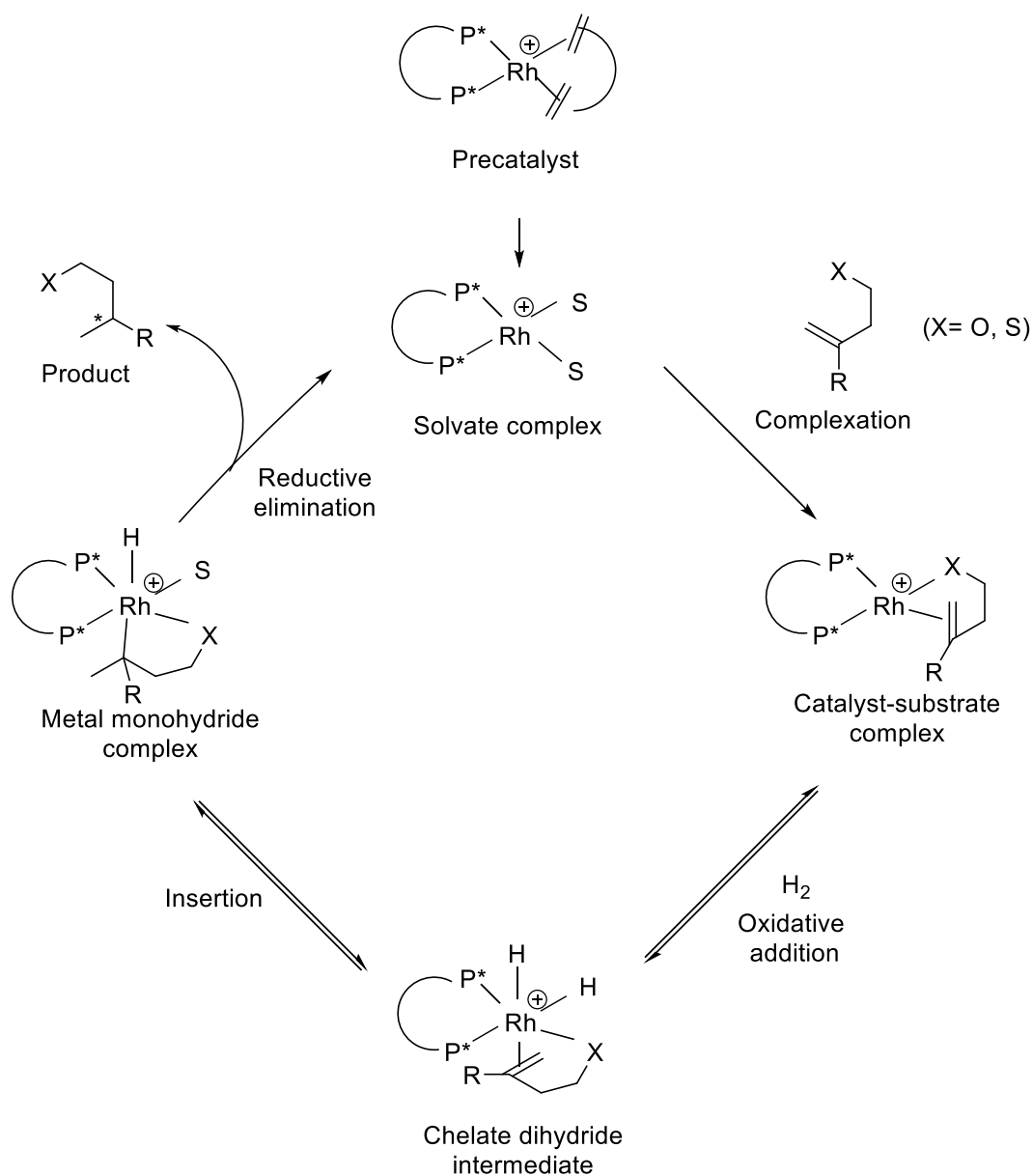
Fig. 14. A typical Rh catalysed asymmetric hydrogenation.

A number of organometallic asymmetric catalytic reactions have been developed by using P-stereogenic ligands, providing high enantioselectivities mainly in asymmetric hydrogenation.[160,161]

Imamoto et al. have significantly contributed in design and development of P-stereogenic ligands including trialkyl-based ligands, BisP* **99** and MiniPhos **100** and also other ligands, such as QuinoxP* **101** and BenzP* **102** ligands. Many of them are now commercially available (fig. 15).[160,162–165] They have demonstrated efficient application of these ligands in various organometallic asymmetric reactions.
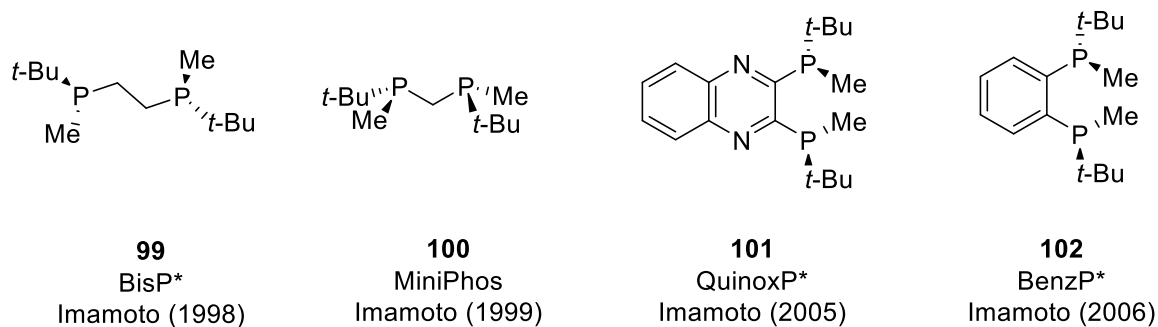
Fig. 15. Some of the important ligands developed by Imamoto et al.

As an example, in 1998, Imamoto et al. prepared the electron rich trialkyl-based diphosphine ligand, called BisP* **99** containing one bulky group, *tert*-butyl and a small group, methyl, attached to each phosphorous atom.[162,166] This diphosphine ligand BisP* **99** forms a rigid complex with the transition metals thus, creating a chiral environment around the metal centre. Using BisP*/Ru complex, asymmetric reduction of β-ketoesters **103** have been reported with very high enantioselectivities (up to 98%) (scheme 20).[162,166]
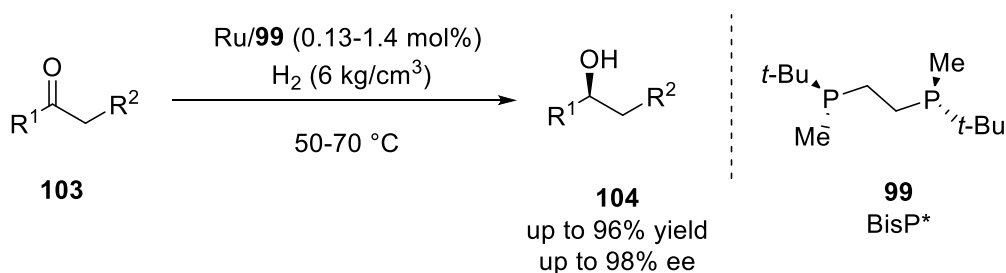
Scheme 20. Asymmetric reduction of ketones using Ru/BisP* catalyst.

Also, using BisP*/Rh complex, an efficient asymmetric hydrogenation of dehydroamino acid derivatives **105** have been described (scheme 21).[162,166] The corresponding products **106** were obtained with up to > 99% ee.
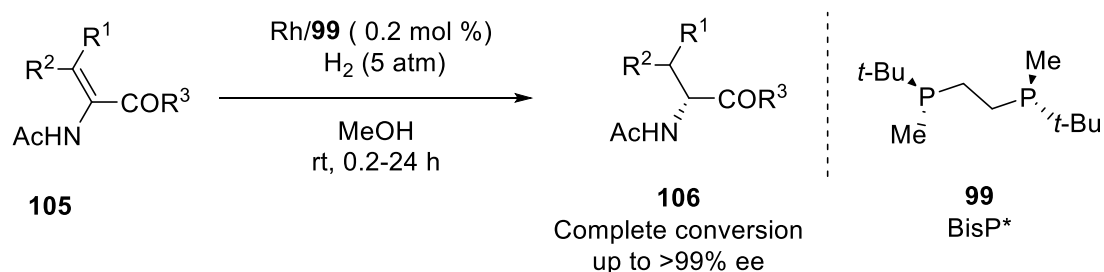
Scheme 21. Asymmetric hydrogenation of dehydroamino acid derivatives using Rh/BisP* catalyst.

In 1999, Imamoto et al. developed another electron rich trialkyl-based diphosphine ligand with a methylene bridge, called MiniPhos **100**.[163] They reported a highly efficient asymmetric hydrogenation of dehydroamino acids and their derivatives **107** using Rh/MiniPhos catalyst with very high enantioselectivities and very good yields (scheme 22).

Scheme 22. Asymmetric hydrogenation of dehydroamino acid derivatives using Rh/Miniphos catalyst.

Moreover, it was found that this catalyst was effective in asymmetric reduction of β,β-disubstituted enamides, which are considered as the challenging substrates with respect to the difficulty in obtaining high enantioselectivities. MiniPhos ligand **100** forms an optically active dinuclear palladium complex **109** bearing Pd-Pd bond. These complexes with some additives, such as silver triflate, are able to catalyse asymmetric ring opening reaction of azabenzonorbornadienes **107** affording the corresponding products **108** with very high enantioselectivities (up to 99%) (scheme 23).[167]

Scheme 23. Asymmetric ring opening reaction of azabenzonorbornadienes using Miniphos-Pd(I) complex.

In 2004, Hoge et al. developed a ligand based on MiniPhos structure, called Trichickenfootphos **113**, which was found to be highly efficient and useful for the asymmetric hydrogenation of α-acetamido dehydroamino acids.[157] Pregabalin **112**, an optically active γ-

amino acid, an anti-epileptic drug, has been produced on industrial scale using Trichickenfootphos/Rh catalyst, with an excellent enantioselectivity and a very good yield (scheme 24).[157] The key intermediate, 2-cyano-4-methylpent-2-enoate **111** is obtained by Trichickenfootphos/Rh catalysed asymmetric hydrogenation with more than 98% conversion and with 99 % ee.
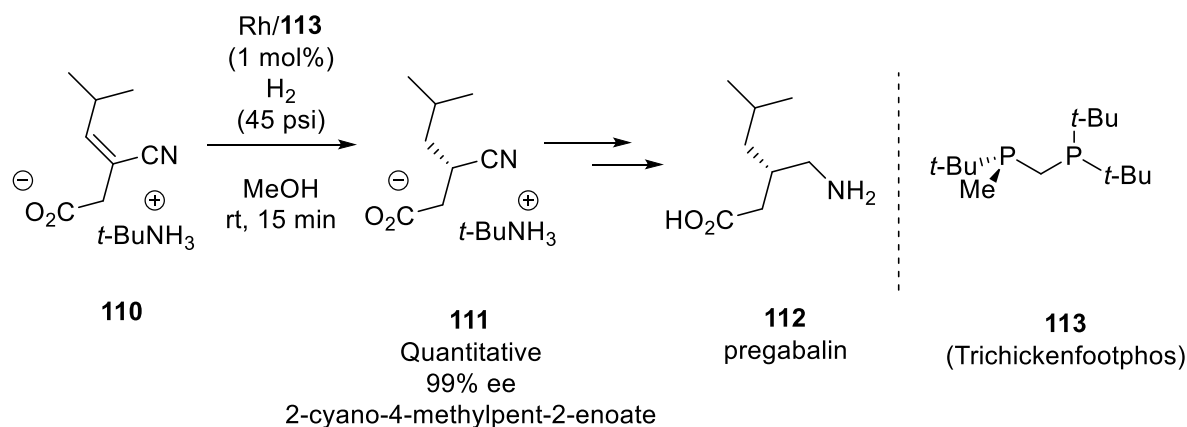
Scheme 24. Synthesis of pregabalin using Trichickenfootphos ligand.

Based on quinoxaline backbone and BisP* moiety, in 2005, Imamoto et al. reported another air stable and configurationally more rigid ligand, called QuinoxP* **101**.[168] This ligand has been utilised in asymmetric hydrogenations of prochiral amino acids and amine derivatives, such as dehydroamino acid esters and α-enamides with very high enantioselectivities (up to 99.9%) (scheme 25).
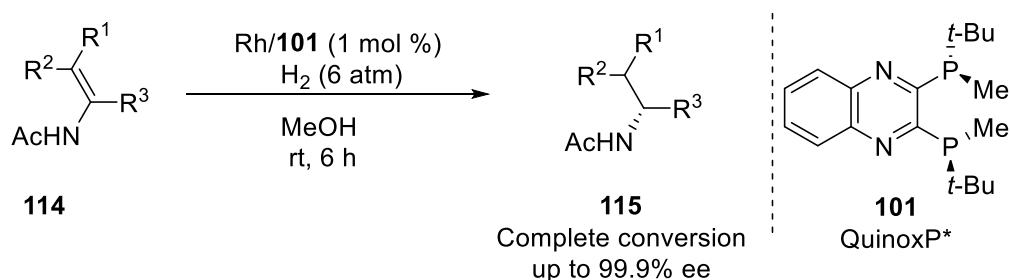
Scheme 25. Asymmetric hydrogenations of dehydroamino acid esters/α-enamides by Rh/QuinoxP* complex.

Moreover, versatility of this QuinoxP* catalyst was described in palladium catalysed asymmetric alkylating ring opening reactions yielding the corresponding alkylated product with very good yields and very high enantioselectivities (scheme 26).[168]
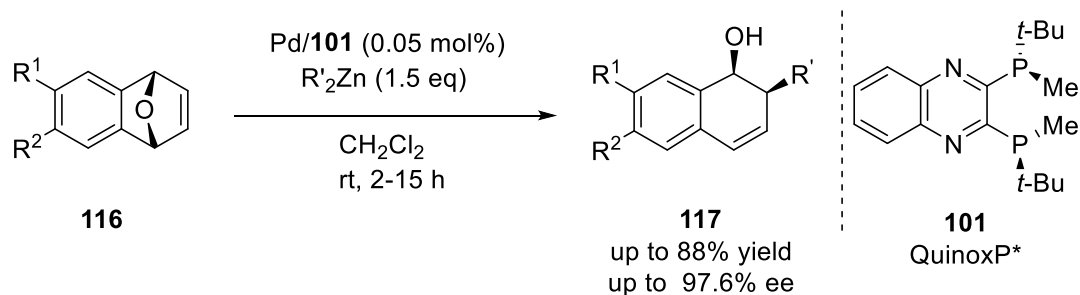
Scheme 26. Asymmetric alkylative ring opening by Pd/QuinoxP*.

In 2006, Imamoto et al. prepared another diphosphine ligand based on two *t*-butylmethyl phosphino groups attached to a phenyl group, called BenzP* **102** ligand (fig. 15).[169] This ligand has been utilised in a number of useful asymmetric hydrogenation reactions, such as Rh/BenzP* catalysed asymmetric hydrogenation of α-dehydroamino acids and derivatives (scheme 27).[170] Remarkably, a very low catalyst loading can be used to achieve the desired product with a very high yield and an excellent enantioselectivity.
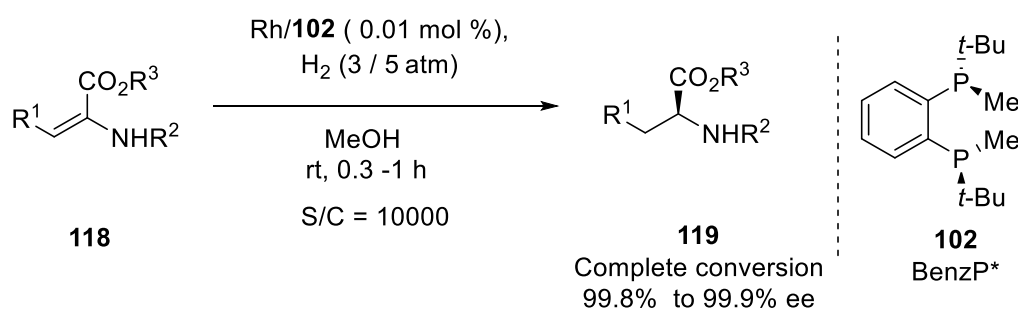
Scheme 27. Rh/BenzP* catalysed asymmetric hydrogenation of α-dehydroamino acids.

More recently, in 2017, A. Börner et al. synthesised a series of P-stereogenic xantphos ligands **122**. They demonstrated an efficient application of these ligands in Rh catalysed asymmetric hydrogenation of isophorone **120** to obtain industrially useful chiral ketones **121** almost in quantitative yields and with very high enantioselectivities of up to 96% ee (scheme 28).[159] It is interesting to note that the hydrogenation of such substrates is particularly challenging, concerning the chemoselectivity (i.e. reduction of keto group can also be observed) as well as the enantioselectivity.
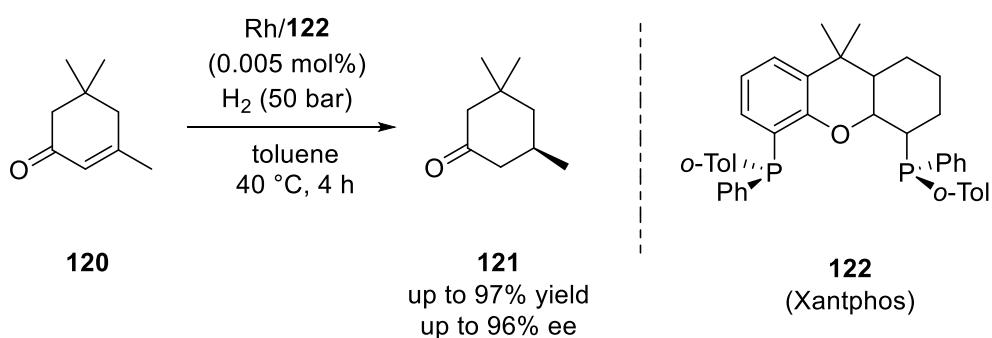
Scheme 28. Asymmetric hydrogenation of isophorone **120** using P-stereogenic xantphos ligands/Rh.

Moreover, the group of X. Zhang et al. have developed a number of efficient P-stereogenic ligands in particular, TangPhos **123** (2002), DuanPhos **124** (2005) and ZhangPhos **125** (2010) (fig. 16).[155,171,172] These ligands were found to be highly efficient in many asymmetric hydrogenation reactions.
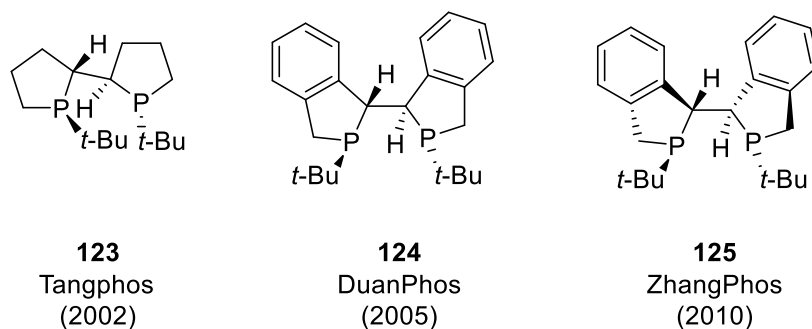
Fig. 16. Representative examples of important ligands developed by X. Zhang.

TangPhos **123**, containing biphospholane ring on its backbone, was expected to be conformationally rigid, which could lead to high enantioselectivity in asymmetric reactions. In fact, theoretical calculations revealed that Rh/TangPhos should be structurally more rigid in chiral environment, compared to Rh/BisP*. Moreover, TangPhos ligand was easy to access from readily available starting materials. Since, its first report in 2002 by X. Zhang, as an efficient chiral ligand in Rh catalysed asymmetric hydrogenation reactions of α-(acylamino)acrylic acids and their esters **126** (scheme 29) and asymmetric hydrogenation of α-arylenamides **128** were conducted in high yield and enantioselectivity (scheme 30).[155,173]
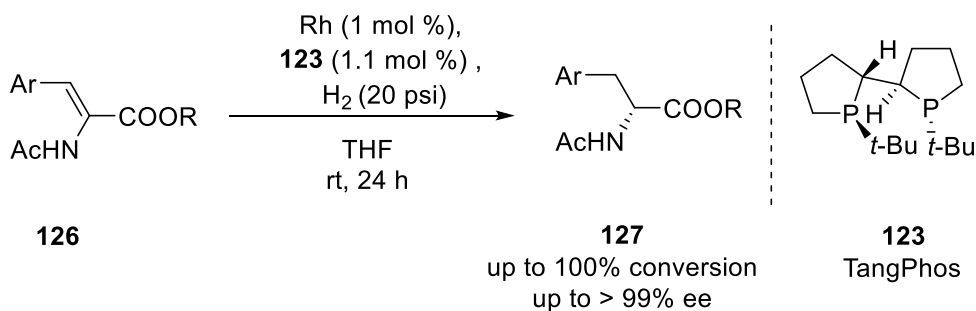
Scheme 29. Asymmetric hydrogenation of α-(acylamino)acrylic acids and their esters using TangPhos/Rh.
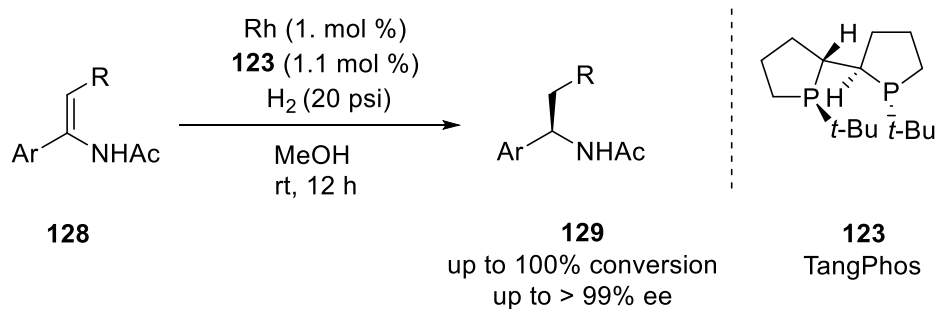
Scheme 30. Asymmetric hydrogenation of α-arylenamides using TangPhos/Rh.

TangPhos **123** has been found to be effective in an array of asymmetric reactions. Rh/TangPhos complex was reported to be an efficient catalyst for asymmetric hydrogenations of β-amino acid derivatives **130**, providing high enantioselectivities and high turnover numbers (scheme 31).[173]
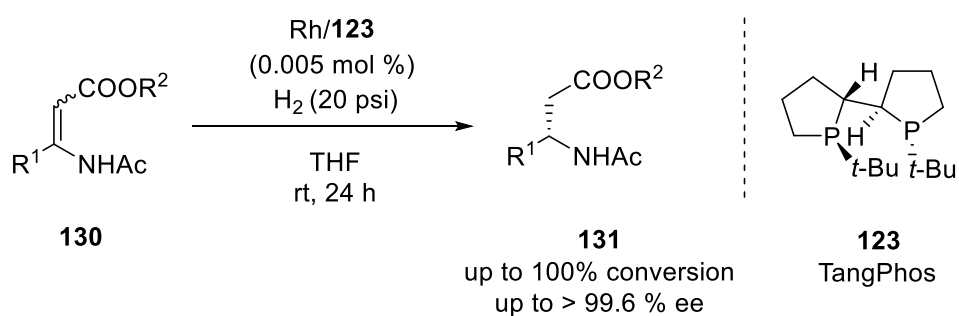
Scheme 31. Asymmetric hydrogenation of β-amino acid derivatives using TangPhos/Rh.

This Rh/TangPhos catalyst has also been successfully used in asymmetric hydrogenations of itaconic acids **132** and enol acetate **134**, providing high enantioselectivities up to 99% ee, and high turnover numbers (scheme 32).[174]

R^2

R^{1}OOC

COOH

132
itaconic acid

Rh/**123**
(0.5 mol %)
H$_2$ (20 psi)

THF
rt, 24 h

R^2

R^{1}OOC

COOH

133
up to 100% conversion
up to > 99% ee

OAc

Ar

134
enol acetate

Rh/**123**
(1 mol %)
H$_2$ (20 psi)

EtOAc
rt, 24 h

OAc

Ar

135
up to 100% conversion
up to > 99.6 % ee

H

P H   P
t-Bu t-Bu

123
TangPhos
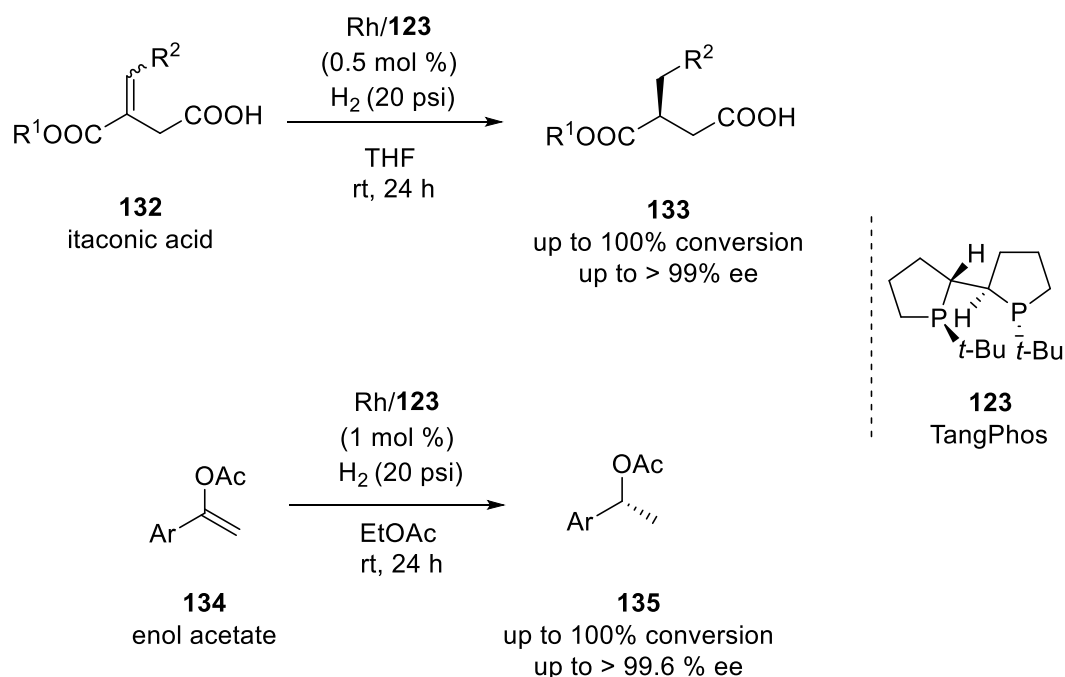
Scheme 32. Asymmetric hydrogenations itaconic acids **132** and enol acetate **134** using TangPhos/Rh.

Also, a highly enantioselective synthesis of arylglycine derivatives **137** was reported in 2006 (up to 95% ee), by asymmetric hydrogenations of *N*-PNP protected α-aryl imino esters **136** using Rh/TangPhos catalyst (scheme 33).[175]

NPMP

Ar   OR
      O

136

Rh/**123**
(1 mol %)
H$_2$ (30-70 atm)

CH$_2$Cl$_2$, rt, 24 h

NHPMP

Ar   *   OR
      O

137
up to > 99 % conversion
up to 95% ee

H

P H   P
t-Bu t-Bu

123
TangPhos
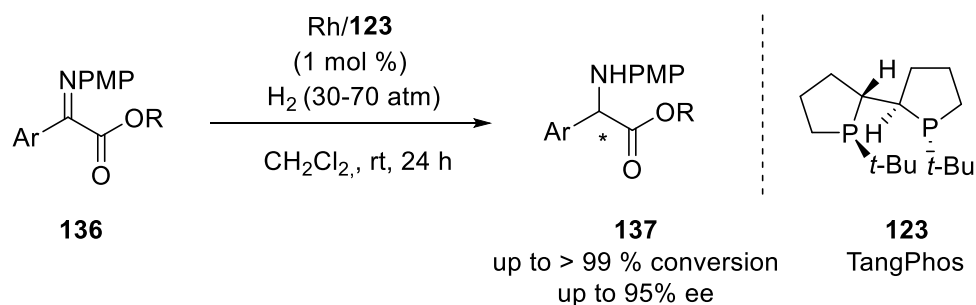
Scheme 33. An enantioselective synthesis of arylglycine derivatives **137** using TangPhos/Rh.

In 2005, Zhang further developed a conformationally more rigid ligand, called DuanPhos **124** (fig. 16) based on previously designed ligand, TangPhos **123** .[171] In case of TangPhos **123**, only one of the enantiomers, TangPhos (1*S*,1*S'*,2*R*,2*R'*) was readily available due to synthetic limitations, while both enantiomers are readily available with DuanPhos **124**. Moreover, this newly developed DuanPhos **124** was found to be highly effective in Rh catalysed asymmetric hydrogenation of functionalised alkenes, providing very high enatioselectivities (up to >99% ee) and turnover numbers (scheme 34).
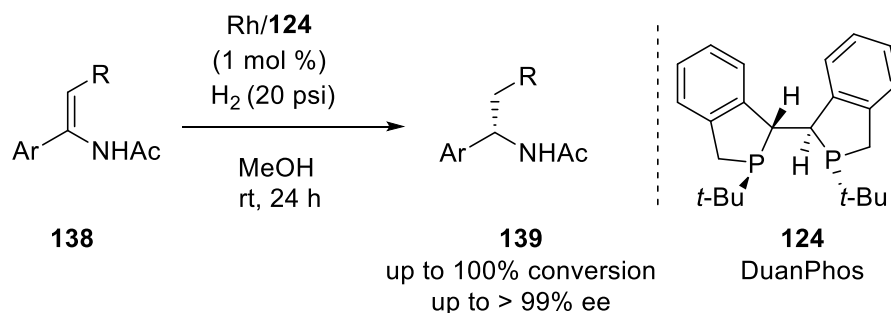
Scheme 34. Rh/DuanPhos catalysed asymmetric hydrogenation of functionalised alkenes.

Besides, Rh/DuanPhos catalyst allowed a very short and efficient synthesis of enantiopure N-monosubstituted γ-amino alcohols.[176] Several β-secondary-amino ketone hydrochlorides (**140** and **143**) were asymmetrically hydrogenated using Rh/DuanPhos catalyst to furnish the corresponding γ-amino alcohols with very high enatioselectivities (up to > 99% ee) and good yields (scheme 35). The resulting amino alcohols (**141** and **144**) find important applications in pharmaceutical industry.
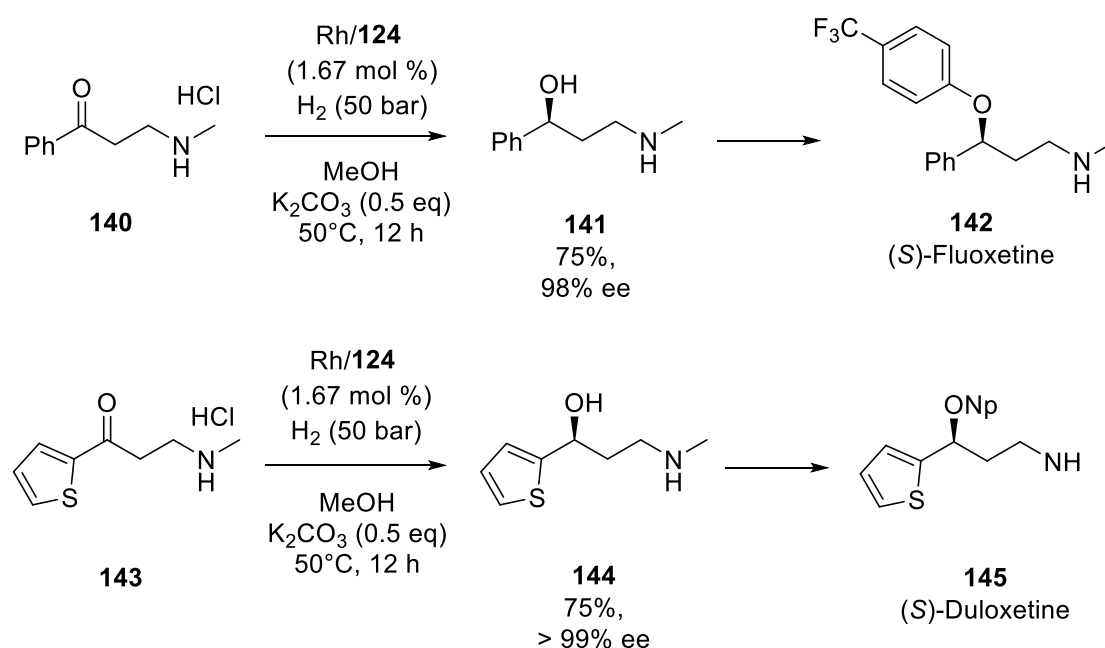
Scheme 35. Rh/DuanPhos catalysed enantioselective synthesis of N-monosubstituted γ-amino alcohols and important pharmaceutical intermediates.

Recently, Rh/DuanPhos catalysed pyridine-directed asymmetric hydrogenation of challenging substrates 1,1-diarylalkenes **146**, has been reported, providing pharmaceutically important intermediates with excellent yields and very high enantioselectivities (scheme 36).[177] This efficient methodology is very useful in accessing chiral 2- (1-arylethyl)pyridines and their derivatives **147**.
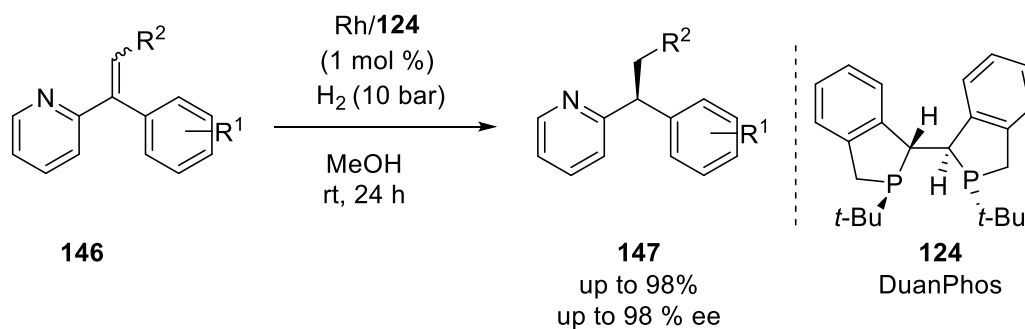
Scheme 36. Rh/DuanPhos catalysed asymmetric hydrogenation of 1,1-diarylalkenes.

In 2011, Zhang et al. reported a synthetic process which is useful for the industrial production of ramipril **150**, a drug used for the treatment of hypertension and congestive heart failure (scheme 37).[161,178]
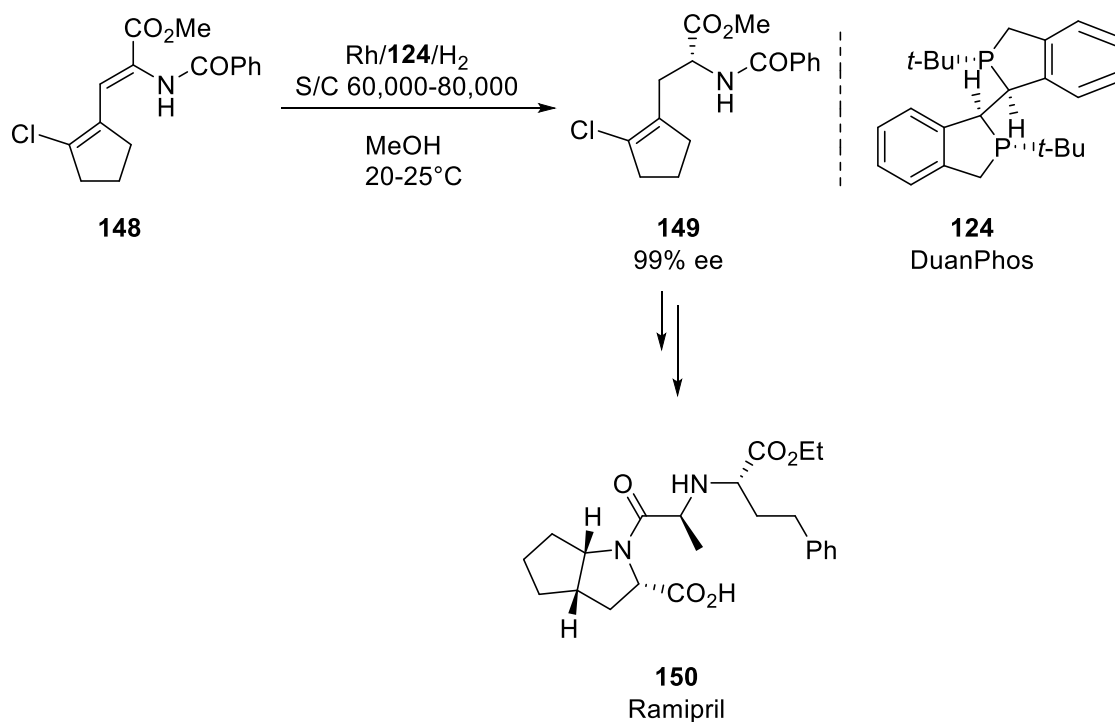
Scheme 37. Synthesis of Ramipril using Rh/DuanPhos catalyst.

The α-dehydroamino acid methyl ester derivative **148** can efficiently be hydrogenated with a rhodium/DuanPhos catalyst to provide the corresponding intermediate compound **149** with 99% ee, which upon further functionalisation provides ramipril.

In 2010, ZhangPhos **125**, another important P-stereogenic biphospholane scaffold-based ligand, was developed by X. Zhang et al.[172] Compared to previously developed biphospholane ligands, such as TangPhos **123** and DuanPhos **124**, this ligand was expected to be conformationally more rigid, and more electron donating in nature. Thus, It has been described that more conformational rigidity leading to a well-defined organometallic system enhances higher enantioselectivity.[179] The two chiral fused cyclohexane rings on the backbone of ZhangPhos **125**, were expected to enhance further conformational rigidity and electron donating ability of the ligand. The applications of this ligand in many Rh catalysed asymmetric reactions has been reported. For example, Rh/ZhangPhos catalyst was found to be highly effective in asymmetric hydrogenation of α-arylenamide and α-(acylamino)acrylic acids and esters **138/152**, the corresponding products **151** and **153** were obtained in very high yields and with excellent enantioselectivities (scheme 38 and 39).[172]
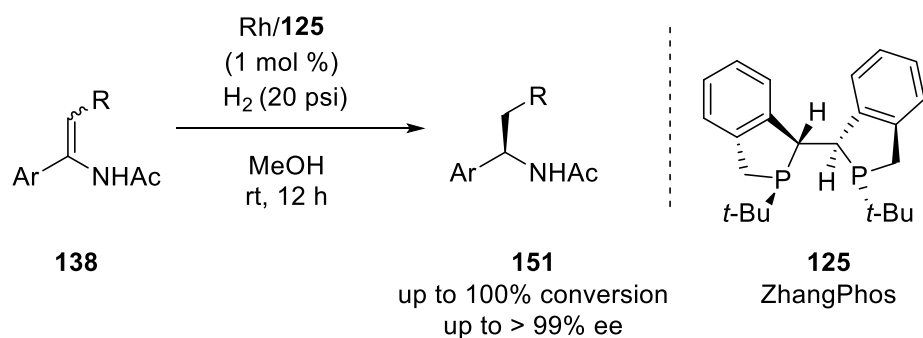
Scheme 38. Rh/ZhangPhos catalysed asymmetric hydrogenation of α-arylenamide.
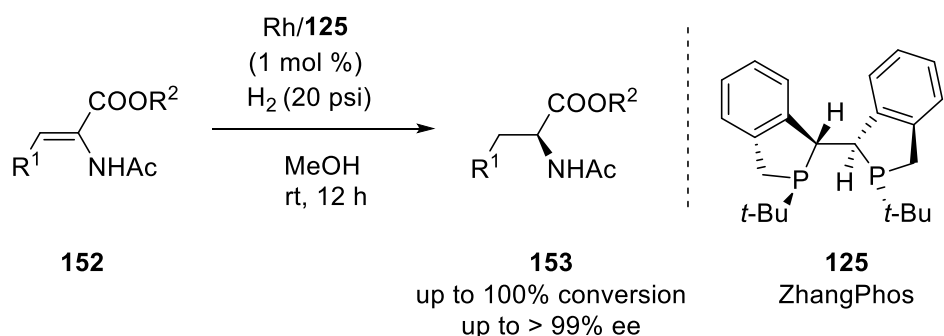
Scheme 39. Rh/ZhangPhos catalysed asymmetric hydrogenation of α-(acylamino)acrylic acids and esters.

A highly enantioselective hydrogenation of β-ketoenamides **154** was also reported by using Rh/ZhangPhos catalyst, providing several optically active β-amino ketones **155** or chiral 1,3-amino alcohols **156** with very good yields and excellent enantiomeric excess (up to 99%) (scheme 40).[180] This synthesis is highly useful in direct synthesis of chiral 1,3-amino alcohols from β-ketoenamides.
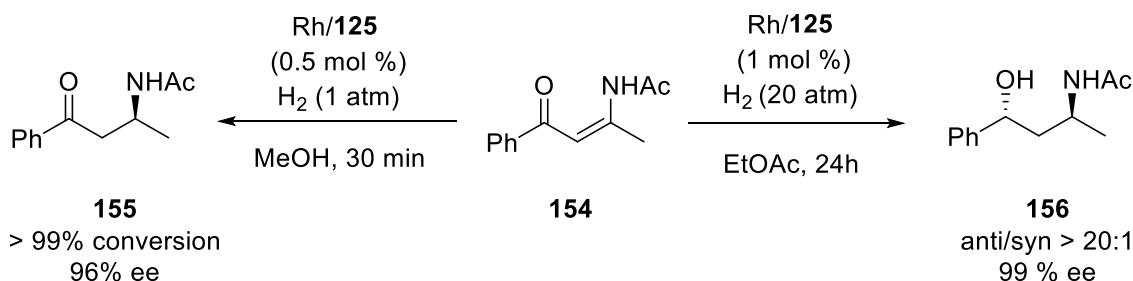
Scheme 40. Synthesis of optically active β-amino ketones and chiral 1,3-amino alcohols using Rh/ZhangPhos.

W. Tang et al. recently used P-stereogenic biaryl ligands, such as BI-DIME **160** and AntPhos **161** in palladium catalysed asymmetric alkene aryloxyarylation reactions.[181] They obtained a series of 1,4-benzodioxanes, 1,4-benzooxazines and chromans (**159**) having quaternary centres with very high enantiomeric excess (scheme 41). They postulated a stereo model for the mechanism of the reaction explaining the high reactivity and enantioselectivity due to sterically bulky and conformationally well-defined ligands.
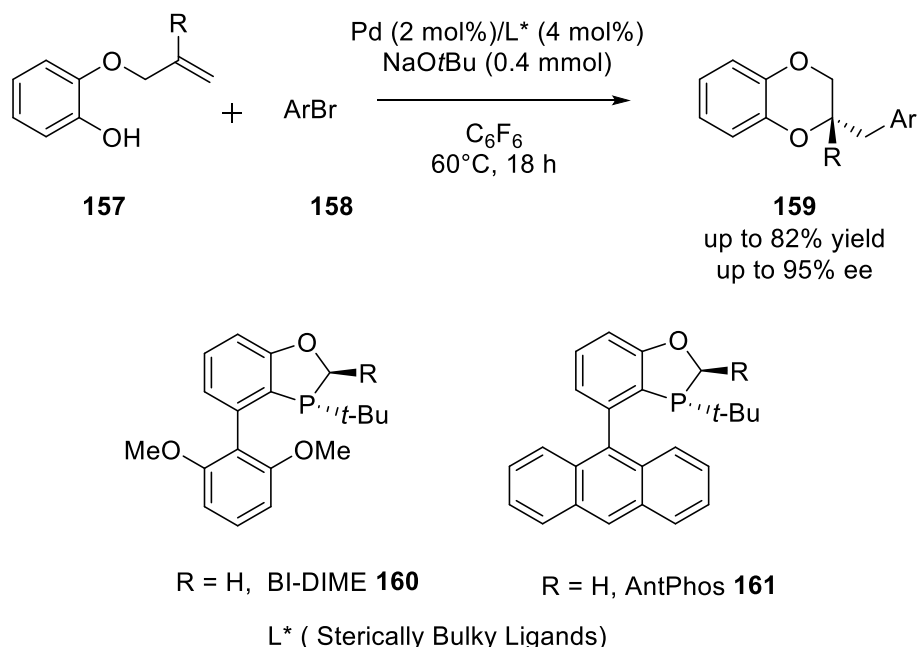
Scheme 41. Palladium/L* catalysed asymmetric alkene aryloxyarylation reactions.

3.3.6.2 Asymmetric Cross coupling reactions

Apart from asymmetric hydrogenation/reduction reactions, P-stereogenic ligands have also been used for asymmetric cross-coupling reactions, such as asymmetric C-C and C-B cross coupling reactions. This subsection would briefly present some examples of asymmetric alkylation, hydroboration and arylation reactions.

Nakamura et al. reported an eco-friendly iron catalysed asymmetric cross-coupling reaction between an aryl Grignard reagent and an electrophile based on α-chloro and α-bromoalkanoates **162**. They obtained the corresponding cross-coupling products **163** with very good yields (up to 92%) and high enantioselectivities (up to 91/9 er) (scheme 42).[182]
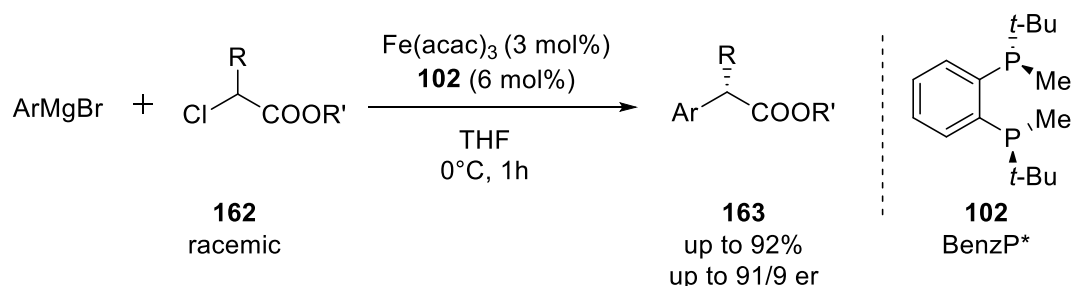
Scheme 42. BenzP*-Iron-catalysed asymmetric cross-coupling reaction.

Very recently, Imamoto et al. reported a highly efficient QuinoxP* derived ligand **167** which catalysed Markovnikov hydroboration of aliphatic terminal alkenes **164**, with very high enantioselectivities of up to 99% ee (scheme 43).[183] It was described in the paper that along with the experimental optimisation study, computational modelisation facilitated the design of the final ligand, which led to the successful asymmetric hydroboration reaction of aliphatic terminal alkenes.
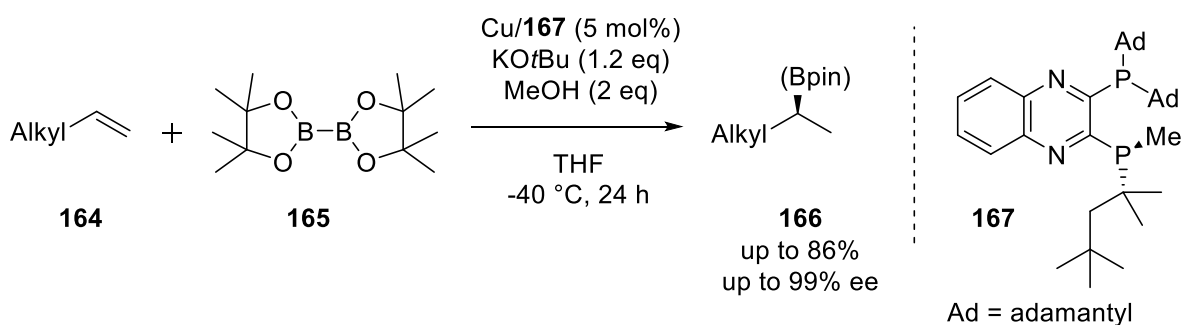
Scheme 43. Asymmetric Markovnikov hydroboration of aliphatic terminal alkenes by Cu/QuinoxP* derivative.

This QuinoxP* **113** ligand was found to be highly effective in transition metal catalysed carbon-carbon bond forming cross coupling reactions, for example, Quinox/Rh catalyst

catalysed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds **168** with very good yields (up to 92%) and high enantioselectivities (up to 99.4%) (scheme 44).[168]
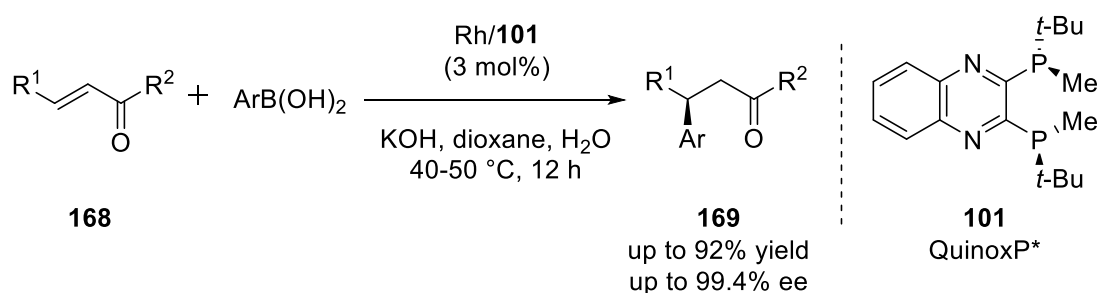
Scheme 44. Asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds by Rh/QuinoxP*.

Thus, to conclude, P-stereogenic compounds are widely used in agrochemistry as pesticides and in pharmacy as biologically active molecules, in coordination chemistry where, these compounds help in determination of three dimensional structure of the metal complex and in asymmetric catalysis by transition metal complexes as a very important class of chiral ligands.[26,27,46] The most important application of P-stereogenic compounds is in organometallic asymmetric catalysis, particularly in asymmetric hydrogenation/reduction reactions, as chiral ligands. These ligands are also widely employed in industry, in particular in the asymmetric hydrogenation reactions of some important pharmaceutical substrates.

3.4 Access to P-stereogenic Compounds:

P-stereogenic organophosphorous compounds barely exist in nature. However, these compounds find several important applications in different fields of science[1,3,13,92,113,115,119,156]. Therefore, a number of methods to build up P-stereogenic compounds have been developed with time. This section first highlights the historical background and later, some of the important methodologies to prepare P-stereogenic organophosphorous compounds.

3.4.1 Historical Background

The first successfully resolved P-stereogenic compound **170**, was obtained by Meisenheimer and Lichtenstadt in 1911.[44]
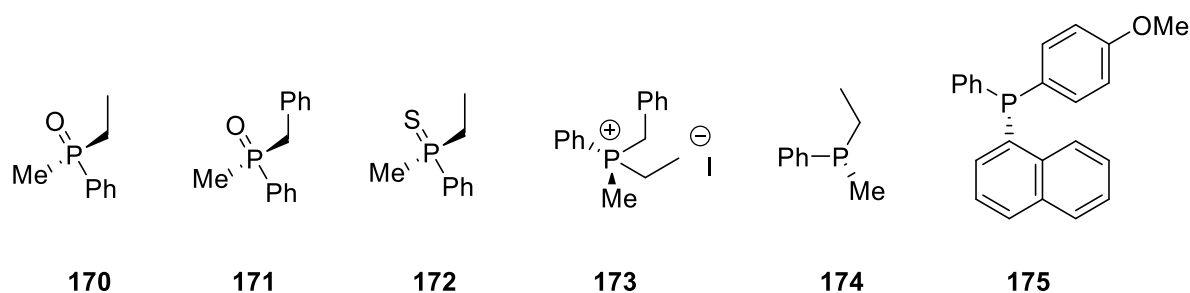
Fig. 17. Examples of P-stereogenic compounds resolved before the work of Mislow (1967-1968).[133,136– 139]

But it was in 1967-1968 that Mislow and co-workers reported a more reliable and relatively easy method based on the use of menthol as a chiral auxiliary providing access to scalemic menthylphosphinates. After the separation of the two diastereomers of menthylphosphinates, a stereospecific reduction was carried out to finally obtain optically pure phosphines.[104,187] Though, this method was based on a tedious multi-step procedure

17
DiPAMP

93
CAMP

94
PAMP

176

177

178
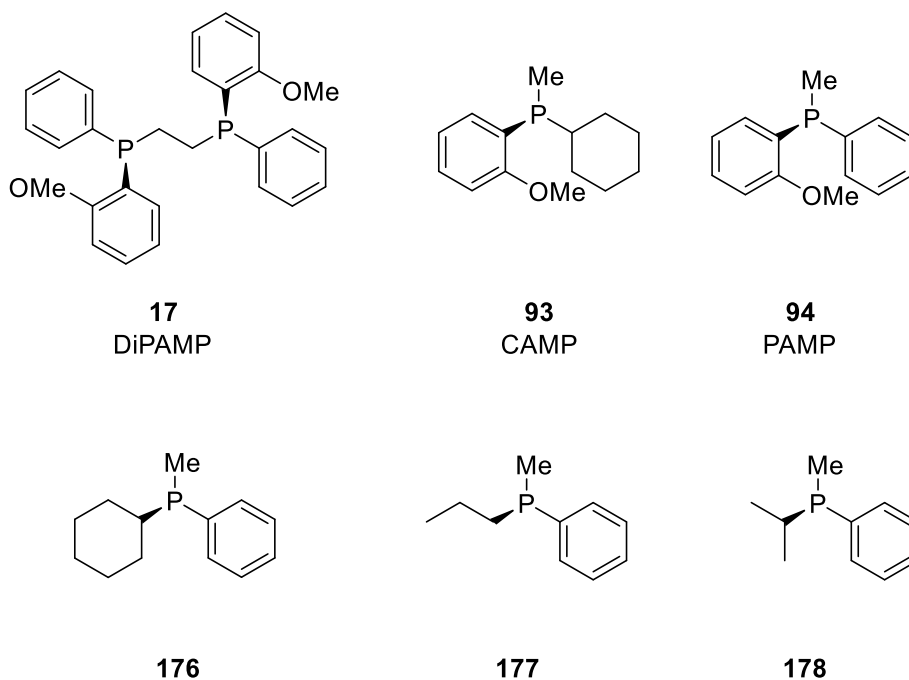
Fig. 18. Examples of P-stereogenic compounds prepared based on Mislow's procedure.

and provided the final optically pure phosphines with very less yields, it promoted further development in the synthetic procedures. Indeed, Horner and Knowles (Nobel Prize 2001) utilised this menthol based methodology in order to develop a large number of optically pure phosphines (fig. 18).[12,13] This greatly contributed in design of P-stereogenic ligands, such as popular ligand DiPAMP, and their applications in asymmetric catalysis.[57,57,59,60,125]

Development towards the synthetic methodologies to access the P-stereogenic compounds and therefore their applications, was hampered and slowed down due to mainly two important reasons. Firstly, soon after the pioneering DiPAMP report, many important reports concerning the synthesis of chiral phosphine ligands featuring backbone chirality and their successful applications in asymmetric catalysis were published, such as DIOP, CHIRAPHOS, DUPHOS and the more popular being BINAP.[61,62,64,65] And secondly, compared to the organic compounds with C-centred chirality, compounds with P-centred chirality are difficult to synthesise. One reason is the abundant availability of C-centred chiral compounds in nature. And, the inherent difficulty to transfer this chiral information from a C-centred chiral compound to another compound with phosphorous atom.

However, since last few decades, the interest of organic chemists has extensively been growing towards the synthesis and application of these P-stereogenic compounds due to their promising applications in various scientific fields.[1] P-stereogenic compounds are generally prepared as phosphine oxides or phosphine boranes, in order to avoid any racemisation process during the multi-step procedures.[70,97,101,111,188–190]

The following flow chart represents different methodologies to access P-stereogenic organophosphorous compounds, which would be discussed in this section. The sub-sections with chiral auxiliary methods in particular, menthol and ephedrine based methodologies, would be discussed in more details.

Access to P-stereogenic compounds

Chiral Resolution	Chiral Auxiliary	Deracemisation	Asymmetric Oxidation	Asymmetric Catalysis
• Diastereomeric Salt Formation • Chiral Metal Complexes • Chiral HPLC	• Menthol • Chiral Amines • Ephedrine			• Organometallic Catalysis • Biocatalysis
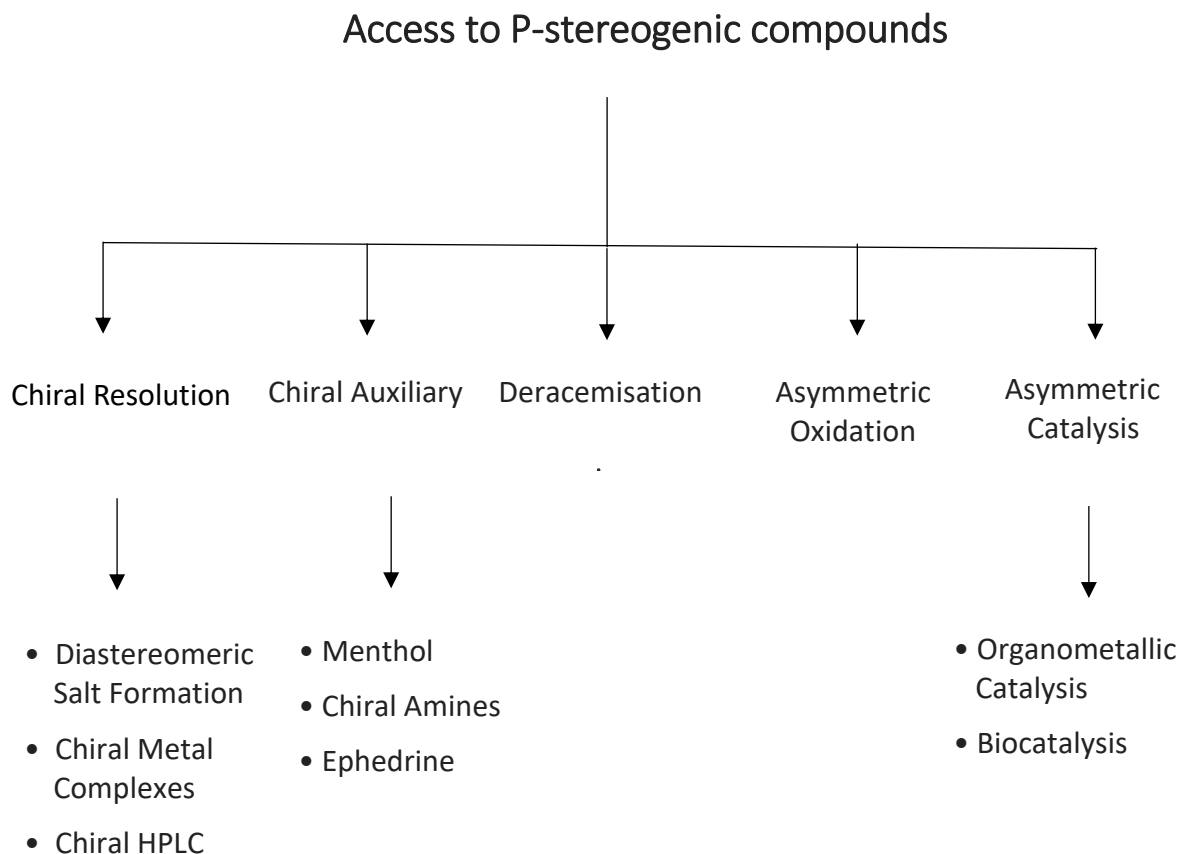
3.4.2 Chiral Resolution

Preparation of the P-stereogenic organophosphorous compounds by chiral resolution is one of the oldest methods.[44] Chiral organophosphorous compounds can be resolved using different resolving techniques, such as using chiral resolving agents or chromatographic separation using a chiral stationary phase. Generally, the preparation of P-stereogenic compounds by this method requires the matching between an organophosphorous compound to be resolved and the resolving agent. This method is rather expensive (maximum theoretical yield of an enantiopure product is limited to 50%), but sometimes useful for an industrial scale synthesis of specific P-stereogenic compounds. Otherwise, this method has several limitations, such as multi-step tedious recrystallisations, difficult chromatographic separations and the fact that the success of this concept relies upon the compatibility of the functional groups present at phosphorous atom and on the resolving agents, in order to form corresponding separable diastereomeric complex/salt.

3.4.2.1 Diastereomeric Salt Formation

This process is based on the formation of diastereomeric salts of a racemic organophosphorous compound using a suitable chiral resolving agent, such as dibenzoyl tartaric acid (DBTA), cinchonine, BINOL, camphor sulfonic acid and their derivatives etc. These diastereomeric complexes/salts exhibit different physical properties, such as solubility and retention time on column chromatography. Thus, diastereomeric complexes/salts are selectively separated and later, treated with a suitable acid/base to finally provide optically pure organophosphorous compounds. Indeed, the first known example for the obtention of an optically active organophosphorous compound, ethylmethyl phenylphosphine oxide, was based on this concept.[44,111] Ethylmethyl-phenyl oxide **170** was directly resolved into two separable diastereomers using (+)-bromocamphor sulfonic acid by Meisenheimer and Lichtenstadt.

More recently in 2004, Imamoto reported a direct resolution of a very hindered diphosphine oxide **179** using DBTA as resolving agent.[45]
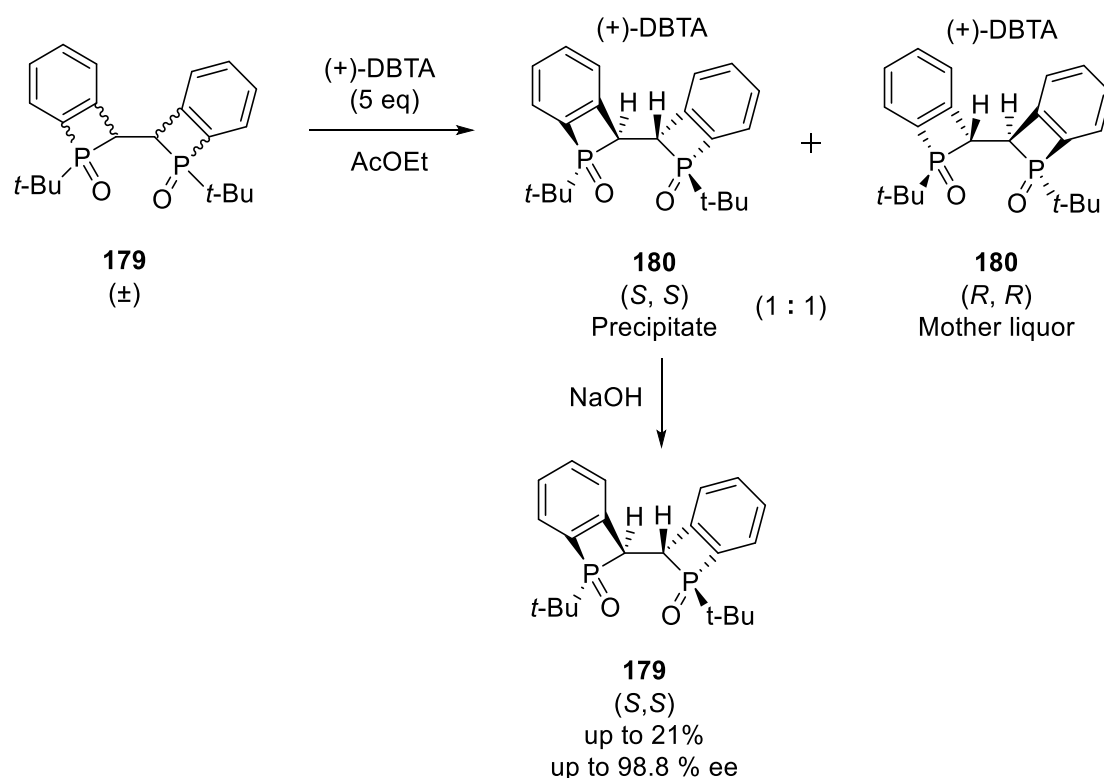
Scheme 45. Direct Resolution of a diphosphine oxide **179** using (+)-DBTA.

They dissolved (+)-DBTA and the corresponding diphosphine oxide **179** in hot ethyl acetate, and on cooling, a precipitated crystalline solid was obtained after filtration. They could obtain the resolved diphosphine oxide **179** (*S*, *S*) with up to 21% yield and with up to 98.8% ee (scheme 45).

In 2007, phosphinous acid boranes **181** have also been directly resolved by using cinchonine **182** as a resolving agent.[191] The corresponding diastereomeric salts (**183**) of phosphinous acid boranes and cinchonine, were obtained with up to 34% yield and with up to 100% optical purity. The salts were subsequently, successfully hydrolysed into the corresponding phosphinous acid boranes **181** with very good yields and retention of its optical purity (scheme 46).
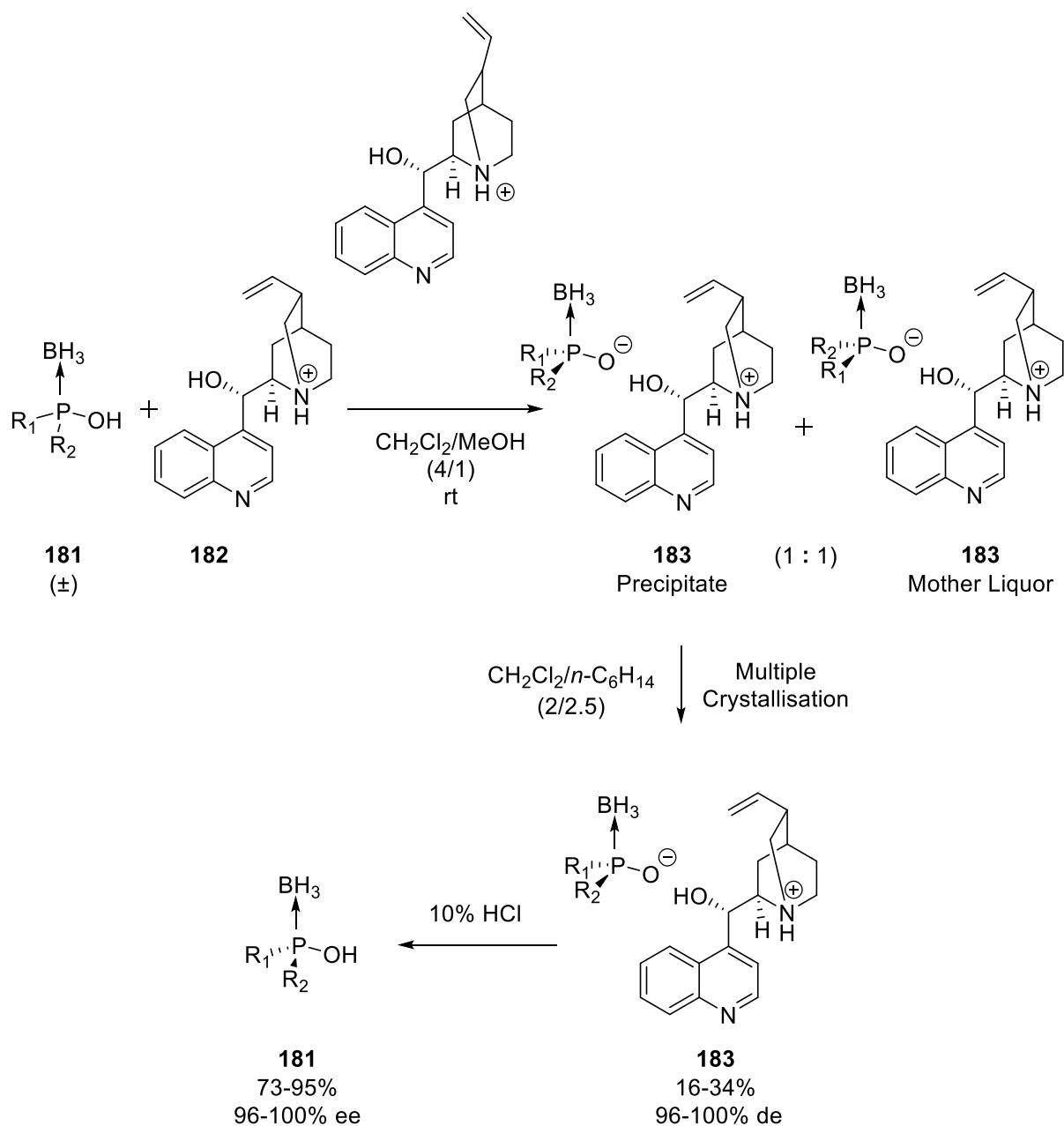
Scheme 46. Direct Resolution of phosphinous acids **181** using (+)-Cinchonine **182**.

3.4.2.2 Chiral Metal Complexes

Chiral metal complexes such as orthometallated palladium complexes are well known as resolving agents for phosphine compounds.[192] For example, palladium complexes with 1-phenylethylamine and 1-naphthylethylamine have been reported to be efficient in resolving some phosphines.[193,194] The basic principle is simple; the racemic phosphine substrate **185** reacts with the chiral palladium complex **184** to form through coordination of palladium to phosphorus atom the corresponding two diastereomers **186** in 1/1 dr which have different physical properties and thus, can be separated by recrystallisation or column chromatography (scheme 47).
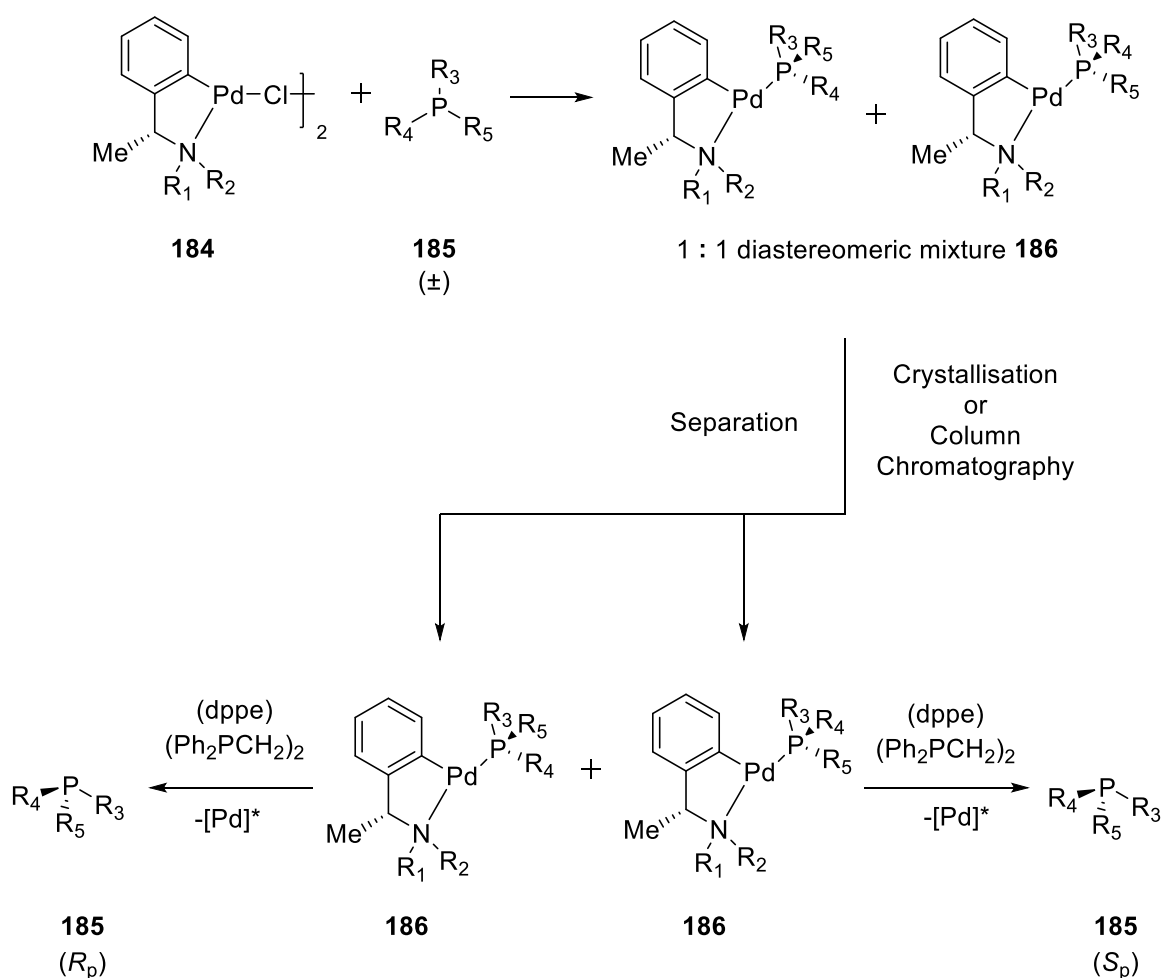
Scheme 47. Resolution of phosphines by orthometallated chiral palladium complexes.

After the separation of the two diastereomers, phosphine is released from the complex by using a strongly coordinating agent such as 1,2-bis(diphenylphosphino)ethane (dppe). Many phosphines have been successfully resolved with this method with high enantioselectivities. Also, the so obtained palladium metallacycles can also be directly used in catalysis, such as in hydrovinylation.[46,48] However, for as successful resolution of phosphines, a matching between the chiral metal complex and the phosphine is required, which can be a tedious process.

3.4.2.3 Chiral Column Chromatography

This technique of resolution utilises a chiral stationary phase which selectively interacts with the two enantiomers of the P-stereogenic compound and thus directly provides an access to both enantiomers of a P-stereogenic compound. Generally, P(V) compounds are utilised with this methodology to avoid any possibility of racemisation process that can occur with P(III) compounds.[49,195–197] This chiral column chromatography technique generally requires use of a large amount of solvent during the separation of enantiomers of a compound and use of a chiral preparative column. However, many organophosphorous compounds have been resolved using this technique in particular, using commercially available chiral columns (fig. 19).[106,198–202]
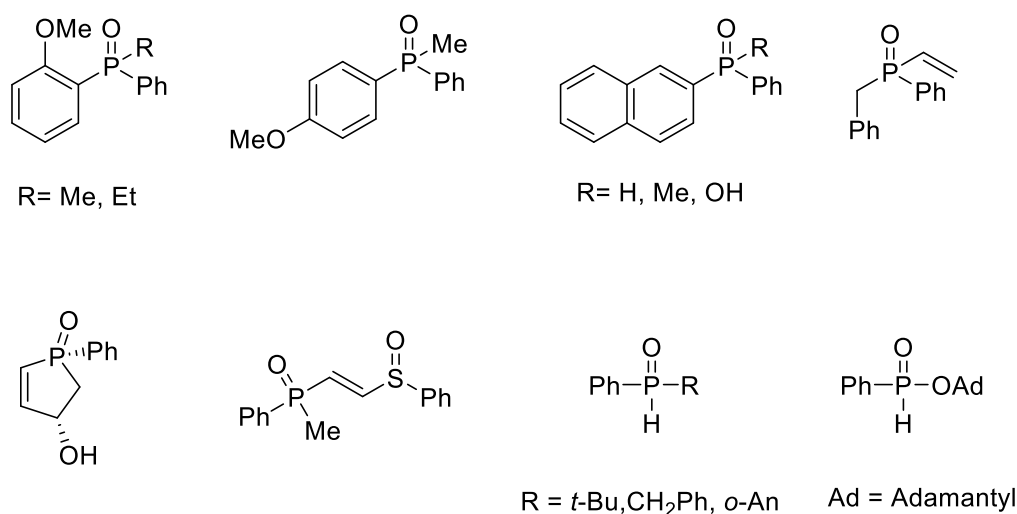
Fig. 19. Representative examples of organophosphorous compounds resolved by chiral column chromatography.

3.4.3 Chiral Auxiliary Method: formation of a covalent bond with a chiral auxiliary and post-functionalisation

Chiral auxiliary based synthesis is one of the most widely used methodologies to prepare P-stereogenic organophosphorous compounds, both on laboratory scale, as well as on industrial scale. Indeed, the first practical synthesis of P-stereogenic organophosphorous compounds by Mislow, was based on this concept.[104,187] Using this concept, a chiral auxiliary is employed in stoichiometric amount, which reacts with a racemic organophosphorous compound to form the corresponding two diastereomers by formation of a covalent bond and thus, inducing chirality on P-atom. These diastereomers on the basis of differences in their physical properties, are then separated by column chromatography or recrystallisation techniques, and later, the chiral auxiliary is cleaved by using a suitable organometallic reagent, often Grignard / lithium reagents, thus delivering the enantiopure organophosphorous compound with a new P-C bond formation. The most popular chiral auxiliaries used for the synthesis of P-stereogenic organophosphorous compounds include menthol and ephedrine.[143,162–165]

3.4.3.1 Menthol as a chiral auxiliary

L-menthol is a classical chiral auxiliary used for the synthesis of P-stereogenic organophosphorous compounds. It serves as a cheap and easily available chiral auxiliary. This section describes the synthesis of P-stereogenic compounds, such as menthylphosphinates, menthylphosphinite-boranes, H-menthylphosphinates/H-menthylphosphinite-boranes.

3.4.3.1.1 Menthylphosphinates

Mislow and Cram first reported the pioneering and practical syntheses of P-stereogenic organophosphorous compounds using menthol (scheme 48).[104,187,203] The unsymmetrically substituted two diastereomers of menthylphosphinates **191** can be separated by recrystallisation. Usually, one of the diastereomers is obtained by recrystallisation, while other one remains in mother liquor. In many cases, the crystallisation process can be troublesome multi-step procedure, yielding the diastereopure menthylphosphinates in very low yields.

Scheme 48. Synthesis of menthylphosphinates by Mislow.

After obtaining diastereopure menthylphosphinates, a range of optically active phosphine oxides can be prepared by stereospecific nucleophilic substitution reaction of menthylphosphinates using Grignard's or lithium reagents. This reaction often proceeds with inversion of configuration at phosphorous atom. With this strategy Horner and others succeeded to prepare some other menthylphosphinates.[59,60] Indeed, Knowles used this concept to prepare the pioneering P-stereogenic ligand, DiPAMP 17 (scheme 49).[63,204]

PhMgBr (4-5 eq)
benzene
reflux, 18 h

Crystallisation
in hexane

191
S_p

40
R_p

LDA (1.2 eq)
CuCl$_2$ (0.2 eq)

THF
0-25 °C, 2-3 h

HSiCl$_3$ (5.8-6 eq)
(*n*-Bu)$_3$N (7 eq)

CH$_3$CN
65-70 °C

193

17
(*R,R*-DiPAMP)

Scheme 49. Synthesis of DiPAMP by Knowles.

This nucleophilic substitution reaction of menthylphosphinates with Grignard or lithium reagents requires higher temperature and excess of Grignard or lithium reagents. Also, the stereoselectivity of this step depends on the substituents attached to P atom and the reaction conditions, such as temperature, reagents etc. However, due to the cheap and easily accessible menthol as chiral auxiliary, a large number of menthylphosphinates and their derivatives have been prepared using this concept.

Imamoto reported a reductive stereoselective method to remove menthyl group at phosphorous atom, while preserving the configuration at phosphorous atom. They found that lithium 4,4-di-*tert*-butyldiphenylide (LDBB), a one electron reducing agent, was able to generate the anionic phosphorus species at 0 °C, which reacted with alkyl halide at the same temperature (scheme 50).[205,206]

1. *sec*-BuLi
-78 °C

2. CuCl$_2$
-78 to 0 °C

191
R_p

194
(R_p,R_p)

1. LDBB (4 eq)
0 °C, 40 min

2. MeI
(excess)

195
(*R,R*)
29-54%
95-98% optical purity
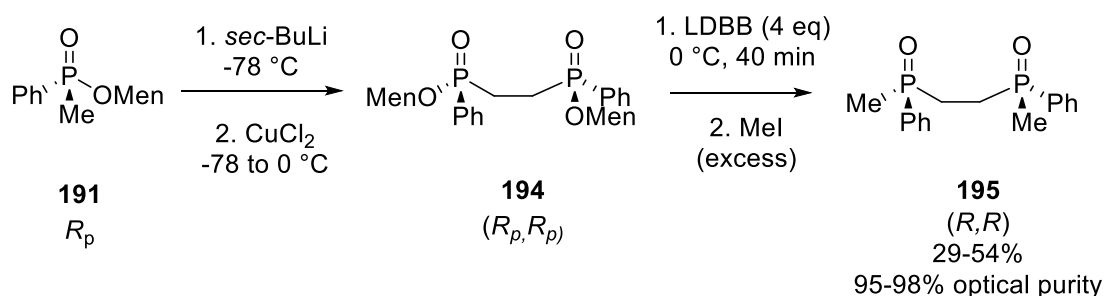
Scheme 50. Imamoto's strategy for removal of menthyl group .

3.4.3.1.2 Menthylphosphinite boranes

Since the 1985ah, the use of menthylphosphinite boranes has exceeded the use of menthylphosphinates.[47,86,118,207,211,212,424,425] Scheme 51 represents the general procedures for borane protection for tertiary phosphine oxides **28** and chlorophosphines **32**.
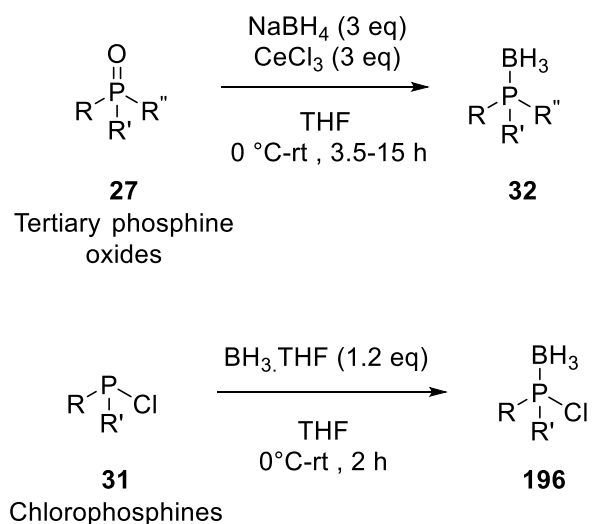
Scheme 51. General procedures for borane protection for tertiary phosphine oxides and chlorophosphines.

The authors described the importance of $CeCl_3$ for the borane protection of tertiary phosphine oxides as, no reaction was observed in the absence of $CeCl_3$. It was assumed that $CeCl_3$ activated both phosphine oxide, as well as $NaBH_4$ through its coordination properties.

In a typical synthetic procedure for menthylphosphinates, Imamoto et al. replaced phosphine oxide with phosphine-boranes as shown in the following scheme 52. [207,211]
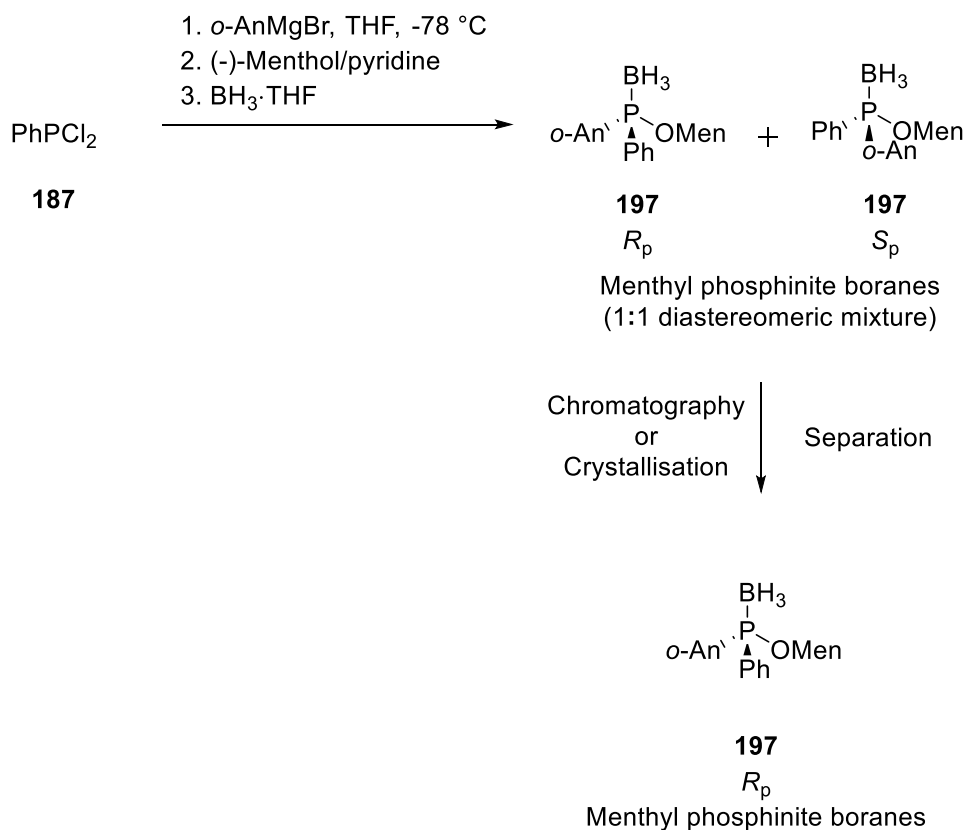
Scheme 52. Synthesis of menthylphosphinite boranes.

These menthylphosphinite boranes are generally crystalline, resistant to racemisation, easy to handle and do not necessarily require handling under inert atmosphere. Moreover, the borane group from phosphine boranes can easily be removed under mild conditions.[73,207,213–218] Imamoto used this menthylphosphinite boranes strategy to prepare DiPAMP ligand as well (scheme 53).[207]
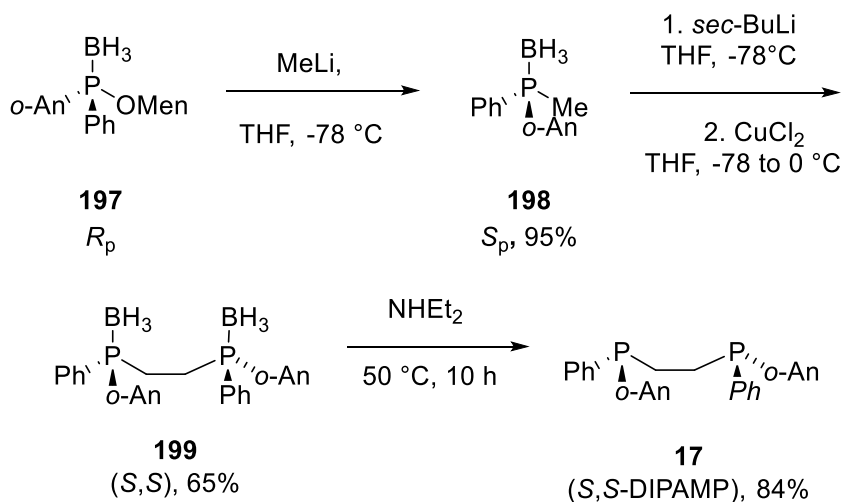
Scheme 53. Synthesis of DiPAMP using menthylphosphinite-borane strategy.

3.4.3.1.3 H-menthylphosphinates / H-menthylphosphinite-boranes

H-menthylphosphinates serve as cheap and classical P-stereogenic precursors for the preparation of complex P-stereogenic compounds. In 1968, Letsinger and co-workers reported the synthesis of H-menthylphosphinates.[112] Unfortunately, they could not separate the mixture of two diastereomers.[87] However, Mislow and co-workers in 1970, were able to obtain H-menthylphosphinates **200** with high diastereomeric excess of up to 90% to 98% after fractional crystallisation of diastereomeric mixture of H-menthylphosphinates, but without mentioning the yield in their report (scheme 54).[87]

PhPCl$_2$

187

1. (-)-Menthol
   pyridine benzene or ether
2. H$_2$O, -78 °C

3. Multiple re-crystallisation
   at -78 /-30 °C

$$\underset{H}{\overset{O}{\underset{\|}{Ph\cdots P\cdots OMen}}}$$

200

R_p

90% to 98% de
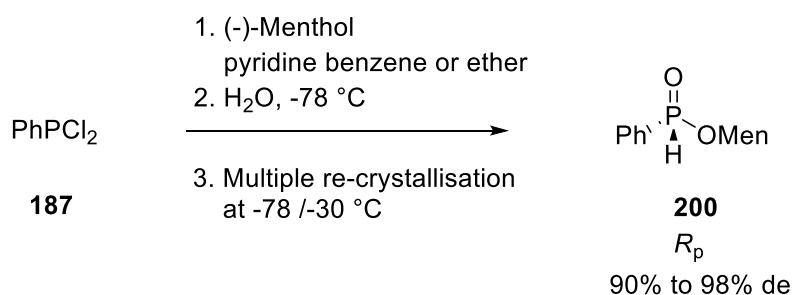
Scheme 54. Preparation of H-menthylphosphinates **200** by Mislow and co-workers.

Hammer and co-workers were able to separate mixture of two diastereomers of H-menthylphosphinates using a chiral HPLC method.[219] Han and co-workers have been utilising H-menthylphosphinates as the P-stereogenic precursors for preparation of complex P-stereogenic organophosphorous compounds.[10,80,220–222] In 2015, they described a detail procedure for the synthesis of H-menthylphosphinates **200** and the crystallisation procedure with good yield and with an excellent diastereomeric excess (scheme 55).[223]
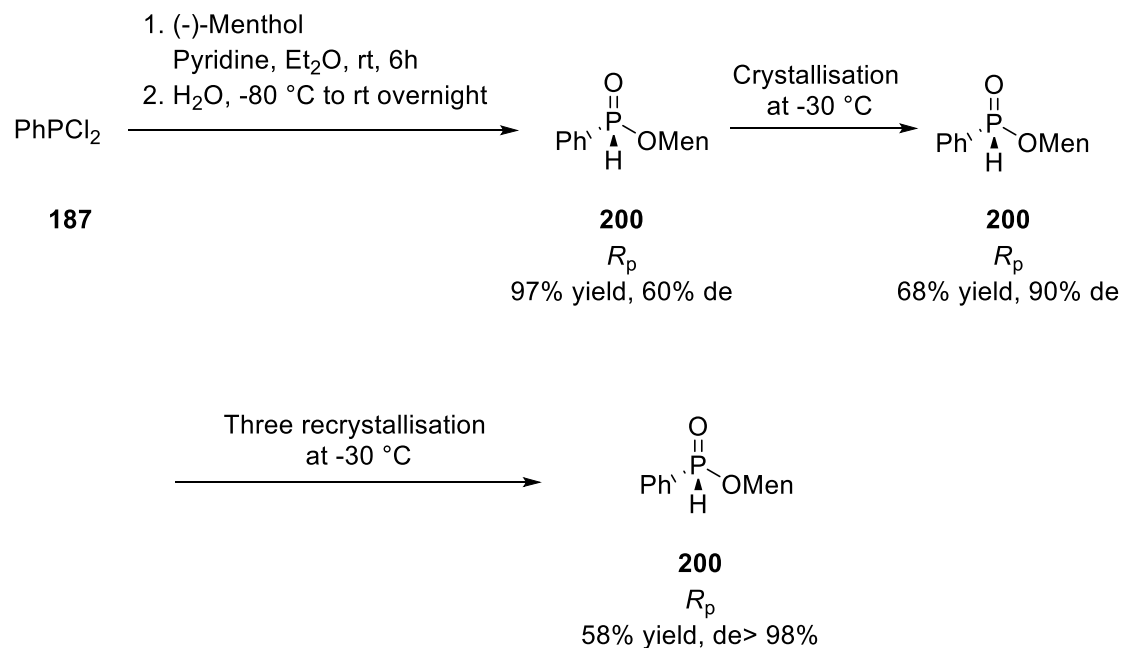
Scheme 55. Detailed procedure for preparation of H-menthylphosphinates described by Han and co-workers.

Recently, Montchamp et al. reported with an excellent diastereomeric excess a variant synthesis of (hydroxymethyl)-H-menthylphosphinates **202** on multigram scale, starting from hypophosphorous, formaldehyde and L-menthol (scheme 56).[224]
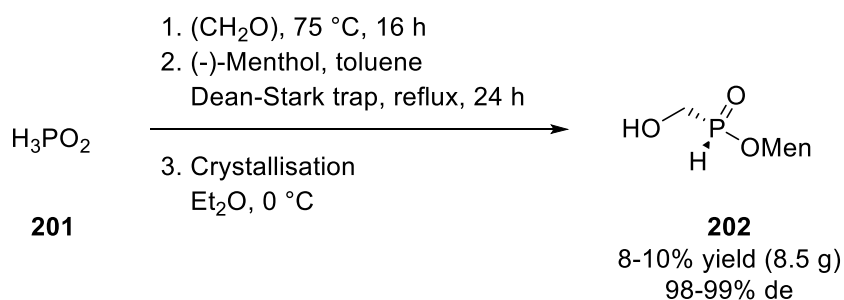
Scheme 56. Synthesis of (hydroxymethyl)-H-phosphinates **202** by Montchamp et al.

They demonstrated that this reagent, (hydroxymethyl)-H-menthylphosphinates **202**, can be converted into various menthyl phosphinate derivatives via undergoing many useful reactions, such as sila-Arbuzov alkylation, palladium-catalysed cross-coupling, and manganese catalysed / promoted radical hydrophosphinylation / arylation.

Today, H-menthylphosphinates and H-menthylphosphinite-boranes are used in preparation of a number of P-stereogenic organophosphorous derivative. Some of the representative examples are provided in scheme 57.[225,226] H-menthylphosphinite-boranes are prepared according to the general preparation of H-menthylphosphinates. These H-menthylphosphinite-boranes (scheme 57) undergo subsequent reaction with methyl iodide and sodium hydride to provide menthyl methylphenylphosphinite borane **233** with 100% diastereomeric excess.[80] Under palladium catalysed reaction, H-menthylphosphinite-boranes undergo coupling reaction either with retention or inversion at phosphorous atom, depending on the use of solvent.[225,226] Menthylphosphinites were also used to prepare P-stereogenic ligands such as DiPAMP by Imamoto et al.[207]
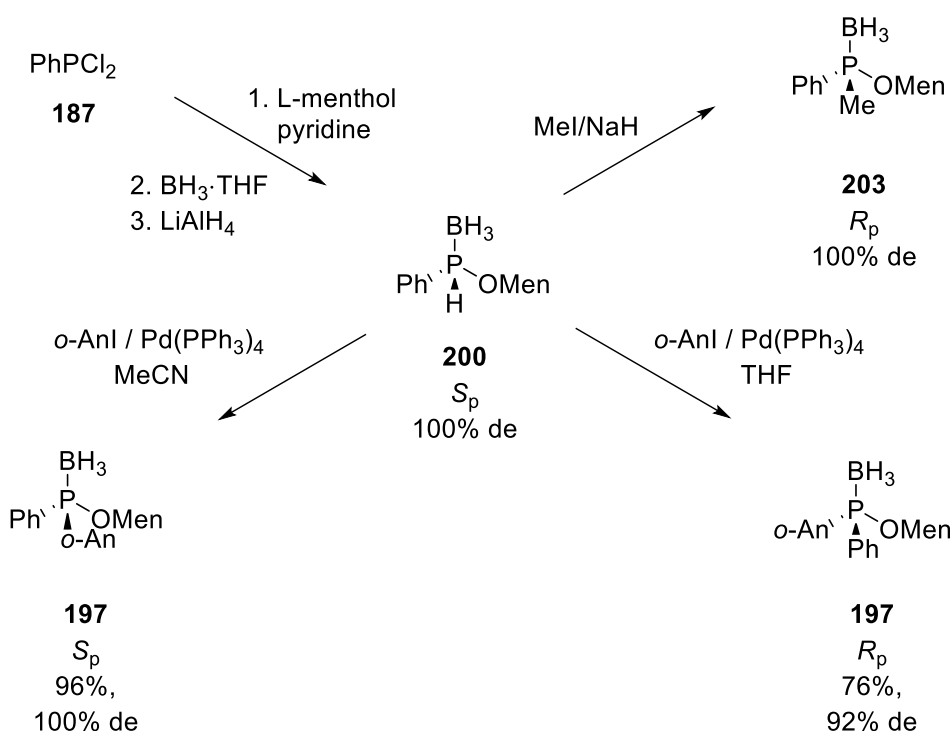
Scheme 57. Synthesis of menthyl H-phosphinite-boranes and their subsequent reactions.

Thus, L-menthol is a classical chiral auxiliary for the synthesis of P-stereogenic compounds. It serves as a cheap and easily available chiral auxiliary. However, using this menthol-based methodology usually one of the diastereomers of menthylphosphinate is obtained by recrystallisation while other one remains in the mother liquor. And, in many cases, the crystallisation process can be a troublesome multi-step procedure, yielding the diastereomerically pure menthylphosphinates in a very low yield.

3.4.4 Optically Active Amines

Some of the optically active amines are useful chiral auxiliaries for preparation of P-stereogenic organophosphorous compounds.[227,228] Chiral amines, such as amino acid esters and 1-methylbenzylamine undergo N-P coupling reactions with asymmetric chlorophosphine and chlorophosphine oxides to form chiral aminophosphines as a mixture of diastereomers with high diastereomeric excess of up to 80%. These diastereomers can be separated by crystallisation with high diastereomeric purity of up to 100% de. For example, (*S*)-1-methylbenzylamine **204** reacts with unsymmetrically substituted chlorophosphine in the presence of a base to form chiral aminophosphines **205** with good yields of up to 80% and high diastereomeric excess of up to 80% (scheme 58).[227] The aminophosphines **205** are then

204
(±)

205
75-80%
up to 80% de
(diastereomeric mixture)
(R_pS + S_pS)

206
Quantitative
(diastereomeric mixture)
(R_pS + S_pS)

Separation
(crystallisation in hexane)

Borane deprotection
(Et$_2$NH)

205
R_pS, 100% de

206
Major diastereomer
R_pS, 100% de
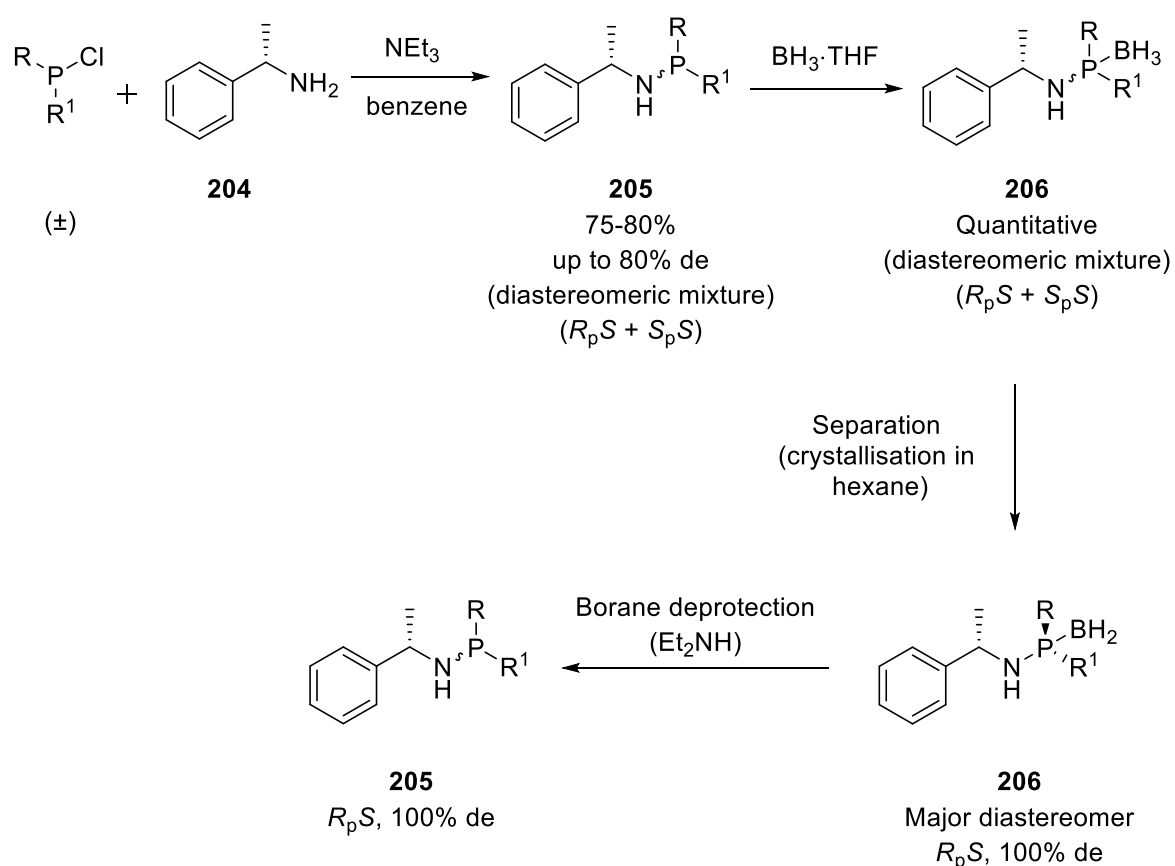
Scheme 58. Synthesis of chiral aminophosphines.

protected with borane group to form crystalline solid aminophosphines boranes **206**, which are crystallised in hexane to obtain the diastereomerically pure product. Moreover, the borane group is easily removed from the aminophosphines boranes using diethylamine as a base, with almost complete retention of stereoselectivity.

These aminophosphines serve as P-stereogenic precursors to undergo various reactions (scheme 59). The Aminophosphine **205** reacts with methanol to provide enantiopure methyl (*S*)-(−)-*tert*-butylphenylphosphinate **208**. On hydrolysis, aminophoshine **205** gives enantiopure (*S*)-*tert*-butyl(phenyl)phosphine oxide **207**. The oxidation of aminophoshine **205** takes place stereospecifically to afford the corresponding aminophoshine oxide **209**. In thiophination reaction of aminophosphine **205**, diastereomerically pure thioaminophosphine **210** is obtained.

207 (R= Ph, R^1= *t*Bu)
S_p

HCOOH

MeOH

208 (R= Ph, R^1= *t*Bu)
S_p

H$_2$O$_2$

205
R_pS

S$_8$

209 (R= Ph, R^1= *t*Bu)
S_pS

210 (R= Ph, R^1= *t*Bu)
S_pS
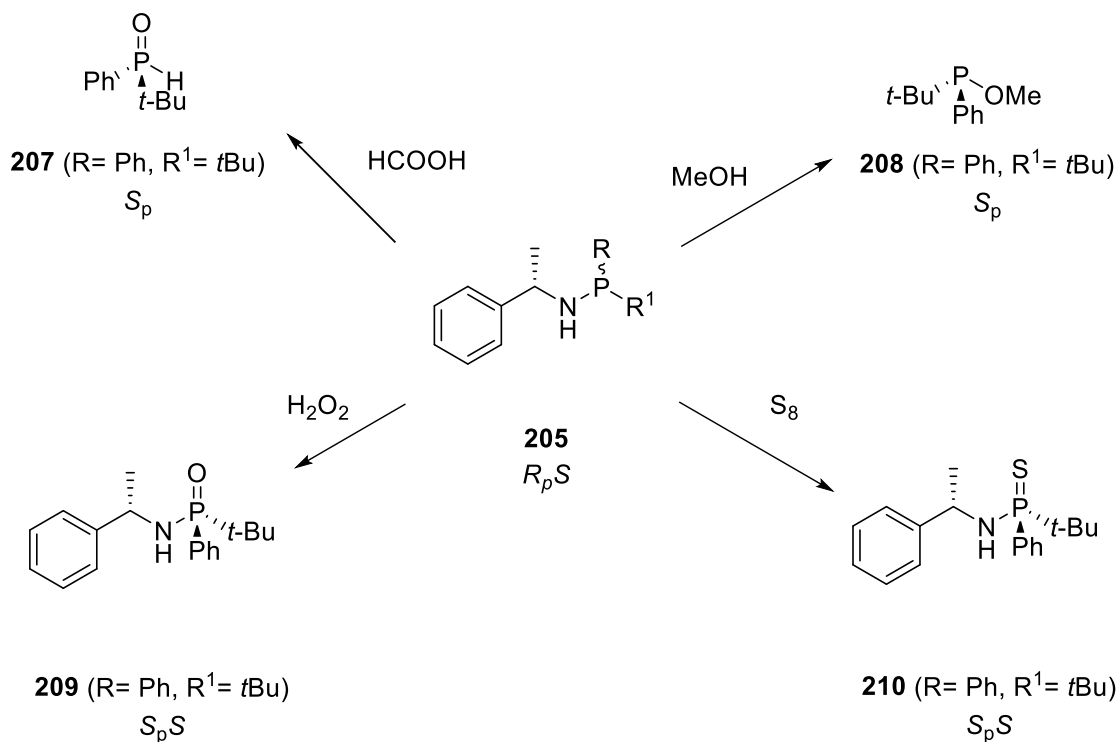
Scheme 59. Representative examples of reactions of chiral aminophosphines.

Chiral aminophosphines with P-stereogenic centre allow further reactivity due to the presence of the amino group. They are used as precursors for the synthesis of new types of ligands possessing N and S atoms with P-centred chirality (scheme 60).[154,156,229,230] Their applications were demonstrated in asymmetric catalytic hydrogenations.
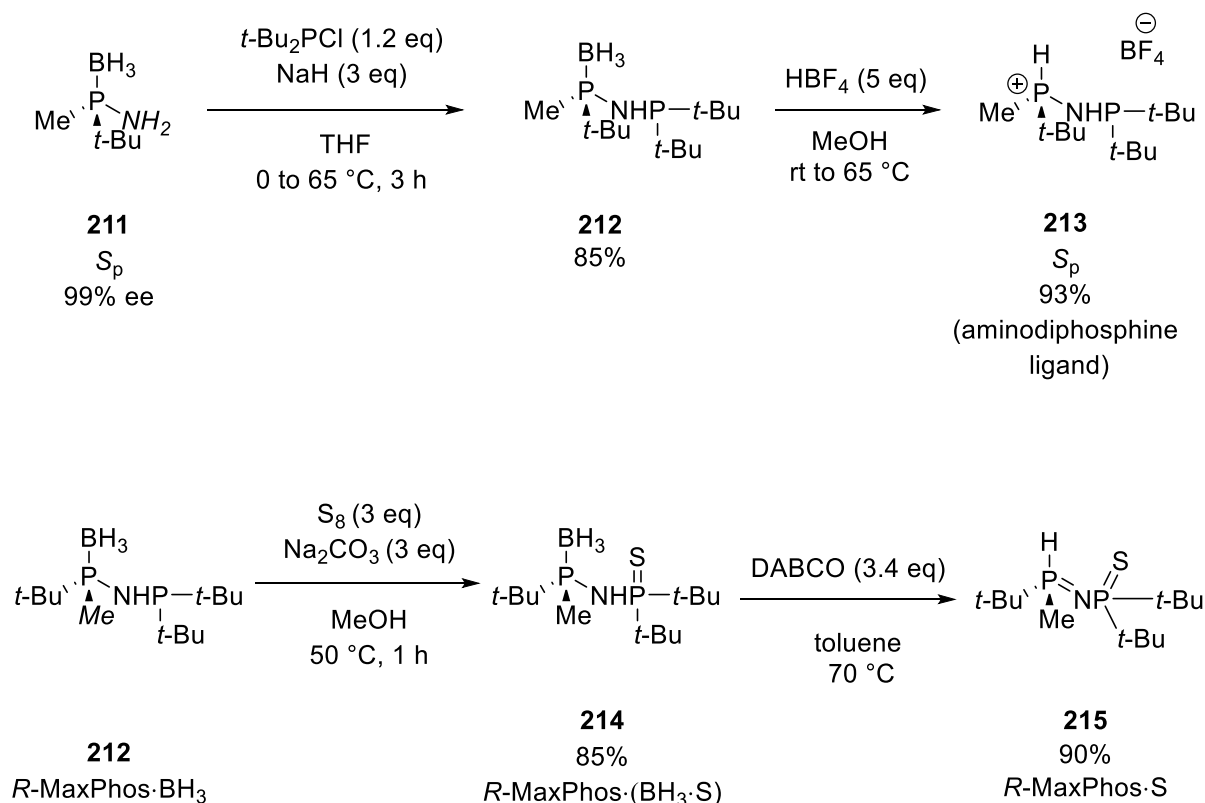
Scheme 60. Synthesis of aminodiphosphine and *R*-MaxPhos·S ligands using aminophosphines.

Chiral oxazolidinones **216** have also been used to prepare several P-stereogenic organophosphorous compounds **218** with good yields and high enantioselectivities (scheme 61).[231]
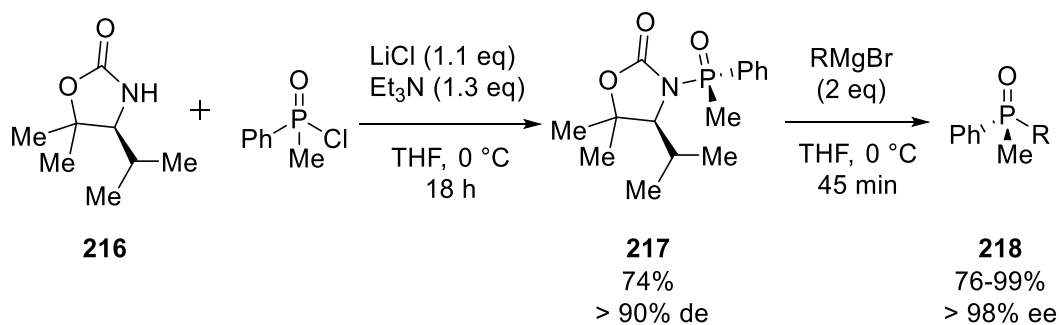
Scheme 61. Synthesis of P-stereogenic phosphine oxides by oxazolidinone method.

In presence of a suitable base and a lithium salt, oxazolidinone **216** undergoes N-phosphorylation using a chlorophosphine oxide to form the corresponding N-phosphinoyl oxazolidinone **217** with a good yield and a high diastereoselectivity. The major diastereomer can be separated by column chromatography or crystallisation. Later, the diastereopure N-phosphinoyl oxazolidinone can be converted into various P-stereogenic phosphine oxides

218. The main step for this methodology relies on the stereoselective formation of N-phosphinoyl oxazolidinone **217**.

Han reported an efficient method for the synthesis of sterically hindered P-stereogenic phosphine oxides based on the formation of a highly diastereoselective benzoxazaphosphinine oxides **220** under mild conditions.[103] These cyclic intermediates, benzoxazaphosphinine oxides **220**, undergo stepwise stereoselective P-N and P-O cleavages using Grignard reagents or alkyl lithium reagents to form the corresponding P-stereogenic phosphine oxides **222** in good yields and high enantioselectivities (scheme 62). Both steps, P-N and P-O cleavages involve inversion of configuration at phosphorous atom.
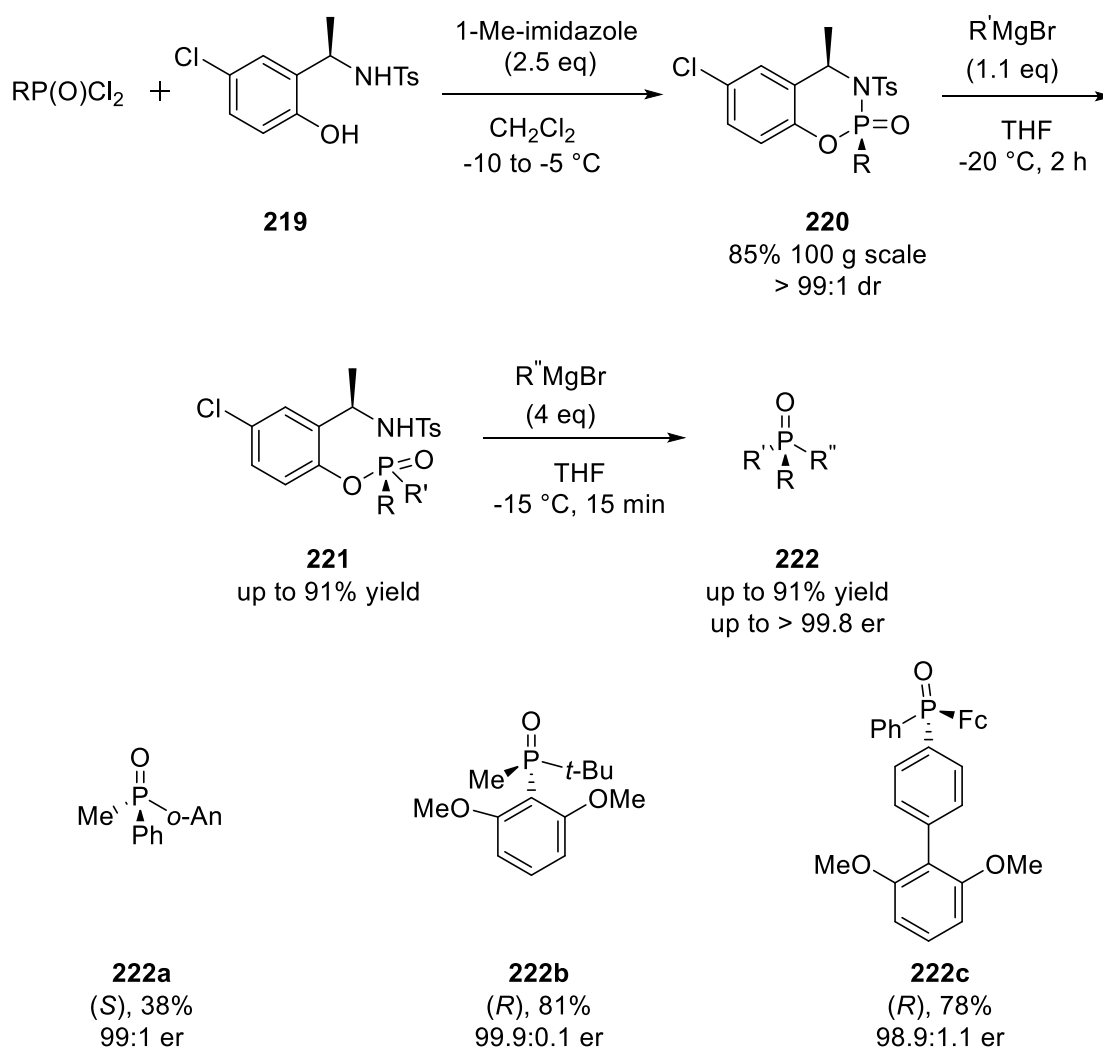
Examples of P-stereogenic phosphine oxides

Scheme 62. Synthesis of P-stereogenic phosphine oxides by Han's strategy .

Recently, Andrioletti et al. reported the enantioselective synthesis of P-stereogenic phosphine oxides using D-glucosamine and 2-aminocyclohexanol scaffolds as chiral auxiliaries.[234,235] As in case of Han's work, their work essentially involves formation of the highly stereoselective cyclic oxazaphospholidines **260**, following two subsequent P-N and P-O cleavages using Grignard or alkyl lithium reagents to form the corresponding P-stereogenic phosphine oxides **262** in good yields and with high enantioselectivities (scheme 63).

N-MeIm = *N*-methylimidazole
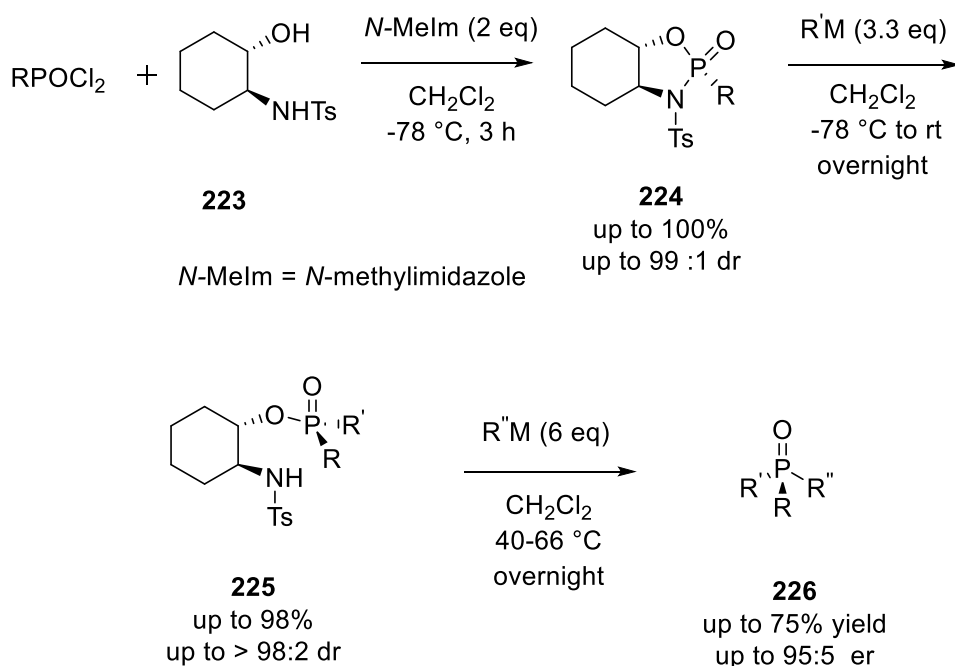
Scheme 63. Synthesis of P-stereogenic phosphine oxides using 2-aminocyclohexanol scaffolds.

Thus, some of the optically active amines are useful chiral auxiliaries for the preparation of P-stereogenic organophosphorous compounds. Also, chiral aminophosphines are used for the preparation of chiral P-N-P ligands.

3.4.5 Ephedrine Method (Jugé Method)

Jugé reported an excellent method to prepare P-stereogenic phosphines based on the use of commercially available cheap chiral auxiliary, ephedrine.[85,85,210,236–240] The principle of his methodology is based on two fundamental steps; first step involves a highly diastereoselective one pot synthesis of oxazaphospholidines boranes **228** by using ephedrine and, the second step involves regio and stereoselective ring opening of oxazaphospholidine boranes **228** to form the compound **229** (scheme 64).

RPN(Met)$_2$

227

1. (-)-ephedrine
toluene
105 °C, 5 h

2. BH$_3$·Me$_2$S
(1 eq)
in Toluene
rt, 4 h

228

oxazaphospholidines
boranes
(*R*$_p$)
up to 84% yield
up to 90% de

1. R'Li (1 or 2 eq)
THF, -78 °C
2. H$_2$O

Retention of
configuration

229

55-96% yield
up to 92 : 8 dr

MeOH/H$^+$
0 °C to rt
over night

inversion of
configuration

230
up to 95%

R"Li (1/2 eq)

inversion of
configuration

231
up to 92%
up to 100% ee

DABCO (4 eq)
toluene, rt
over night

Retention of
configuration

232
(*S*$_p$)
quantitative
83-99% ee

Scheme 64. Synthesis of P-stereogenic phosphines using Jugé method.

Ultimately, the product **229** obtained after the ring opening step of oxazaphospholidine is transformed into several useful P-stereogenic compounds by using suitable nucleophiles or electrophiles. Currently, this method is considered as one of the most efficient methods providing P-stereogenic tertiary phosphines with very high enantioselectivities and with up to 55% overall yield (starting from ephedrine).

The first step involves the highly diastereoselective formation of oxazaphospholidine ring **228** with up to 84% yield and 90% de. There is a *trans* relationship between R group of phosphorous and both Me and Ph substituents of ephedrine at C4 and C5 positions (fig. 20).[209]

228
R, Me (C4) and Ph (C5) are in
trans relation to each other
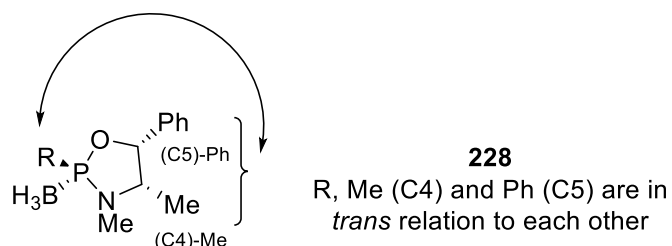
Fig. 20. A *Trans* relationship between R and Me (C4) /Ph (C5) in oxazaphospholidine ring **228**.

The ring opening reaction of oxazaphospholidines **228** proceeds with retention of configuration at P-centre.[208,209] The organometallic reagent attacks on less hindered oxygen atom compared to the more hindered nitrogen having a methyl substituent. Acidic methanolysis of aminophosphine borane **229** occurs under mild conditions with inversion of configuration providing phosphinite borane **230** with a high yield and excellent enantioselectivity. Next, a suitable alkyl lithium reagent reacts with phosphinite borane **231** to form the corresponding tertiary phosphine borane **232** in good yield and with high enantioselectivity (> 90% ee). This step takes place with inversion of configuration at P-centre.[210] After isolating optically pure phosphine borane by recrystallisation, the borane can easily be decomplexed using DABCO or other suitable reagents.[211,214,216,217,242,244] In general, both the enantiomers of P-stereogenic compound can be obtained using (-)-ephedrine or (+)-ephedrine. Moreover, it was reported that by changing the order of the reagents, both enantiomers of P-stereogenic phosphine could also be obtained.[426]

Using ephedrine method, synthesis of optically pure DiPAMP **17** was achieved with a good yield. After the two subsequent P-N and P-O cleavages of oxazaphospholidine boranes **233** with the corresponding alkyl lithium reagents, PAMP-borane **198** was obtained, which underwent copper catalysed homocoupling to form DiPAMP-borane. Finally, borane was decomplexed using DABCO to provide optically pure DiPAMP **17** (scheme 65).
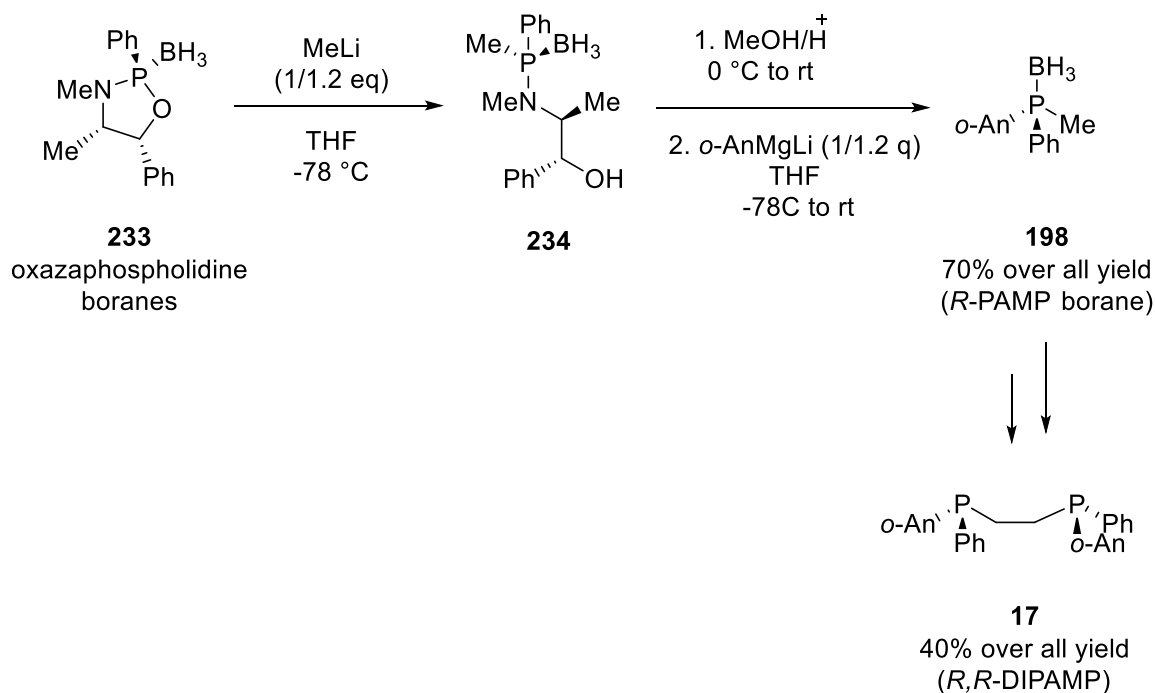
Scheme 65. Synthesis of optically pure DiPAMP **17** using Jugé method.

Ephedrine methodology has been used to synthesise the large bite-angle P-stereogenic diphosphonic ligands supported on the upper rim of calix[4]arene by using two equivalents of oxazaphospholidines borane **233** complex and lithiated calix[4]arene **235** (scheme 66).[246] This reaction takes place regio and stereoselectively by P-O bond cleavage of oxazaphospholidines ring **2633**. Subsequent steps with HCl, organometallic reagent and DABCO afford calix[4]arenyl diphosphine **236**. This calix[4]arenyl diphosphine ligand **236** has been used in Rh catalysed asymmetric hydrogenation of α-acetamidocinnamates to provide phenylalanine derivatives with up to 99% ee.[246]
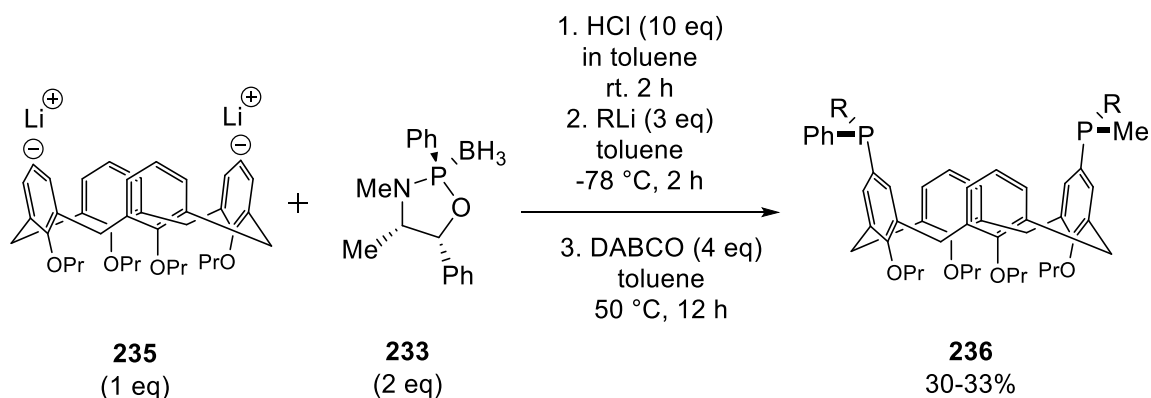
Scheme 66. Synthesis of calix[4]arenyl diphosphine **236**.

Based on ephedrine methodology, in 2013 Bickelhaupt reported an interesting example of stereodivergent ring opening of 2-phenyl oxazaphospholidines **238** with alkyl lithium reagents (scheme 67).[247]
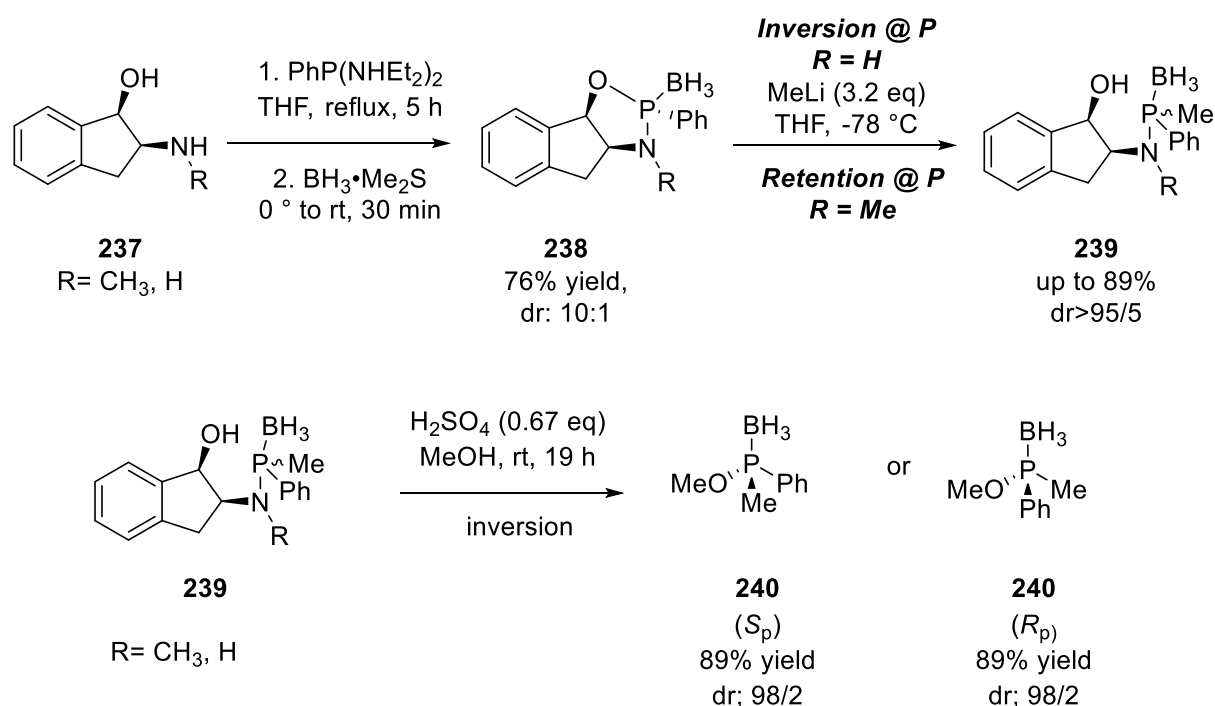
Scheme 67. Synthesis of P-stereogenic compounds using Bickelhaupt' strategy.

The formation of oxazaphospholidine ring takes place with a high stereoselectivity (dr: 10:1) and a good yield (76%). N-H and N-Me oxazaphospholidines **238** undergo highly stereoselective ring opening reactions with alkyl lithium with inversion and retention of configuration at phosphorus centres. Thus, both the enantiomers of corresponding P-stereogenic compound **240** can be obtained with this methodology. The acid catalysed methanolysis finally provides P-stereogenic compound with high yield and excellent diastereoselectivity.

The ephedrine method is considered as one of the most efficient methods to prepare P-stereogenic compounds, providing P-stereogenic tertiary phosphines with very high enantioselectivities and up to 55% over all yield (starting from ephedrine) and therefore, a number of P-stereogenic compounds have been prepared. However, some limitations have been observed. For example, it was observed that oxazaphospholidine borane complex **228** of ephedrine did not undergo ring opening reaction (P-O bond cleavage) with *o,o'*-disubstituted aryl lithium reagents (scheme 68).[240]
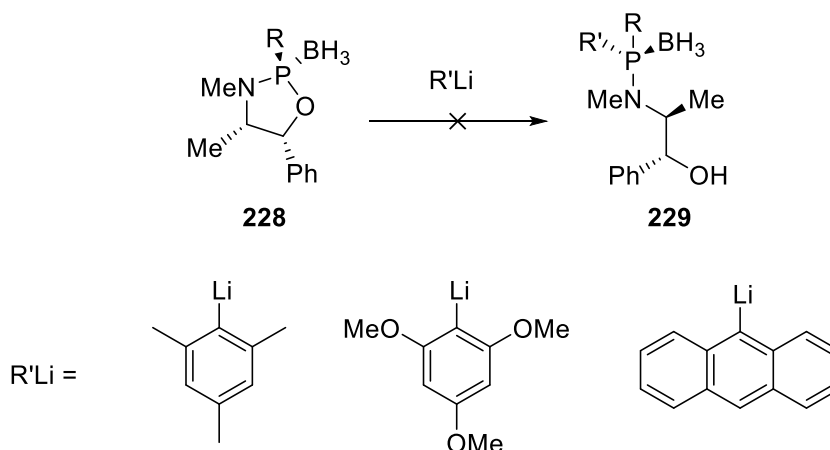
Scheme 68. Unsuccessful attempt to cleave oxazaphospholidine borane complex of ephedrine with *o,o*-disubstituted aryl lithium reagents

Acidic methanolysis of aminophosphine borane generally occurs under mild conditions. But, it was found that when aminophosphine boranes with *tert*-butyl substituent attached to phosphorous atom **241** subjected to this step, methanolysis did not take place (scheme 69).[249]
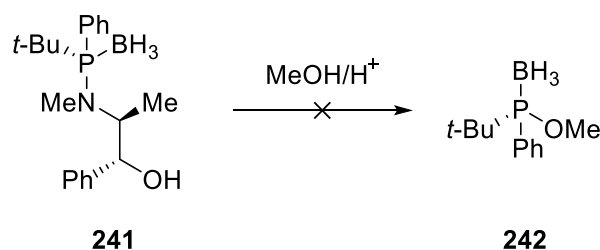
Scheme 69. Unsuccessful attempt-acidic methanolysis of aminophosphine borane.

Also, resistance to reactivity of alkylarylmethoxy phosphane borane **230** complex towards soft nucleophiles for example, cyclopentadienyl anion and phenates/phenolates (salts of phenols for example, sodium phenoxide) creates another limitation. In order to overcome this limitation, use of more reactive chlorophosphine boranes has been reported.[84,208,216,250] Chlorophosphines in general, are prone to racemisation under ambient conditions.[84,251–253] However, chlorophosphines in coordination with borane group are configurationally more stable, but their reactivity is similar to that of parent chlorophosphines.[208]

The chlorophosphine boranes **244** are easily obtained using ephedrine methodology by acidolysis of aminophosphine boranes (R = phenyl) **233** with a toluene solution of HCl, cleaving P-N bond with inversion of configuration at phosphorous atom (scheme 70).[208,216,238,244] The success of acidolysis step depends upon the steric hinderance of the

substituents at phosphorous atom, concentration of reagents, amount of HCl and the reaction time. For example, on changing substituents from methyl to naphthyl at phosphorous atom, the yield of the reaction gets lower, while no reaction take place with the bulkier substituents, such as *tert*-butyl. The best results are obtained when chlorophosphine boranes are prepared in situ and handled under inert atmosphere.

243
Aminophosphine from
(-)-ephedrine

244
Chlorophosphine
borane
up to 99% yield
up to 99% ee

245
Tertiary phosphine
boranes
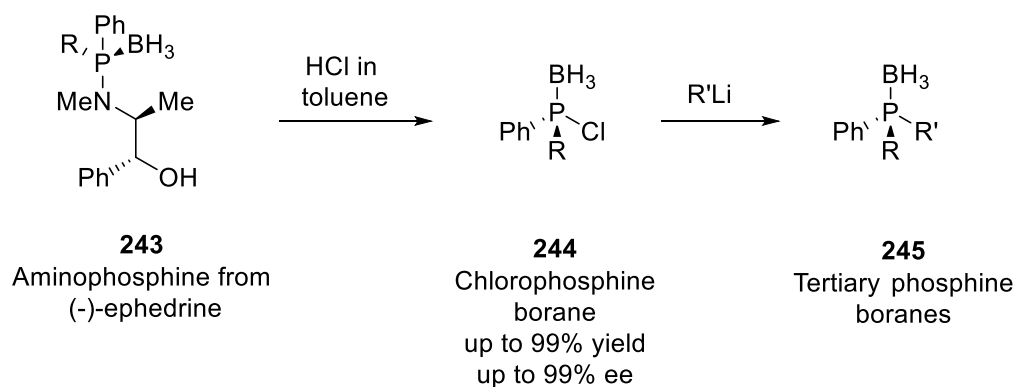
Scheme 70. Synthesis of chlorophosphine borane from ephedrine-method.

The chlorophosphine boranes **244** are efficient P-stereogenic precursors to prepare a number of useful P-stereogenic compounds. They undergo nucleophilic substitution reactions with carbanions, phenoxides, phenylthiolates or amides to afford the corresponding P-stereogenic compounds (scheme 71).[208,237,254]

246
(S_p)
87%
60% ee

247
R= alkyl, ary
70-80%
80-99% ee

244
(R_p)
R'= *n*-alkyl,*t*-Bu, Ar

248
R= alkyl, aryl
53-75%
98-99% ee

249
R' = Me, *o*-An
55-99%
87-99% ee
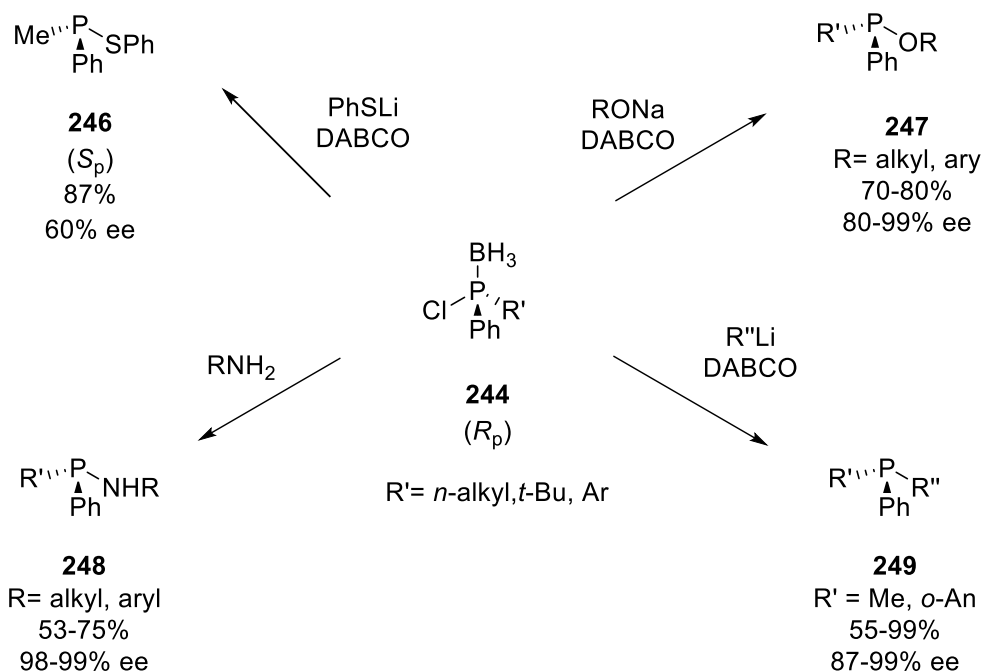
Scheme 71. Chlorophosphine boranes as P-stereogenic precursor.

74

An unusual result was reported by Jugé et al. (scheme 72) when *tert*-butyl lithium was added to the chlorophosphine borane **244** in toluene at -85 °C, metal-halide exchange took place in the formation of the corresponding P-stereogenic phosphide borane **250**.[237] This phosphide borane **250** was later, converted to the corresponding P-stereogenic phosphine borane **251** by addition of THF, followed by addition of an alkyl halide. These phosphine boranes **251** were obtained in good yield of up to 75% and with a high enantioselectivity of up to 99% ee.

$$
\begin{array}{ccccc}
& & & & BH_3 \\
BH_3 & t\text{-BuLi (3 eq)} & BH_3 & RX \text{ (excess)} & | \\
| & \longrightarrow & \ominus\ | & \longrightarrow & P \\
C & & P & & R \diagdown | \diagdown R' \\
Cl \diagup | \diagdown R' & \text{toluene} & \diagup | \diagdown R' & \text{THF} & Ph \\
Ph & -85\ ^\circ C & Ph & & \\
\mathbf{244} & \text{Retention@ P} & \mathbf{250} & & \mathbf{251}
\end{array}
$$

BH₃ / C / Cl, Ph, R' — **244**

t-BuLi (3 eq), toluene, -85 °C, Retention@ P

BH₃ / P⁻ / Ph, R' — **250**

RX (excess), THF

BH₃ / P / R, Ph, R' — **251**
up to 75% yield
up to 99% ee
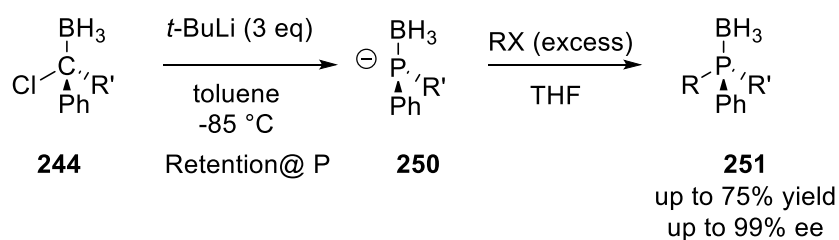
Scheme 72. The unusual reaction of chlorophosphine boranes **244** with *t*-BuLi.

3.4.6 Deracemisation Using Sparteine

3.4.6.1 Historical Background

The initial reports by Mislow and co-workers on the acidic character and the stereoselective deprotonation of methyl protons of methylphosphine oxides led to the current strategy for the preparation of P-stereogenic compounds by enantioselective deprotonation of methyl protons of alkyl or aryl dimethyl phosphine boranes.[104,204] In 1985/1990, Imamoto et al. reported that dimethylphosphine boranes could be easily deprotonated by a strong base,[207,211] the borane group attached to the phosphorous atom activating the methyl protons. Next, in 1995, Evans and co-workers used alky lithium reagents and (-)-sparteine as a chiral auxiliary for the enantioselective deprotonation of aryldimethyl phosphine boranes **252** (scheme 73).[255] This combination of using alkyl lithium reagents   and (-)-sparteine, provides a chiral environment for enantioselective deprotonation of the methyl protons, yielding a stereogenic α-carbanion **253** which can either react with an electrophile or undergo a homocoupling reaction in presence of a copper salt.[256,257]

BH$_3$
|
R ⸍P⸍ Me
  |
  Me

252
(±)

sec-BuLi
(-)-sparteine

Et$_2$O, -78°C

→

BH$_3$
|
R ⸍P⸍ CH$_2$Li
  |
  Me

253

⊕
E, THF
-20 °C
or

Cu(II)
THF

→

BH$_3$
|
R ⸍P⸍ CH$_2$E
  |
  Me

254
up to 84% yield
up to 87% de

or

BH$_3$ BH$_3$
| |
R ⸍P⸍ CH$_2$ ⸍P⸍ Me
  | |
  Me   R

255
up to 58.9% yield
up to 99% de
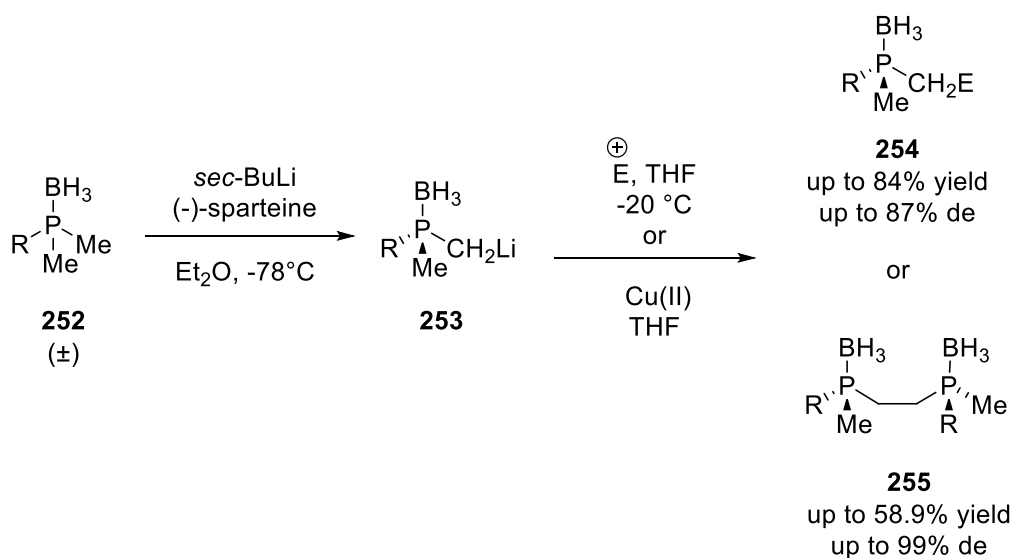
Scheme 73. Enantioselective deprotonation of methyl protons by *sec*-BuLi and (-)-sparteine.

3.4.6.2 Principal

Alkyl lithium reagents, such as *n*-BuLi and (-)-sparteine, can enantioselectivity deprotonate one of the methyl groups of alkyldimethyl phosphine boranes **252** to form the corresponding α-carbanion **253** , which can either react with an electrophile or undergo a homocoupling reaction catalysed by a copper salt (scheme 73).[255]

With this methodology, P-stereogenic compounds are obtained in good yields and with up to very high enantioselectivities.[256,257] Today, numerous P-stereogenic phosphines and diphosphines have been prepared by this methodology with good yields and high enatioselectivities (scheme 74).[162,163,168,207,218,240,245,255,258–261]
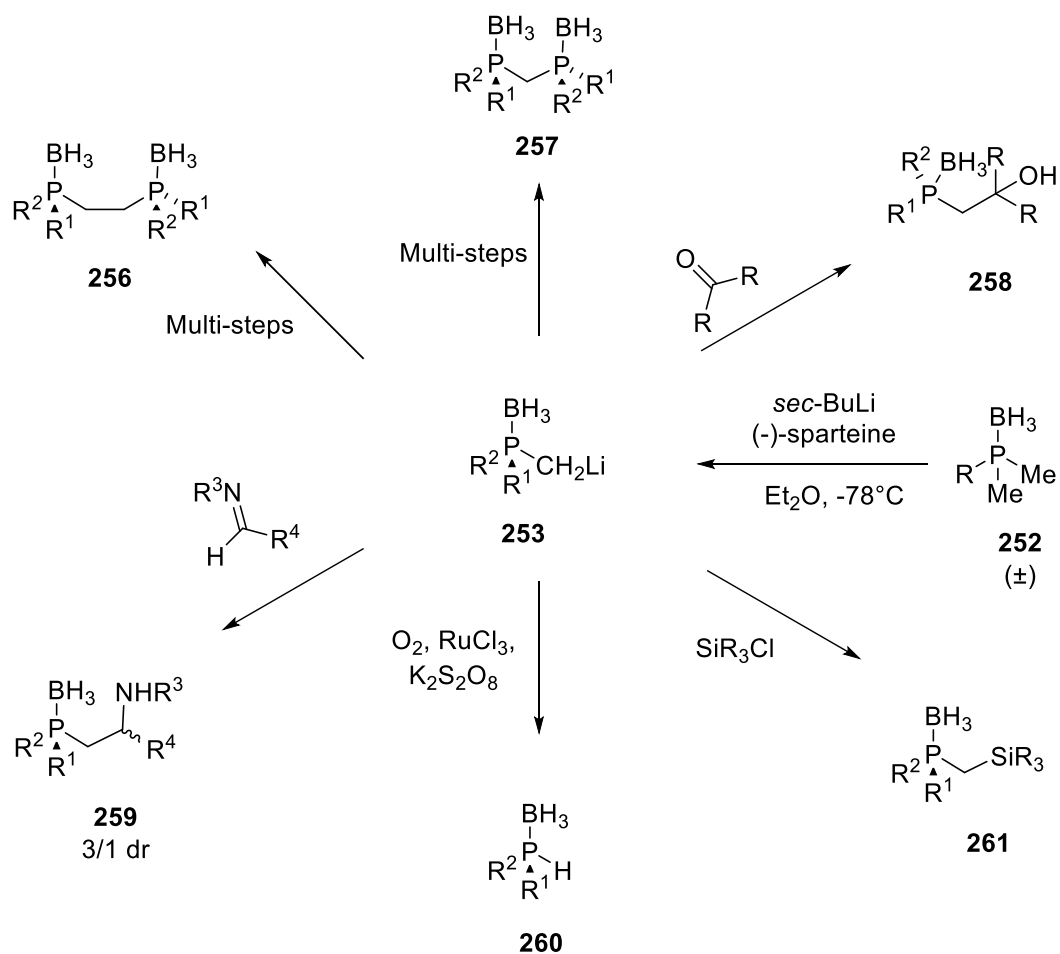
Scheme 74. Access to various P-stereogenic compounds using sparteine based methodology.

Using sparteine based methodology, Imamoto et al. also prepared an electron rich trialkyl-based diphosphonine ligand, called BisP* **99**, containing one bulky group, *tert*-butyl and a small group, methyl, attached to each phosphorous atom (scheme 75).[162] This biphosphine ligand BisP* **99** was obtained in high enantiomeric excess and good yields. This ligand BisP* **99** forms a rigid complex with the transition metal thus, creating a chiral environment around the metal centre. Using BisP*/Ru complex, many asymmetric catalytic reactions have been reported such as asymmetric reduction of β-ketoesters with very high enantioselectivities (up to 98%) and asymmetric hydrogenation of dehydroamino acid derivatives.[162,166]
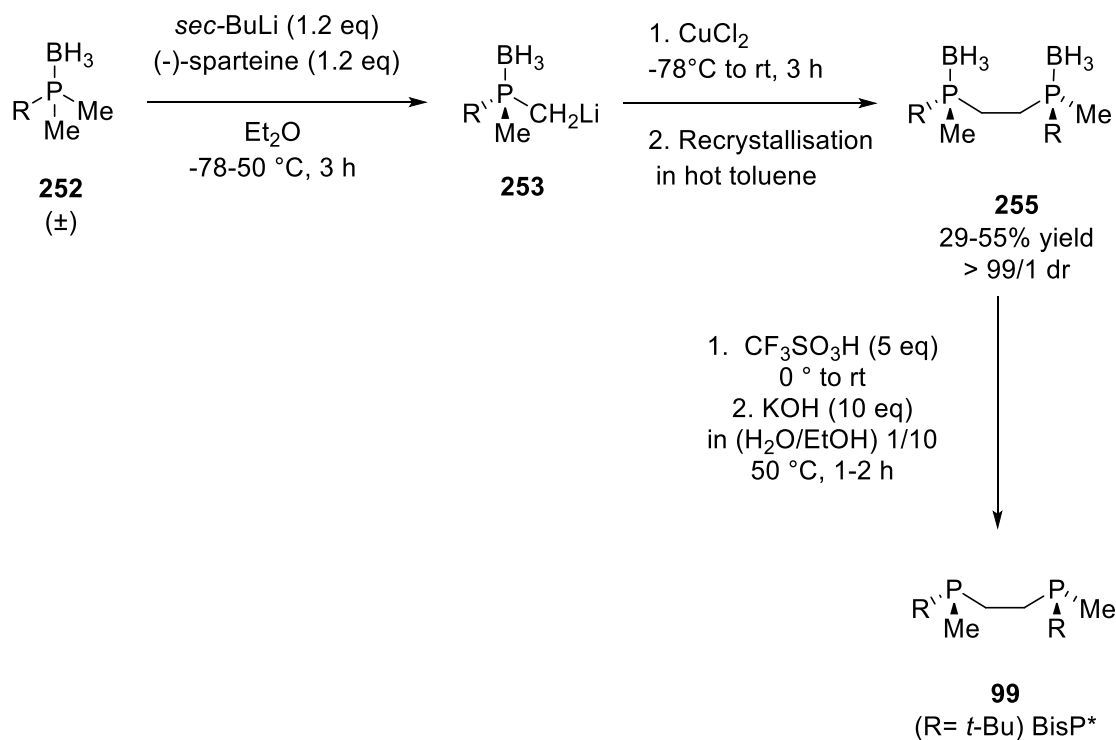
Scheme 75. Synthesis of BisP* ligand using sparteine based methodology.

Also, using the similar strategy, Imamoto et al. prepared another diphosphine ligand with methylene bridged, MiniPhos **100** (scheme 76).[163] This ligand has been used in several transition metal catalysed asymmetric reactions, such as efficient asymmetric hydrogenation of dehydroamino acids and their derivatives using Rh/MiniPhos catalyst with very high enantioselectivities and very good yields.[163]
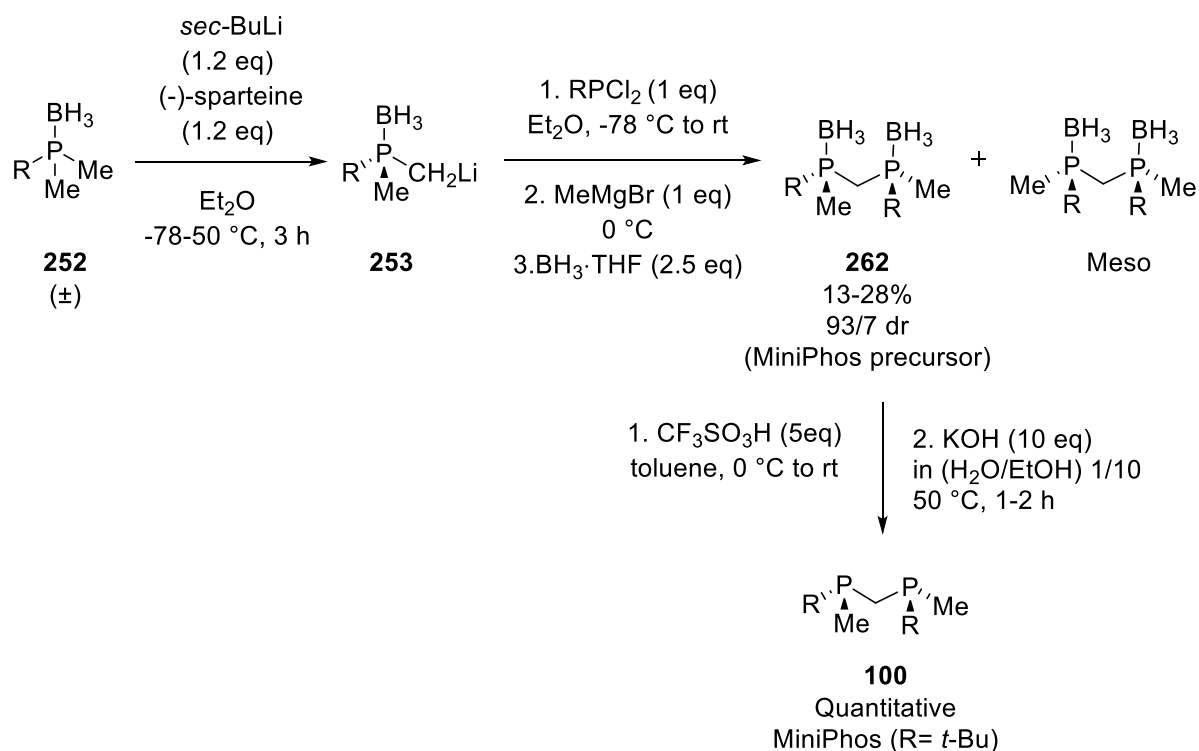
Scheme 76. Synthesis of MiniPhos ligand using sparteine based methodology.

Secondary phosphine boranes are an important class of P-stereogenic precursors and can easily be obtained by sparteine based methodology.[262] The secondary phosphine boranes bearing a *t*-butyl and a methyl groups, have been used for the synthesis of an air stable and configurationally more rigid ligand, called QuinoxP* **101** (scheme 77).[168] This ligand has been utilised in a number of asymmetric catalytic reactions, such as the efficient asymmetric hydrogenations of prochiral amino acids and amine derivatives with very high enantioselectivities (up to 99.99 %) and asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds with very good yields and high enantioselectivities.[168,183]
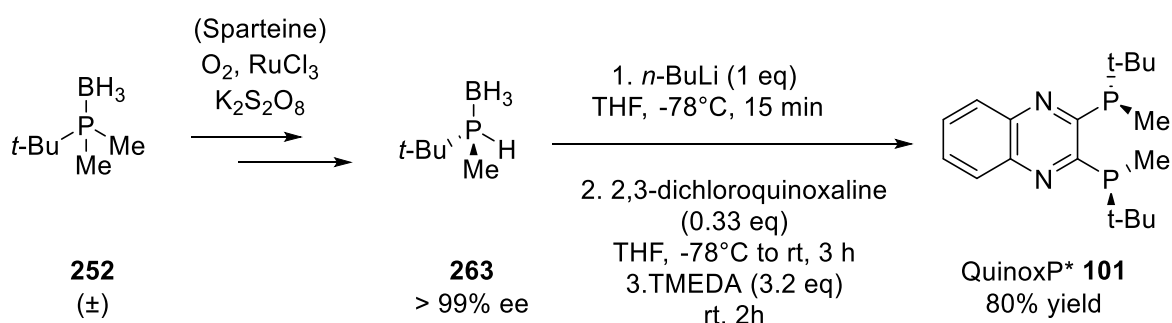
Scheme 77. Synthesis of QuinoxP* ligand using sparteine based methodology.

Another important diphosphine ligand, Trichickenfootphos **113** has been prepared using sparteine based methodology with a very good yield (71%) and with an excellent enantiomeric excess (96% ee) (scheme 78).[263]
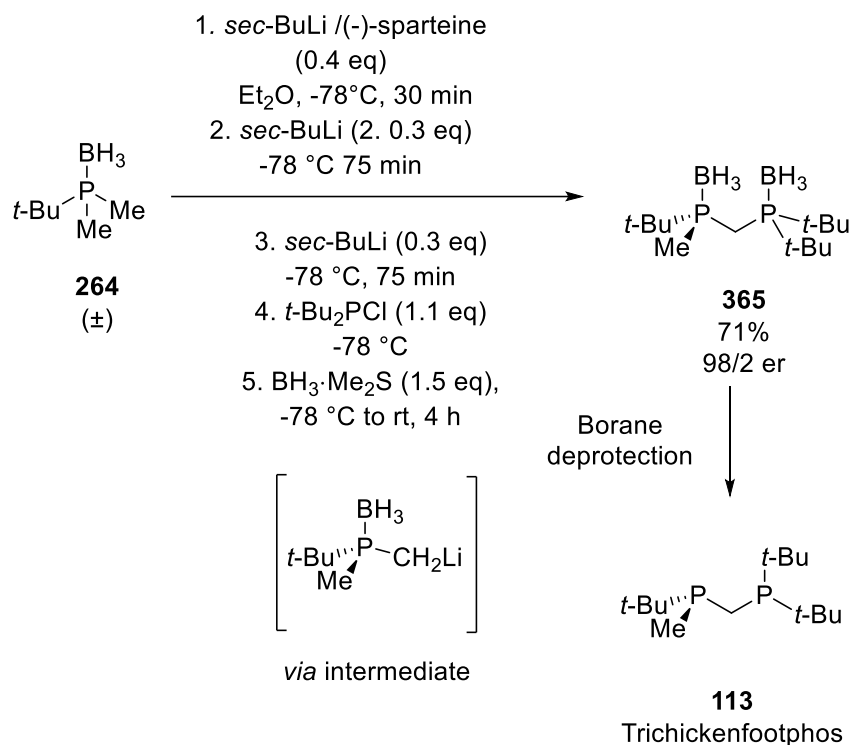
Scheme 78. Synthesis of Trichickenfootphos ligand using sparteine based methodology.

Thus, using this sparteine based methodology, numerous P-stereogenic phosphines and diphosphines have been prepared with good yields and high stereoselectivities. However, only alkyldimethyl phosphine boranes or aryldimethyl phosphine borane derivatives can be prepared by this method.

3.4.7 Asymmetric Oxidation of P(III) Compounds

This method deals with the stereoselective oxidation of an asymmetrically substituted P(III) organophosphorous compound by using a suitable oxidant or a complex, providing the corresponding optically active P(V) organophosphorous compound. Although, the methodology is appealing, it has seldomly been exploited for the synthesis of P-stereogenic compounds. Some successful examples of the enantioselective oxidation of tertiary phosphines and aminophosphines have been reported with good yields and with moderate to high enantiomeric excess.[264,265]

Gilheany et al. successfully carried out asymmetric Appel reaction i.e. the enantioselective oxidation of tertiary phosphines **266** using polyhaloalkanes, such as tetrachloromethane, and L-menthol as a chiral auxiliary.[266–272] They obtained the corresponding tertiary phosphine oxides **26** with very good yields and with high enantiomeric excess. They were also able to carry out an efficient homo coupling of the tertiary phosphine oxides **268** in order to get the corresponding diphosphine oxides **269** with good yields and very high enantiomeric excess (scheme 79).
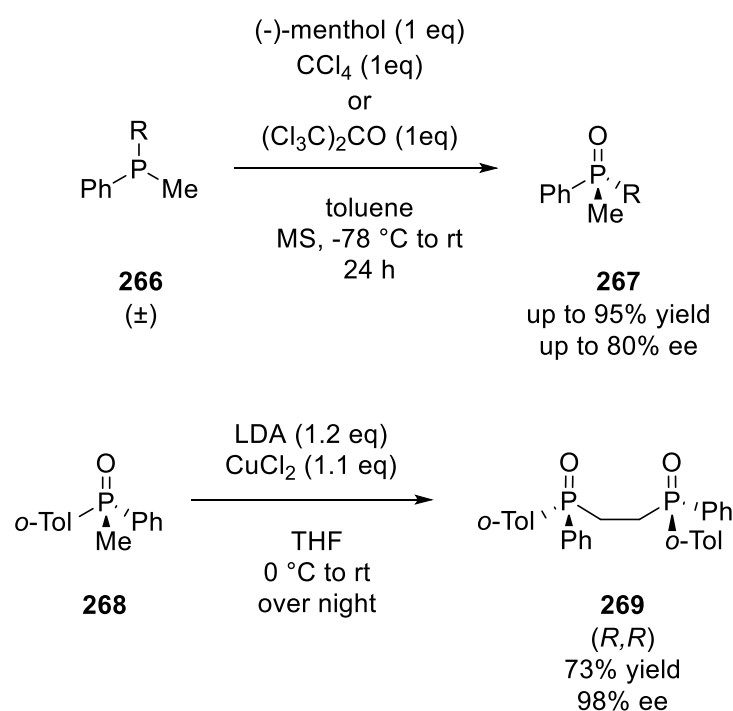
Scheme 79. Asymmetric oxidation of tertiary phosphines and synthesis of diphosphine oxide.

Also, the same group reported another interesting achievement in asymmetric Appel reaction. They were able to obtain both the enantiomers of the tertiary phosphine oxide by bifurcation of the reaction pathway, which proceeded through a common intermediate **270**. Under the controlled conditions, they described an Arbuzov-type collapse of the common intermediate which took place *via* nucleophilic attack of Cl⁻ ion on menthyl group (C-O bond fission leading to release of menthyl chloride) with retention of configuration at phsohphorous atom. However, an alkaline hydrolysis of the common intermediate proceeded *via* breaking of P-O bond with inversion of the configuration at phosphorous atom (scheme 80).[268]
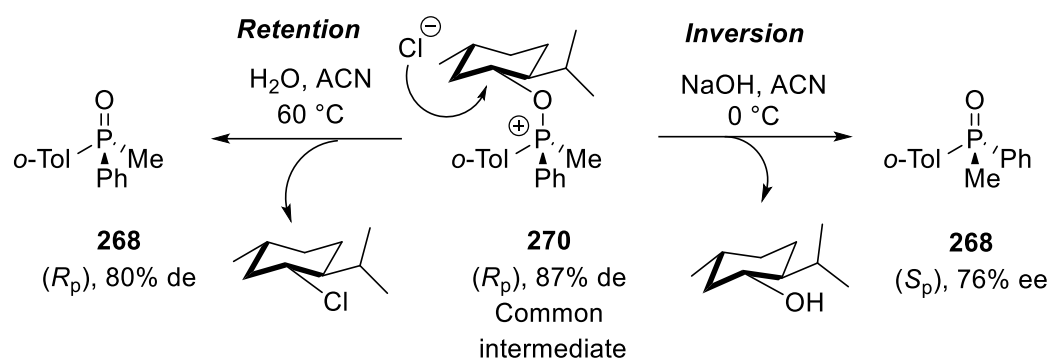
Scheme 80. Resolution of tertiary phosphine oxides.

3.4.8 Synthesis of P-stereogenic compounds by Asymmetric Catalysis / Biocatalysis

3.4.8.1 Asymmetric Catalysis by Transition Metals

Secondary phosphines in particular undergo organometallic catalysed asymmetric substitution reactions with aryl halides or triflates in order to get transformed into various P-stereogenic tertiary phosphines and their derivatives.[273–279,427] A racemic secondary phosphine can coordinate with a metal centre of chiral metal complex, in order to form the corresponding diastereomeric metal complexes. One of these complexes selectively undergoes an addition reaction with another coupling partner such as an aryl halide and thus, subsequent elimination step leads to the formation of the corresponding P-stereogenic tertiary phosphine (scheme 81).

(±)

X= lone pair, O, BH$_3$
Y= halide or trflate
[M]= chiral metal-complex

(a)

(S_p)

X= lone pair, O, BH$_3$
[M]= chiral metal-complex

(R_p)

(b)
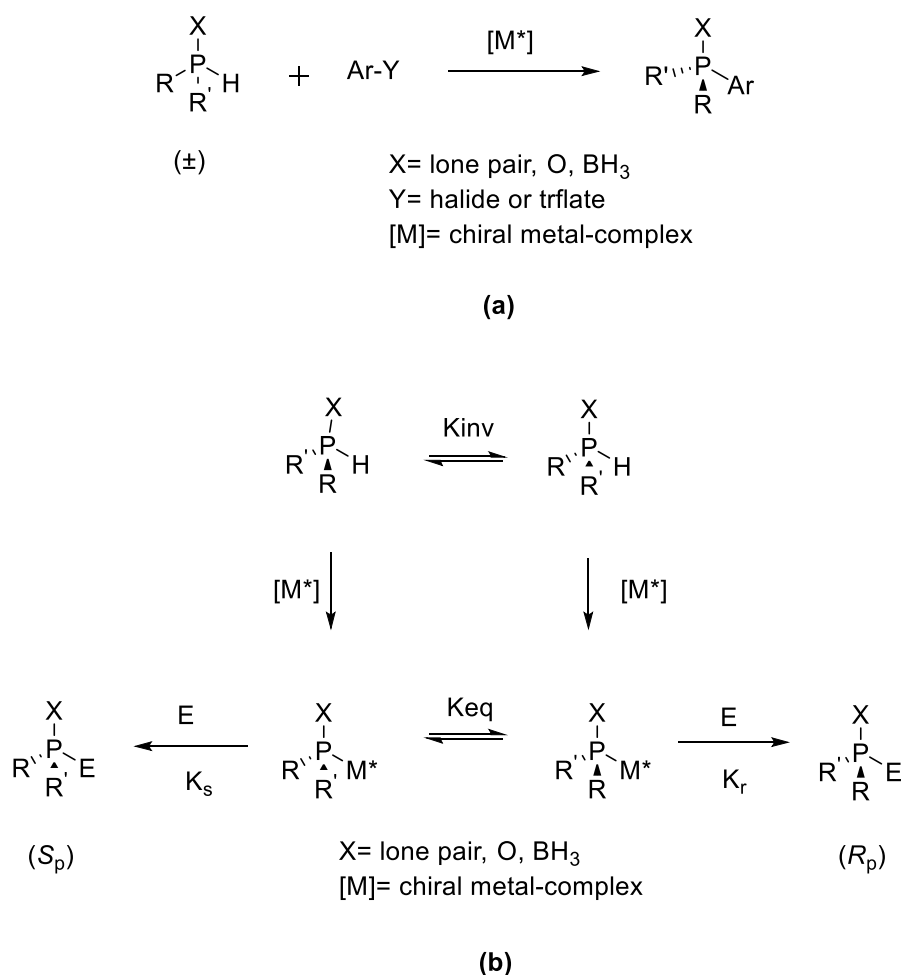
Scheme 81. a) Transition metal catalysed asymmetric reaction with secondary phosphine and b) the proposed mechanism.

In 2006, D. Toste et al. reported an efficient enantioselective alkylation of secondary phosphines **271** by using Ru/*i*Pr-PHOX complex. The corresponding tertiary phosphine boranes **272** were obtained with very high yields (up to 91%) and high enantioselectivities (up to 95% ee) (scheme 82).[280]
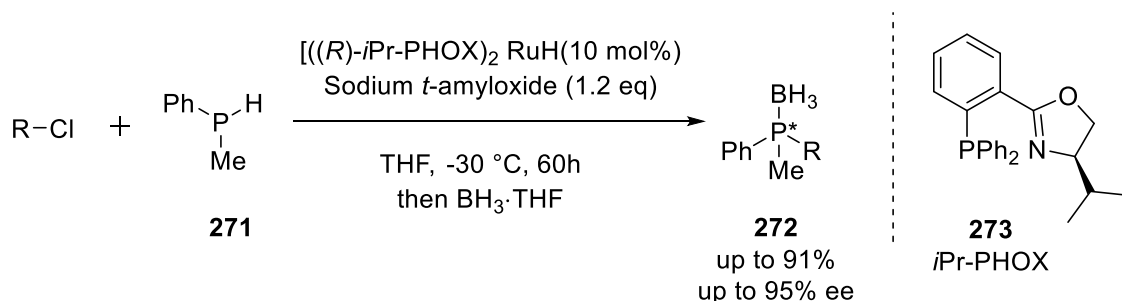
Scheme 82. Ru/iPr-PHOX complex catalysed enantioselective alkylation of secondary phosphines.

Also, an efficient Ir(III) catalysed C-H amidation of aryl phosphoryl bearing a chiral auxiliary **274**, have been reported by Chang et al. in 2014.[281] When chiral auxiliary happened to be C_2-symmetric chiral pyrrolidine, the corresponding products **276** were obtained with good yields and high diastereoselectivities (up to 90% de) (scheme 83).
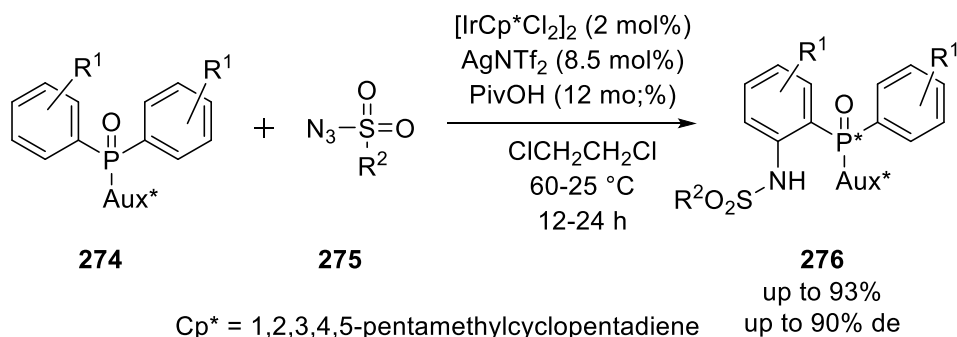
Scheme 83. Ir(III) catalysed C-H amidation of aryl phosphoryl.

Very recently Cramer et al. have published several reports for the stereoselective synthesis of various P-stereogenic compounds using Rh/Ir catalysed stereoselective C-H activation method.[282–285] For example, in 2016, they described an efficient stereoselective synthesis of P-stereogenic cyclic phosphinamides **279** using a chiral Rh(III)-complex **280** that catalysed the enantiotopic C-H activation of one of the aryl group attached to the phosphinamides **277** (scheme 84).[285]
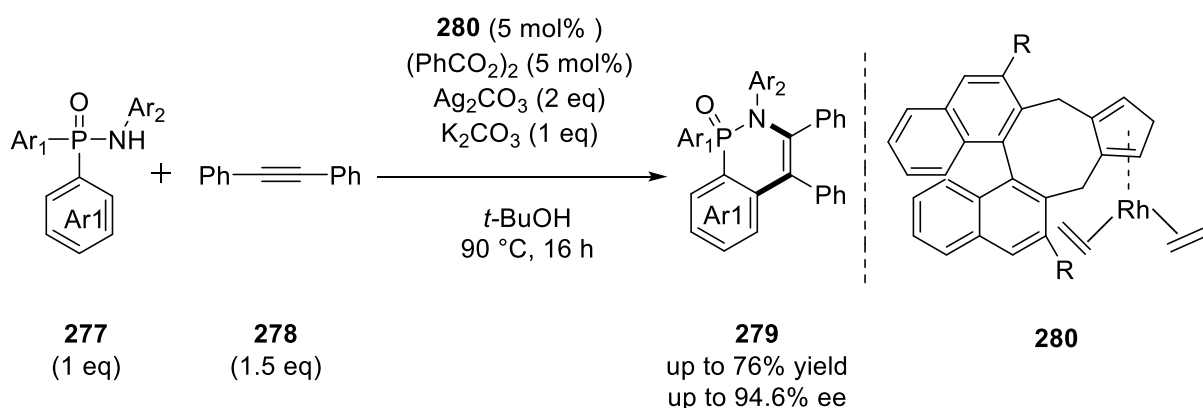
Scheme 84. Stereoselective synthesis of P-stereogenic cyclic phosphinamides using a chiral Rh(III)-complex.

Other interesting examples for the synthesis of P-stereogenic compounds with C-H activation include the Pd catalysed enantioselective intramolecular C-H arylation of phoshphinic amide derivatives and Pd catalysed desymmetric *ortho* C-H arylation of diarylphosphinamides with boronic acids.[286–288] In 2012, Leung et al. developed a methodology, in which a chiral palladium-complex **284** catalysed a highly stereoselective hydrophosphination of enones **281** to prepare C-stereogenic and P-stereogenic tertiary phosphines **283**.[289] The corresponding tertiary phosphines **283** were obtained with excellent yields and diastereoselectivities / enantioselectivities (scheme 85).
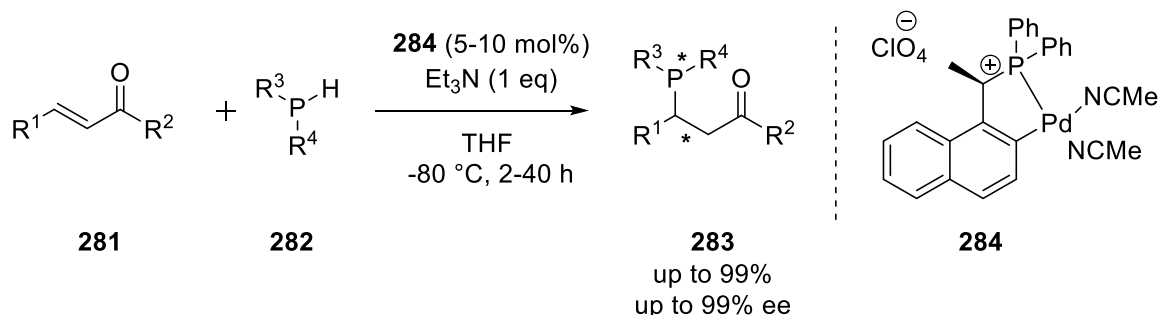
Scheme 85. Chiral Palladium-complex catalysed Stereoselective hydrophosphination of enones.

Another very interesting example reported by Cramer et al. for the stereoselective synthesis of P-stereogenic biaryls **287** by Ir-complex **288** catalysed C-H arylation of phosphine oxides **285** and *o*-quinone diazides **286** (scheme 86).[283]
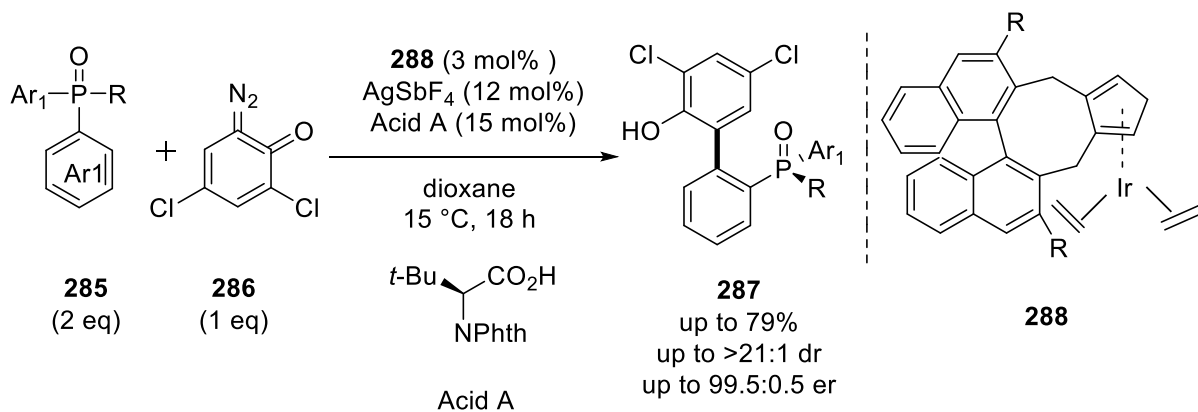
Scheme 86 . Synthesis of of P-stereogenic biaryls by [Ir*] catalysed C-H arylation of phosphine oxides and *o*-quinone diazides.

The palladium catalysed enantioselective intra-molecular C-H arylation of N-(2-haloaryl)-P,P-diphenylphosphinic amides **289** have also been reported with excellent yields (up to 99%) and enantioselectivities (97% ee) (scheme 87).[288]
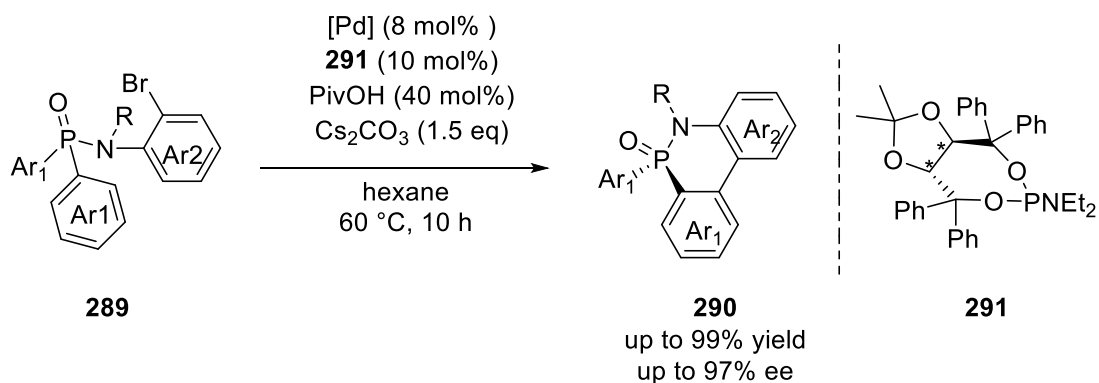
Scheme 87. Pd catalysed intra-molecular C-H arylation of diphosphonic acid amide derivatives.

3.4.8.2 Asymmetric Synthesis Using Enzymatic Transformations

This is another appealing alternative method to prepare P-stereogenic compounds using enzymes. Commercially available enzymes, such as hydrolases and lipases, are able to behave differently with different stereoisomers of a given organophosphorous compound. As a result, some enzymatic asymmetric biocatalysis have been reported for the synthesis of P-stereogenic compounds.[290,291] Mikołajczyk et al. described a PLE (Pig Liver Esterase)

catalysed asymmetric transformation of bis(methoxycarbonylmethyl)phenylphosphine oxide **292**, in order to get the corresponding monoacetate product **293** with up to 92% yield and with up to 72% ee (scheme 88). [291]

292

293
92% yield
72% ee
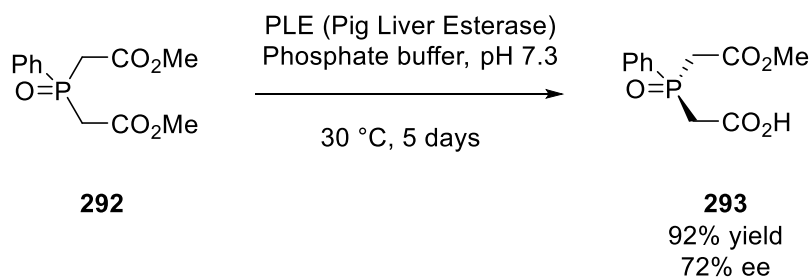
Scheme 88. PLE (Pig Liver Esterase) catalysed asymmetric synthesis of P-stereogenic compounds.

They also reported the desymmetrisation of bis(hydroxymethyl)phenylphosphine oxide **295** and (phenylphosphoryl)bis(methylene) diacetate **397** i.e. a lipase catalysed acetylation/hydrolysis of **295/297** to obtain the corresponding P-stereogenic monoacetate product **296** with up to 76% yield and with up to 79% ee (scheme 89).[291]

294
(10.84 mmol)

295
(1 mmol)

296
up to 76% yield
up to 79% ee

297
(1 mmol)
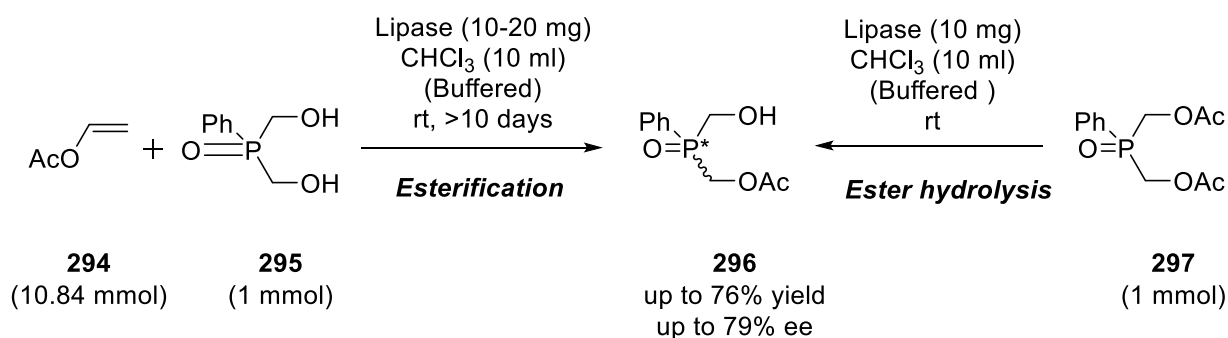
Scheme 89. Lipase catalysed asymmetric synthesis of P-stereogenic compounds.

Also, the phosphine boranes have been reported for the lipase-catalysed asymmetric desymmetrisation of pro-chiral diols **299** or diacetate **301** starting materials in order to obtain the corresponding monoacetate product **300** with up to 98% ee (scheme 90).[290] Both the enantiomers of the final desymmetrised product **300** were simply obtained either by acetylation of dihydroxyphosphine boranes **299** or hydrolysis of the diacetatephosphine boranes **301**. This further made it easier to recycle the substrates.
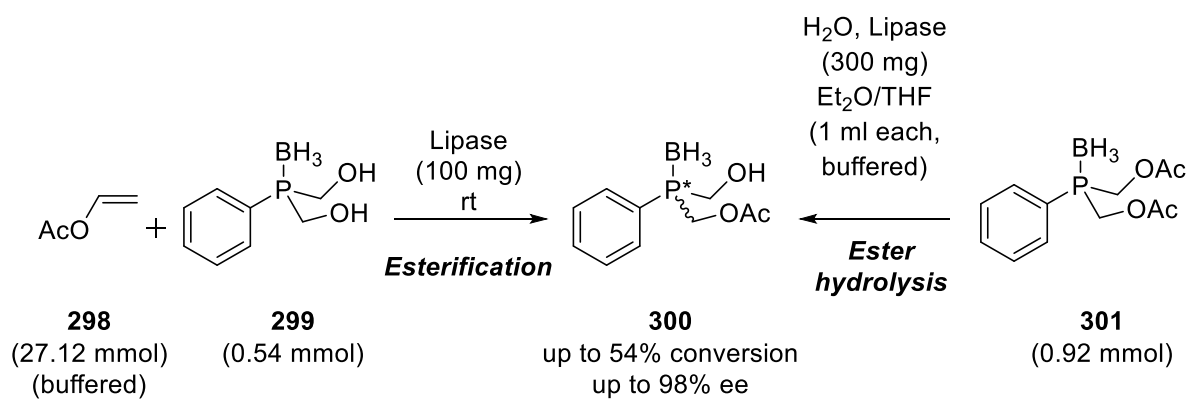
Scheme 90. Lipase catalysed asymmetric synthesis of P-stereogenic phosphine boranes.

Thus, to conclude, the preparation of P-stereogenic compounds by asymmetric catalysis is one of the most appealing methods. In last decades, some reports have been published with this methodology, providing P-stereogenic compounds in good to high yields and high to excellent stereoselectivities. However, very often, this methodology is applicable for a narrow range of organophosphorous substrates, as organometallic catalysts and enzymes are highly substrate specific. Therefore, the process is rather tedious as a large number of screening is needed to achieve the right combination of organometallic catalysts / enzymes and an organophosphorous substrate.

4 Diastereoselective Phosphorylation of Phenols via Dynamic Kinetic Resolution (DKR)

4.1 Introduction: Scope of The Thesis

As we have discussed in the previous chapter, P-stereogenic compounds are an important class of chemical compounds, which find several valuable applications in various fields of science such as agrochemistry as pesticides[2–5], pharmacy as biologically active molecules[6–9], coordination and material chemistry[10,11,292] and organometallic asymmetric catalysis as one of the most important class of chiral ligands [1,3,12–14,92,113,115,119,156]. Therefore, a number of methodologies to synthesise P-stereogenic compounds have been under steady development with time.[44,64,70,73,87,95–104] Moreover, synthetic routes to access P-stereogenic compounds based on the chiral auxiliary synthetic methodologies and in particular, employing menthol and ephedrine, remain the most popular choice for both, laboratory scale as well as for the industrial scale purposes. Menthol and ephedrine are easily available and cheap chiral auxiliaries, and a large number of P-stereogenic compounds and their precursors have been synthesised based on these methodologies. Although, these strategies are useful for the preparation of P-stereogenic compounds, but there are stil several limitations associated with these strategies and the synthesis of P-stereogenic compounds stil remain a challenging task.

This thesis aims to develop a novel methodology to build up such P-stereogenic scaffolds, based on the use of sulfoxide as chiral auxiliary. The methodology relies on an O-P coupling reaction, between an easily accessible enantiopure phenol bearing a sulfoxide chiral auxiliary, and a commercially available or easily accessible racemic H-phosphinate as an organophosphorous precursor, resulting in the formation of a new chiral (*P-stereogenic)* centre on phosphorus atom (scheme 91).

(±)
H-phosphinate   FG* : Sulfoxide   O-P coupling product
                         Chiral Auxiliary   (P-stereogenic molecule)
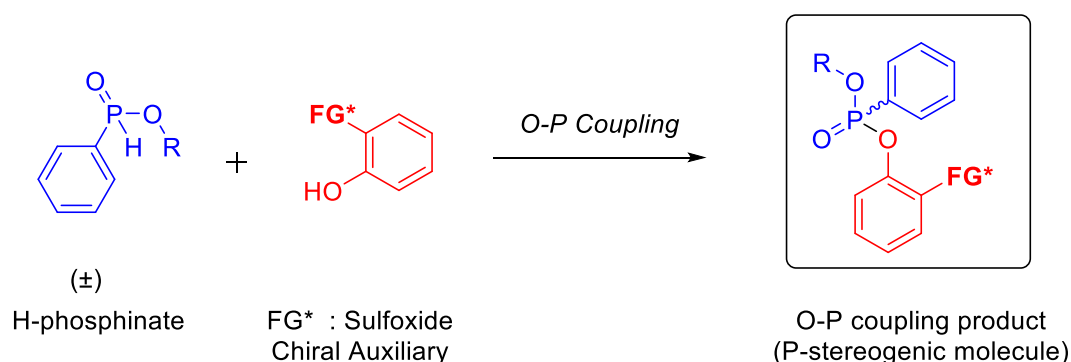
Scheme 91. O-P coupling reaction.

The main advantage of such an approach is the possibility of post functionalisation *i.e.* the newly obtained P-stereogenic compounds can potentially be transformed into a variety of

original P-stereogenic scaffolds by using organolithium or Grignard reagents and in addition, the enantiopure phenol bearing chiral sulfoxide would also be released during the process (scheme 92). Thus, these enantiopure phenols are expected to be recyclable and would further strengthen the synthetic value of this research project.
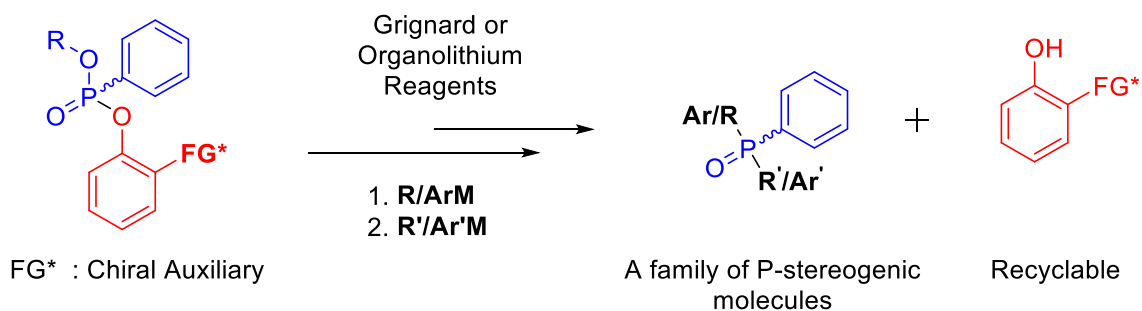
Scheme 92. Post-functionalisation of O-P coupling molecules.

This section of the thesis will first briefly discuss the two classes of the substrates or starting materials used in this project *i.e.* racemic H-phosphinates and enantiopure phenols. It would be followed by a brief review of Atherton-Todd reaction. The next part i.e. results, and discussions will first briefly highlight the attempted synthesis of axially chiral biaryls using hypervalent iodine reagents subsequently, a detailed discussion on P-stereogenic organophosphorus chemistry i.e. O-P coupling reactions between an easily accessible enantiopure phenol bearing a sulfoxide chiral auxiliary, and a commercially available or easily accessible racemic H-phosphinate would be presented. For example, initial screening of the sulfoxide chiral auxiliary substrates, various types of reactions adopted (for example, metal catalysed reaction, Atherton-Todd reaction) during the course of the project will be discussed with the initial results and optimisation of the reaction. Studies for the attempted separation of the newly obtained diastereomers of P-stereogenic compounds will also be highlighted. And the effect of substituents of H-phosphinates on diastereoselectivity of the reaction with the scope of the reaction, will be presented. Finally, the post-functionalisation step, and a concluding remark with the future perspectives will be discussed.

4.2 H-phosphinates

H-phosphinates are pentavalent organophosphorous compounds, and they are represented by a general formula, HRP(=O)(OR) (fig. 21).
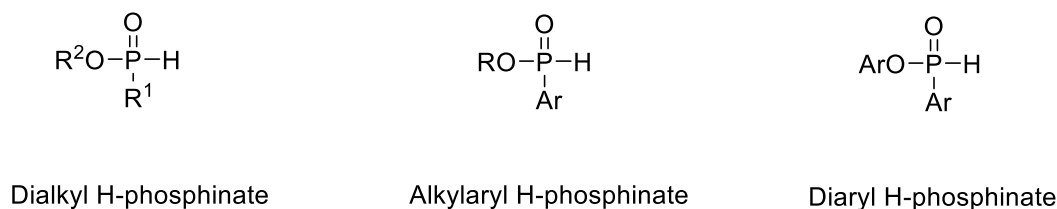
Fig. 21. General structure of H—phosphinates.

Like secondary phosphine oxides, these H—phosphinates are known to tautomerise with their trivalent phosphinic acid counterpart (scheme 93).[293,294] Equilibrium being mainly shifted to the H-phosphinate **29**, as they are more stable than their corresponding phosphinic acid counterpart **302**.
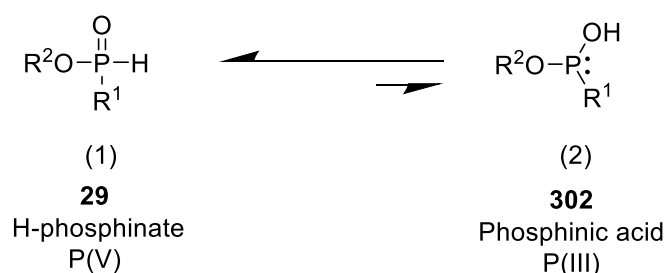
Scheme 93. Tautomeric equilibrium of H-phosphinate.

H-phosphinates , along with H-phosphonate and secondary phosphine oxides, are mainly used as important organophosphorous precursors for the synthesis of phosphinates and tertiary phosphine oxides. These precursors undergo various types of coupling reactions such as, P-C coupling and O-P coupling reactions, often involving deprotonation of the P-H containing compound.[79,80,295,296,298-301] There has been seldom experimental data available for pKa values of these compounds due to the high instability of P-centred anionic species. The general predicted relationship between their pKa values in DMSO is shown in fig. 22.[294]

28
Secondary phosphine
oxides
pKa = 20.6-26.9

29
H-phosphinate
pKa = 17.9-22

25
Phosphonate
pKa = 9-18.4

Decreasing order of pKa values
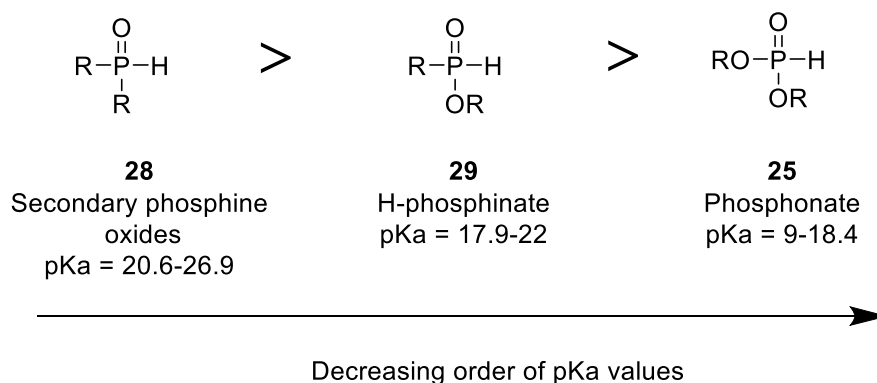
Fig. 22. Predicted trend in pKa values of secondary phosphine oxides **28**, H-phosphinates **29** and H-phosphonates **25** in DMSO.

The pKa values for H-phosphinates lie in between the pKa values of secondary phosphine oxides and H-phosphonates. Moreover, pKa values of H-phosphinates do not depend much on the substituents attached to P atom. For example, lowest and highest predicted pKa values for phenyl phenylphosphinate **303** and methyl methylphosphinate **304** are 22 and 17.9 respectively (fig. 23).[294]

303
Phenyl phenylphosphinate

pKa = 17.9
(Lowest pKa value
for phosphinates)

304
Methyl methylphosphinate

pKa = 22
(Highest pKa value
for phosphinates)
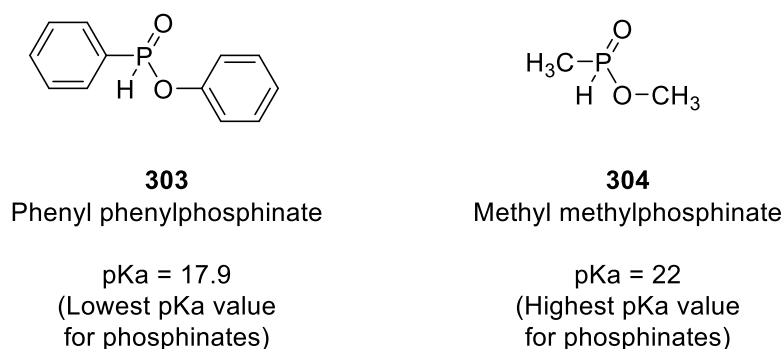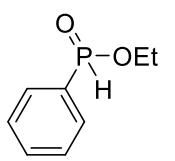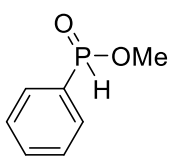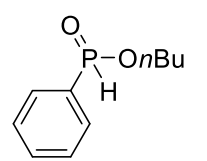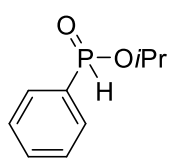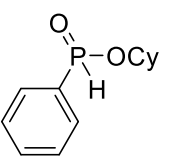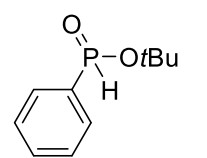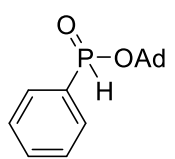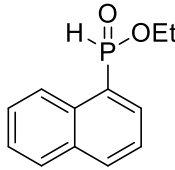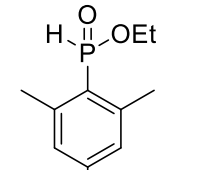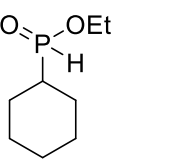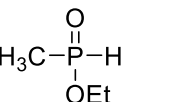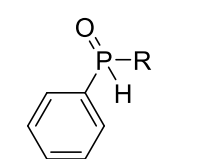
Fig 23. The highest and lowest predicted pKa values for H-phosphinates in DMSO.

H-phosphinates are less sterically hindered compared to tertiary phosphine oxides (TPOs). Therefore, they are less configurationally stable than TPOs, but they are more stable than the corresponding phosphines. The configurational stability of H-phosphinates depends on the substituents attached on P atom, temperature, acid-base conditions.[106] For example, ethylphenyl H-phosphinate **41a** and isopropyl H-phosphinate **41b** are less configurationally stable compared to the sterically more hindered *tert*-butyl H-phosphinate **41c** and adamantly H-phosphinate **41c** (fig. 24).

O
‖
Ph►P−H   <   Ph►P−H   <   Ph►P−H   Ph►P−H
OEt   O-*i*Pr   O-*t*Bu   OAd

Ad = Adamantyl

41a   **41b**   **41c**, **41d**
Racemisation in several   Racemisation in several   Configurationally stable
minutes at room temperature hours at room temperature   at room temperature

→

Increasing order of configurational stability

Fig. 24. Some examples of configurational stability trend of alkylphenyl H-phosphinates.

H-phosphinates possess several advantages over other organophosphorous precursors such as, they are in general more stable than their corresponding trivalent phosphorous compounds and chloro derivatives. They have quenched volatility and possess lower danger, they can be handled without the inert conditions and generally they have no or lower odour.[302] Moreover, some of them are also commercially available.

Alkylphenyl H-phosphinates (table 1) are one of the most commonly utilised H-phosphinate substrates for the synthesis of phosphinates and tertiary phosphine oxide, as the phenyl group attached to the phosphorous atom is present in most of these final organophosphorous compounds.[14,69,80,87,106] Furthermore, some of these alkylphenyl H-phosphinates are commercially available. For our research project, commercially available ethylphenyl H-phosphinate **41a** was considered as a standard H-phosphinate substrate. Following table 1 represents various H-phosphinate substrates along with the secondary phosphine oxides used in this project.

Table. 1. H-phosphinates and secondary phosphine oxides utilised in this project.

(commercially available)

41a
ethyl
phenylphosphinate

41e
methyl
phenylphosphinate

414f
n-butyl
phenylphosphinate

41b
isopropyl
phenylphosphinate

41g
cyclohexyl
phenylphosphinate

41c
tert-butyl
phenylphosphinate

41d
adamantyl
phenylphosphinate

41h
ethyl
naphthalen-1-ylphosphinate

41i
ethyl
mesitylphosphinate

41j
ethyl
cyclohexylphosphinate

41k
ethyl
methylphosphinate

secondary
phosphine oxide

41l: R = CH$_3$
41m: R= C$_4$H$_9$

4.2.1 General Synthetic methods:

Alkyl phenyl H-phosphinates are generally prepared from commercially available starting materials i.e. phenylphosphinic acid, dichlorophenyl phosphine, triethyl phosphite etc.[76,79,106,301,303–306] For example, microwave assisted synthesis of alkylphenyl H-phosphinate **306** is carried out using phenylphosphinic acid **305** and primary/secondary haloalkanes in the presence of a base, triethylamine (scheme 94).[76]
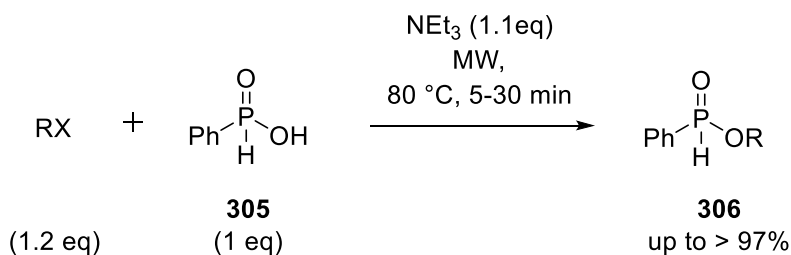
Scheme 94. Microwave assisted synthesis of H-phosphinates.

To obtain, more hindered H-phosphinate such as, *t*-butylphenyl H-phosphinate, propylphosphonic anhydride is used to facilitate the esterification reaction between the phenylphosphinic acid and the corresponding alcohol (scheme 95).[305]
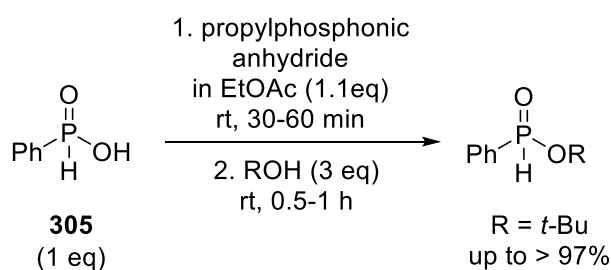
Scheme 95. The propylphosphonic anhydride catalysed synthesis of H-phosphinates.

Montchamp et al. have also introduced a modified method based on the use of orthosilicate for the preparation of H-phosphinates. Several H-phosphinates can be prepared using monosubstituted phosphinic acid and orthosilicate in good yields (scheme 96).[306]

(R'O)₄Si
(0.5/1 eq))

toluene
reflux, 24 h

80-100%
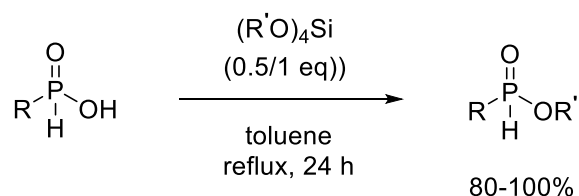
Scheme 96. Synthesis of H-phosphinates using orthosilicates.

The method which utilises dichlorophenyl phosphine **187** as a starting material for the preparation of H-phosphinates, is more commonly utilised, as a number of H-phosphinates can be prepared using this method.[79,104,106,307] For example, scheme 97 describes the methodology of Buono et al. using dichlorophenyl phosphine **187** and the corresponding alcohol in the presence of pyridine. During our experimental part, we found this methodology quite useful for the preparation of various H-phosphinates.

1. Pyridine (1eq)
   CH₂Cl₂
   0 °C-rt, 15 h

ROH + PhPCl₂

2. H₂O (excess)
   0 °C

187

306
up to > 95%
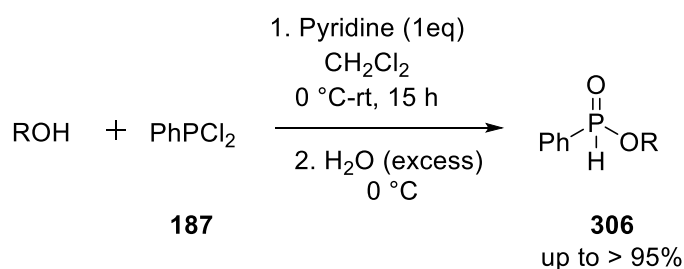
Scheme 97. Synthesis of H-phosphinates using dichlorophenyl phosphine and the corresponding alcohol.

4.3 Chiral Sulfoxides

4.3.1 Introduction:

Chiral sulfoxides are widely used in asymmetric synthesis in particular, as an important class of chiral auxiliaries and chiral ligands (fig. 25).[308–316]
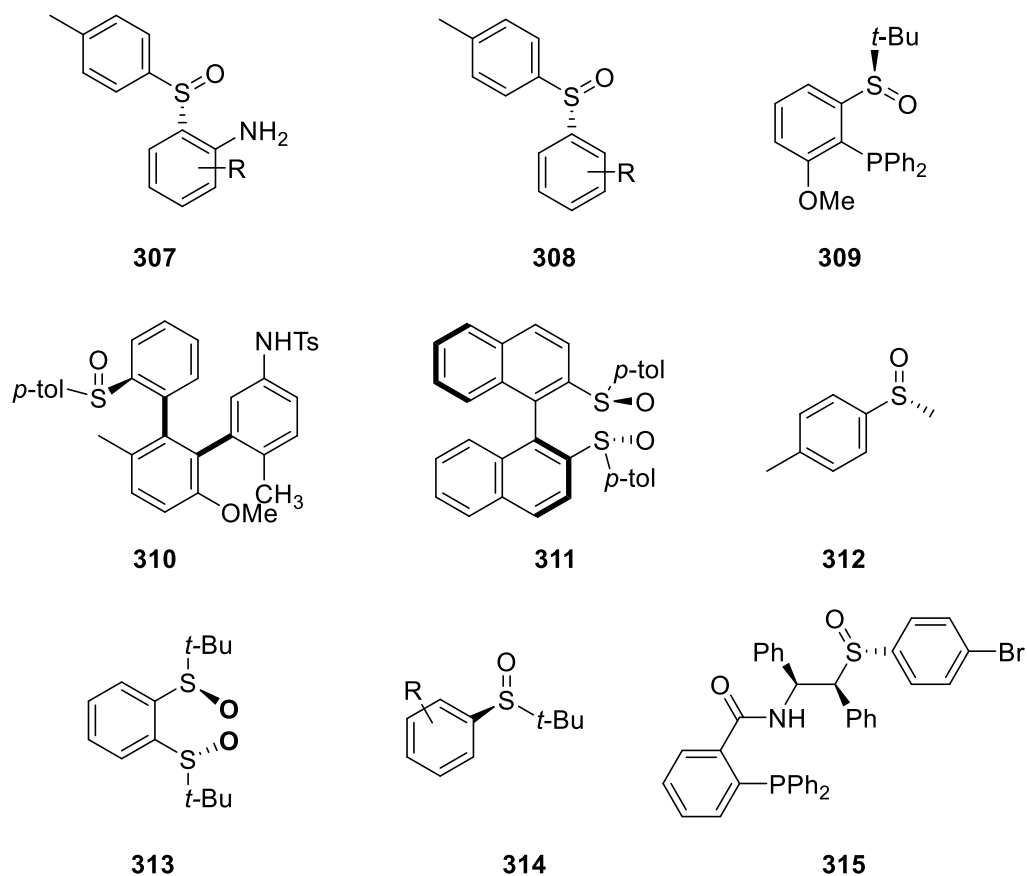
Fig. 25. Some examples of chiral sulfoxides used as chiral auxiliary and ligands in asymmetric synthesis.

Chiral sulfoxides are also used as biologically active molecules like drugs: esomeprazole **316** and armodafinil **317** (fig. 26).[317,318]

316
Esomeprazole

317
Armodafinil
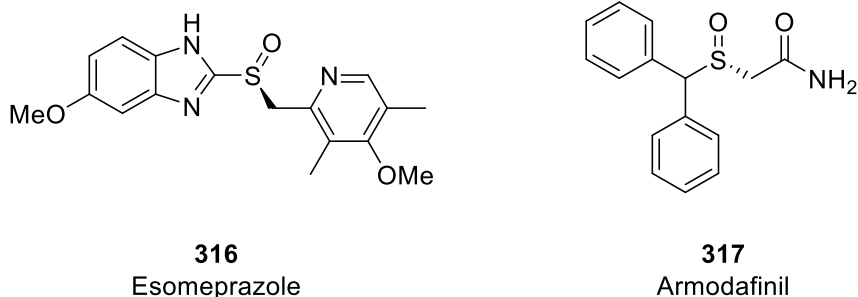
Fig. 26. Chiral sulfoxides as biologically active molecules.

Sulfoxides can be represented by Lewis structures, where in fact, S-stereogenic atom is sp^3 hybridised and the lone pair of S atom occupies the fourth orbital (fig. 27).
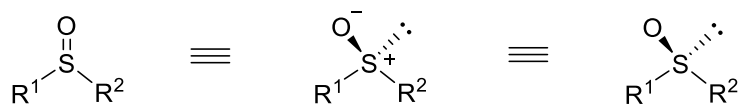
Fig. 27. Typical Lewis structures of chiral sulfoxides.

Chiral sulfoxides are in general conformationally stable at room temperature. Their typical pyramidal inversion barrier is around 38-41 kcal/mol.[319–323] However, they can racemise under harsh reaction conditions such as temperature exceeding 200 °C, irradiation with UV radiations and in the presence of radical transfer agents.[319]

4.3.2 General Synthesis of Chiral Sulfoxides

Chiral sulfoxides are mainly prepared either by Anderson's methodology using menthol and *p*-toluenesulfinyl chloride (for the synthesis of *p*-toluenesulfinyl derivatives) or by metal catalysed enantioselective oxidation of sulfides.[324–326]

1.1.1.1 Anderson's Method

This method is based on the synthesis of menthyl sulfinates as a mixture of diastereomers **319** using menthol and *p*-toluenesulfinyl chloride **318**.[327,328] Generally, one of the diastereomers of menthyl sulfinate is crystalline, while the other one is oily. Therefore, these diastereomers are separated by crystallisation. Optically pure menthyl sulfinates can further be obtained by means of multiple recrystallisations (scheme 98). Later, the nucleophilic

substitution reaction proceeding *via* inversion of configuration at S atom, using a Grignard reagent providing the corresponding enantiopure sulfoxide **320** (scheme 98).
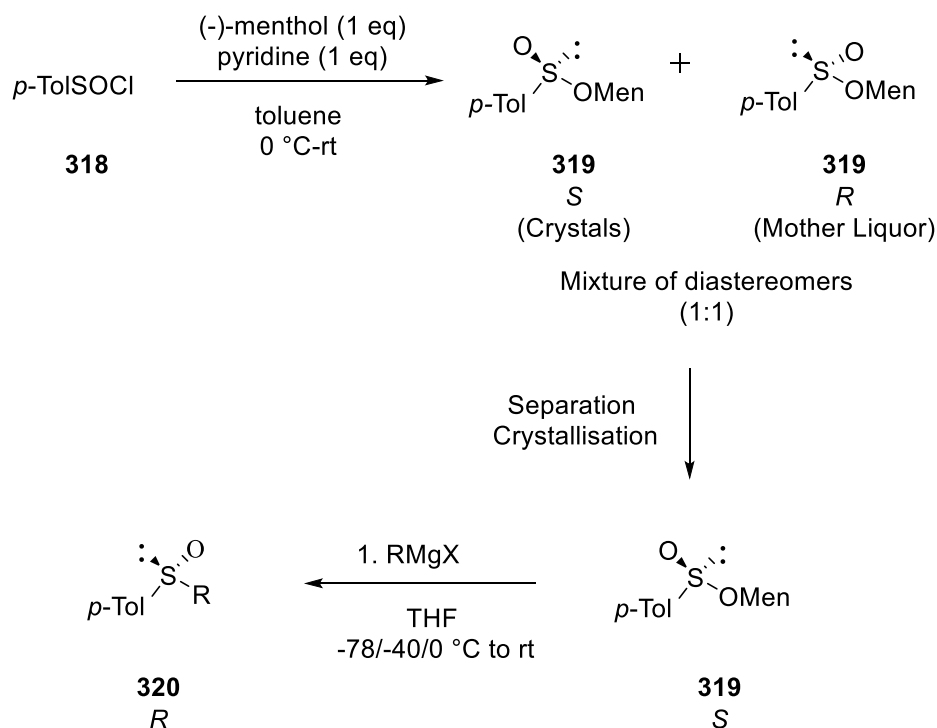
Scheme 98. Synthesis chiral sulfoxides with Anderson's method.

Solladié et al. further improved this methodology of preparing menthyl sulfinates with up to 90% yield *via* inducing an epimerisation equilibrium of menthyl sulfinate diastereomeric mixture. A catalytic amount of HCl is added to the mother liquor that is left after the first crystallisation step causing racemisation of remaining (*R*)-menthyl sulfinate. Thus, crystalline(*S*)-menthyl sulfinate is finally obtained in more quantity. This process is repeated several times to finally get the optically pure (*S*)-menthyl sulfinate in high yields (scheme 99).[329,330]

This methodology is widely applicable to the synthesis of chiral aryl sulfoxides, since they can be crystallised easily, but not applicable for the preparation of chiral alkyl sulfoxides due to the difficulty of separation of diastereomers of the corresponding menthyl sulfinate.
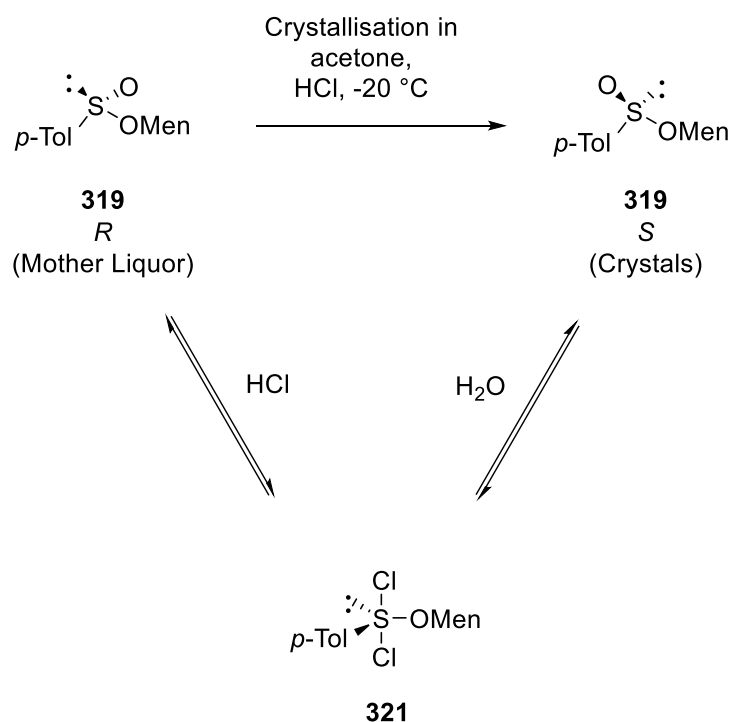
Scheme 99. HCl catalysed epimerisation equilibrium of menthyl sulfinate.

1.1.1.2 Metal Catalysed Asymmetric Oxidation of Sulfides

This method is one of the most straightforward methods to access enantiopure arylalkyl sulfoxides as well as dialkyl sulfoxides. Moreover, some of the industrially relevant enantiopure sulfoxides have also been produced using this method. However, the success in achieving high enantiomeric excess depends on the substituents attached to the S atom. Another challenge is the competitive overoxidation of sulfides to sulfones.

4.3.2.1.1 Titanium Based Complexes of Tartaric Acids

In 1984, Kagan and Modena independently reported the enantioselective oxidation of sulfides to sulfoxides using a modified version of Sharpless oxidation conditions (scheme 100).[331–333] They obtained the corresponding sulfoxides **323** with up to 88-91% ee. There were minor differences in reaction conditions described by Kagan and Modena (scheme 100). Kagan used 1 equivalent of Ti(OiPr)$_4$, 2 equivalents of DET (diethyl tartrate), 1 equivalent of t-BuOOH and 1 equivalent of H$_2$O and obtained the corresponding sulfoxide **323** with up to 91% ee, while Modena reported similar conditions, except using 4 equivalents of DET and no use of water in the reaction to achieve almost the similar enantioselectivities, as reported by Kagan.

100

Ti(O*i*Pr)$_4$ (1 eq)
R,R-DET (2 or 4 eq)
*t*BuOOH (1 eq)

1) Kagan; -20 °C, H$_2$O, CH$_2$Cl$_2$
2)) Modena; -20 °C, CH$_2$ClCH$_2$Cl

322

323
1) up to 91% ee
2) up to 88% ee

Ar: *p*-Tol, p-MeO$_2$CC$_6$H$_4$, *p*-MeOC$_6$H$_5$,
R; Me, Et, *i*Pr
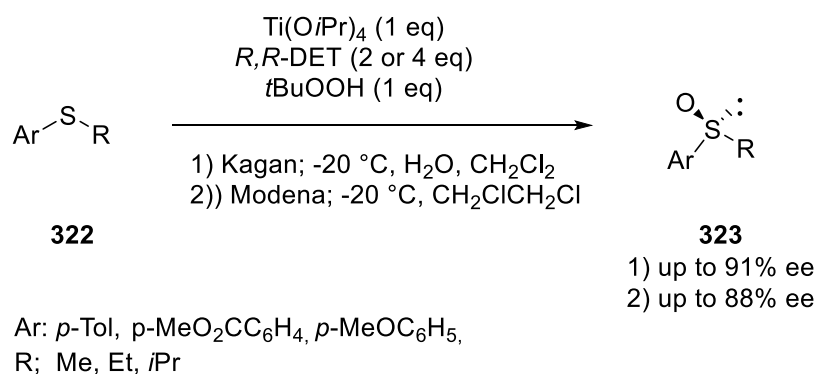
Scheme 100. Enantioselective oxidation of sulfides to sulfoxides using Kagan/Modena strategy.

Today, a number of modified strategies have been developed on the same principle for example, DET have been replaced by other chiral ligands/diols, *t*-BuOOH by cumene hydroperoxide (CHP) etc.[326,334–337]

1.1.1.2.1 Vanadium Based Complexes with Multifunctional chiral ligands

Vanadium is another important metal which form the chiral complexes with multi-functional chiral ligands to catalyse the enantioselective oxidation of sulfides.[338,339] In 1995-1996, Bolm et al. described the catalytic enantioselective oxidation of sulfides **322** into sulfoxides **323** using VO(acac)$_2$, N-salicylidene amino acid ligands **324** and hydrogen peroxide under ambient conditions (scheme 101).[340] They obtained the corresponding sulfoxides **323** with good yields and moderate enantioselectivities.

VO(acac)$_2$ (1%)
324 (1.5%)
H$_2$O$_2$ (1.1 eq)

CH$_2$Cl$_2$
rt

322

323
up to 94%
up to 65% ee

324
X = NO$_2$, *t*Bu
R = *t*Bu, H, SiPh$_2$,*t*-Bu
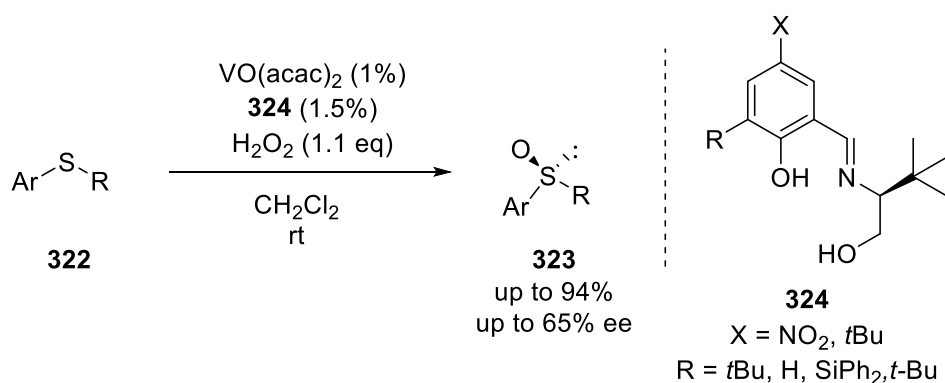
Scheme 101. Enantioselective oxidation of sulfides to sulfoxides with vanadium-complex.

On the basis of this strategy, Ellman et al. developed a method to enantioselectively oxidise disulfides **325** to thiosulfinates **326**, targeting to prepare *t*-butanesulfinamide **327**, useful in asymmetric additions of nucleophiles to imines (scheme 102).[341–344] They described a kilogram scale procedure for the highly efficient catalytic enantioselective oxidation of di-*t*-

butyl disulfides to *t*-butylthiosulfinate, using easily accessible and cheap reagents/ligands under ambient reaction conditions.
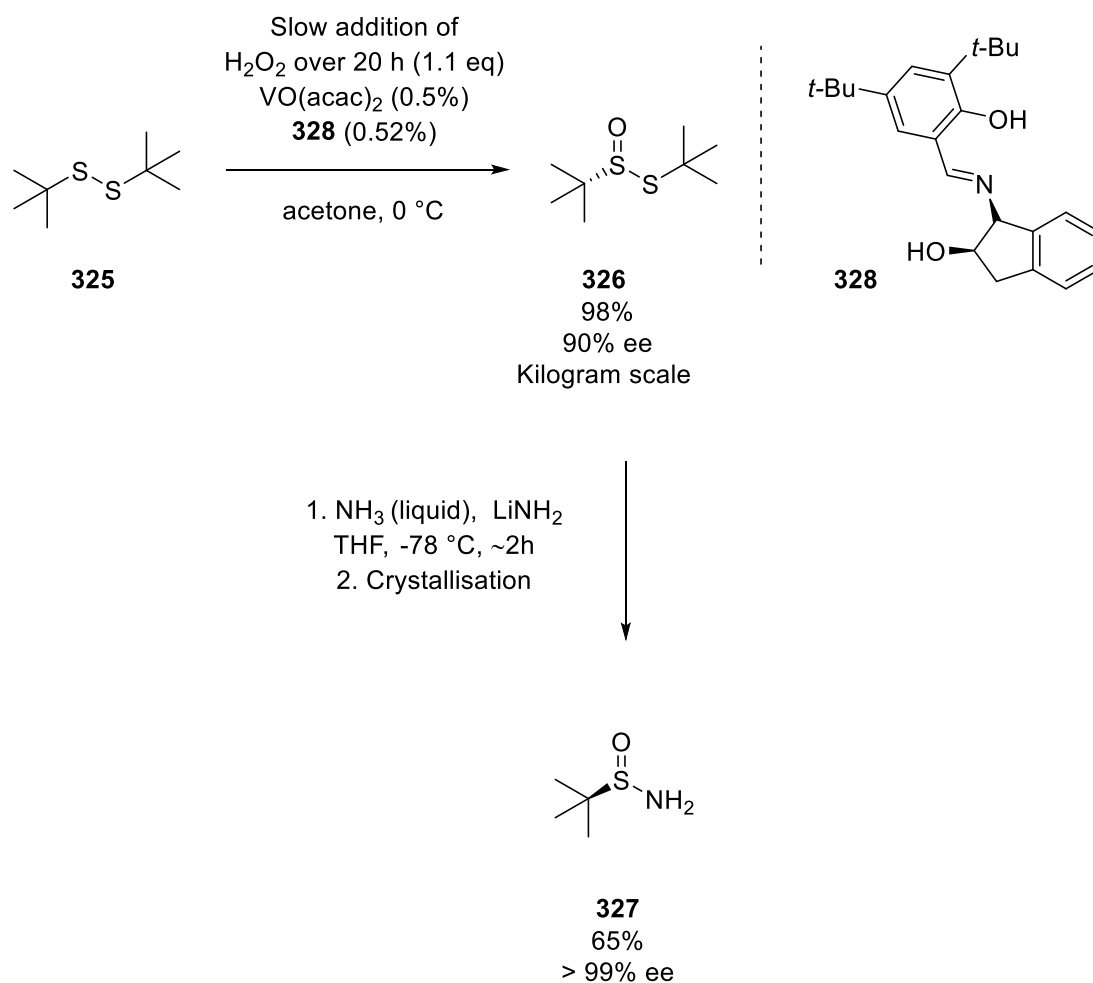
Scheme 102. An enantioselective oxidation of di-*tert*-butyl disulfide **325** and subsequent synthesis of *tert*-butanesulfinamide **327**.

4.3.3 Application of chiral sulfoxides as ligands and chiral auxiliaries

Chiral sulfoxides are mainly used in asymmetric synthesis as chiral ligands and chiral auxiliaries. In this section, some examples of application of chiral sulfoxides as ligands and chiral auxiliaries will be presented.

In 2005 Nguyen et al. described an efficient Rh catalysed asymmetric cyclopropanation of olefins using a monodentate chiral sulfoxide, (*R*)-1-methyl-4-(methylsulfinyl)benzene **312** as a ligand (scheme 103).[308] The reaction was carried out in neat styrene *i.e.* without any solvent

to provide the corresponding cyclopropane derivatives **330** in high yields and high enantiomeric excess.
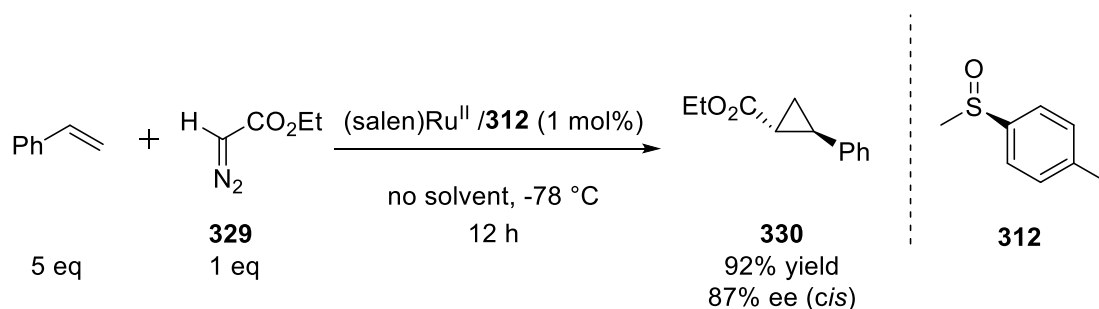
Scheme 103. Rh catalysed asymmetric cyclopropanation of olefins using a chiral sulfoxide ligand.

In 2008, Dorta et al. reported an excellent example of Rh/bis-sulfoxide catalysed asymmetric 1,4-addition of arylboronic acids to cyclic double bonds. As a result, the corresponding arylated cyclic ketones **332** were obtained in very high yields and in excellent enantiomeric excess (scheme 104).[345]
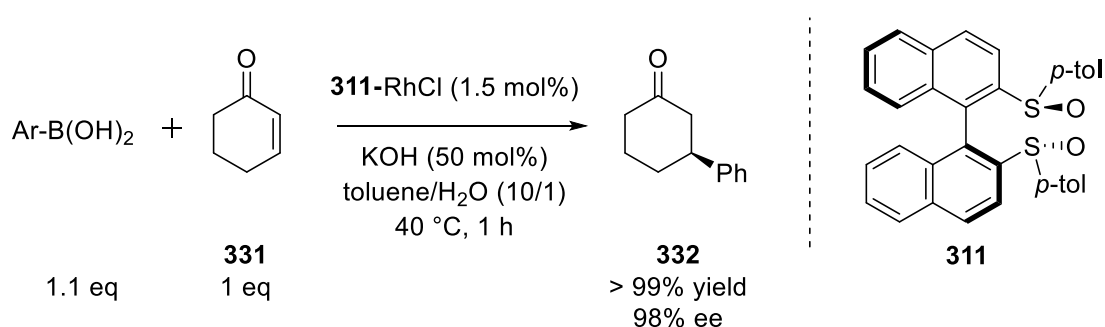
Scheme 104 . Rh/bis-sulfoxide catalysed asymmetric 1,4-addition of arylboronic acids.

In 2015, Liao et al. described a highly efficient and enantioselective pinacolboryl addition of *N*-Boc imines **333** catalysed by Cu(I) using a chiral sulfoxide phosphine ligand **336**.[346] They noted an interesting observation that when a smaller counter ion of Cu catalyst for example, Cl⁻ ion was used, the corresponding α-amino boronic ester was obtained with (*S*) configuration, while a larger counter ion *i.e.* BARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) provided the corresponding α-amino boronic ester with the opposite configuration of (*R*) (scheme 105).
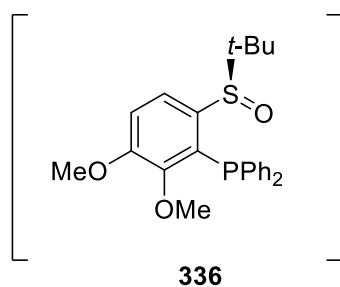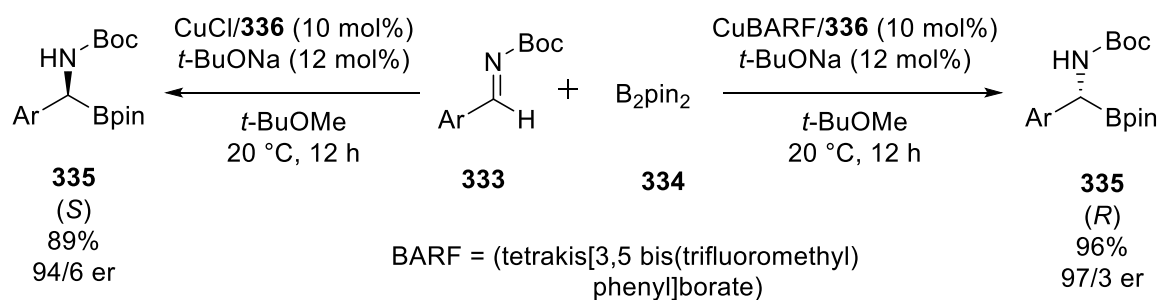
Scheme 105. Cu/sulfoxide-phosphine catalysed enantioselective pinacolboryl addition of *N*-Boc imines.

Sulfoxides are also used as an important class of chiral auxiliaries, as well as traceless directing groups in various asymmetric synthesis.[311,311,313–315,347,348] Our team has published several reports on this topic. For example, in 2014, we reported a highly efficient Pd-catalysed and sulfoxide-directed asymmetric acetoxylation and iodination of biaryls under mild conditions (scheme 106 and 107).[349]
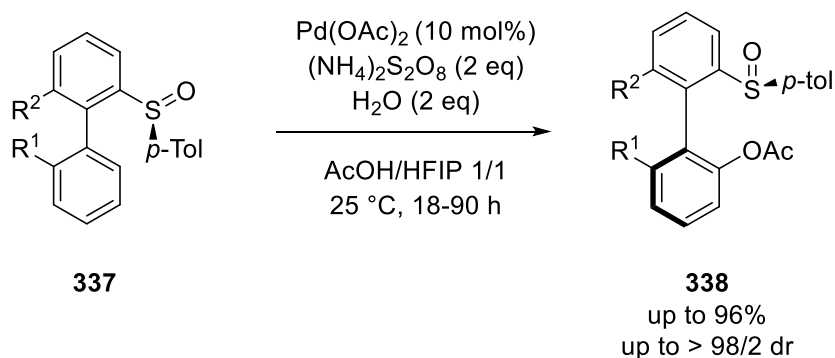
Scheme 106. Sulfoxide directed asymmetric acetoxylation.
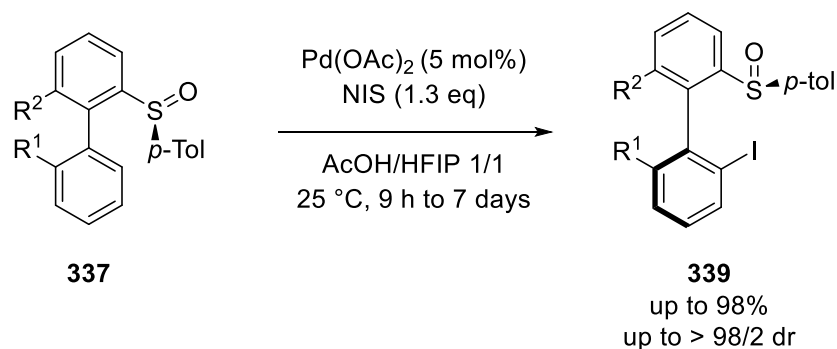
Scheme 107 . Sulfoxide directed asymmetric acetoxylation.

The sulfoxide group in biaryl was easily removed using t-BuLi in THF and the resulted lithiated biaryl was trapped with CO_2 (g) generated from dry ice (scheme 108). The corresponding biaryl-carboxylic acid **340** was obtained with good yield and very high enantioselectivity.
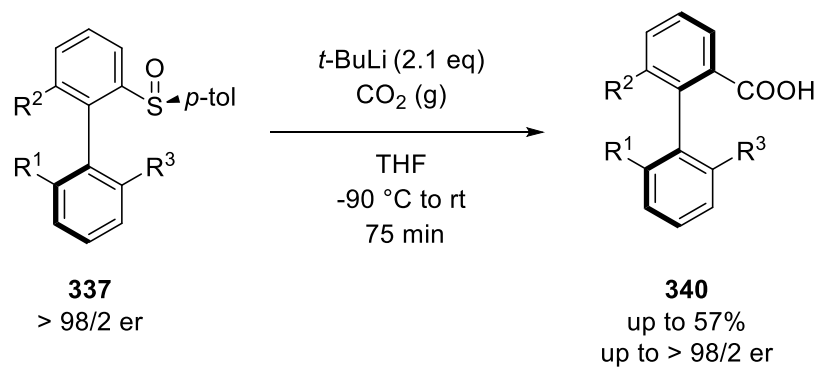
Scheme 108. An example of transformation of sulfoxide group in biaryl.

Very recently, we reported a bidentate directing group chiral auxiliary based on sulfinyl aniline moiety.[311] And, this bidentate ligand was used in Pd catalysed diastereoselective functionalisation of cyclopropane carboxylic acid derivatives (scheme 109).
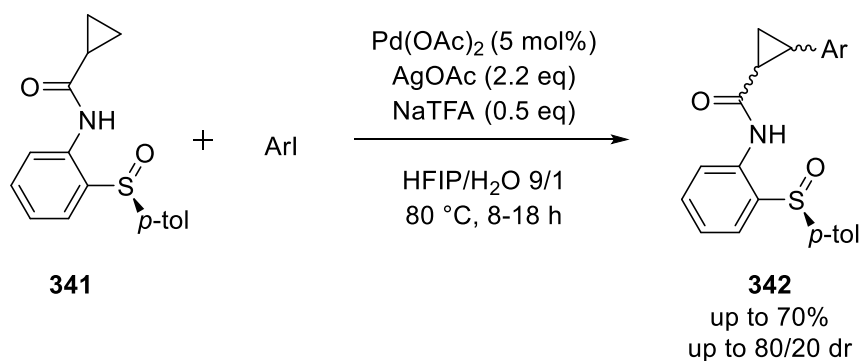
Scheme 109. Enantiopure sulfinyl aniline directed functionalisation of cyclopropane carboxylic acid derivatives.

Moreover, sulfinyl-aniline moiety was easily removed from the corresponding cyclopropane acid derivative **342** under mild conditions i.e. by carrying out a simple work up with KOH (1 M) in EtOH at 80 °C (scheme 110). Functionalised cyclopropane carboxylic acid **343** and sulfinyl-aniline chiral auxiliary **344** were obtained without any loss of chirality.
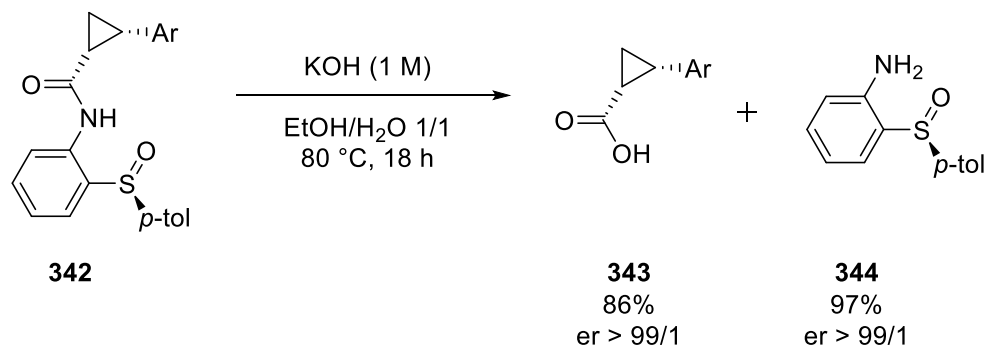
Scheme 110. Removal of sulfinyl-aniline chiral auxiliary.

Thus, to conclude, chiral sulfoxides are widely used in asymmetric synthesis, mainly as an important class of chiral auxiliaries and chiral ligands.

4.4 Atherton Todd (AT) Reaction: O-P/N-P Coupling

Atherton-Todd (AT) reaction is one of the classical synthetic methods to prepare phosphoramidates, phosphonates and other organophosphorous derivatives.[26,350–357] The reaction corresponds to a N-P coupling or an O-P coupling reaction. Indeed, the reaction was discovered by serendipity by Atherton-Todd group, in 1945.[350,351] They observed the formation of *o,o*-dibenzyl phosphoramidate **346** during the attempted purification of dibenzyl phosphite **345** in the presence of aqueous ammonia in carbon tetrachloride (scheme 111).

345
dibenzyl phosphite

346
o,o-dibenzyl phosphoramidate
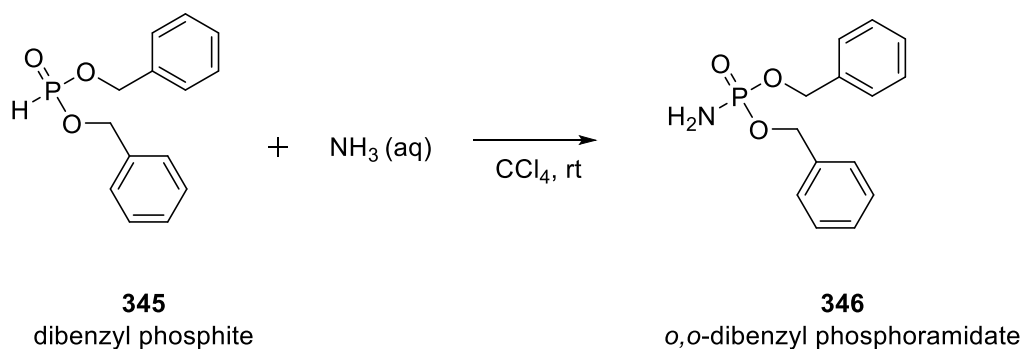
Scheme 111. Synthesis of phosphoramidate observed by Atherton-Todd group.

Generally, the reaction takes place between an organophosphorous precursor such as H-phosphinate / H-phosphonate and a nucleophile such as an amine/alcohol in the presence of a base, which is usually a trialkyl amine, in carbon tetrachloride solvent. Carbon tetrachloride plays dual role in the reaction *i.e.* it acts as a solvent as well as a halogenating agent. The reaction is usually carried out under anhydrous condition, to avoid any possible hydrolysis of the chloro phosphate derivative reaction intermediate, during the reaction.

4.4.1 Stereochemistry and Mechanism of the Reaction

There are several studies which have been carried out to understand the mechanism of Atherton-Todd reaction. Today, the most widely accepted mechanism of the reaction suggests the formation of a chlorophosphate derivative intermediate **347**.[357–361]

In the presence of a suitable base in carbon tetrachloride, an organophosphorous precursor is converted into the corresponding chlorophosphate derivative intermediate **347**, which is a highly reactive species, the electrophilic centre being on P atom. This step is proposed to proceed through *retention of configuration* on P atom.[352] The reaction intermediate **347**, subsequently undergoes a nucleophilic substitution reaction with a suitable nucleophile, to provide the final corresponding product. This final step proceeds through *inversion of configuration* on P atom (scheme 112).[25,252,352,362]
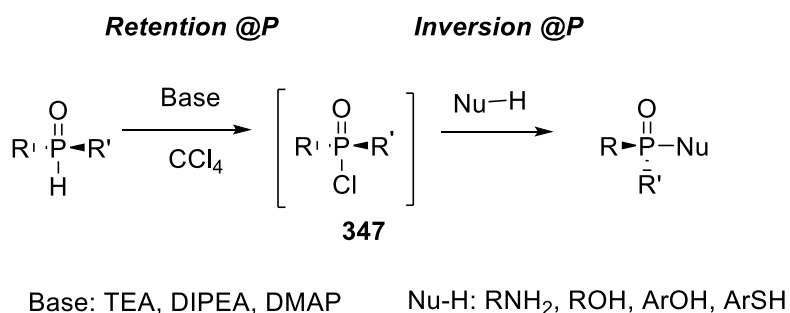
Scheme 112. A general proposed mechanism for Atherton-Todd Reaction.

Considering the stereochemistry of Atherton-Todd (AT) reaction, limited studies have been carried so far. Aaron et al. reported the first investigation on stereochemistry of AT reaction.[363] They carried out the stereospecific AT reaction using an enantiopure (R)-isopropylmethyl phosphinate **348** and aniline to form the corresponding anilide **349** under the standard AT reaction conditions (scheme 113).
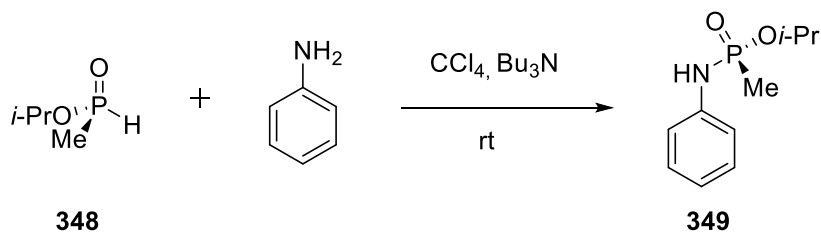
Scheme 113. Stereospecific AT reaction reported by Aaron et al.

However, they reported a rapid racemisation of (R)-isopropylmethyl phosphinate in a mixture of MeOH and MeONa. This loss of optical purity can be attributed to the formation of a configurationally unstable iso-propyl (R)-methylphosphonite anion **350** (scheme 114).
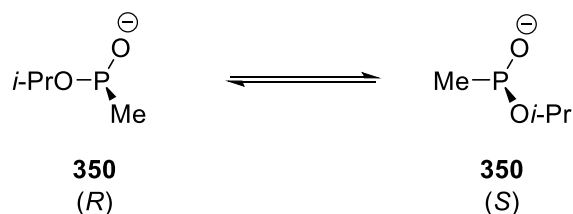
Scheme 114. Racemisation of (R)-isopropylmethyl phosphinate **348** via formation of isopropyl (R)-methylphosphonite anion **350** in a methanol/sodium methoxide mixture.

Following this lead, Mikolajczyk et al. also described the stereochemical studies on cyclic organophosphorous compounds.[364] They reported that the *trans* isomer of cyclic H-phosphinate compound **351** underwent the stereospecific Atherton-Todd reaction to form the corresponding chloro derivative **352** with *trans* geometry *i.e.* without any loss of optical purity. While the *cis* isomer of the cyclic H-phosphinate **351** underwent Atherton-Todd reaction yielding both, the corresponding chloro derivative **352** with *cis* and *trans* geometry respectively in 70/30 ratio (scheme 115). The racemisation observed with the *cis* isomer of cyclic H-phosphinate **351** was explained on the basis of its decreased stability, compared to the *trans* isomer which hence underwent no racemisation during the reaction.
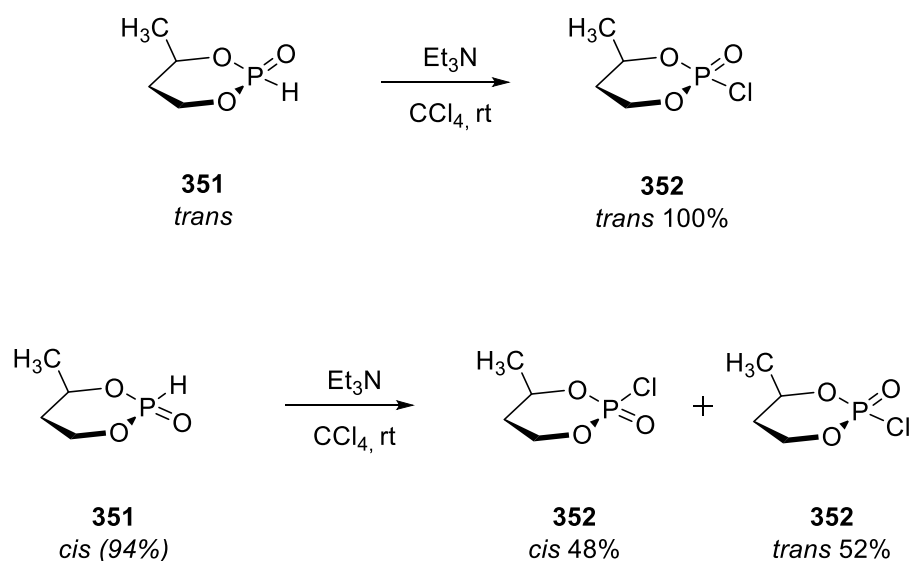
Scheme 115. Synthesis of *cis/trans* 2-chloro-2-oxo-4-methyl- 1,3,2-dioxaphosphorinans under Atherton-Todd reaction conditions.

Han et al. demonstrated that P-stereogenic H-phosphinates bearing a menthyloxy group and secondary phosphine oxides underwent Atherton-Todd reaction diastereoselectively.[25,365] The corresponding N-P coupling or O-P coupling products **353** are obtained in high yields with inversion of configuration on P atom (scheme 116).
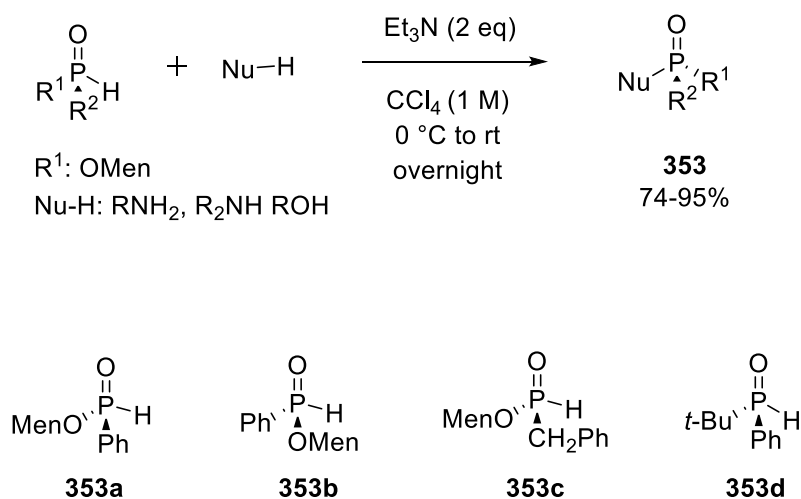
Scheme 116. Stereospecific Atherton-Todd reaction described by Han et al.

Thus, Atherton-Todd reactions in general are diastereoselctive the first step of formation of chlorophosphate derivative intermediate, proceeds through the retention of configuration on P atom, while the second and final step *i.e.* nucleophilic substitution takes place with inversion of configuration on P atom.

4.4.2 Scope of Atherton-Todd Reaction

With time, the classical Atherton-Todd reaction conditions were modified to broaden the scope of the reaction such as types of organophosphorous precursors, nucleophiles and solvents etc (scheme 117).[25,352,362,365–373]

X = Z = R, Ar , OR, OAr   Base = TEA, DIPEA,DMAP etc

Nu-H = RNH_2,R_2NH Solvent = CCl_4, CH_2Cl_2, $CHCl_3$,
 ROH, ArOH, ArSH CH_3CN, THF, Et_2O
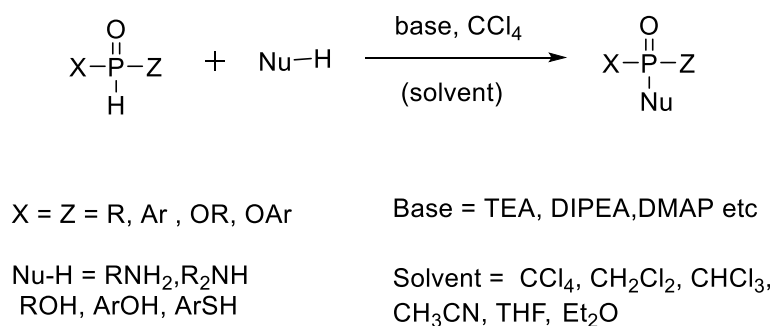
Scheme 117. Modified Atherton-Todd reaction.

Different organophosphorous compounds with P-H bonds such as, H-phosphinates, H-phosphonates and secondary phosphine oxides, have been utilised for the reaction.[356,374,375] The most commonly used nucleophiles under Atherton-Todd reaction condition are primary and secondary dialkylamines. Today, a number of nucleophiles have been successfully used for the reaction (aniline, hydrazine, alcohols, azides, nitriles and thiols).[373,376,376–381] Less nucleophilic amines such as, aniline also undergoes the reaction, but it may require the pre-activation of the aniline substrate with sulfonamide or acetamide groups for example (scheme 118).[370,371,382]
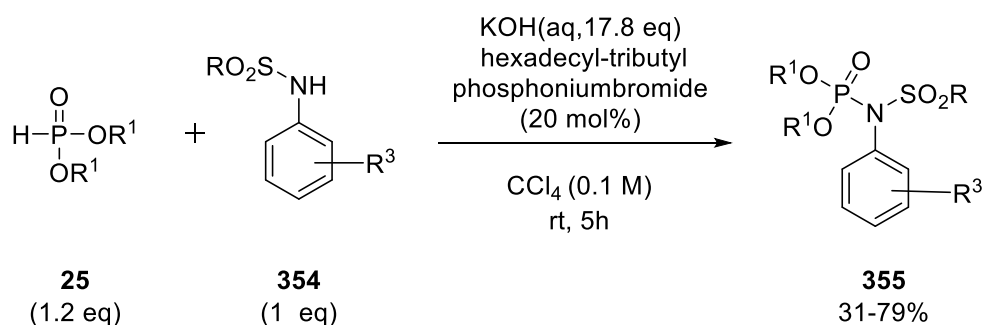
Scheme 118. Atherton-Todd reaction of activated aniline.

Use of alcohols as nucleophile in the reaction is seldomly reported due to its less nucleophilic character, compared to the amines. Phenols preferably undergo AT reaction under milder conditions. For example, Silverberg et al. described an efficient modified AT reaction with phenols and H-phosphonates , using 5 equivalents of carbon tetrachloride, DIPEA as a base, with catalytic amount of DMAP, in acetonitrile solvent (scheme 119).[369]
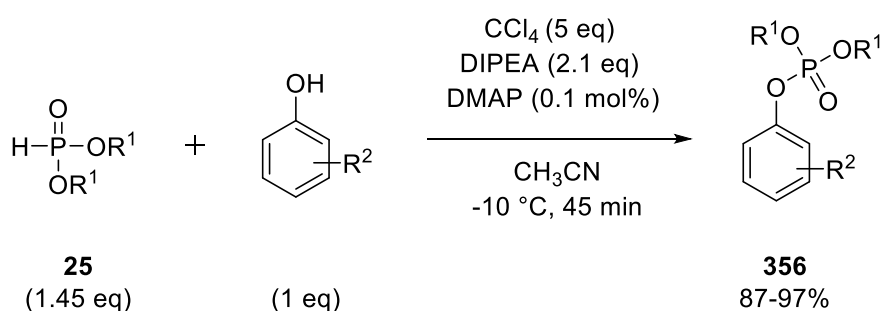
Scheme 119. Atherton-Todd reaction with phenols and H-phosphonates.

Initially, carbon tetrachloride was used as a solvent of choice, as it plays dual role in AT reaction; as a solvent as well as a halogenating agent to produce the reaction intermediate, the chlorophosphate derivative. Several other solvents such as, THF, diethyl ether,

dichloromethane, chloroform, acetonitrile etc have also been used in the reaction.[25,352,362,362,366] Generally, CCl$_4$ is the halogenating agent of choice, however, other halogenating agents such as, CBrCl$_3$, CBr$_4$ and CHI$_3$ have also been used in place of CCl$_4$.[350,367,368] For example, Lopusińki et al. prepared various phosphoramidates **357** using iodoform as a halogenating agent (scheme 120).[367]
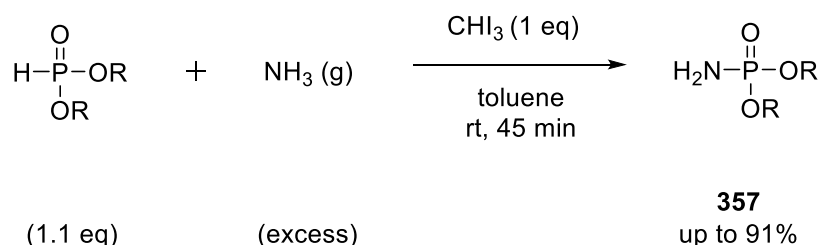
Scheme 120. Synthesis of phosphoramidates using iodoform as a halogenating agent.

The most widely used base in AT reaction is trialkyl amine, in particular, triethyl amine and diisopropylethylamine (DIPEA, Hünig's base). However, the use of other bases, such as DMAP (4-dimethylaminopyridine) and inorganic bases for examples NaOH and K$_2$CO$_3$ with a suitable phase transfer reagent such as triethylbenzylammonium chloride, have also been reported.[367,369,383] Very recently, Sharapova et al. reported the first base free example of AT reaction under thermal conditions.[384] They carried out the phosphorylation of alcohols (1.1 equivalent) with secondary phosphine chalcogenides **358** (1 equivalent) in carbon tetrachloride (41.45 equivalent) at 80-82 °C, for a duration of about 12-74 h (scheme 121).
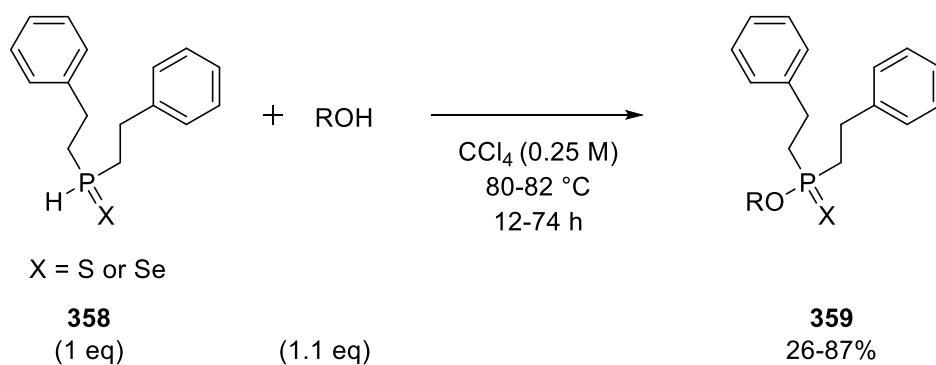
Scheme 121. Base free Atherton-Todd reaction.

Thus, Atherton-Todd reaction is widely employed as an O-P coupling or N-P coupling reaction.

4.5 Results and Discussion

4.5.1 Synthesis of Aryl-Sulfoxide Substrates

This section describes the synthesis of aryl-sulfoxide substrates which are used in the project.

4.5.1.1 Biarylphenol-sulfoxide 363
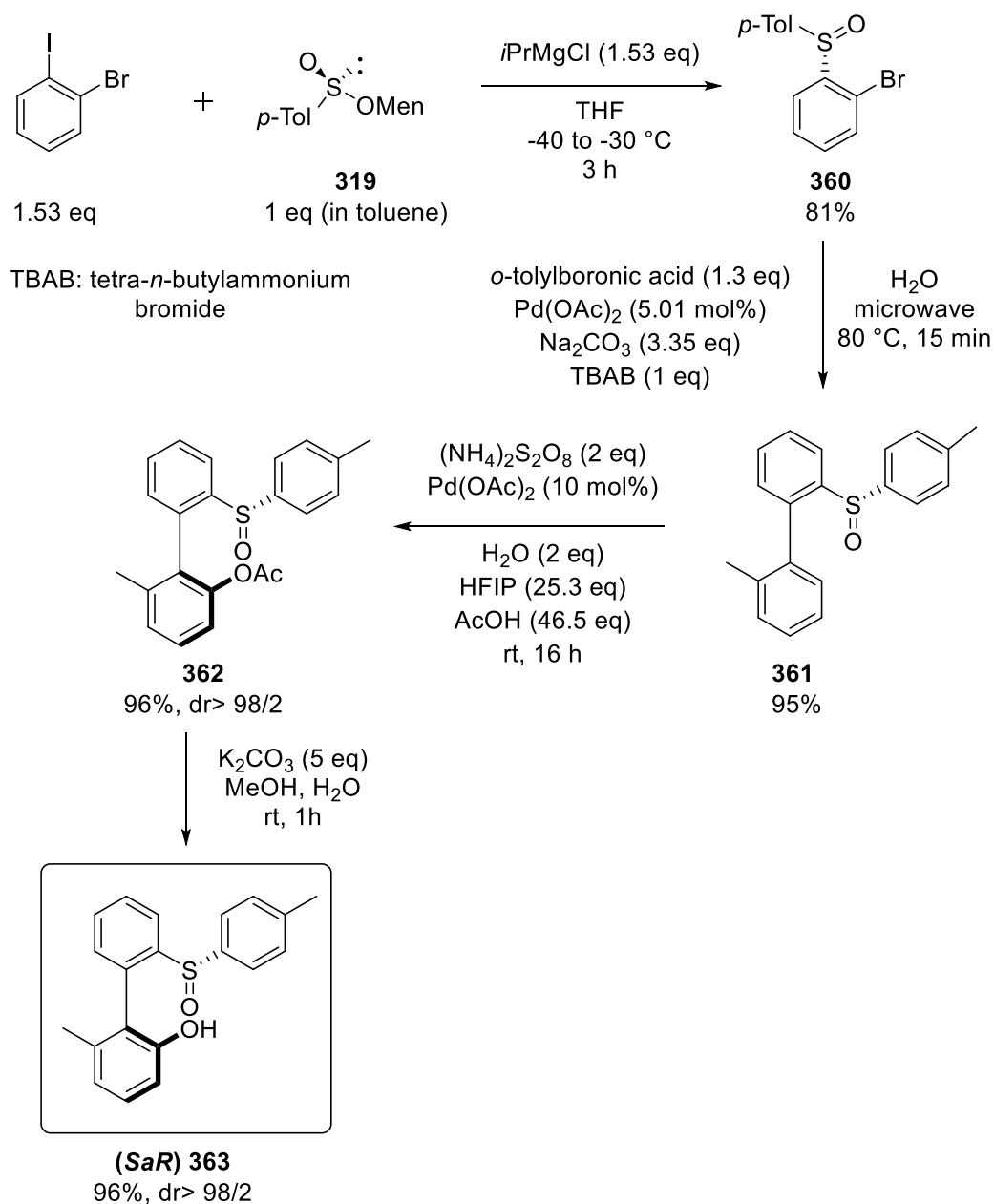
Scheme 122. Synthesis of biaryl phenol **363**.

Biarylphenol sulfoxide **363** was prepared according to the previously developed methodology in our team (scheme 122).[314] The first step involves the lithiation of iodobromobenzene that is followed by quenching with (-)-menthyl (*S*)-*p*-toluenesulfinate **319**. After the work up, the crude product **360** is crystallised with CH_2Cl_2/*n*-hexane (1:10) affording pure product **360** in about 81% yield. Next, under the microwave conditions compound **360** is subjected to Suzuki-Miyaura coupling with *o*-tolylboronic acid affording the compound **361** in almost quantitative yield. A palladium catalysed acetoxylation of the biaryl compound **361** affords the compound **362** with a very good yield of about 95% and with a very high diastereomeric ratio of more than 98/2 dr. Finally, hydrolysis of compound **362** affords the final product **363** in a very good yield of about 96% and with almost full retention of diastereoselectivity.

4.5.1.2 (*S*)-2-(*p*-tolylsulfinyl)phenol 366
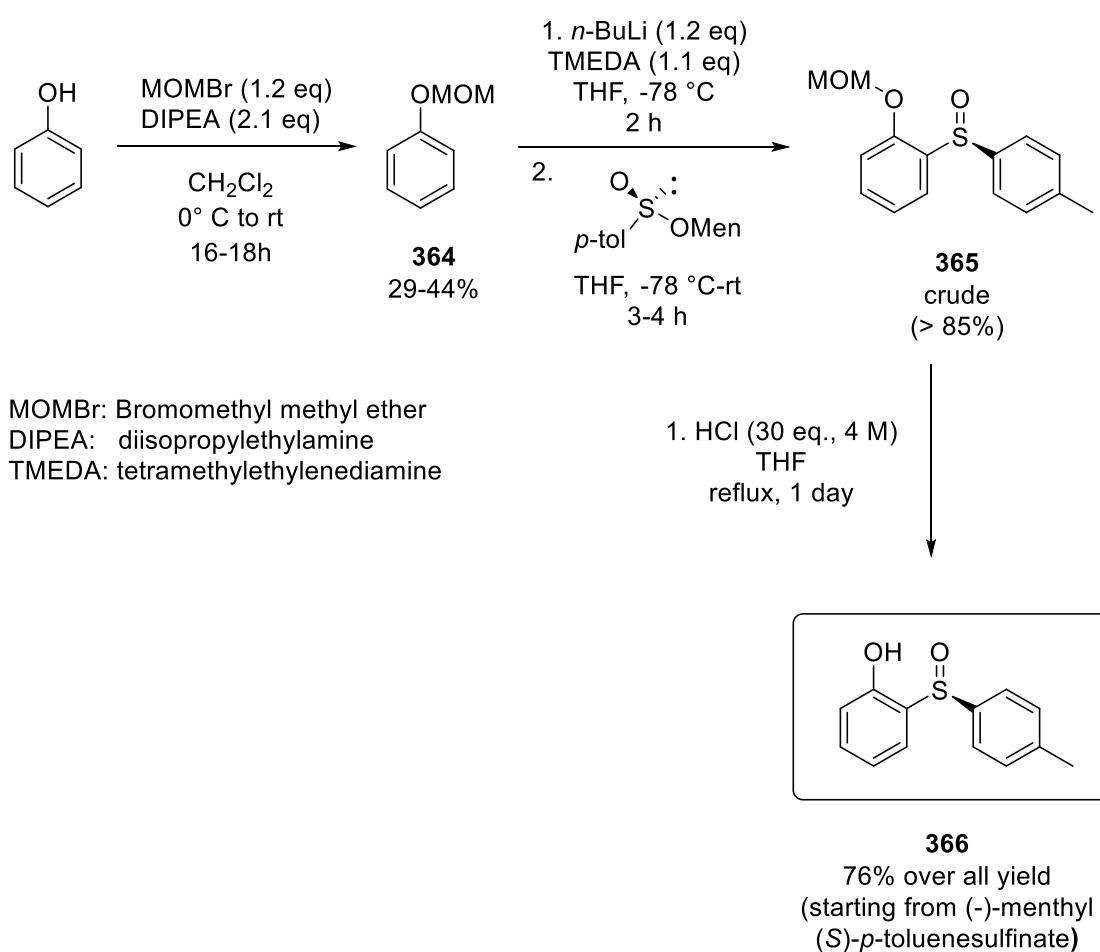
Scheme 123. Synthesis of substrate, (*S*)-2-(*p*-tolylsulfinyl)phenol **366**.

Compound **366** was first synthesised according to the literature.[385] i.e. using the strategy depicted in above scheme 123. First, phenol is protected with MOM group to afford the compound **364** in 29% yield (44% yield with second attempt). This compound **364** undergoes

ortho-lithiation in the presence of *n*-BuLi and TMEDA (tetramethylethylenediamine), followed by quenching with (-)-menthyl (*S*)-*p*-toluenesulfinate **319**. After the work up, the crude containing product **365** is subjected to deprotection of MOM group in the presence of HCl (30 eq., 4 M) under reflux conditions to finally obtain the product **366** in about 76% over all yield after the purification by chromatography (starting from (-)-menthyl (*S*)-*p*-toluenesulfinate) .

However, the first step of MOM protection of phenol provided compound **364** in quite less yield of 29% (44% yield in second attempt). Therefore next, we slightly changed our strategy for the synthesis of compound **366** targeting the higher yield of MOM protected phenol derivatives (scheme 124).[310]

MOMBr: Bromomethyl methyl ether
DIPEA: diisopropylethylamine
TMEDA: tetramethylethylenediamine
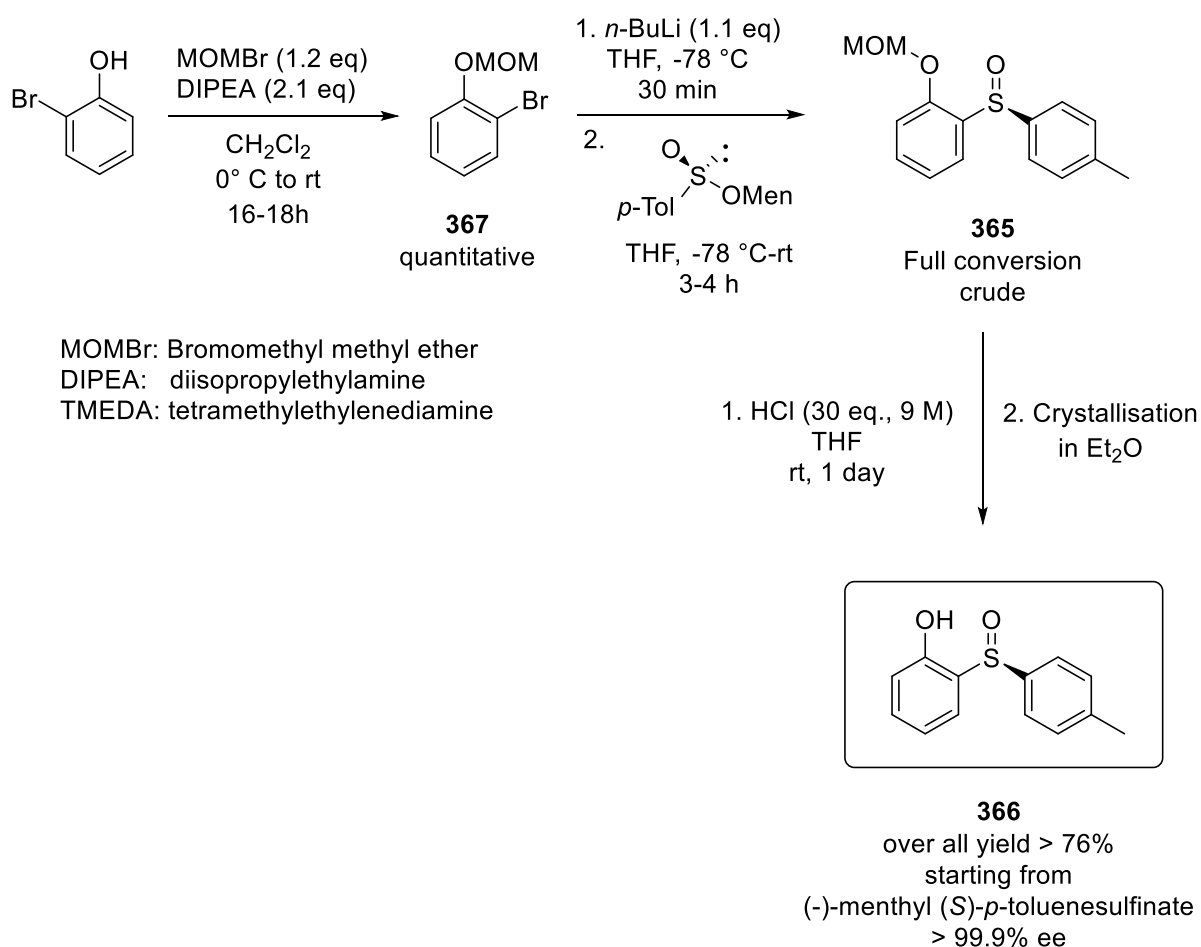
Scheme 124. Synthesis of substrate, (*S*)-2-(*p*-tolylsulfinyl)phenol **366**.

This strategy works quite well i.e. MOM protection step of bromophenol works quantitatively. Bromine-lithium exchange step of compound **367** in the presence of *n*-BuLi is conducted for about 20-30 min, which is followed by quenching with (-)-menthyl (*S*)-*p*-toluenesulfinate **319**. The crude obtained **365** after the work up is directly subjected to deprotection of MOM group in the presence of HCl (30 eq., 9 M) at room temperature. After

the work up, the product **366** is isolated by crystallisation in about 76% over all yield (starting from (-)-menthyl (*S*)-*p*-toluenesulfinate) and with > 99.99% ee.

4.5.1.3 (*S*)-2-(*tert*-butylsulfinyl)phenol 468a and derivatives.

MOMBr: Bromomethyl methyl ether
DIPEA: diisopropylethylamine
TMEDA: tetramethylethylenediamine
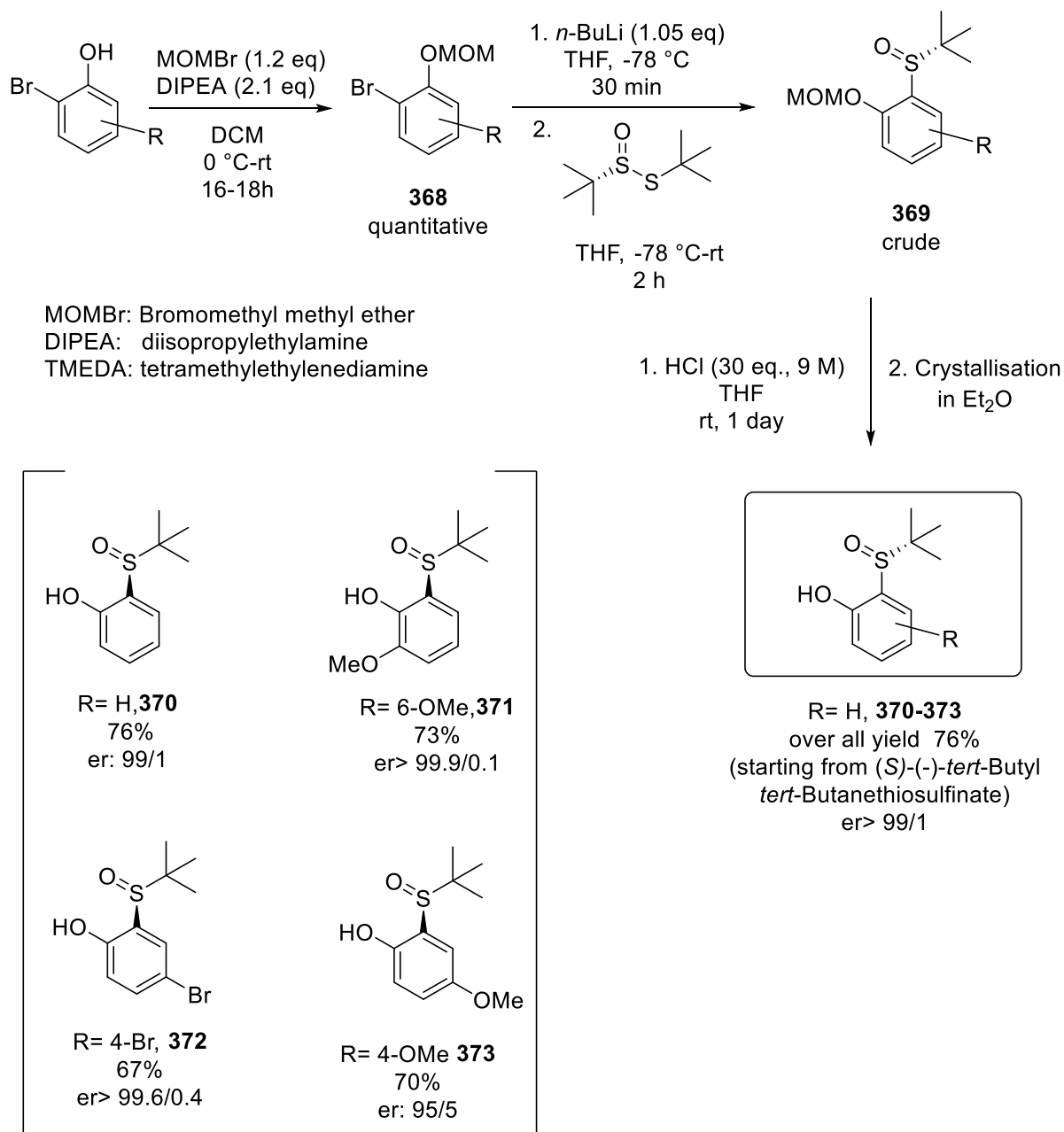
Scheme 125. Synthesis of substrate, (*S*)-2-(*tert*-butylsulfinyl)phenol derivatives **370-373**.

Following the similar strategy used for the synthesis of compound **366**, compounds **370-373** were easily prepared in about 67-76% over all yield (starting from (*S*)-(-)-*tert*-Butyl *tert*-

Butanethiosulfinate, which was prepared by literature procedure[342]) and with er ranging from 95/5 to more than 99/1 (scheme 125).

4.5.1.4 Adamant-1-yl sulfinyl phenol 378

First, adamantan-1-yl adamantane-1-sulfinothioate **376** was prepared as shown in the following scheme 126.[386,387]
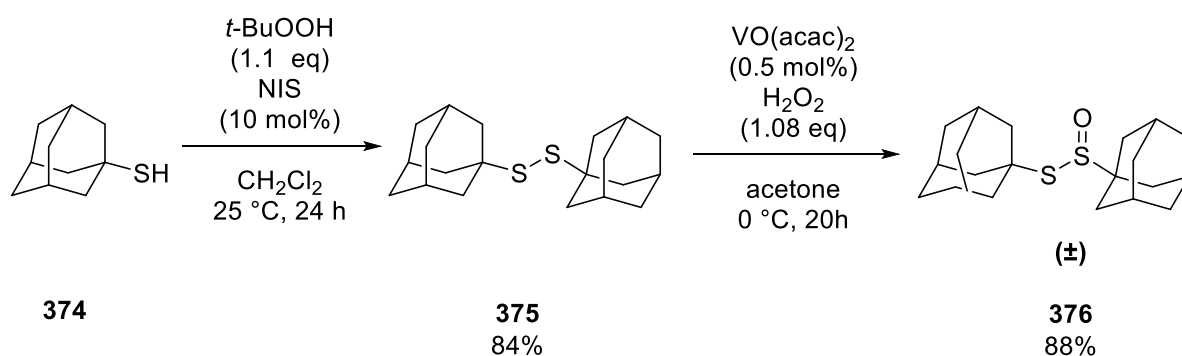
Scheme 126. Synthesis of adamantan-1-yl adamantane-1-sulfithioate **376** precursor.

MOMBr: Bromomethyl methyl ether
DIPEA: diisopropylethylamine
TMEDA: tetramethylethylenediamine
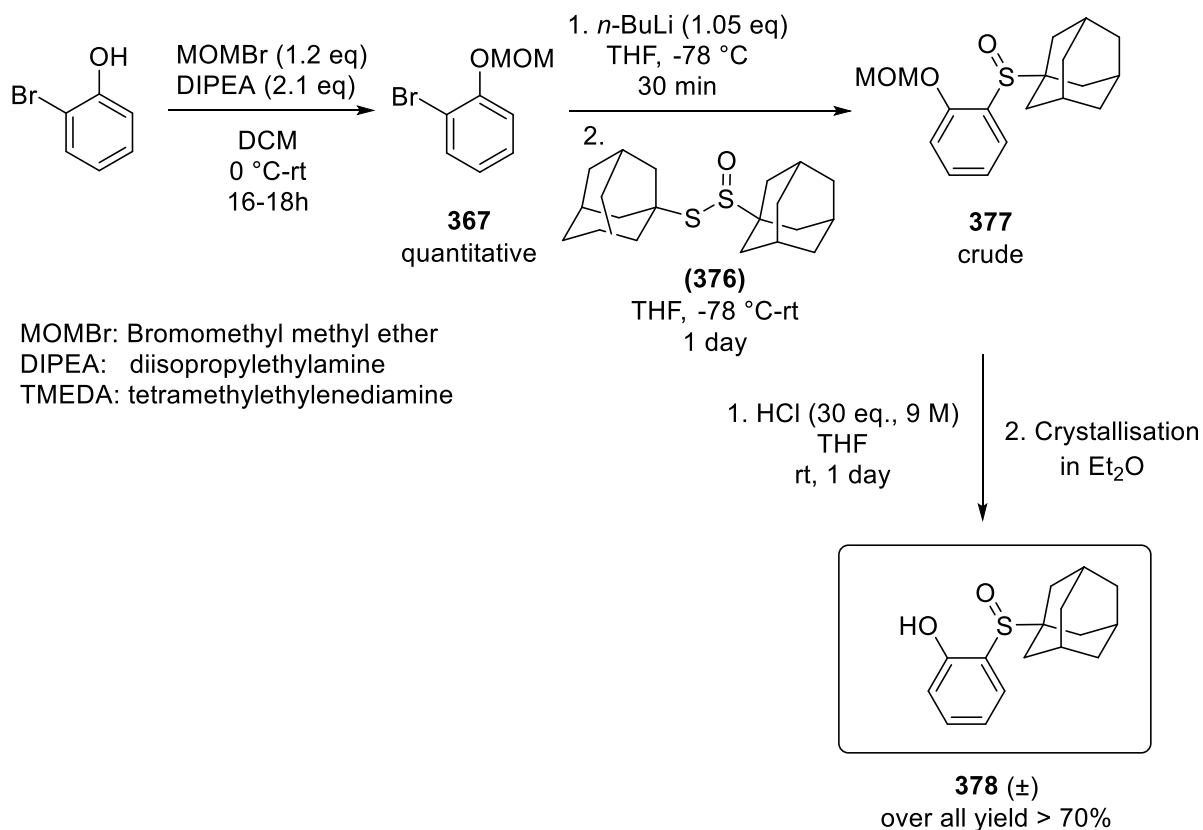
Scheme 127. Synthesis of compound **378.**

Later, following the similar strategy as used in scheme 125, compound **378** was easily obtained in a good yield (scheme 127).[310]

4.5.2 Hypervalent Iodine Chemistry

Our doctoral research project commenced under the Cefipra (Centre Indo-Français pour la Promotion de la Recherche Avancée) framework in 2015, with the Indian collaborator, Dr. Rajender Reddy, from IICT-Hyderabad, India.

The initial goal of the project was to develop the unprecedented stereoselective oxidative cross couplings based on a merge of a C-H activation and a radical chemistry strategy under metal free conditions. Such oxidative couplings of two non-prefunctionalised coupling partners was expected to provide an easy access to the high value-added chiral scaffolds, such as axially chiral biaryls, in a facile and direct way, and under relatively mild reaction conditions.[314,388–390] The main challenge of this project, a chiral induction, was speculated to achieve using a chiral sulfoxide moiety, which would act as both, a traceless directing group, as well as a chiral auxiliary.[311,313,314,391]

To fulfil this purpose, we initially focussed on the extraordinary progress that had been achieved in *hypervalent iodine* chemistry. Therefore, we turned directly our attention to the metal free atropo-selective arylation, using hypervalent iodine compounds as coupling partners.[15–19]

In order to accomplish the goal, we tried several reaction conditions using both chiral sulfoxide based biaryls **361** and monoaryls **312** and hypervalent iodine compounds **379**.
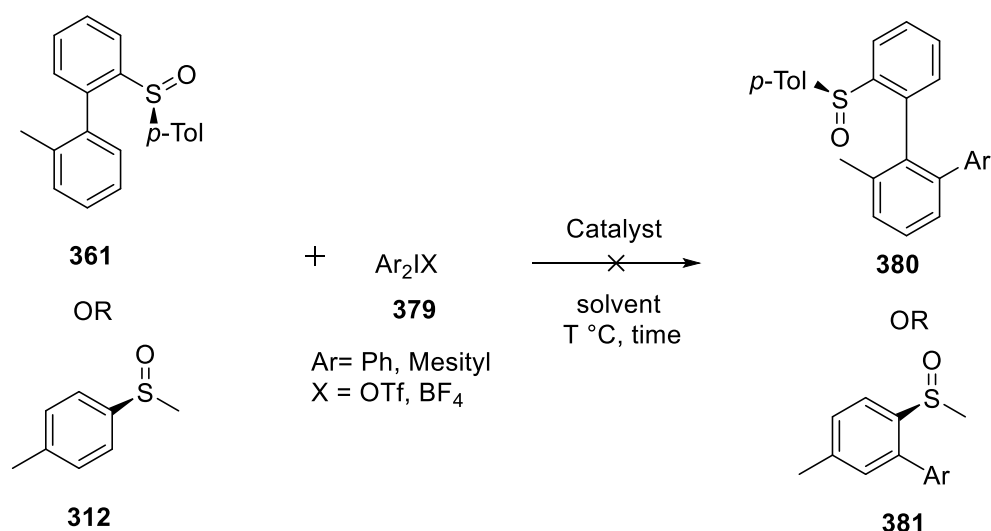
Scheme 128. Attempted arylation of biaryls/monoaryls bearing chiral sulfoxide with hypervalent iodine reagents.

Taking the advantage of sulfoxide chiral auxiliary attached to a biaryl compound such as **361**, an axial chirality could be induced in the corresponding product **380** during such arylation reactions. Unfortunately, the expected results could not be obtained (scheme 128).[15,20,21]

Following table 2 represents some of the reaction conditions which were employed for the arylation of both biaryls **361** and monoaryls **312** with hypervalent iodine reagents. In all the cases, desired product formation was not observed, instead starting material **361** and **312** were recovered.

Table 2.

S. No.	Catalyst	Temperature (°C)	Solvent	Time (day)	Comment
1	na	rt	HFIP	1	sm **361/312** recovered
2	na	rt	DCM	1	sm **361/312** recovered
3	TMSOTf	rt	DCM	1	sm **361/312** recovered
4	na	80	DCE	1	sm **361/312** recovered
5	na	80	HFIP	1	sm **361/312** recovered
6	na	80	TFE	1	sm **361/312** recovered
7	na	110	TFE	2	sm **361/312** recovered
8	TMSOTf	110	HFIP	2	sm **361/312** recovered

sm: starting material, HFIP: hexafluoro isopropanol, DCM: dichloromethane, DCE: dichloroethane, TFE: trifluoroethanol, TMSOTf: trimethylsilyl trifluoromethanesulfonate

Next, we decided to change our approach; we speculated that hypervalent iodine species bearing a chiral sulfoxide moiety in *ortho* position could be highly appealing reactants for asymmetric arylation reactions.[392,393] Therefore, we planned to carry out the synthesis of a chiral hypervalent iodine compound bearing a sulfoxide chiral auxiliary **383** (scheme 129).

382   **383**
                                sulfones
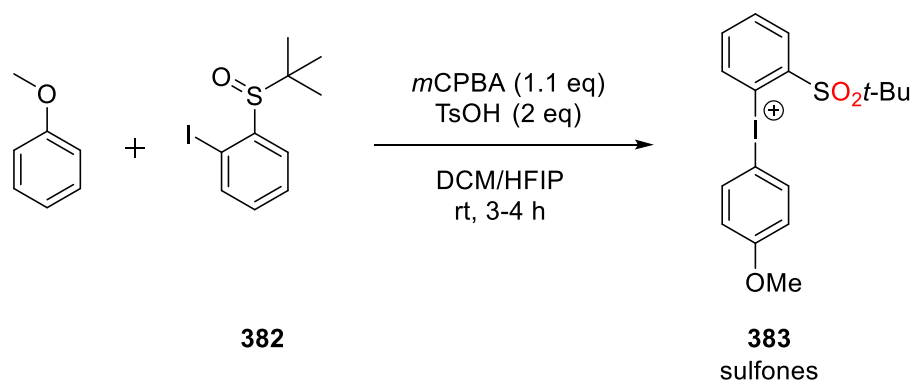
Scheme 129. Attempted synthesis of a chiral hypervalent iodine.

Unfortunately, under the experimental conditions we adopted, the corresponding hypervalent iodine could not be obtained and rather the compound **383** was obtained with a sulfone moiety instead of a sulfoxide i.e. sulfoxide was oxidised during such transformation.

In the meantime, a colleague in our team, Dr. James Rae, succeeded to synthesise the chiral hypervalent iodine **386** using another synthetic route involving ligand exchange with Koser's derivative **385** (scheme 130).[391]

384   **385**   **386**
(1 eq)   (1.1 eq)

TFA: trifluoroacetic acid   Quantitative
                                                   Chiral hypervalent
                                                   iodine
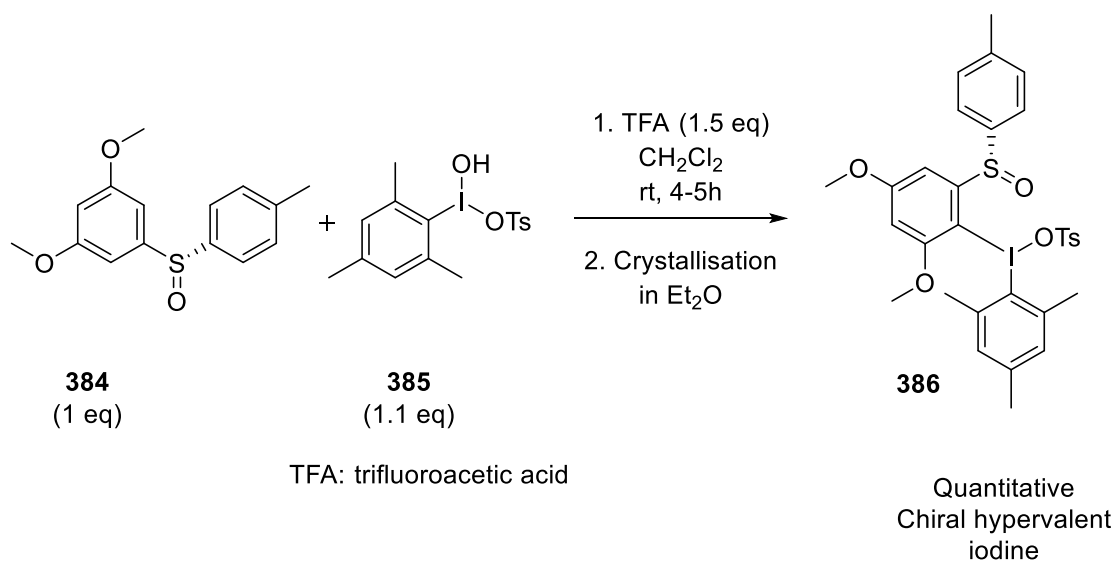
Scheme 130. Synthesis of chiral hypervalent iodine compound.

Drawing an inspiration from the work of Wang and Olofsson, who had reported non-asymmetric arylation of ethyl 2-methylcyanoacetate and nitroesters respectively under metal free conditions using hypervalent iodine reagents.[22,23]

We next explored the potential applications of the chiral hypervalent iodine compound developed in our team as a stereogenic arylating agent under metal free conditions. We hypothesised that the chiral hypervalent iodine compound could react with coupling partners, such as nitroesters and cyanoacetate derivatives. We were particularly interested to know if these transformations would afford the corresponding arylated products with quaternary chiral C-centres, which would be highly valuable compounds in fine organic chemistry.

Several experiments were carried out in order to achieve the desired arylation of nitroesters and cyanoacetate derivatives coupling partners using chiral hypervalent iodine compounds **386** and **387** . A number of reaction parameters were changed during the investigation: coupling partners, bases, solvents, temperature and duration of the reaction (table 3). However, we only observed the three main side products: reduced products **390** and **391**, together with a side product **392** resulting from an intra-molecular arylation of chiral hypervalent iodine **386/387**(scheme 131).
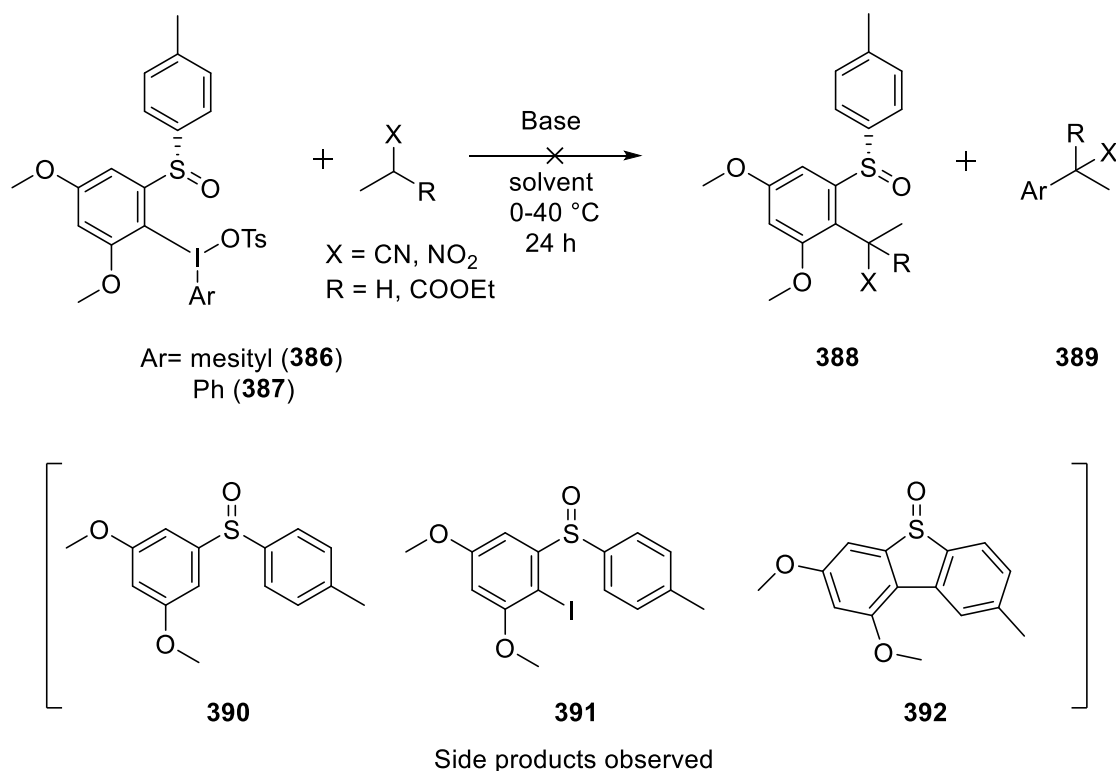
Scheme 131. Attempted arylation of nitro/cyano derivatives with a chiral hypervalent iodine compound.

Table 3.

S. No.	X	Ar	Base	Temperature (°C)	Solvent
1	CN	mesityl	t-BuOK	0/rt	DCM
2	CN	mesityl	t-BuOK	0/rt	DCM
3	CN	mesityl	t-BuOK	0/rt	DCM/THF
4	CN	mesityl	t-BuOK	40/rt	DCM
5	CN	mesityl	t-BuOK	0/rt	toluene
6	CN	mesityl	Cs_2CO_3	0/rt	DCM
7	CN	mesityl	Cs_2CO_3	40/rt	HFIP
8	CN	mesityl	NaH	0/rt	DCM/THF
9	NO_2	mesityl	t-BuOK	0/rt	DCM
10	NO_2	mesityl	Cs_2CO_3	0/rt	DCM
11	CN	phenyl	t-BuOK	40/rt	DCM
12	CN	phenyl	Cs_2CO_3	0/rt	DCM
13	CN	phenyl	NaH	0/rt	DCM/THF
14	CN	phenyl	Cs_2CO_3	40/rt	DCM
15	NO_2	phenyl	t-BuOK	0/rt	DCM
16	NO_2	phenyl	Cs_2CO_3	40/rt	DCM

HFIP: hexafluoroisopropanol, DCM: dichloromethane, THF: tetrahydrofuran

To investigate further about the side reaction products, stability tests of the hypervalent iodine reagents under various basic conditions were conducted. Thus, it was revealed that the presence of a base in the reaction mixture led to the formation of all the three side products **390-392**. At the end, unfortunately we did not observe any of the expected coupling products during our investigation.

Kita et al. published several reports on metal free arylations to access biaryls using hypervalent iodine reagents.[16,17,21] We tried to explore the potential of these coupling reactions using the chiral hypervalent iodine compound **386** (scheme 132). Herein, TMSOTf acts as a Lewis acid catalyst activating (causing hypervalent iodine to be more electrophilic) hypervalent iodine **386** and triggering a transfer of one of its aryl groups to a more electron rich coupling partner and releasing an aryl iodide (ArI). However, under our experimental conditions, the desired products **393/394** could not be obtained in this case too.
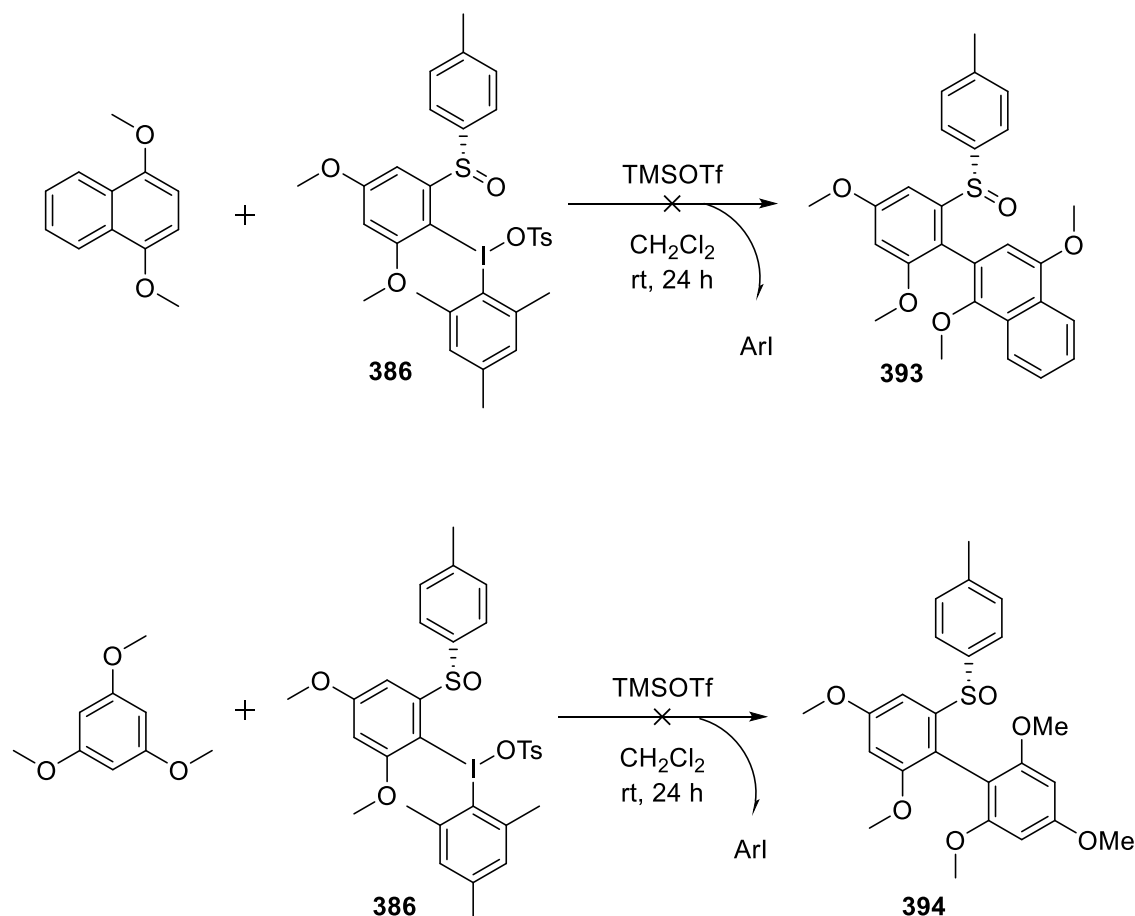
Scheme 132. Attempted arylation using chiral hypervalent iodine

In the meantime, our CEFIPRA collaborator, Dr. Rajender Reddy visited our laboratory in Strasbourg. This scientific meeting gave us an opportunity for sharing the most recent works

of both the research groups. We were particularly interested in the O-P coupling reactions developed at that moment in the group of Dr. Rajender Reddy. The details would be discussed in the coming section.

4.5.3 P-stereogenic phosphorous Chemistry

Under the conditions developed in Dr. Reddy's team at IICT-Hyderabad, India, for the O-P coupling reaction, commercially available substrates i.e. a phenol **396** and an H-phosphonate **395** undergo O-P bond-formation/coupling in the presence of lithium iodide as a catalyst and *t*-butyl hydroperoxide as an oxidant in acetonitrile at room temperature under air (scheme 133). The corresponding products **397** are generally obtained in quantitative yields.
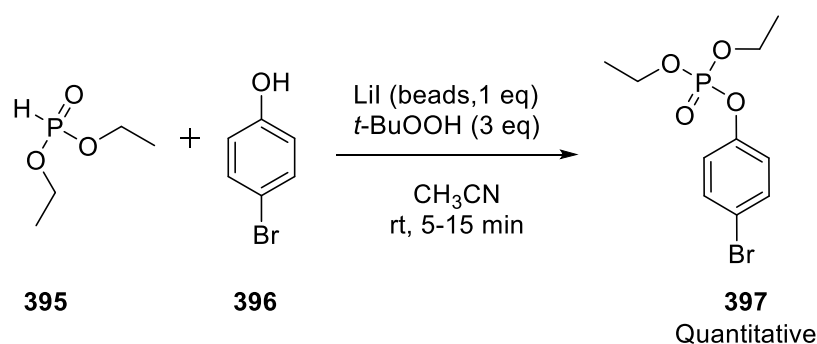
Scheme 133. O-P coupling reaction developed by Dr. Reddy and co-workers (unpublished results).

Inspired by this work, and targeting a fully collaborative project, we decided to investigate the potential of phenols bearing a chiral sulfoxide moiety in such O-P coupling reactions. We specifically targeted the potential of accessing P-stereogenic compounds *via* such transformations. Despite the tremendous importance of these P-stereogenic compounds in several fields of science, access to them is still challenging and limited.[1,3,70,92,101,156]

Initially, we selected a commercially available and an easily accessible racemic ethylphenyl H-phosphinate **41a**, as a model substrate and together with a diastereopure biaryl phenol **363** bearing a chiral sulfoxide moiety.

H-phosphinates possess several advantages over other organophosphorous precursors, such as they are, in general more stable than their corresponding trivalent phosphorous compounds and chloro derivatives, lower volatile with reduced hazardous properties, can be handled without the inert conditions and generally have less or no odour.[302] In particular, alkylphenyl H-phosphinates are amongst the most commonly utilised H-phosphinate substrates for the synthesis of phosphinates and tertiary phosphine oxide, as the phenyl group attached to the phosphorous atom is present in most of well-known

organophosphorous compounds.[14,69,80,87,106] Moreover, some of them are also commercially available such as ethylphenyl H-phosphinate **41a**.

Ethylphenyl H-phosphinates **41a** can also be easily prepared from the commercially available starting materials, such as phenylphosphinic acid dichlorophenyl phosphine **(**scheme 128).[76,79,106,301,303–306] Other coupling partner, diastereopure biaryl phenol **363** bearing a chiral sulfoxide moiety, was chosen for the project considering the high importance of biaryl scaffolds in various fields of science such as biology, ligand-design etc [389,394,395]. Moreover, it can easily be prepared on gram scale using a previously developed methodology in our team.[349]
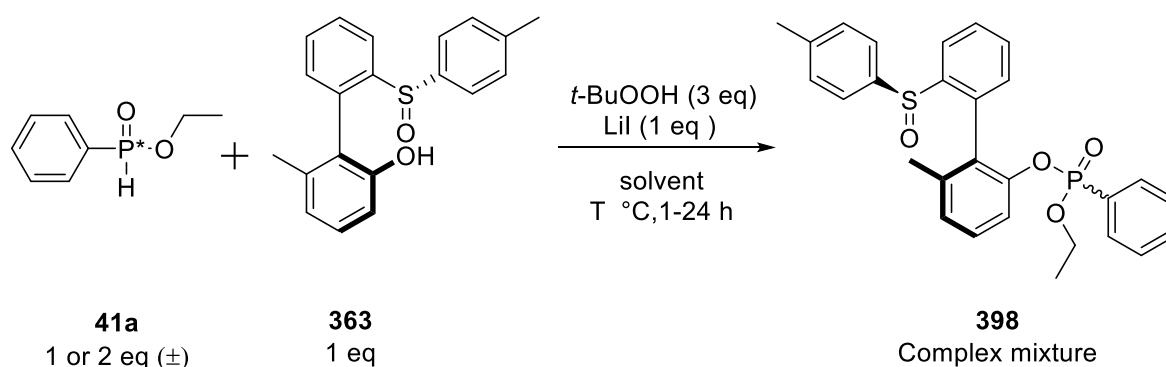
Scheme 134. Attempted O-P coupling reaction between **354a** and **432**.

Table 4

S. No.	Temperature (°C)	Solvent	Conversion (%)	Comment
1	rt	ACN	0	No reaction
2	40	ACN	0	No reaction
3	60	ACN	0	No reaction
4	rt	DCM	100	Complex nmr
5	rt	DCM/ACN	0	No reaction
6	rt	DCM/toluene	0	No reaction

DCM: dichloromethane, ACN: acetonitrile

Under the O-P coupling reaction conditions developed by Dr. Reddy indeed, the desired reaction did not work (scheme 134). By changing the reaction parameters, such as temperature, solvent etc, the complex reaction mixture was obtained (entry 4, table 4), and it was challenging to isolate the desired product **398**.

Therefore, we turned our attention to other available methodologies for the O-P coupling reactions. Rewardingly, it was found that under Atherton-Todd (AT) reaction conditions, the desired reaction proceeded well (scheme 135).[24–26] The reaction works well with a range of temperature with almost full conversion of starting material **363** and affording the desired product **398**.

41a 1 or 2 eq (±)   **363** 1 eq   NEt$_3$ (2 eq)   CCl$_4$ (0.2 M)   T °C,1 day   R = CH$_3$, CF$_3$ T (°C) = -78, 0   **398** 44-56%   50/50 dr
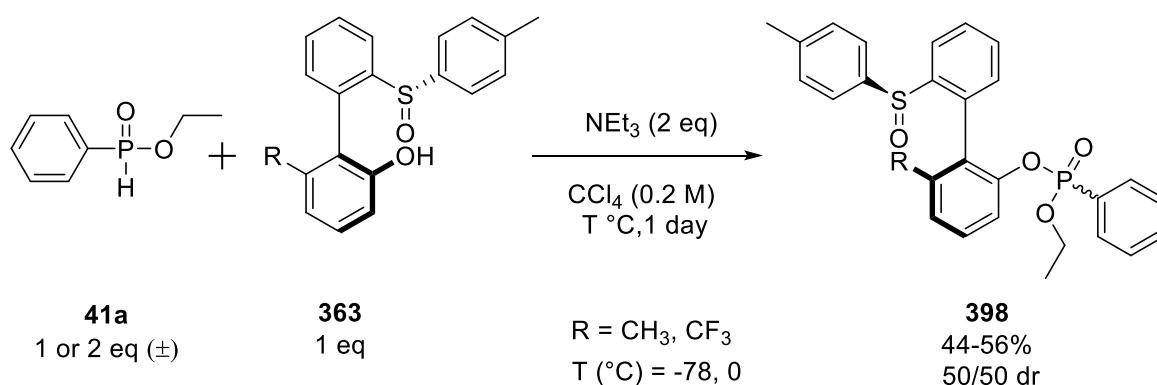
Scheme 135. Atherton-Todd reaction for O-P coupling between **41a** and **363**.

However, we obtained both the diastereomers of the corresponding product **398** (scheme 135) in about 50/50 diastereomeric ratio (dr).

Therefore, we hypothesised that the sulfoxide chiral auxiliary should be in a close proximity to the phenolic group, in order to favour the expected chiral induction at P atom during the O-P coupling reaction. And hence, in our next set of experiments, we installed a chiral sulfoxide group on *ortho* position of the phenol to get the substrate (*S*)-2-(*p*-tolylsulfinyl)phenol **366** (scheme 136), which was easily prepared using following strategy described in scheme 124.[310,385]

Under the optimised conditions, the desired O-P coupling reaction proceeded smoothly, providing the corresponding product **399** in 83% yield, but with 60/40 dr(scheme 136).
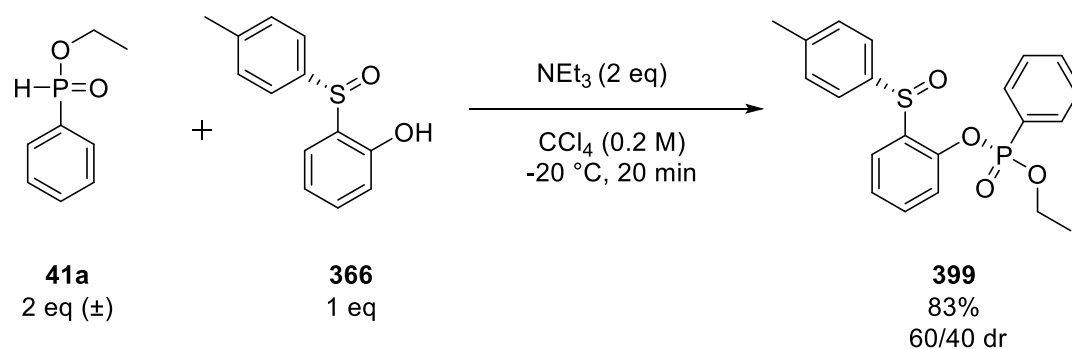
Scheme 136. Atherton-Todd reaction for O-P coupling between **41a** and **399**.

The expected result of the O-P coupling product **399** with stereoinduction of 60/40 obtained under AT reaction condition, prompted us to use more hindered *t*-butylsulfoxide chiral auxiliary on *ortho* position of the phenol. In order to carry out the preliminary investigation of the desired O-P coupling reaction, we first prepared an easily accessible racemic 2-(*tert*-butylsulfinyl)phenol **370** according to the literature procedure (scheme 125).[310]

The substrate, 2-(*tert*-butylsulfinyl)phenol **370** was subjected to AT reaction. To our delight, we succeeded in carrying out the diastereoselective O-P coupling or phosphorylation of **370** to obtain the desired product **400**, with diastereomeric ratio of up to 90/10 (scheme 137).
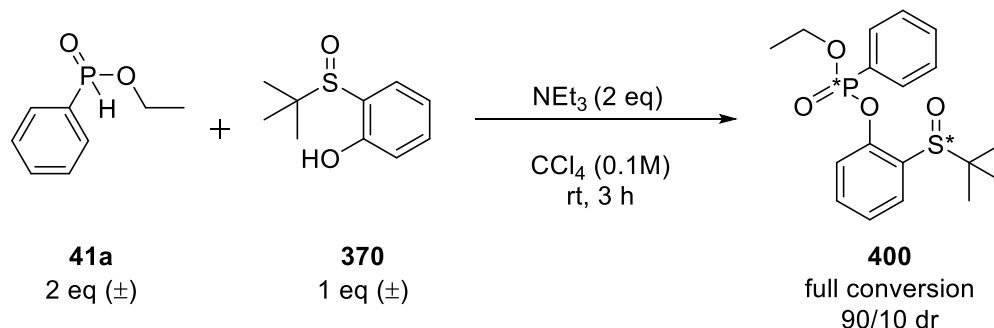
Scheme 137. Atherton-Todd reaction for O-P coupling between **41a** and **370.**

Under the reaction condition, 2 equivalents of ethylphenyl H-phosphinate **41a** reacts with 1 equivalent of racemic *t*-butylsulfinylphenol **370** in the presence of 2 equivalents of triethylamine in carbon tetrachloride at room temperature under air. Moreover, we were delighted to separate the major diastereomer-d1 of the O-P coupling product **400** in about 78% yield by direct crystallisation of the reaction crude in dichloromethane/pentane mixture.

The dr of the product was determined using ^{31}P NMR and chiral HPLC spectra (fig. 28 and fig. 29).

a   b
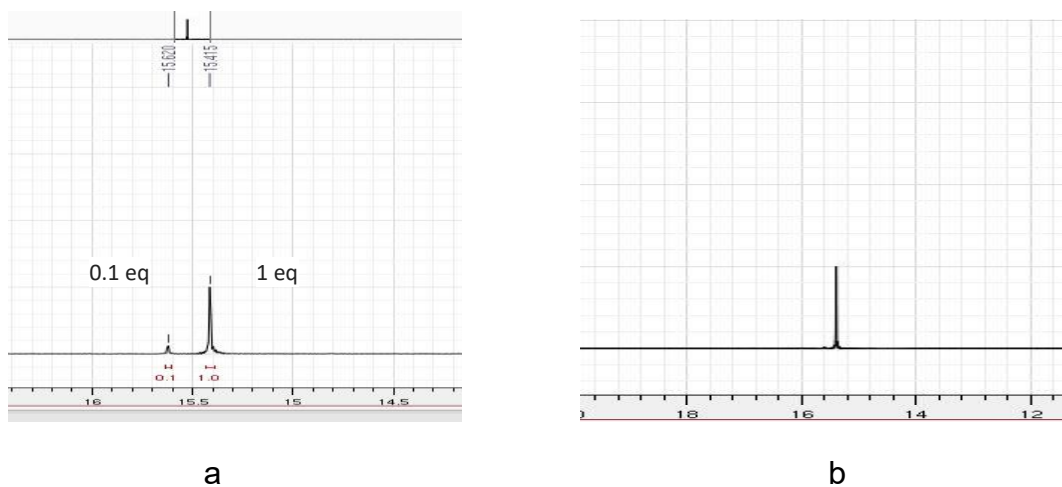
Fig. 28. ^{31}P NMR spectra of a) mixture of diastereomers of compound **400** d1/d2: 90/10. b) Major diastereomer d1.

As it can be seen in fig. 28a that two ^{31}P NMR signals at 15.4 ppm and 15.6 ppm with a ratio of 1/0.1 equivalent, correspond to the two diastereomers d1 and d2 of the O-P coupling product **400**. After separation of the major diastereomer d1 by crystallisation, ^{31}P NMR spectrum (fig. 28b) shows only one signal at around 15.4 ppm, indicating presence of a single major diastereomer.

a   b
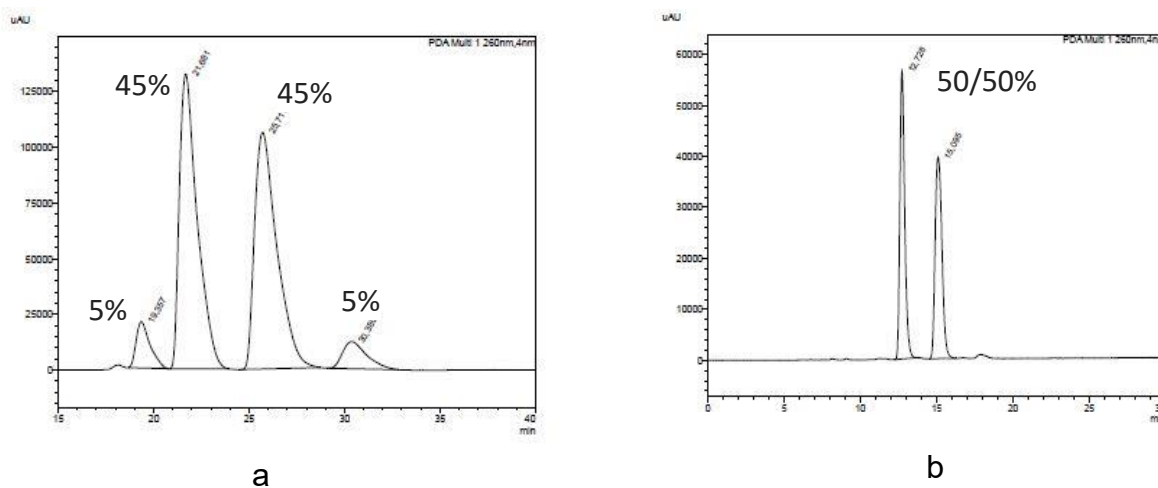
Fig. 29. Chiral HPLC spectra of a) mixture of diastereomers of **400** d1/d2: 90/10. b) Major diastereomer d1.

Furthermore, fig. 29a shows chiral HPLC spectrum of a mixture of diastereomers of the compound **400** in 90/10 ratio (each diastereomer of the compound **400** is composed of two

enantiomers. After the separation of the two diastereomers by crystallisation, a chiral HPLC spectrum was obtained for the major diastereomer shown in fig. 29b.

363

(50/50 dr)

366

(60/40 dr)

370

(90/10 dr)

Increasing order of effect of chiral auxiliary on stereo induction on P atom

Scheme 138. Trend of different chiral auxiliaries on stereo induction on P atom in AT reaction.

Thus, by comparing the three substrates bearing sulfoxide chiral auxiliary i.e. biaryl phenol **363**, monoaryl phenol **366** and *t*-butylsulfinylphenol **370**, used in the AT reactions, the most hindered one i.e. *t*-butylsulfoxide phenol **370**, produced the maximum stereo induction on P atom (scheme 138).

Next, we prepared the enantiopure substrate, (*S*)-2-(*tert*-butylsulfinyl)phenol **370** (previously described in scheme 125).[310]

We carried out the AT reaction with the enantiopure (*S*)-2-(*tert*-butylsulfinyl)phenol **370** substrate, under the optimised reaction conditions (scheme 139). To our surprise, we observed a decrease in diastereoselectivity of the reaction i.e. dr of 71/29 dr was measured.

41a
2 eq (±)

370
1 eq

400
Full conversion
71/29 dr

Scheme 139. AT reaction with enantiopure (*S*)-2-(*tert*-butylsulfinyl)phenol **370** and ethylphenyl phosphinate **41a**.

However, by adding the molecular sieves (MS) in the reaction, the diastereoselectivity could be improved up to 83/17 dr while achieving a full conversion of starting material **370** with a reduced reaction time i.e. from 3 to 2 h(scheme 140).
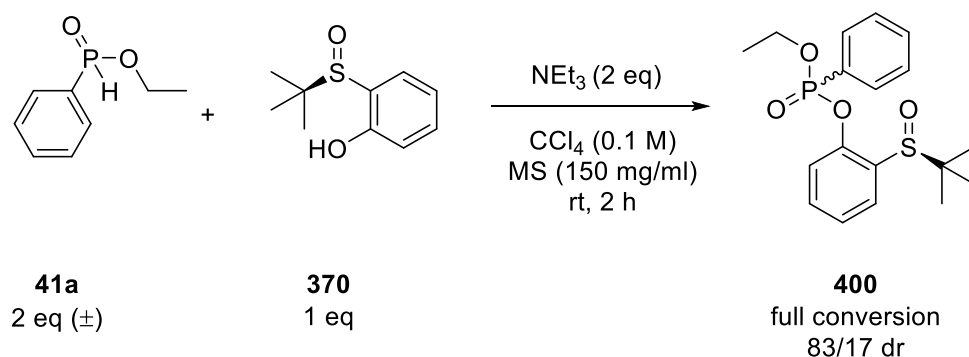
Scheme 140. AT reaction with molecular sieves in the reaction.

Furthermore, we wanted to replace the solvent carbon tetrachloride with other less toxic organic solvents. Therefore, we modified a number of parameters for the classical Atherton-Todd (AT) reaction.

In all of the following screening reactions, the reaction mixtures were stirred under the specified conditions, until almost complete consumption of starting materials was observed by TLC. Following table 5 represents the screening of various solvents.

Table 5. Effect of solvent on diastereoselectivity of the modified Atherton-Todd (AT) reaction.

S. No.	Solvent	Time (h)	dr
1	THF	1	77/23
2	toluene	1	77/23
3	trifluorotoluene	1	77/23
4	dioxane	1	77/23
5	diethyl ether	1	77/23
6	dimethoxy ethane	1	77/23
7	acetonitrile	1	71/29
8	dichloromethane	1	71/29
9	chloroform	2	58/42
10	cyclohexane	2	67/33

As it can be seen in the table 5, modified AT reaction works well in most of all the solvents tested. Finally, as an easily accessible dry solvent, THF (entry 1) was selected as the solvent for further screening of the other reaction parameters with 77/23 observed dr.

Table 6. Effect of temperature on diastereoselectivity of the modified Atherton-Todd (AT) reaction.

41a
2 eq (±)

370
1 eq

CCl$_4$ (10 eq)
NEt$_3$ (2 eq)

THF (0.1 M)
MS
T °C, time (h)

400
full conversion
83/17 dr
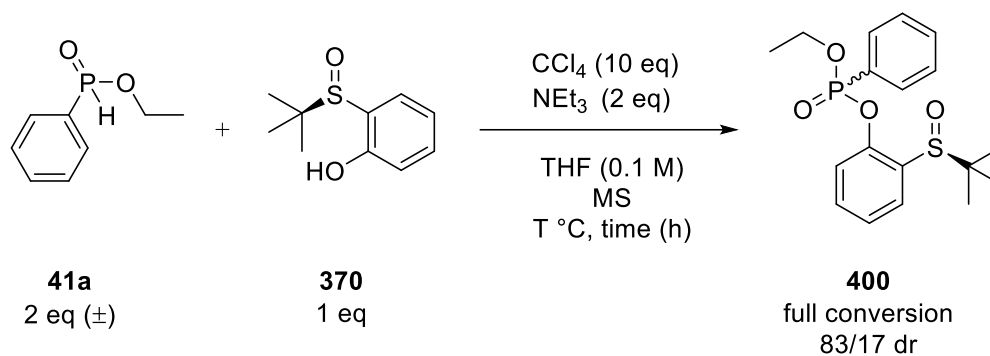
S. No.	Temperature (°C)	Time (h)	Conversion (%)	dr
1	-40	4.5	90	58/42
2	0	2	93	71/29
3	rt	1	100	71/29
4	30	1	100	83/17
5	50	1	100	83/17

During the study of impact of temperature on reaction, an interesting trend was noticed; on going from a lower temperature (-40 °C) to a higher temperature (30 °C) (table 6, entries 1-4), diastereoselectivity of the reaction increased up to a level, and after that, further increase in the temperature did not affect the diastereoselectivity of the reaction (table 6, entries 4 and 5). Accordingly, for the practical reasons, we decided to follow up this reaction at room temperature.

Table 7. Effect of concentration on diastereoselectivity of the modified Atherton-Todd (AT) reaction.
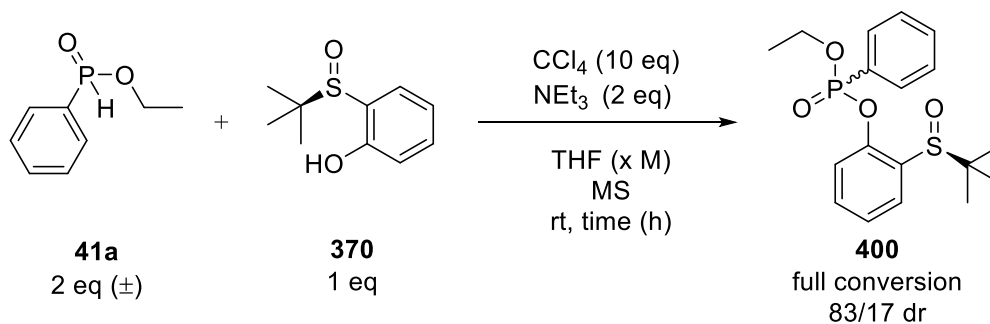
S. No.	Concentration (x M)	Time (h)	Conversion (%)	dr
1	0.2	0.5	100	77/23
2	0.1	1	100	77/23
3	0.05	2	100	83/17
4	0.025	6	90	83/17

Also, it was observed that when the concentration of the reaction was decreased from 0.2 M to 0.05 M, the diastereoselectivity of the reaction increased from 77/23 to 83/17 dr (table 7). Therefore, rest of the screening experiments were carried out with 0.05 M concentration.

Table 8. Effect of different bases on diastereoselectivity of the modified Atherton-Todd (AT) reaction.

41a
2 eq (±)

370
1 eq

400
full conversion
83/17 dr

S. No.	Base	Time	Conversion	dr
	(2 eq)	(h)	(%)	
1	triethylamine	2	100	83/17
2	DBU	1	100	50/50
3	DMAP	2	85	50/50
4	2,6-lutidine	2	0	na
5	DIPEA*	24	100	90/10

4 equivalents of DIPEA were used. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP: 4-dimethylaminopyridine, DIPEA: diisopropylethylamine

It was found that trialkylamine bases worked well for the reaction, in particular diisopropylethylamine (DIPEA). The highest diastereoselectivity was observed with DIPEA i.e. 90/10 dr however, use of 4 equivalents of DIPEA and a prolonged reaction time i.e. 24 h, was necessary to achieve the full conversion of the starting material (table 8).

Finally, under the optimised reaction conditions i.e. using 2 equivalents of racemic ethylphenyl H-phosphinate **41a**, 1 equivalent of enantiopure (*S*)-2-(*tert*-butylsulfinyl)phenol **370**, 10 equivalents of carbon tetrachloride, 4 equivalents of diisopropylethylamine and 75 mg/ml of solvent molecular sieves (MS) in THF under argon at room temperature for about 24 h, the maximum diastereomeric ratio of 90/10 was achieved with up to 85% yield (scheme 141).

Scheme 141. An Optimised modified Atherton-Todd reaction.

Next, considering the effect of the steric hindrance of the substituent on the sulfoxide i.e. *t*-butyl instead of *p*-tolyl substituent, we wanted to evaluate what would be the diastereoselectivity of the AT reaction with use of an adamantly substituted sulfoxide **378**.

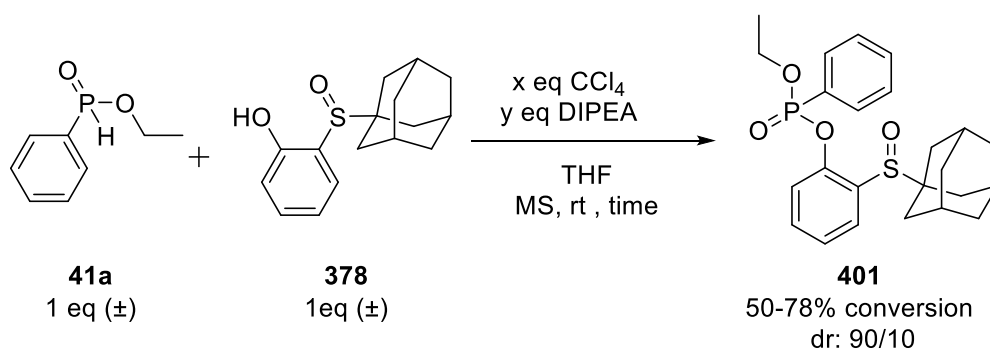Surprisingly, we obtained the corresponding product **401** with lower yields (50-78% conversion) and with 90/10 dr (scheme 142 and table 9) i.e. same dr compared to the reaction in scheme 142, with *t*-butyl group being attached to sulfoxide.

Scheme 142. Effect of adamantly substituted sulfoxide group on diastereoselectivity of the reaction.

Under the previously optimised reaction condition, compound **401** was obtained with about 67% conversion and with 90/10 dr (entry 1). By changing various reaction parameters such as reaction time, amount of CCl$_4$/DIPEA etc compound **401** was obtained with up to 78% conversion and with up to 90/10 dr (entry 2).

Table 9.

S. No.	DIPEA (x eq)	CCl$_4$ (y eq)	Concentration (p M)	Time (q h)	Conversion (%)	dr
1	4	10	0.05	24	67	90/10
2	4	10	0.05	60	78	90/10
3	4	10	0.1	24	68	83/17
4	6	10	0.05	24	67	90/10
5	8	20	0.05	24	70	90/10
6*	4	10	0.05	24	50	77/23

*0.2 eq. DMAP (dimethylaminopyridine) was added

4.5.3.1 Dynamic kinetic resolution (dkr)

 Dynamic kinetic resolution (dkr) is one of the highly valuable tools in asymmetric synthesis, where a single enantiomer or diastereomer of a compound can selectively be obtained from a racemic mixture of the starting material.[396,397] Contrary to the kinetic resolution, where maximum yield of accessing an enantiomer or a diastereomer is only 50%, in case of dynamic kinetic resolution (dkr) the corresponding product may be obtained in 100% yield. This powerful concept can help in overcoming the challenges and difficulties associated with the asymmetric synthesis.[398,399] Following energy diagram shows typical energy profiles for *R* and *S* enantiomers of a compound in a chemical reaction.
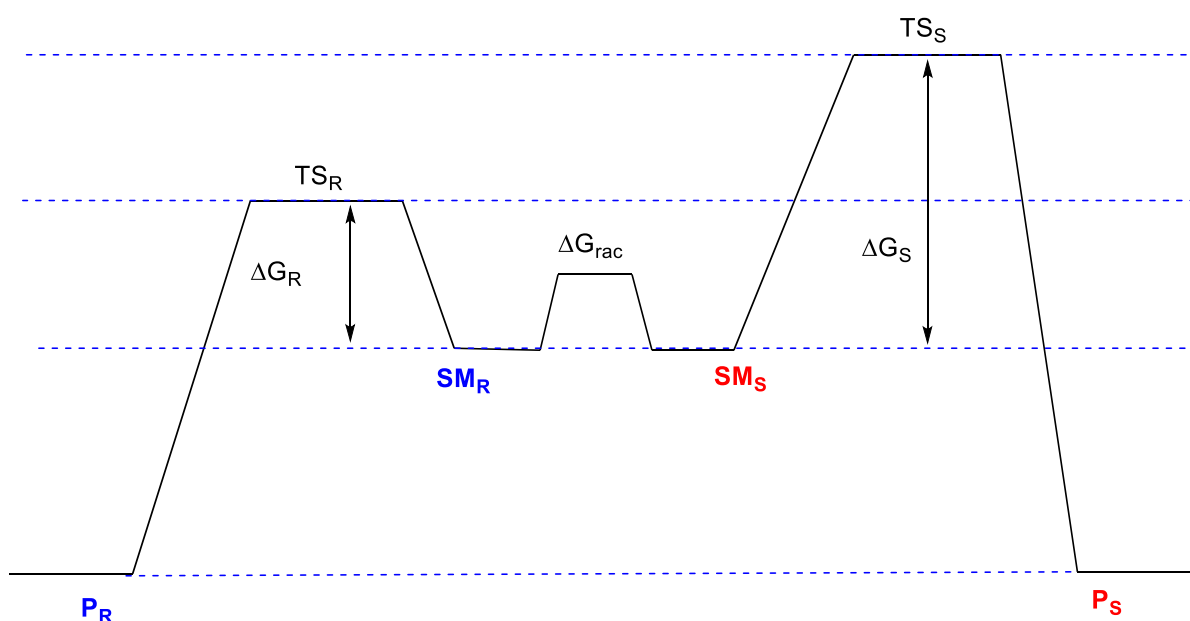

SM$_R$: Starting material with *R*-configuration, SM$_S$: Starting material with *S*-configuration

P$_R$: Product with *R*-configuration,P$_S$: Product with *S*-configuration,

ΔG_R : Energy barrier to form P$_R$ from SM$_R$, ΔG_{rac} :Energy barrier of racemisation of SM$_R$

and SM$_S$, ΔG_S :Energy barrier to form P$_S$ from SM$_S$, TS$_R$: Transition state of *R* isomer

TS$_S$: Transition state of *S* isomer

Scheme 143. A general energy diagram of *R* and *S* enantiomer of a compound.

During a *dynamic kinetic resolution (dkr)* process in a chemical reaction, both the enantiomers, *R* and *S* of a compound/an intermediate are in equilibrium due to the low inversion energy barrier resulting in racemisation and thus, under the reaction conditions, one of the enantiomers having a lower reaction energy barrier (ΔG) is predominantly converted into the final product while the other enantiomer of the substrate is easily racemised. Thus, this process ideally allows the access of a single enantiomer or diastereomer of a compound in a chemical reaction.

Today, *dynamic kinetic resolution (dkr)* concept is applied in several important asymmetric transformations such as asymmetric hydrogenations, asymmetric reductions, asymmetric aldol reactions and a number of enzyme/metals catalysed asymmetric reactions.[349,400–407]

Noyori's asymmetric hydrogenation *via* dkr mechanism includes the Ru/BINAP catalysed asymmetric hydrogenation of keto-lactones **401** where, under the reaction conditions the keto-lactone is selectively reduced to one of the diastereomers **402** (scheme 144).[400]
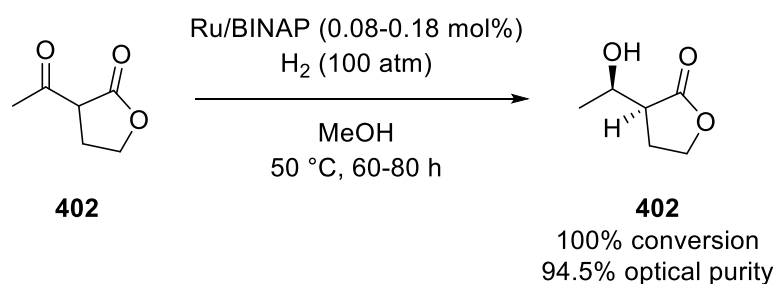

Scheme 144. Ru/BINAP catalysed asymmetric hydrogenation of keto-lactone.

Akinnusi et al. described a proline catalysed asymmetric aldol reaction between an aldehyde **404** and a ketone **403** which proceeded *via* dkr.[408] They obtained the corresponding aldol product **405** with very high enantiomeric excess (scheme 145). It was assumed that the aldehyde **404** underwent a rapid racemisation in the presence of proline what finally allowed a dynamic behaviour of the system.
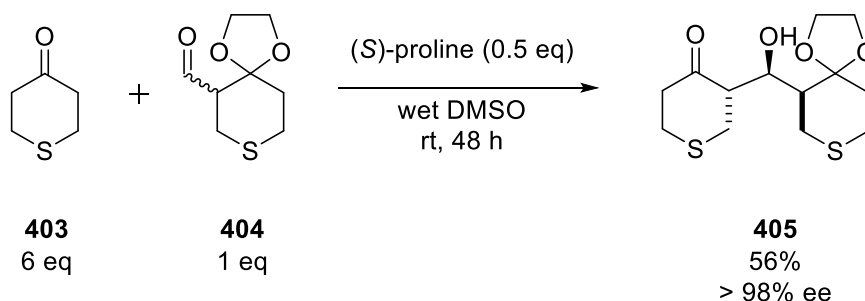
Scheme 145. (*S*)-proline catalysed asymmetric aldol reaction *via* dkr.

Kim et al. reported a lipase catalysed asymmetric transesterification of acyclic allylic acetate **406**, coupled with the palladium catalysed racemisation of the acetate that enabled the reaction to proceed *via* dkr (scheme 146).[406] The corresponding product **407** was obtained in a good yield and with an excellent enantiomeric excess.
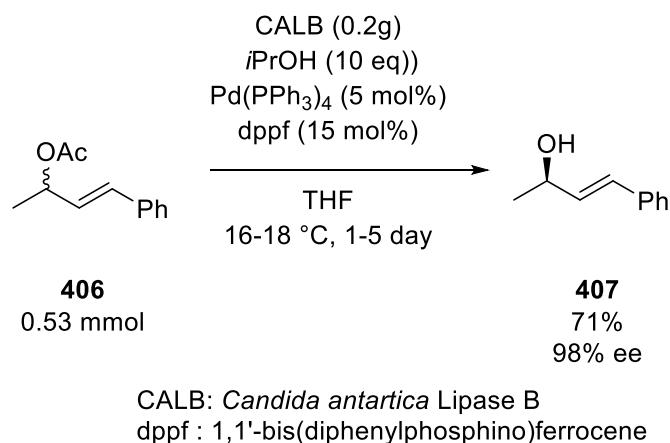
Scheme 146. Lipase catalysed asymmetric transesterification of acyclic allylic acetate.

Indeed, in case of the herein presented AT reaction, the racemisation of substrate **41a** should be relatively easy and thus, the reaction might involve a dynamic kinetic resolution process.[106] In accordance with this hypothesis, It was later revealed that the optimised O-P coupling between racemic ethylphenyl H-phosphinate **41a** and enantiopure (*S*)-2-(*tert*-butylsulfinyl)phenol **370** proceeded *via* dynamic kinetic resolution (dkr) i.e. using only 1 equivalent of each, racemic ethylphenyl H-phosphinate **41a** and enantiopure (*S*)-2-(*tert*-butylsulfinyl)phenol **370**, providing the desired product **400** with up to 80% yield and with up to 83/17 dr (scheme 147).
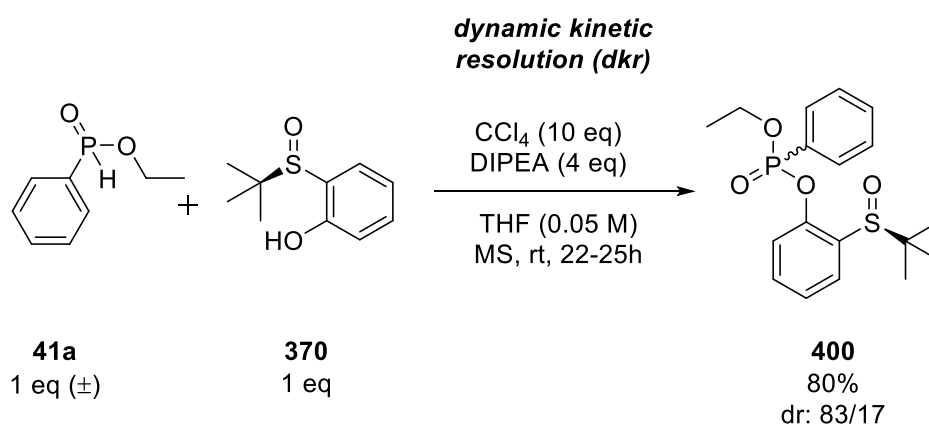
Scheme 147. O-P coupling *via* dynamic kinetic resolution (dkr).

Once we confirmed this phenomenon of dynamic kinetic resolution (dkr), several reaction parameters such as, base, temperature, molecular sieves etc, were further screened in order to improve the diastereoselectivity of the reaction. Despite the extensive optimisation study performed, the diastereoselectivity of the reaction could not further be improved (table 10).
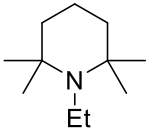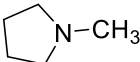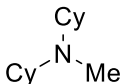
Table 10.
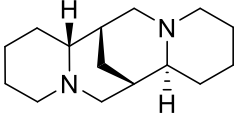
S. No.	DIPEA (eq)	CCl$_4$ (eq)	Concentration (M)	Temperature (° C)	Conversion* (%)	dr
1	4	10	0.0125	rt	60	83/17
2	4	10	0.05	rt	90	83/17
3	4	10	0.1	rt	90	83/17
4	2	5	0.05	rt	85	83/17
5	4	10	0.05	0	90	80/20
6	4	10	0.05	20	85	83/17
7	4	10	0.05	40	85	83/17

*determined by ^{1}H NMR

The best result was obtained under the optimised condition (entry 2) i.e. compound **400** was obtained in 80 % yield and with 83/17 dr.

A study on effect of hindered bases on the diastereoselectivity of the reaction was also carried out (table 11). 1-ethyl-2,2,6,6-tetramethylpiperidine (entry 1 table 11) afforded the product **400** with slightly higher dr of 86/14 with 85% conversion, however a complex reaction mixture was obtained at the end of the reaction rendering isolation of the product **400** very challenging (entry 1 table 11). With other bases such as DABCO, Me-pyridine, N-cyclohexyl-N-methylcyclohexanamine and sparteine, no improvement in diastereoselectivity was observed (entry 2-5 table 11).

Table 11.

S. No.	Base (4 eq)	Conversion (%)	dr
1	N–Et (tetramethylpiperidine, N-Et)	85*	86/14
2	DABCO	45	62/38
3	N–CH₃ (N-methylpyrrolidine)	85	77/23
4	Cy–N(Cy)–Me	90	77/23
5	sparteine	90	77/23

*complex nmr was obtained

Next, we focused on the separation of diastereomers of the product **400** mainly using different crystallisation techniques as well as using column chromatography. Though, a rigorous work was carried out to separate the diastereomers, it remained however, a challenging and undone task.

Moreover, separation by means of resolving agent techniques was tested on the diastereomers of **400**.[409–413]
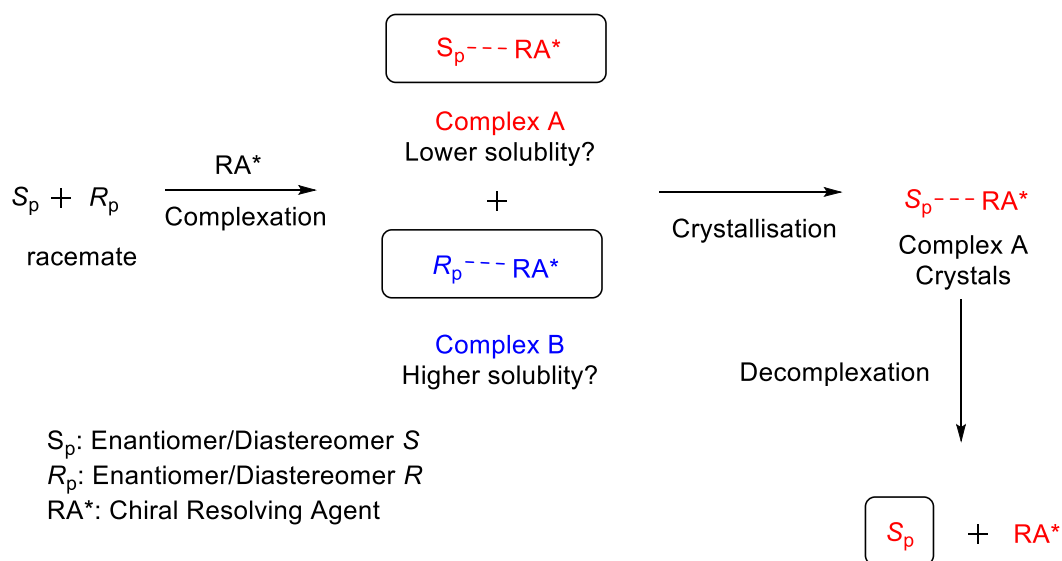
Scheme 148. An outline of basic principle of resolution of a racemate by a resolving agent.

Scheme 148 depicts the basic principle of resolution of a racemate by a suitable resolving agent. In a typical procedure, a suitable resolving agent form the corresponding complexes with enantiomer or diastereomers of a compound. Later, these complexes are usually separated by crystallisation process. Finally, decomplexation step provides the desired enantiopure/diastereopure compound. Following fig. 30 represents different resolving agents which were utilised in order to achieve the separation of the diastereomers of compound **400**.
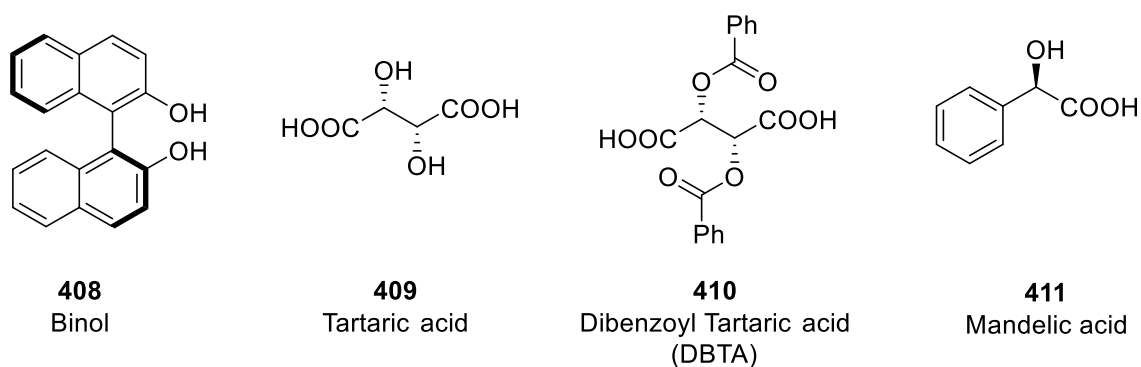

| **408** | **409** | **410** | **411** |
| Binol | Tartaric acid | Dibenzoyl Tartaric acid (DBTA) | Mandelic acid |

Fig. 30. Different resolving agents used for resolution of compound **400**.

Table 12

S. No.	Resolving Agent	Complexation	Crystallisation	Change in dr
1	(+)/(-)-Mandelic Acid	✓	✓	X
2	(-)-Binol	X	X	na
3	(+)-Cinchonine	X	X	na
4	(-)-DBTA	X	X	na

Reaction parameters such as temperature, solvents system and different techniques of crystallisation were tested in order to resolve the compound **400**. However, only in case of mandelic acid **411**, complexation between **400** and **411** took place and the resulting complex was crystallised in solvent systems; dichloromethane/*n*-pentane, dichloromethane/cyclohexane, chloroform/*n*-pentane utilising double layer diffusion or vapour diffusion techniques and keeping the mixture in fridge for about 1-2 days. However, the process was non-diastereoselective i.e. the same diastereomeric ratio (83/17) of the complex **400**-**411** was observed as diastereomeric ratio of compound **400** (83/17). Moreover, yield of the crystals was significantly low (about 20%). Therefore, this technique of crystallisation was finally abandoned.

Nonetheless, we forwarded and explored the potential of the reaction with various H-phosphinates as well as differently substituted phenol derivatives.
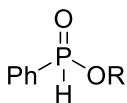
4.5.4 Scope of Atherton-Todd (AT) Reaction

tert-butylsulfinylphenol derivatives bearing mainly, methoxy or bromo group on the phenyl ring, were prepared according to the previously described strategy for (*S*)-2-(*tert*-butylsulfinyl)phenol **370** and derivatives in good yields and high enantiomeric excess (scheme 125).[310]

In parallel, several types of H-phosphinates were prepared using a variety of different procedures, which are briefly presented below. For example, ethyl, isopropyl and butyl derivatives of H-phosphinates were prepared according to the literature procedure (see scheme 94) under microwave conditions (table 13).[76]

Table 13. Synthesis of ethyl, *iso*propyl and butyl derivatives of H-phosphinates under microwave condition.

S. No.	RX	O‖Ph–P(–OR)–H	Time (min)	Yield (%)
1	EthI	Ethyl (**41a**)	30	97
2	*i*PrBr	*i*Pr (**41b**)	15	76
3	*n*-BuBr	*n*-Bu (**41f**)	15	95

H-phosphinate bearing a *tert*-butyl and methyl group (**41c** 70% and **41e** 73%) for example were prepared using propylphosphonic anhydride as a condensing agent under mild reaction conditions (see scheme 95).[305]

H-phosphinates bearing a cyclohexyl and adamantyl group (**41g** and **41d**) were prepared according to the strategy described in scheme 97, and the corresponding H-phosphinates were obtained in quantitative yields.[106]

Ethylcyclohexyl H-phosphinate **41j** was prepared following the procedure described by Gaunt et al. (scheme 149).[79,306,414]
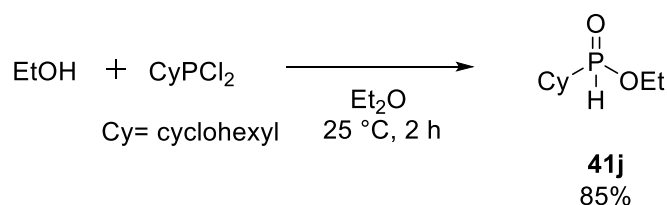
Scheme 149. Synthesis of ethylcyclohexyl H-phosphinate **41j**.

Ethylmesityl H-phosphinate **41i** was prepared according to the literature procedure (scheme 150).[415]
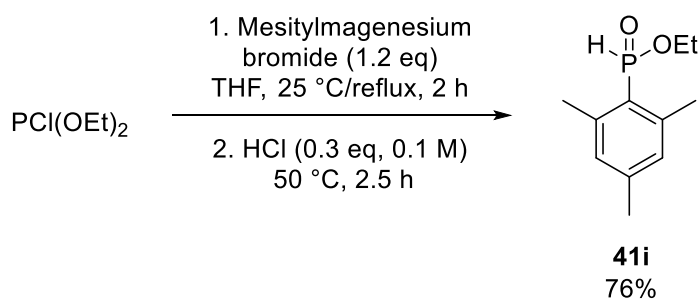
Scheme 150. Synthesis of ethylmesityl H-phosphinate **41i**.

Ethylnaphthalenyl H-phosphinate **41h** was prepared following the literature strategy (scheme 151).[77]
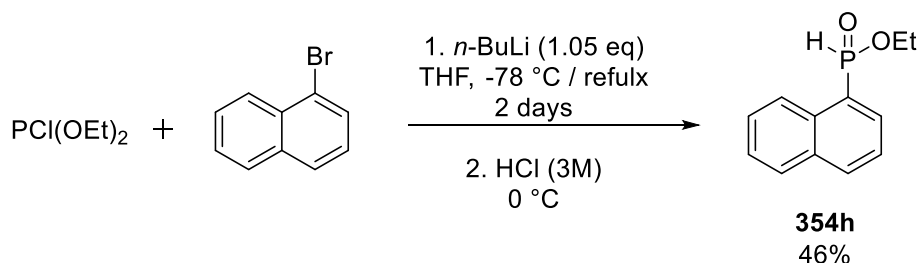
Scheme 151. Synthesis of ethylnaphthalenyl H-phosphinate **41h**.

Ethyl methylphosphinate **41k** was prepared using the literature procedure in a quantitative yield (scheme 152).[416]
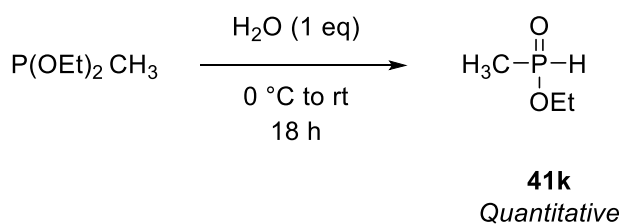
Scheme 152. Synthesis of ethyl methylphosphinate **41k**.

Secondary phosphine oxides were prepared following the procedure described by Gaunt et al. (scheme 153).[79]
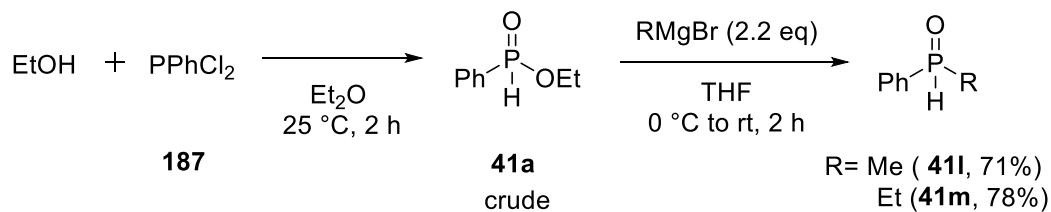
Scheme 153. Synthesis of secondary phosphine oxides **41l** and **41m**.

With the panel of different coupling partners, scope of this AT reaction was investigated. Following table 14 represents the scope of the reaction.

Table 14.
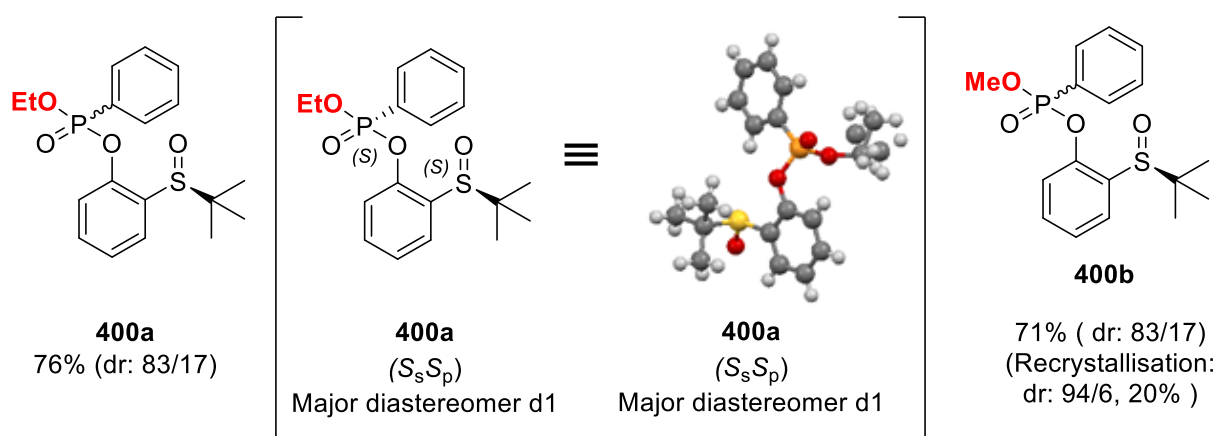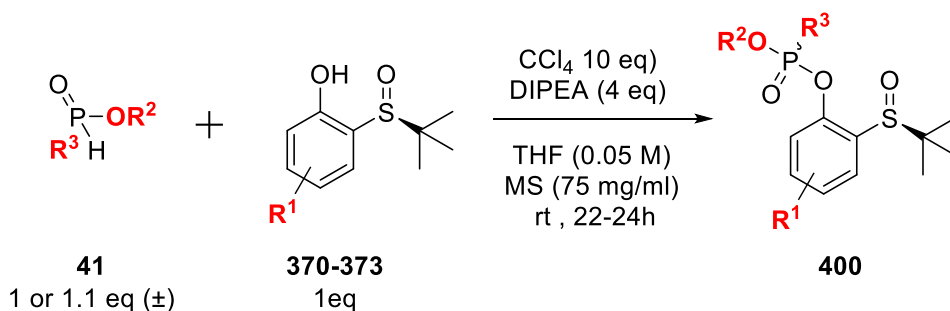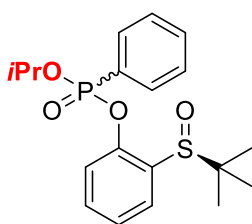
400c

total 64%
(crude dr: 77/23)
d1 (28%) : dr: 98/02
fr2 (24%) : dr: 62/38
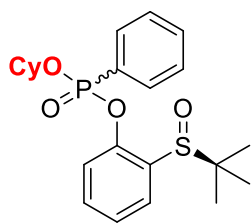
400d

total 67%
(crude dr : 60/40)
d1 (41%): 97/3
d2 (26%): 85/15
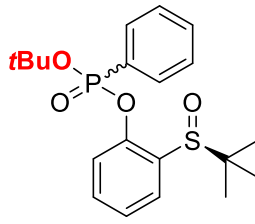
400e

dr: 60/40
d1 (22%): 90/10
d2 : impure
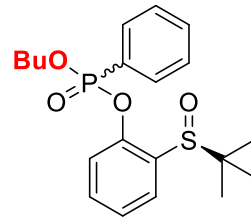
400f

80% (dr: 71/29)
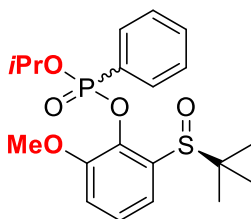
400g
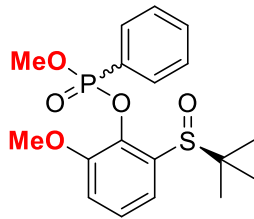
52% (dr: 78/22)

400h

58% (dr: 80/20)
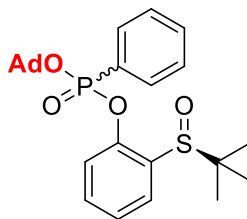
400i

total 68%
(crude dr : 50/50)
d1: 35%
d2: 33%
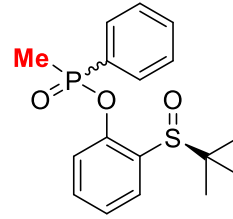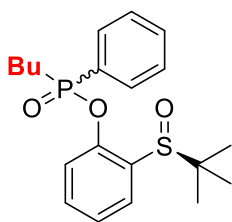
400j

total 67%
(crude dr: 55/45)
d1: 31%
d2: 26%

400k

total 75%
(dr crude: 51/49)
d1: 34%
d: 41%

400l

72%
(dr; 83/17)
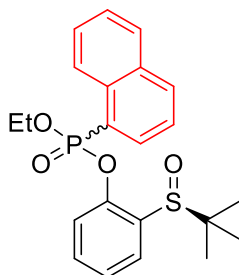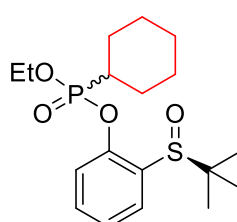
400m

34%(dr: 78/22)
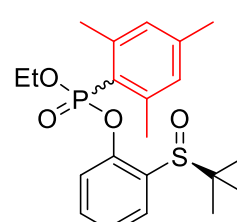
400n

34%(dr: 72/28)
inseparable from sm
(sm = ethyl mesitylphosphinate)
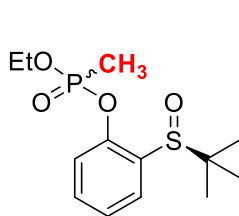
400o

80%(dr: 70/30)
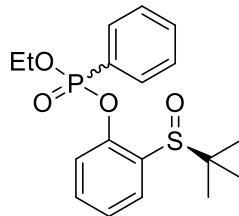
400p

64% (dr: 77/23)
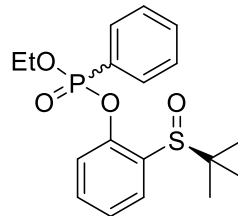
400q

68% (dr: 66/34)
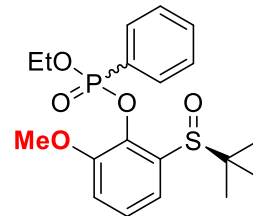
400r

78% (dr: 83/17)

Indeed, the AT reaction works smoothly for a wide variety of H-phosphinates as well as for the secondary phosphine oxides. In general, as the steric hindrance of the alkoxy group attached to P atom in H-phosphinates increases (**400a-400e**, **400i**, table 14), yield and diastereoselectivity of the reaction decrease. For example, when ethylphenyl H-phosphinate was used in the reaction, the corresponding product **400a** was obtained in about 80% yield and with 83/17 dr. While, more sterically hindered H-phosphinates such as, isopropylphenyl H-phosphinate **41c**, cyclohexylphenyl H-phosphinate **41g** and adamantylphenyl H-phosphinates **41d** provided the corresponding products **400c** (64% 77/23 dr) , **400d** (67% 60/40 dr) and **400i** (67% 50/50 dr) in lower yields and with lower diastereoselectivities.

When, the phenyl ring attached to P atom in H-phosphinate was replaced with another aromatic ring or simply by an alkyl group, there was either no significant change or some decrease in yield and in diastereoselectivity of the reaction. For example, when ethylcyclohexyl H-phosphinate **41j** and ethylmesityl H-phosphinate **41i** were used, the corresponding products **400m** (34% 78/22 dr) and **400n** (34% 72/28 dr) were obtained in lower yields, as well as with lower diastereoselectivities. In case of ethyl methylphosphinate **41k**, (a methyl group being attached to P atom, instead of a phenyl ring), the corresponding product **400o** (80% 70/30) was obtained in a good yield but with lower diastereoselectivity.

Secondary phosphine oxides also undergo the O-P coupling reaction smoothly but, the corresponding products, **41j** (67% 55/45 dr) and **41k** (75% 51/49 dr) were obtained with lower diastereoselectivities.

Also, in case of the products **400j** and **400k**, the crystal structures were obtained for one of their respective diastereomers, having S configurations on both sulphur and phosphorous atoms in case of compound **400j** and having R and S configurations on sulphur and phosphorous atoms for compound **400k** (fig. 31 and 32).

400j-d1 (S_sS_p)
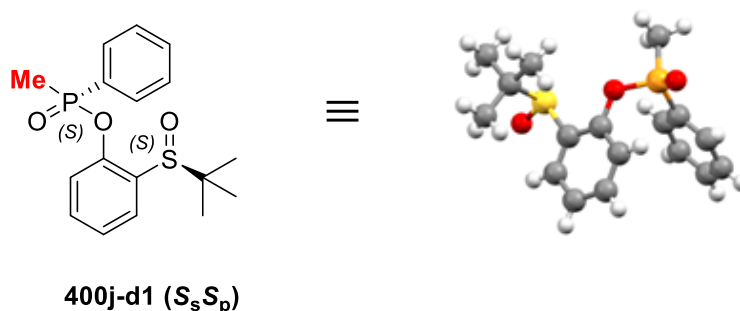
Fig. 31. X-ray crystal structure of compound **400j (d1)**.
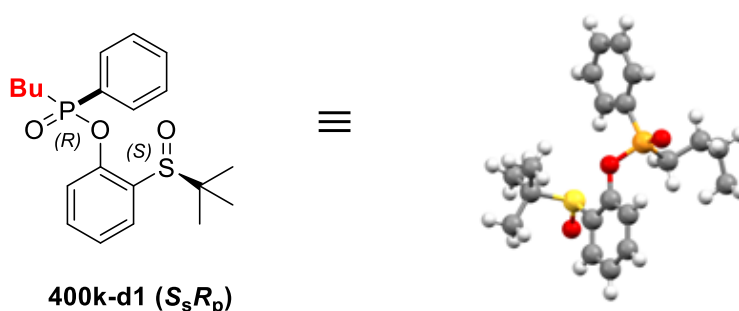
Fig. 32. X-ray crystal structure of compound **400k (d1)**.

4.5.4.1 Absolute Configuration of Major Diastereomer of Compound 400a

The X-ray structure of the major diastereomer of compound **400a** (X-ray crystal sample of the compound **400a** was taken for ^{31}P NMR to determine that it was indeed the major diastereomer of compound **400a**) reveals that both sulphur and phosphorous atoms have *S* configuration, labelled as S_sS_p (table 14).With this information, the configuration of major diastereomers of compounds **400a-400r** could possibly be assigned as S_sS_p.

We also tried to explore the effect of substituents attached to the *t*-butylsulfoxide phenol substrate (**371-373**). In case of the compounds **371-373**, bearing methoxy or bromo group on phenol ring, the reaction proceeded equally well, providing the corresponding products **400p** (64%, 77/23 dr), **400q** (68%, 66/34 dr) and **400r** (78%, 83/17 dr). However, compared to *t*-butylsulfinyl phenol **370**, no increment in diastereoselectivity was observed with hydroxyaryl sulfoxides **371-373**.

Also, substrate **412**, bearing a methyl group on *ortho* position of phenol, did not undergo the O-P coupling reaction, even on higher temperature, showing that the more hindered phenols were difficult to react with a H-phosphinate substrate (scheme 154).
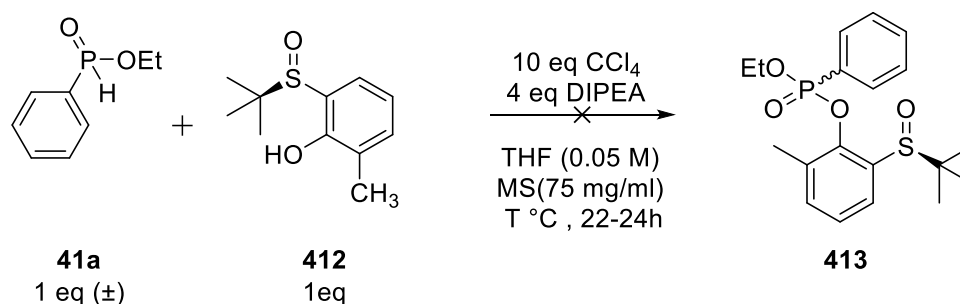
Scheme 154. Attempted O-P coupling reaction with substrate **412.**

As in previous case with the O-P coupling product **400a**, the tremendous efforts were put in separating the diastereomers of various O-P coupling products **400a-400r** reported in table 14, either by column chromatography or by crystallisation. However, the complete or partial separation of the diastereomers could be achieved in case of the following compounds presented in table 15.

Table 15.

S. No.	Compound	dr (d1+d2 mixture)	Separation Technique	dr: d1/d2 (yield %)	dr: d2/d1 (yield %)
1	**400b**	83/17	Crystallisation in Et$_2$O	94/6 (20)	na
2	**400c**	77/23	Chromatography	98/2 (28)	na
3	**400d**	60/40	Chromatography	97/3 (41)	85/15 (26)
4	**400e**	60/40	Chromatography	90/10 (22)	na
5	**400i**	50/50	Chromatography	100/0 (35)	100/0 (33)
6	**400j**	55/45	Chromatography	100/0 (31)	100/0 (26)
7	**400k**	51/49	Chromatography	100/0 (34)	100/0 (41)

The compound **400b** (entry 1) was crystallised in Et$_2$O affording the major diastereomer d1 in about 20% yield and with 94/6 dr. All other diastereomers of the compounds (entry 2-7) were separated employing column chromatography technique. The major diastereomer d1 of compound **400c** (entry 2) was obtained in about 28% yield and with 98/2 dr, while other diastereomer d2 was obtained as a mixture in about 24% yield with 62/38 dr. The major diastereomer d1 of compound **400c** (entry 3) was obtained in about 22% yield and with 90/10 dr, while other diastereomer d2 could not be isolated. The major diastereomer d1 of compound **400d** (entry 3) was obtained in about 41% yield and with 97/3 dr, while other diastereomer d2 was obtained in about 26% yield with 85/15 dr. The diastereomers of the compounds **400i**, **400j** and **400k** were successfully separated in good yields and as pure isomers.

4.5.5 Application in Stereoselective Synthesis

Post functionalisation of P-stereogenic compounds/precursors is an appealing step to establish their further importance for the preparation of a wide variety of P-stereogenic scaffolds. Generally, this step is achieved by stereospecific nucleophilic substitution reaction of the P-stereogenic compounds/precursors, using Grignard reagents or organolithium reagents. The reaction conditions are rather harsh i.e. excess of Grignard reagents or organolithium reagents are used, either a very low temperature or a high temperature is usually required, yields and enantioselectivities/stereoselectivities vary depending on the structure of P-stereogenic compounds/precursors and the reaction conditions (scheme 155)[13,87,204,234,365,409,417–419].

1. RMgX (4/5 eq)
benzene
reflux, 18 h

2. Crystallisation
in hexane

191

S_p

192

R_p

yield ~50-55%
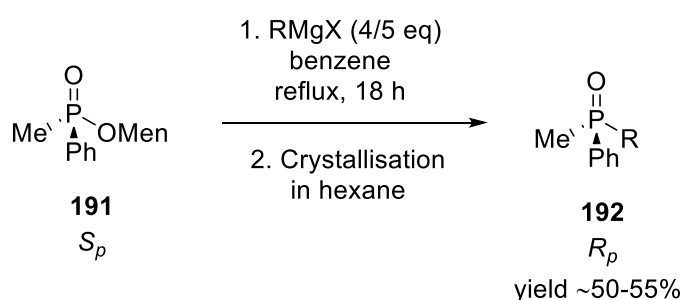
- Excess of Grignard Reagent
- Higher Temperature
- Lower yields
- Crystallisation in Final Step

Scheme 155. A representative example of reaction (O-P cleavage) of P-stereogenic compounds.

In our case, most of the compounds **400a-400r** (table 14) possess one alkoxy group and one (*S*)-2-(*tert*-butylsulfinyl)phenol group, both being attached to phosphorous atom. Indeed, both of these groups can act as leaving groups under nucleophilic substitution reaction conditions with suitable Grignard or organolithium reagents. Thus, this feature of the structures of compounds **400a-400r** provides a high potential to further transform these compounds into various P-stereogenic scaffolds (fig. 33).
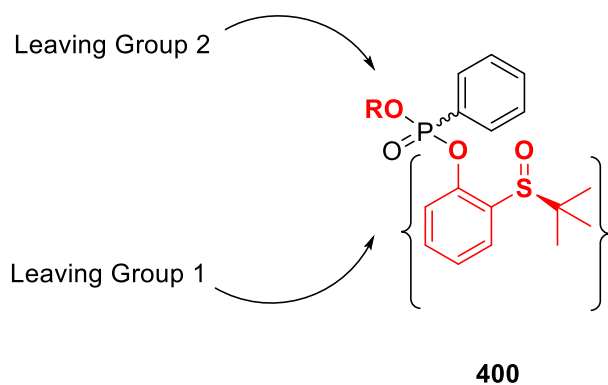
Fig. 33. Leaving groups attached to phosphorous arum in compound 469.

Moreover, the first nucleophilic reaction of these compounds **400a-400r** with a suitable Grignard or organolithium reagent is expected to be chemoselective, as (*S*)-2-(*tert*-butylsulfinyl)phenoxide group should selectively be cleaved (a better leaving group) compared to an alkoxy group, resulting in the formation of P-stereogenic phosphinates. And, these newly formed P-stereogenic phosphinates would possess an alkoxy leaving group, which can further react with another Grignard or organolithium reagent, affording various P-stereogenic tertiary phosphine oxides.

We first carried out the optimisation study for nucleophilic substitution with racemic compound **400a** using MeLi (scheme 156).
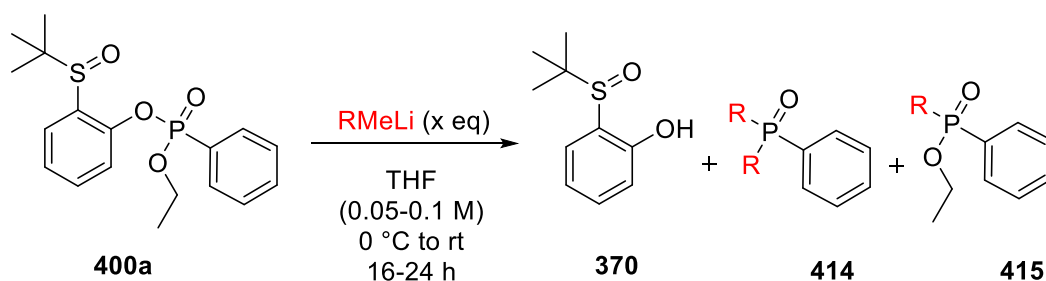
Scheme 156. Nucleophilic substitution of racemic compound **400a**.

Following table 16 depicts some of the experimental results obtained herein.

Table 16.

S. No.	MeLi (x eq)	Temp. (°C)	Conversion (%)	NMR Yield (%) 370: 414: 415	Comment
1	2.2	0/rt	100	na	Complex NMR
2	1.1	0/rt	100	100:100:0	
3	1	0/rt	100	60:0:14	Complex NMR
4	0.9	0/rt	60	60:0:60	Complex NMR

Using 2.2 equivalents of MeLi (entry 1) yielded a complex mixture, which was difficult to analyse. When 1.1 equivalents of MeLi was used (entry 2), formation of dimethyl substituted tertiary phosphine oxide **414** was observed along with the compound **415**. Use of a decreased amount of MeLi (entry 3 and 4) yielded a complex mixture along with the formation of desired compounds **370** and **415**.

Later, we replaced MeLi with MeMgBr. Gladly, we soon succeeded to optimise the desired reaction conditions (scheme 157 and table 17) i.e. using 1 equivalent of MeMgBr and increasing the reaction temperature to 40 °C during 16 h of stirring (entry 4), the compound **400a** got selectively converted into the desired products **415** and **370** in 66% and 94% yields respectively.

400a
racemic

MeMgBr (x eq)

THF (0.05 M)
0/40 °C, 16h

415
66%

370
94%
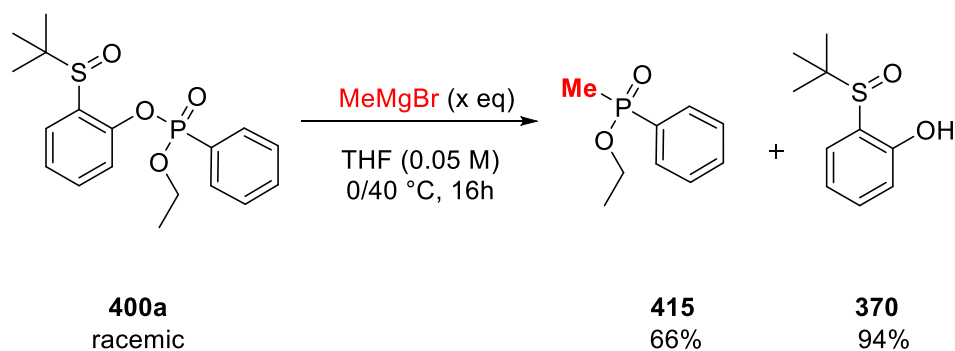
Scheme 157. Post-functionalisation of compound **400a** using MeMgBr.

Table 17.

S. No.	MeMgBr (x eq)	Temp. (°C)	Conversion-415 (%)
1	1	0/rt	20
2	0.95	0/40	70
3	1	0/40	100

With the optimised conditions of the racemic compound **400** in hand, the post-functionalisation reaction was carried out for the diastereomeric mixture of compound **400a** (83/17 dr) (scheme 158). The reaction proceeded with a complete conversion and the corresponding post-functionalised product **415** was obtained with more than 90% retention of chirality, while compound **370** was obtained without racemisation. The enantiomeric ratios of compound **415** and **370** were measured using a chiral HPLC technique.
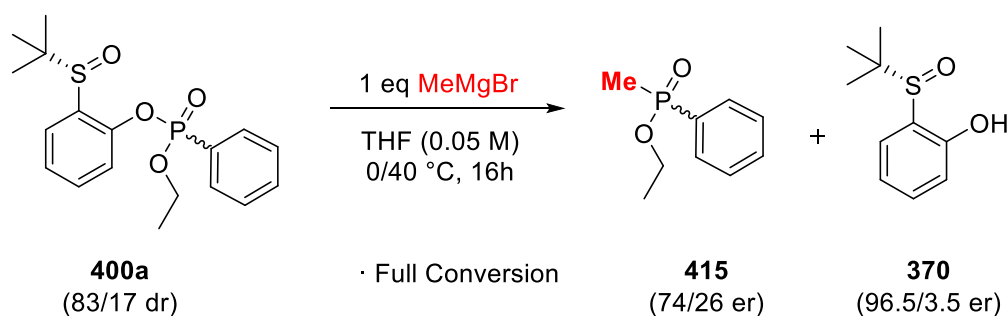
Scheme 158. Optimised reaction conditions for the post-functionalisation of diastereomeric mixture of compound **400a**.

Using similar reaction conditions, post-functionalisation of diastereopure substrate **400i** (diastereomer-d1) was carried out using 1 equivalent of MeMgBr. The desired reaction worked, but with about 45% conversion. Next, considering the impact of steric hindrance of adamantyloxy group attached to phosphorous atom in compound **400i**, an increased amount of Grignard reagent was used i.e. 2 equivalents of of MeMgBr were used resulting in a complete conversion of substrate **400i** into the desired products **416** (64% 90/10 er)and **370** (93% >99/1 er) (scheme 159).
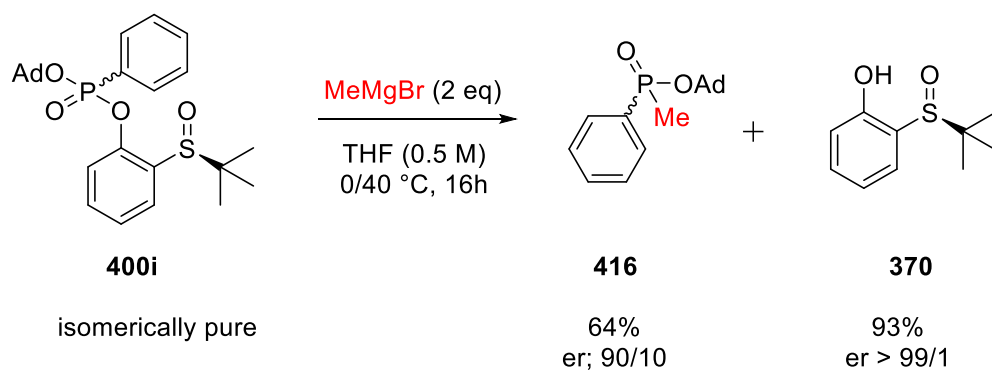
Scheme 159. Post functionalisation of substrate **400i**.

4.5.5.1 Synthesis of (*S*)-PAMPO 40

With the previously optimised conditions for the post-functionalisation in hand, we were able to transform the compound **400j** into an original P-stereogenic scaffolds, (*S*)-PAMPO **40**, which is also a precursor for the synthesis of the pioneer ligand DiPAMP **17**. The reaction worked under milder conditions; only one equivalent of *o*-AnMgBr was used in dry THF containing the substrate **400j** at 0 °C and after the addition of *o*-AnMgBr, the reaction was stirred at room temperature for about 16 h thus, providing (*S*)-PAMPO **40** in 84% yield and with 98/2 er, and (*S*)-2-(*tert*-butylsulfinyl)phenol **370** in 94% yield and with > 99/1 er (scheme 160). And the reaction proceeded with inversion of configuration at P atom. It should be noted here that, the compound, (*S*)-PAMPO **40**, was obtained in a very high yield and with an excellent enantiomeric excess *via* a simple column chromatography, without the need of further crystallisation step, which is generally required at the end of post-functionalisation / O-P cleavage step (scheme 160).
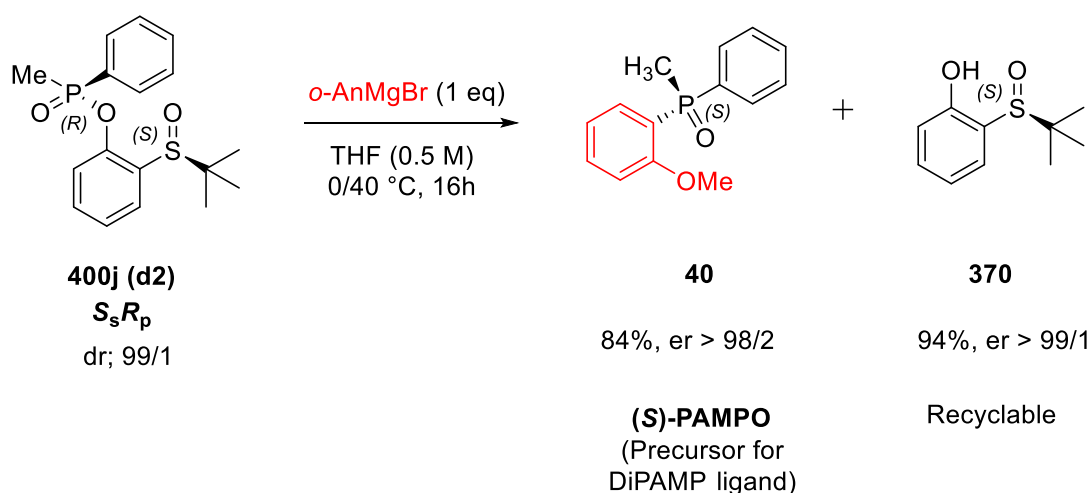
Scheme 160. Post-functionalisation of substrate **400j (d2)** to prepare (*S*)-PAMPO **40**.

4.5.5.2 Determination of Configuration of P atom in (*S*)-PAMPO 43:

The specific optical rotation of *S*-PAMPO **40** was measured as $[\alpha]_D^{20}$. = -9.74 (c 0.5, CHCl$_3$), which on comparing the literature data i.e. $[\alpha]_D^{20}$ = -23.0 (c 1.0 in CHCl$_3$) for *S*-PAMPO, suggested that in our case, the configuration of P atom in compound **PAMPO 40** is *S*.[231,266] And, the optical purity of the **S-PAMPO 40** was determined by chiral hplc technique.

Besides, previously we had obtained the crystal structure of the diastereomer 1 of compound **400j (d1)** (fig. 31), and thus, we knew the configuration of this compound as S$_s$S$_p$ (both the atoms, S and P have configuration S). As a consequence, the configuration of its other diastereomer i.e. **400j (d2),** which was indeed, used in the above post-functionalisation

reaction, would therefore, be *S* and *R* on sulphur and phosphorous atoms respectively (scheme 160).

These data collectively further suggested that the post-functionalisation reaction proceeded *via* inversion of configuration at P atom.

Thus, these O-P coupling compounds **400a-400r** (table 14) bearing a (*S*)-2-(*tert*-butylsulfinyl)phenoxide moiety, can potentially be considered as an important class of P-stereogenic precursors in order to obtain an array of different P-stereogenic scaffolds under milder reaction conditions. In particular, the reaction does not require the use of excess of Grignard reagents and a high reaction temperature condition. The post-functionalisation reaction of compounds **400a** and **400d** proceeds chemoselectivity (i.e. (*S*)-2-(*tert*-butylsulfinyl)phenoxide group is preferentially cleaved, not the alkoxy group) and stereoselectively with inversion of configuration at P atom, providing mainly the corresponding product having a P-stereogenic centre. Also, the chiral auxiliary i.e. *(S)*-2-(*tert*-butylsulfinyl)phenoxide moiety **370**, is recovered in a very high yield and without racemisation. Thus, it can be recycled for the reaction.

5 Conclusion Générale

Les composés P-stéréogènes constituent une classe importante de composés chimiques, qui trouvent plusieurs applications intéressantes dans divers domaines scientifiques tels que l'agrochimie en tant que pesticides, la pharmacie en tant que molécules biologiquement actives, la chimie de coordination et des matériaux et la catalyse asymétrique organométallique en tant que ligands chiraux. Par conséquent, les méthodologies permettant de synthétiser des composés P-stéréogènes ont connu un développement constant avec le temps. De plus, les voies de synthèse pour accéder aux composés P-stéréogénes basées sur des méthodologies utilisant un auxiliaire de chiralité tel que le menthol ou l'éphédrine, ont été reconnues comme très efficaces à la fois en laboratoire et à l'échelle industrielle. Le menthol et l'éphédrine sont des auxiliaires chiraux facilement disponibles et peu coûteux. En outre, un grand nombre de composés P-stéréogénes et leurs précurseurs ont été synthétisés sur la base de ces méthodologies. Cependant, ces stratégies souffrent souvent de plusieurs limitations telles qu'une portée limitée, des rendements faibles, des conditions réactionnelles drastiques, des procédures complexes, fastidieuses et en plusieurs étapes afin de délivrer les composés énantiopurs P-stéréogénes.

Ici, nous avons développé une nouvelle méthodologie pour construire des composés P-stéréogènes, basée sur l'utilisation d'un sulfoxyde en tant qu'auxiliaire chiral, afin de surmonter les difficultés et les limites associées aux méthodologies existantes pour la préparation de composés P-stéréogènes. Notre méthodologie repose sur un couplage O-P via la réaction d'Atherton-Todd (AT) entre un phénol énantiopur facilement accessible portant un auxiliaire chiral de type sulfoxyde et un H-phosphinate racémique disponible commercialement ou facilement accessible, ce qui entraîne la formation d'un nouveau centre chiral sur l'atome de phosphore (schéma 1).
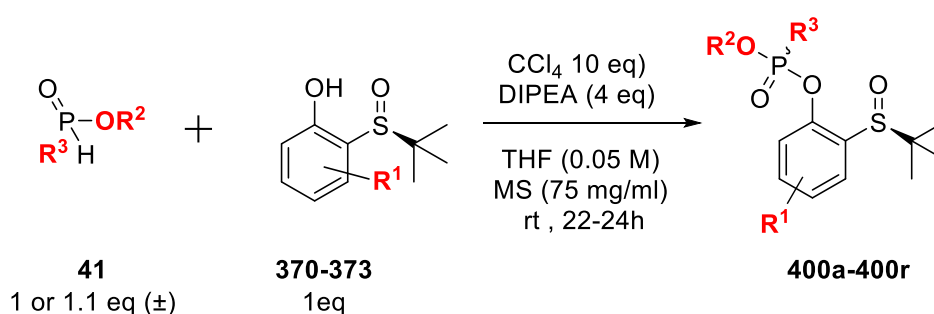
Schéma 1. Schéma général d'une réaction de couplage O-P / Atherton-Todd (AT).

En effet, la réaction AT fonctionne avec une grande variété de H-phosphinates ainsi qu'avec les oxydes de phosphine secondaires. De plus, dans de nombreux cas, la réaction se déroule

via une résolution cinétique dynamique (DKR), donnant le produit de couplage O-P correspondant **400a-400r** avec un bon rendement et une diastéréosélectivité élevée (schéma 2).

Schéma 2. Un exemple représentatif d'une réaction de couplage O-P / Atherton-Todd (AT) se déroulant via une résolution cinétique dynamique (DKR)

Le principal avantage d'une telle approche est la post-modification des composés P-stéréogènes nouvellement obtenus qui peuvent potentiellement être transformés en une variété de dérivés P-stéréogènes via des réactions de substitution nucléophile avec des réactifs organolithiens ou de Grignard; le phénol porteur du sulfoxyde chiral énantiopur doit être libéré au cours du processus (schéma 166) permettant ainsi sa récupération et son recyclage.

Schéma 3. Schéma général de post-fonctionnalisation du composé de couplage O-P.

Ainsi, nous avons pu transformer le composé **400j** en un composé P-stéréogène original, le (S)-PAMPO **40**, précurseur de la synthèse du célèbre ligand DiPAMP **17**. La réaction de post-fonctionnalisation est réalisée dans des conditions douces conduisant au (S) -PAMPO **40** avec un rendement de 84% et un rapport énantiomèrique de 98/2, et le (S)-2-(tert-butylsulfinyl)

phénol **370** est récupéré énantiopur avec un rendement de 94% (schéma 4). Lors de la reaction, une inversion de la configuration de l'atome de phosphore a lieu. Il convient de noter ici que le composé (S) -PAMPO **40** a été obtenu avec un rendement très élevé et avec un excellent excès énantiomérique après une simple chromatographie sur colonne, c'est-à-dire qu'il n'a pas été nécessaire de procéder à une étape de cristallisation supplémentaire, ce qui est généralement le cas dans la literature pour les reactions de coupure O-P.
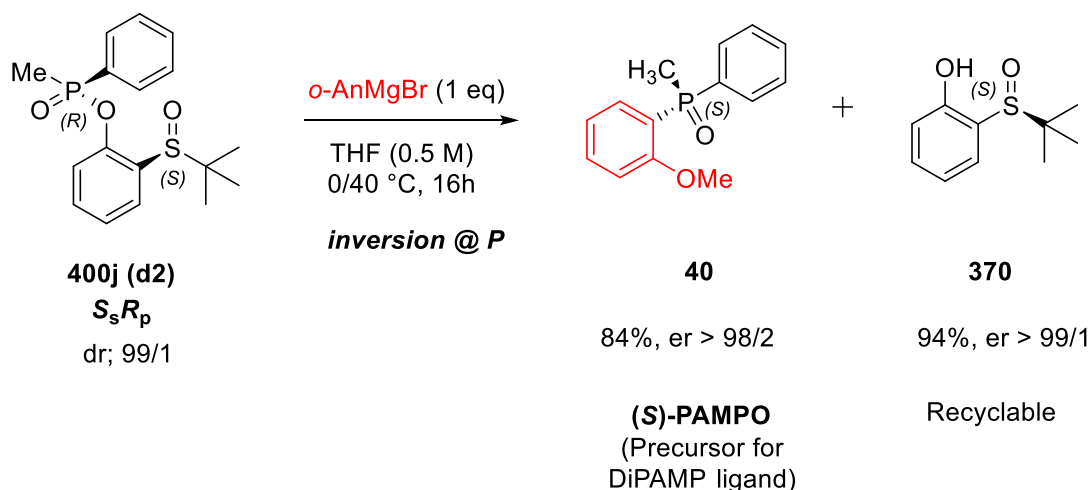
Schéma 4. Post-fonctionnalisation du substrat **400j (d2)** pour préparer du (S) -PAMPO **40**.

De plus, dans des conditions similaires, le substrat **400i** a été transformé avec succès en le produit correspondant **416** avec un rendement de 64% et un rapport énantiomèrique de 90/10 et le substrat **370** énantiopur avec un rendement de 93% (schéma 5).
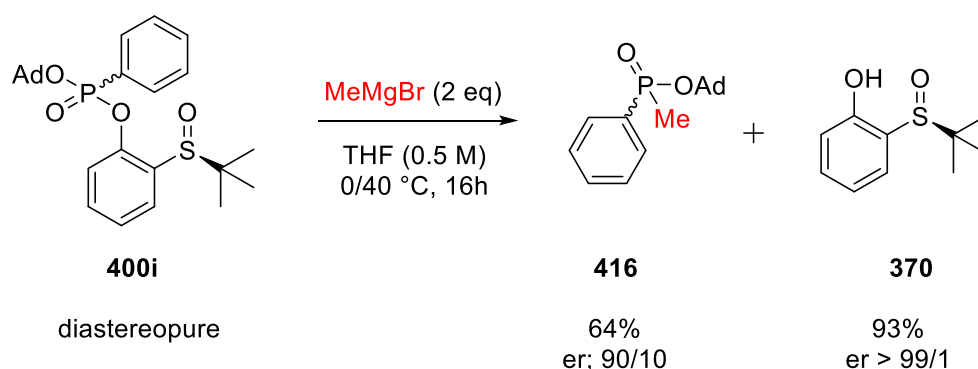
Schéma 5. Post-functionalisation du substrat **400i**.

Ainsi, ces composés de couplage O-P **400a-400r** (tableau 14) portant un fragment phénoxyde de (S)-2-(tert-butylsulfinyle) peuvent potentiellement être considérés comme une classe importante de précurseurs P-stéréogénes obtenus dans des conditions de réaction douces.

En particulier, la réaction ne nécessite pas un excès de réactif de Grignard et une température de réaction élevée. Les réactions de ces composés se déroulent de manière stéréosélective avec inversion de la configuration de l'atome de phosphore, donnant principalement un produit post-fonctionnalisé ayant un centre P-chiral et on récupère l'auxiliaire chiral c'est-à-dire le (S) -2-(tert-butylsulfinyl) phénoxyde **370**.

6 Perspectives Futures

Ainsi, ces composés de couplage O-P **400a-400r** (tableau 14) portant un fragment phénoxyde de (S)-2-(tert-butylsulfinyle) peuvent potentiellement être considérés comme une classe importante de précurseurs P-stéréogénes. En particulier, la réaction ne nécessite pas un excès de réactif de Grignard et une température de réaction élevée. Les réactions de ces composés se déroulent de manière stéréosélective avec inversion de la configuration de l'atome de phsophore, donnant principalement un produit post-fonctionnalisé ayant un centre P-chiral, et la récupération de l'auxiliaire chiral, le (S)-2-(tert-butylsulfinyle) phénoxyde **370**.
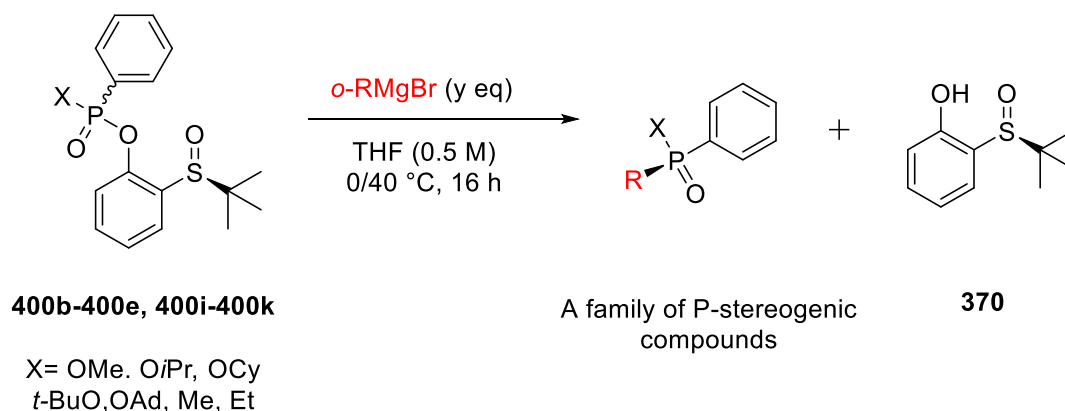

Schéma 1. Synthèse d'une famille de composés P-stéréogénes par post-fonctionnalisation de substrats **400-b-400e, 400i-400k**.

En outre, la principale difficulté rencontrée au cours du projet concerne la séparation des diastéréomères du composé **400a**.
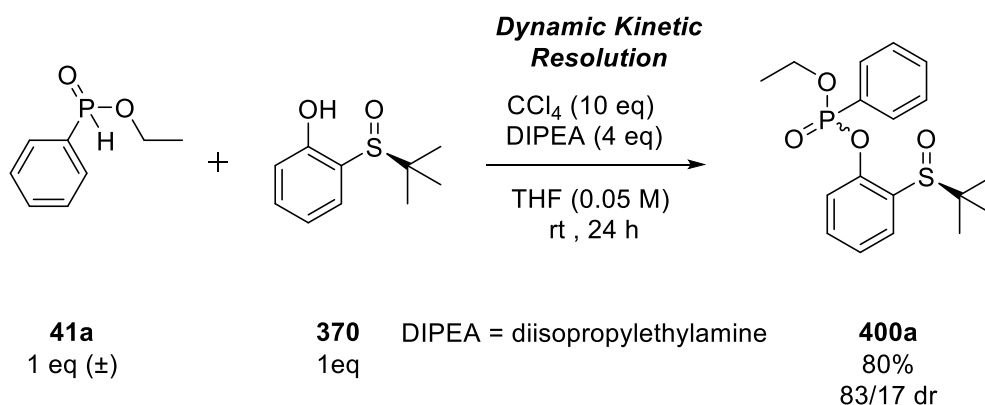

Schéma 2. Couplage O-P via une résolution cinétique dynamique (DKR).

En effet, ce produit **400a** est facilement obtenu en utilisant 1 équivalent de l'éthylphényl H-phosphinate **41a** racémique disponible commercialement et un équivalent du (S)-2-(tert-butylsulfinyl) phénol **370** énantiopur facilement accessible dans nos conditions de réaction, ce qui donne le produit souhaité **400a** avec un rendement allant jusqu'à 80% et jusqu'à 83/17 de rapport diastéréomèrique (schéma 2). La réaction se déroule via une résolution cinétique dynamique (DKR).

Cependant, la séparation des diastéréoisomères du composé **400a** est extrêmement difficile. Étant donné que ce composé **400a** peut être facilement obtenu avec un très bon rendement et un rapport diastéréomèrique élevé, un accès direct au composé diastéréomèriquement pur **400a** améliorerait considérablement l'importance de cette méthodologie pour la préparation de composés P-stéréogénes. Par conséquent, des efforts supplémentaires sont nécessaires pour développer une approche simple et pratique permettant de séparer les diastéréomères du composé **400a**.

Une protection des composés organophosphorés de type H-phosphinite sous forme de boranes **500** pourrait induire une meilleure cristallinité des produits et ainsi une meilleure séparation des diastéréomères. [47,86,118,207,208,208-212, 227].
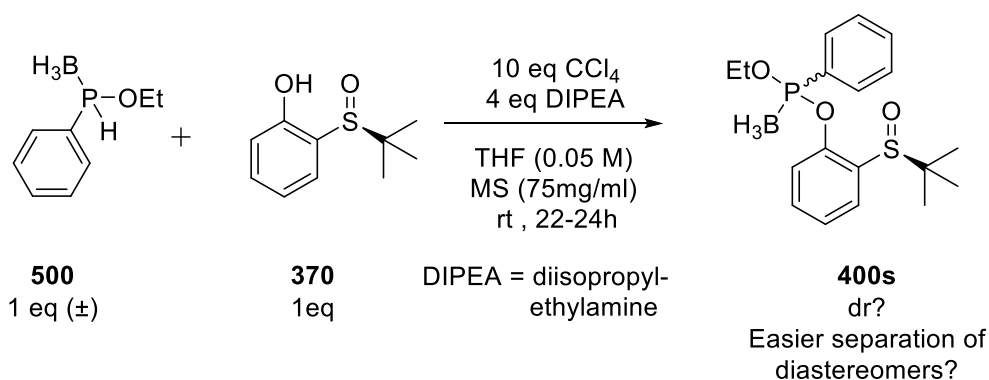
Schéma 3. Couplage O-P entre H-phosphinite borane **500** et **370**.

Une autre approche possible consisterait à effectuer une protection du produit **400a** et à explorer la séparation de ces diastéréoisomères par cristallisation ou chromatographie (schéma 4).
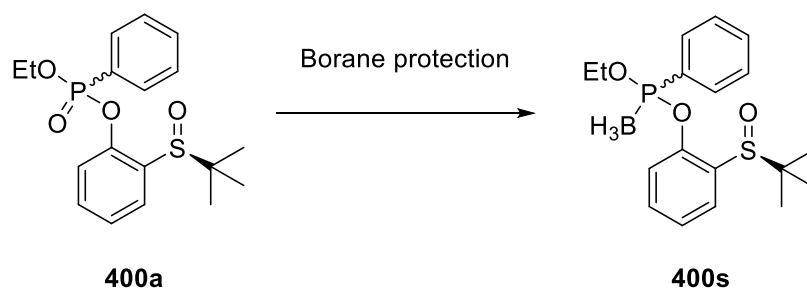
Scheme 4. Protection du produit **400a**.

Une fois que l'on obtient un produit **400** diastereopur, il peut être converti en une famille de molécules P-stéréogènes. L'étape de post-fonctionnalisation (déjà optimisée) sur le composé **400** peut être effectuée à deux reprises, car ce composé **400** possède deux groupes partants, à savoir un groupe éthoxy et un groupe phénoxy (S)-2-(tert-butylsulfinyle) phénoxyde, les groupes étant attachés à l'atome de phosphore, afin d'obtenir les molécules P-stéréogénes désirées (schéma 5).
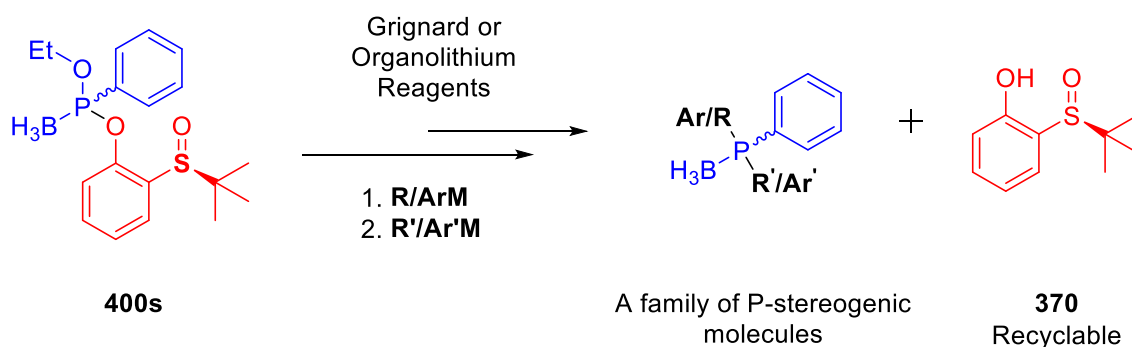
Scheme 5. Post-functionalisation du composé **400s**.

Une autre possibilité pour obtenir une diastéréosélectivité plus élevée dans la réaction de couplage O-P comprend l'utilisation d'organocatalyseurs chiraux (schéma 6). [422,423] Ces organocatalyseurs peuvent vraisemblablement faciliter la formation d'un état de transition bien organisé entre un H-phosphinate et un phénol portant un sulfoxyde chiral qui peut finalement conduire à une réaction de couplage O-P plus diastéréosélective.
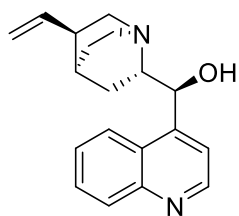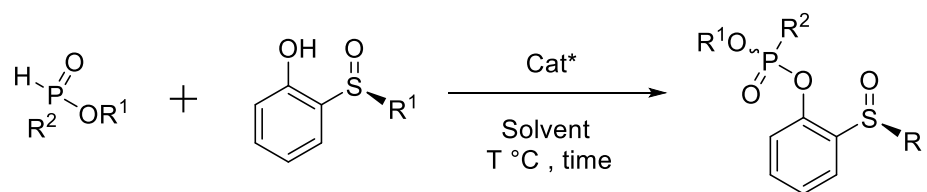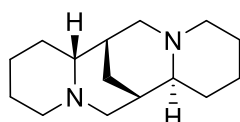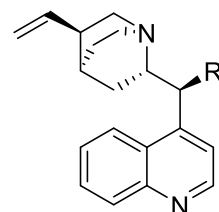
Scheme 6. Réaction de couplage O-P organocatalysée.

7 Experimental Procedure

7.1 General Methods:

All reactions were performed under an argon atmosphere in flame dried glass wares using dry solvents unless and otherwise stated. THF was distillated over Na/benzophenone. Anhydrous CCl_4 was purchased from Sigma Aldrich. Triethyl amine (TEA) was freshly distilled using CaH_2 or NaOH as drying agents and stored under argon over CaH_2 or NaOH.

Technical grade solvents for extraction and chromatography (cyclohexane, dichloromethane, *n*-pentane, ether, toluene, and ethyl acetate etc) were used without purification. All reagents were purchased from commercial suppliers. Analytical thin-layer chromatography (TLC) was performed on silica gel. Flash column chromatography was performed on silica gel 60 (40–63 μm, 230–400 mesh, ASTM) by *Merck* using the indicated solvents. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on *Bruker* AV 300/400/500 instruments. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent resonance as the internal standard ($CHCl_3$ = 7.26 ppm for ^1H NMR and $CDCl_3$ = 77.16 ppm for ^{13}C NMR). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, aq = apparent quartet, brd = broad doublet), coupling constant (Hz) and integration. Infrared (IR) spectra were recorded on Perkin Elmers *Spectrum OneTM* equipped with an ATR unit and are reported (br = broad, vw = very weak, w = weak, m = medium, s = strong) in wavenumbers (cm–1). The spectra were processed with the program Spectrum (Version 5.3.1, Perkin Elmer). High resolution mass spectrometry (HRMS) analysis was performed by the analytical facility at the University of Strasbourg (measurement accuracy ≤15 ppm). Optical rotation was measured on a Perkin Elmer Polarimeter 341 and denoted as specific rotations: $[\alpha]_D^{20}$.

7.2 Substrate Synthesis

7.2.1 (S)-2-(tert-butylsulfinyl)phenol derivatives 370-373

MOMBr: Bromomethyl methyl ether
DIPEA: diisopropylethylamine
TMEDA: tetramethylethylenediamine
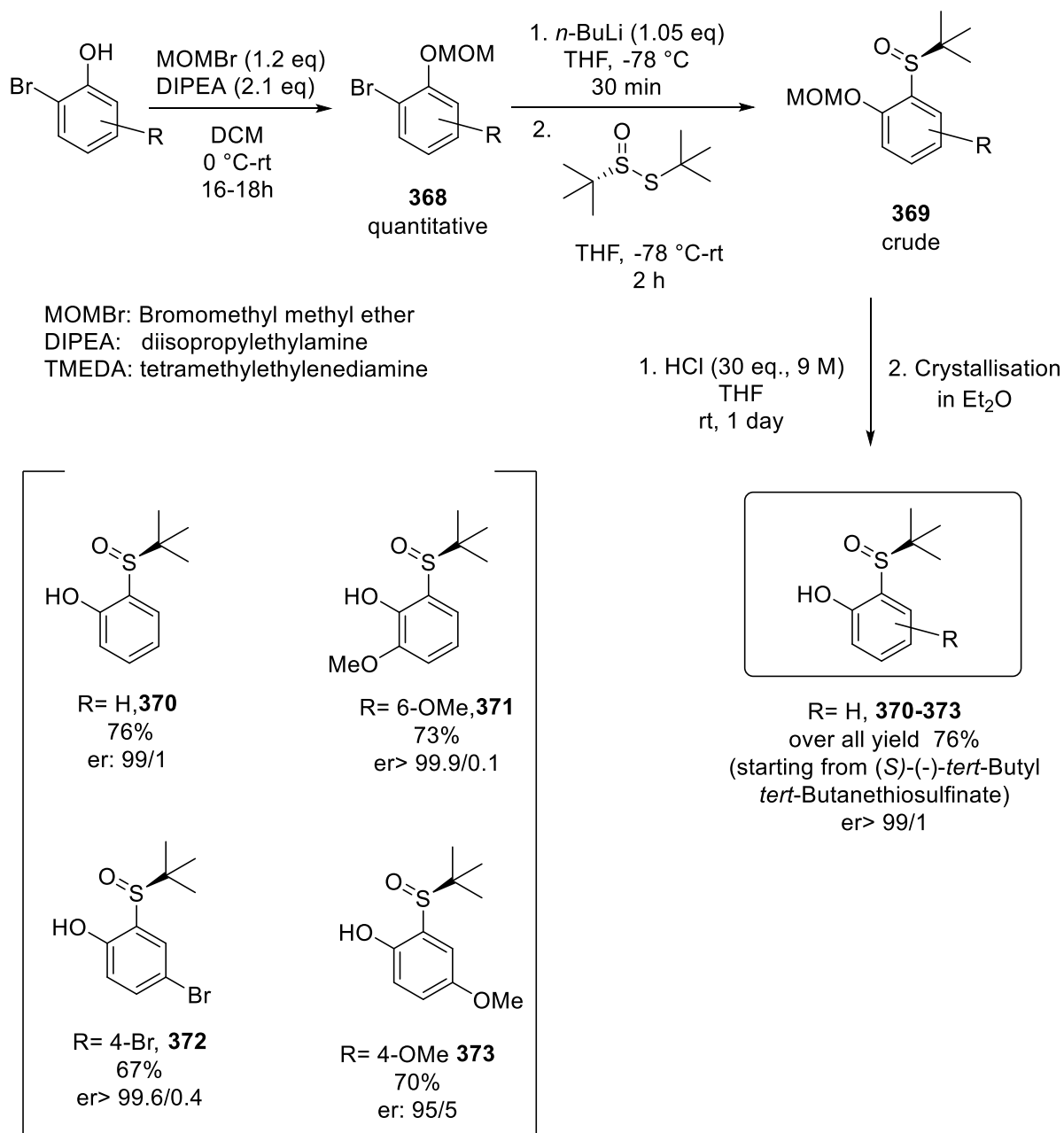
Scheme 1. A general scheme for the preparation of (*S*)-2-(*tert*-butylsulfinyl)phenol derivatives.

7.2.1.1 (S)-2-(tert-butylsulfinyl)phenol 370
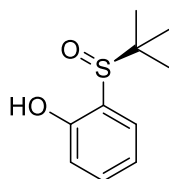
General Procedure A:

(*S*)-2-(*tert*-butylsulfinyl)phenol derivatives were prepared following the literature procedure for the preparation of (*S*)-2-(*tert*-butylsulfinyl)phenol **370**.[310,385][310,385]

Step 1: A flame-dried 250 mL round bottom flask was charged with 1-bromo-2-phenol derivative (1 eq., 7.45 g, 5 mL, 43.1 mmol) and DCM (37.8 ml, 1.14 M) . The solution was cooled to 0 °C in an ice-water bath under Ar protection. *n,n*-diisopropylethylamine (2.12 eq., 11.8 g, 15.1 mL, 91.4 mmol) was added followed by Bromomethyl methyl ether (1.19 eq., 6.4 g, 4.19 mL, 51.2 mmol) slowly. The ice-water bath was removed, and the reaction was stirred overnight at rt.

After about 18 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL).The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford the corresponding product, 1-bromo-2-(methoxymethoxy)benzene derivatives **368** in quantitative yield (>98%).

Step 2: Next, At -78 ∘C, *n*-BuLi (1.05 eq., 1.57 M, 9.24 mL, 14.5 mmol) was added dropwise to the solution of the 1-bromo-2-(methoxymethoxy)benzene **368** (1 eq., 3 g, 13.8 mmol)) in anhydrous THF (53.7 mL)). It might result in pink/orange coloration or simply white turbid appearance.

The resulting mixture was stirred for 30 min at -78 °C and a solution of (*S*)-(-)-*tert*-Butyl *tert*-Butanethiosulfinate (1 eq., 2.69 g, 2.69 mL, 13.8 mmol) in THF (13.8 mL)) was added. The resulting mixture was stirred for 2 h at -78 °C.

The reaction mixture was quenched with water. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product **369** *S*-(*tert*-butylsulfinyl)-2-(methoxymethoxy)benzene hydrate (full conversion) was directly used in the next step of deprotection of MOM group from the aromatic ring.

Step 3: A 500 mL round bottom flask was charged with the crude **369** S-(*tert*-butylsulfinyl)-2-(methoxymethoxy)benzene hydrate (1 eq., 3.35 g, 12.9 mmol) and THF (126 mL) . HCl (30 eq., 9 M, 42.9 mL, 386 mmol) was added while stirring at rt.

After about 24 h, starting material was full consumed (TLC analysis). The reaction was diluted with water and the organic layer was separated. The aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine and dried over anhydrous MgSO$_4$. After filtration, the solvent was removed under reduced pressure.

Et$_2$O was added to the reaction crude and it was placed in a fridge for crystallisation. Next day, solid crystals were filtered off and dried under high vacuum to obtain the pure compound (S)-2-(*tert*-butylsulfinyl)phenol **370**. Over all yield was found to be about 82%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.95 (s, 1H), 7.36 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.93 – 6.83 (m, 2H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 161.84, 133.04, 127.95, 119.68, 118.84, 116.48, 58.89, 22.99. HRMS (ESI-TOF): m/z calculated for C$_{10}$H$_{15}$O$_2$S; 199.0782, found 199.0787. er: 99/1. IC column, solvent: 80/20 hexane/*i*PrOH, Flow rate: 0.5ml/min t= 20.74 min(R enantiomer) / 25.25 min (S enantiomer) min. [α]$_D^{20}$= - 99.36 (C= 0.99, CHCl$_3$).

The compound **370** can also be resolved under following chiral hplc conditions: ODH, solvent: 95/5 hexane/iPrOH, Flow rate: 0.5ml/min, t= 13.4 min (S enantiomer) / 15.2 min (R enantiomer).

7.2.1.2 2-bromo-1-(methoxymethoxy)benzene 368a
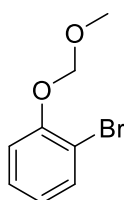
This compound was prepared according to the general procedure A. A dark brown oily liquid in appearance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.27 (ddd, *J* = 8.3, 7.3, 1.6 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.91 (ddd, *J* = 7.9, 7.4, 1.5 Hz, 1H), 5.27 (s, 2H), 3.54 (s, 3H).

7.2.1.3 2-bromo-4-methoxy-1- (methoxymethoxy)benzene 368b
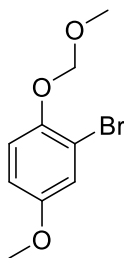
This compound was prepared according to the general procedure A. A dark brown oily liquid in appearance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.10 (d, *J* = 3.0 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.79 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.15 (s, 2H), 3.76 (s, 3H), 3.52 (s, 3H).

7.2.1.4 2-bromo-6-methoxy-1-(methoxymethoxy)benzene 368c
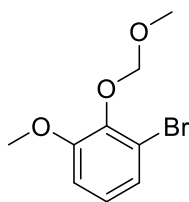
This compound was prepared according to the /general procedure A. A yellowish-brown oily liquid in appearance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.5 Hz, 1H), 5.19 (s, 2H), 3.87 (s, 3H), 3.69 (s, 3H).

7.2.1.5 2,4-dibromo-1-(methoxymethoxy)benzene 368d
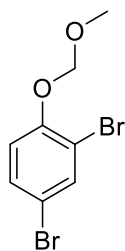
This compound was prepared according to the literature procedure/general procedure A. A dark brown oily liquid in appearance ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.68 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 5.22 (s, 2H), 3.50 (s, 3H).

7.2.1.6 (*S*)-(-)-tert-Butyl *tert*-Butanethiosulfinate
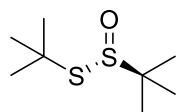
This compound was prepared according to the literature.[342] ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 1.51 (s, 9H), 1.33 (s, 9H). $[\alpha]^{20}{}_D$ -148.0° (c=0.51, CH$_2$Cl$_2$).

7.2.1.7 2 (*S*)-2-*(tert*-butylsulfinyl)-4-methoxyphenol 373
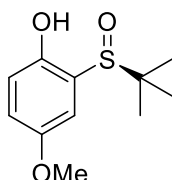
This compound was prepared according to the general procedure A. White solid, overall yield 70% (starting from (*S*)-(-)-*tert*-Butyl *tert*-Butanethiosulfinate). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.41 (s, 1H), 6.95 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.47 (d, *J* = 3.0 Hz, 1H), 3.75 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 155.51, 151.87, 120.32, 119.40, 116.57, 112.29, 59.01, 56.08, 23.09. er: 95/5. Chiral HPLC **Column:** IC, solvent: 95/5 hexane/*i*PrOH, Flow rate: 0. 5 ml/min t= 23.8 (minor)/46.3 (major) . HRMS (ESI-TOF): m/z calculated for C$_{11}$H$_{17}$O$_3$S; 229.0880 , found 229.0893. $[\alpha]_D{}^{20}$= - 138 (C= 1.01 CHCl$_3$).

7.2.1.8 (*S*)-2-(*tert*-butylsulfinyl)-6-methoxyphenol 371
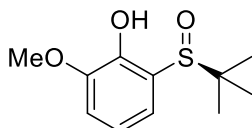
This compound was prepared according to the general procedure A. White solid, overall yield 73% (starting from (*S*)-(-)-*tert*-Butyl *tert*-Butanethiosulfinate).   ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.71 (s, 1H), 6.95 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.4 Hz, 1H), 3.89 (s, 3H), 1.30 (s, 9H).^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 149.21, 119.35 (overlapped C$_{AR}$), 118.62 (overlapped C$_{AR}$), 114.31, 58.94, 56.27, 23.06. >99% ee. Chiral HPLC **Column:** IC, solvent: 80/20 hexane/*i*PrOH, Flow rate: 0.5 ml/min t (min)=

47.90/78.9. HRMS (ESI-TOF): m/z calculated for $C_{11}H_{16}KO_3S$; 267.0442, found 267.0452. $[\alpha]_D^{20}$= -89.63 (C= 1.572, CHCl₃).

7.2.1.9 (S)-4-bromo-2-(*tert*-butylsulfinyl)phenol 372
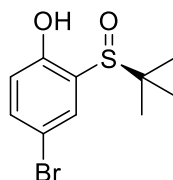
This compound was prepared according to the general procedure A. White solid, overall yield 67% (starting from (S)-(-)-*tert*-Butyl *tert*-Butanethiosulfinate). ¹H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.94 (s, 1H), 7.44 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 1H), 1.32 (s, 9H). ¹³C NMR (101 MHz, Chloroform-*d*) δ (ppm) 160.93, 135.84, 130.01, 121.55, 118.23, 110.52, 59.37, 22.98. er: 99.7/0.3. Chiral HPLC **Column:** IC, solvent: 80/20 hexane/iPrOH, Flow rate: 0.5 ml/min, t (min)= 49.58 (minor)/53.16 (major). HRMS (ESI-TOF): m/z calculated for $C_{10}H_{14}BrO_2S$; 276.9878, found 276.9892. $[\alpha]_D^{20}$= -181.76 (C= 1.01, CHCl₃).

7.2.1.10   (S)-2-[(4-methylphenyl)sulfinyl]phenol 366
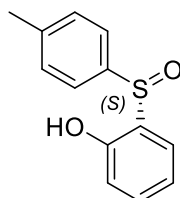
This compound was prepared according to the general procedure A. White solid, over all yield 76% yield (starting from (-)-menthyl (S)-*p*-toluenesulfinate). ¹H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.43 (s, 1H), 7.62 – 7.55 (m, 2H), 7.17 (dd, *J* = 8.1, 1.7 Hz, 1H),7.35-7.27 (m, 3H), 6.93 – 6.85 (m, 2H), 2.38 (s, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ (ppm) 159.41, 142.35, 140.67, 133.08, 130.36, 126.08, 125.10, 119.98, 119.74, 119.71, 21.53. er> 99/1. Chiral HPLC **Column:** , solvent: / hexane/iPrOH, Flow rate: 0.5ml/min, t (min)= 36.2 (minor)/39.97 (major). HRMS (ESI-TOF): m/z calculated for C $_{13}H_{13}O$ ₂S; 233.0631, found 233.0631**.** $[\alpha]_D^{20}$ =+ 99.22 (C= 0.995, CHCl₃).

7.2.1.11   (SaR)-6-Methyl-2'-(p-tolylsulfinyl)-[1,1'-biphenyl]-2-ol[(SaR)-5] 363
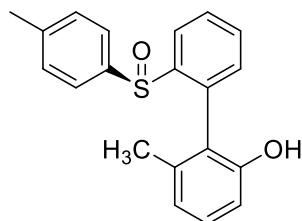
This compound was prepared according to the literature procedure. White solid, over all yield 60% (starting from (-)-menthyl (S)-p-toluenesulfinate).[314] 1H-NMR (CDCl3, 400 MHz) δ (ppm) 8.23 (brd, 1H), 8.29 (dd, J = 7.8, 1.1 Hz, 1H), 7.56 (td, J =7.7, 1.0 Hz, 1H), 7.49 (td, J = 7.5, 1.1 Hz, 1H), 7.15 (dd, J = 7.4, 1.1 Hz, 1H), 7.08 (t, J = 7.7 Hz,3H), 7.02 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 7.5 Hz, 1H), 2.32 (s, 3H), 1.29(s, 3H) ppm. [α]$_D^{20}$ = −153 (c = 1, CHCl$_3$).

7.3   Hydrogen Phosphinate Substrates

7.3.1.1   Ethyl phenylphosphinate 41a
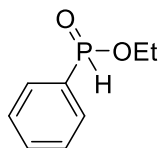
This compound is commercially available and can also be prepared according to the literature procedures.[76,79] A colourless oily liquid, 97% yield. 1H NMR (400 MHz, Chloroform-d) δ (ppm) 7.86 − 7.74 (m, 2H), 7.65 − 7.45 (m, 3H), 7.58 (d, J = 562.79 Hz, 1H, PH), 4.26 − 4.05 (m, 2H), 1.37 (dt, J = 9.3, 7.0 Hz, 3H). 31P NMR (CDCl3) δ (ppm) 24.59.

7.3.1.2   Methyl phenylphosphinate 41e
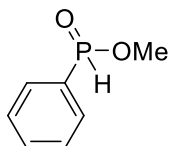
This compound was prepared according to the literature procedure.[305] A colourless oily liquid, 73% yield. 1H NMR (400 MHz, Chloroform-d) δ (ppm) 7.85 − 7.73 (m, 2H), 7.66 − 7.56

(m, 1H), 7.56 – 7.45 (m, 2H), 7.52 (d, *J*= 566.12 Hz, 1H, PH), 3.80 (d, *J* = 12.0 Hz, 3H). ^{31}P NMR (CDCl3) δ (ppm) 27.18.

7.3.1.3 Butyl phenylphosphinate 41f

This compound was prepared according to the literature procedures.[76] A colourless oily liquid, 95% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.78 (ddt, *J* = 13.7, 8.0, 1.2 Hz, 2H), 7.64 – 7.55 (m, 1H), 7.6 (d, *J*= 562.3, 1H, PH), 7.51 (tdd, *J* = 7.0, 3.5, 1.3 Hz, 2H), 4.17 – 3.99 (m, 2H), 1.76 – 1.64 (m, 2H), 1.50 – 1.33 (m, 2H), 0.92 (td, *J* = 7.4, 1.1 Hz, 3H). ^{31}P NMR (CDCl3) δ (ppm) 24.83.

7.3.1.4 Isopropyl phenylphosphinate 354b
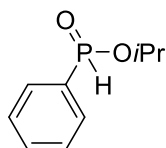
This compound was prepared according to the literature procedure.[76] A colourless oily liquid, 76% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.32 (s, 0.5, PH), 7.84 – 7.74 (m, 2H), 7.64 – 7.46 (m, 3H), 6.92 (s, 05, PH), 4.72 (dhept, J = 9.3, 6.2 Hz, 1H), 7.62 (d, *J*= 559.2, 1H, PH) 1.43 (d, J = 6.2 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H). 31P NMR (CDCl3) δ (ppm) 22.18.

7.3.1.5 Cyclohexyl phenylphosphinate 41g

This compound was prepared according to the literature procedures.[81,106] A colourless oily liquid, 93% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.91 – 7.70 (m, 2H), 7.64 – 7.53 (m, 1H), 7.56 – 7.36 (m, 2H), 7.63 (d, *J*= 564 Hz, 1H, PH) 4.45 (qt, *J* = 9.2, 3.9 Hz, 1H),), 2.9-1.86

(m, 2H), 1.84-1.7 (m, 2H), 1.7-1.45(m, 3H), 1.7-1.4(m, 3H). ^{31}P NMR (CDCl3) δ (ppm) 21.91 ppm.

7.3.1.6 *tert*-butyl phenylphosphinate 354c
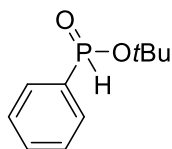
This compound was prepared according to the literature procedures.[305] A colourless oily liquid, 70% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.43 (s, 0.5 PH), 7.81 − 7.71 (m, 2H), 7.61 − 7.52 (m, 1H), 7.74 (d, *J* = 552 Hz, 1H, PH), 7.48 (tt, *J* = 7.2, 3.3 Hz, 2H), 7.05 (s, 0.5 PH), 1.57 (s, 9H). ^{31}P NMR (CDCl3) δ (ppm) 15.12.

7.3.1.7 Adamantan-1-yl phenylphosphinate 354d
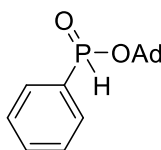
This compound was prepared according to the literature procedure.[106] A waxy white coloured solid, 96% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.83 − 7.73 (m, 2H), 7.61 − 7.44 (m, 3H), 7.79 (d, *J*= 553.3 Hz, 1H, PH), 2.25 − 2.19 (m, 3H), 2.14 (d, *J* = 2.8 Hz, 6H), 1.67 (t, *J* = 3.1 Hz, 6H). ^{31}P NMR (CDCl3) δ (ppm) 14.16.

7.3.1.8 Ethyl naphthalen-1-ylphosphinate 41h
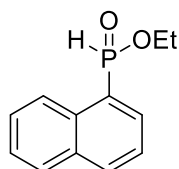
This compound was prepared according to the literature procedures.[77,420] A colourless oily liquid, 46% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.43 (dt, *J* = 8.6, 1.0 Hz, 1H), 8.12 (dd, *J* = 7.0, 1.3 Hz, 1H), 8.11 − 8.02 (m, 1H), 7.93 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.93 (d, *J*= 560 Hz,

1H PH), 7.72 – 7.49 (m, 3H), 4.30 – 4.05 (m, 2H), 1.41 – 1.28 (m, 3H). ^{31}P NMR (CDCl3) δ (ppm) 25.55.

7.3.1.9 Ethyl mesitylphosphinate 41i
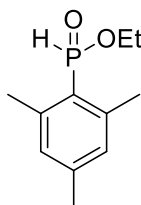
This compound was prepared according to the literature procedure.[421] A colourless oily liquid, 76% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 6.98 (d, J= 1337.5 Hz 1H, PH), 6.87 (d, J = 4.6 Hz, 2H), 4.27 – 4.05 (m, 2H), 2.55 (s, 6H), 2.28 (d, J = 0.9 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).^{31}P NMR (CDCl3) δ (ppm) 23.97.

7.3.1.10 Ethyl cyclohexylphosphinate 41j
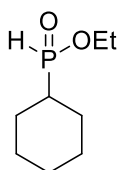
This compound was prepared according to the literature procedure.[305] A colourless oily liquid, 90% yield. ^{1}H-NMR (400 MHz, CDCl3) δ (ppm) 6.81 (d, 1 J = 517.0 Hz, 1H), 4.21-3.99 (m, 2H), 1.90-1.65 (m, 6H), 1.33 (t, 3 J = 7.4 Hz, 3H), 1.29-1.21 (m, 5H). ^{31}P NMR (CDCl3) δ (ppm) 44.02.
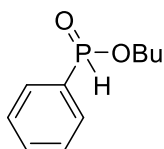
7.3.1.11 Ethyl methylphosphinate 41k
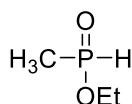
This compound was prepared according to the literature procedures.[416] A colourless oily liquid, 91% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.20 (1H, d, 1JHP 537 Hz, H1),4.23 – 3.97 (m, 2H), 1.56 – 1.40 (m, 2H), 1.38 – 1.26 (m, 3H). ^{31}P NMR (CDCl3) δ (ppm) 33.26.

7.3.1.12   Methyl(phenyl)phosphine oxide 41l
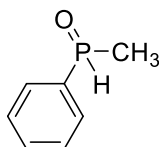
This compound was prepared according to the literature procedure.[79] A colourless oily liquid, 71% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 8.23 (q, J = 3.8 Hz, PH), 7.71 (ddt, J = 13.6, 6.8, 1.5 Hz, 2H), 7.6- 7.45 (m 2H), 7.05 (q, J = 3.8 Hz, PH), 1.79 (dd, J = 13.9, 3.8 Hz, 3H).^{31}P NMR (CDCl3) δ (ppm) 20.21.

7.3.1.13   Butyl(phenyl)phosphine oxide 41m
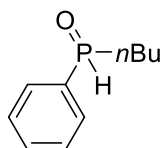
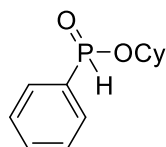
This compound was prepared according to the literature procedure.[79] A colourless oily liquid, 78% yield. 1H NMR (400 MHz, CDCl3) δ (ppm): 7.69 – 7.59 (m, 2H), 7.56 – 7.39 (m, 3H), 7.43 (dt, 1JH-P = 463.0 Hz, J = 3.3 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.62 – 1.46 (m, 2H), 1.44 – 1.31 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H);^{31}P NMR (CDCl3) δ (ppm) 28.6.

7.4 General Procedure B for O-P Coupling/Atherton Todd Reaction Using Racemic 2-(*tert*-butylsulfinyl)phenol and 2 eq. of Ethyl Phenylphosphinate

41a
2 eq
(±)

370
(±)

400a
78%
dr: 90/10
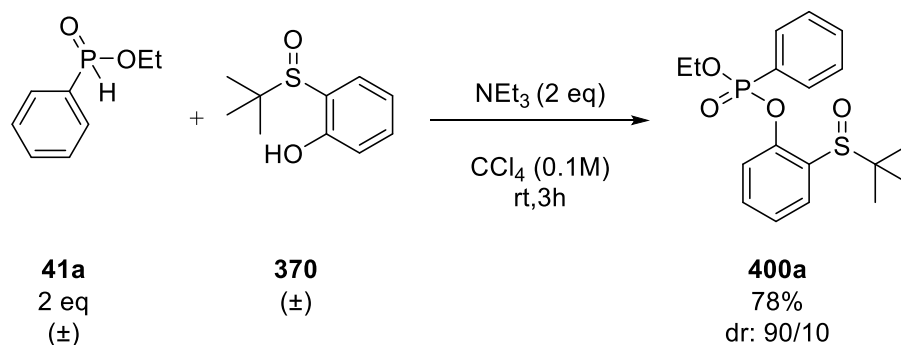
In a round bottom flask ethyl phenylphosphinate **41a** (2 eq., 912 mg, 0.809 mL, 5.04 mmol) and 2-(*tert*-butylsulfinyl)phenol **370** (1 eq., 500 mg, 2.52 mmol) were dissolved in CCl_4 (25 mL) , reaction mixture was stirred for about 5-10 min at rt, followed by fast addition of triethylamine (TEA) (2 eq., 510 mg, 0.701 mL, 5.04 mmol) under argon at rt. The reaction was stirred for 3h.

The reaction was quenched with distilled water and was diluted with EtOAc. Organic layer was separated. Aqueous layer was further extracted with EtOAc (2 times). All organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and major diastereomer was recrystallised in CH_2Cl_2/n-C_5H_{12}.

Recrystallisation Procedure: Reaction crude was dissolved in minimum amount of CH_2Cl_2 and n-C_5H_{12} was added. Both the layers were mixed by shaking and put into the refrigerator for 2 days. White solid, yield = 78%.

Major Diastereomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.00 – 7.91 (m, 2H), 7.82-7.80 (dd, 1H), 7.66 – 7.60 (m, 1H), 7.56 – 7.49 (m, 3H), 7.45 (td, *J* = 8.3, 7.8, 1.7 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 4.25 – 4.13 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 9H). ^{31}P NMR (162 MHz, CDCl$_3$) δ (ppm) 15.41. ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 148.64 (d, *J* = 8.1 Hz), 133.29 (d, *J* = 3.2 Hz), 132.47, 132.07 – 131.95 (m), 131.92, 128.80, 128.65, 127.88, 125.07, 120.09 (d, *J* = 3.1 Hz), 63.78 (d, *J* = 6.2 Hz), 57.96, 22.95, 16.33 (d, *J* = 6.0 Hz). IR: 459.88, 506.26, 599.24, 666.91, 696.04, 750.06, 916.15, **1039.18,** 1066.16, 1131.23, 1161.32, 120.95, 1268.10, 1365.28, 1392.33, 1440.23, 1470.36, 1582.89, 2978.54. HRMS: m/z calculated for $C_{18}H_{23}LiO_4PS$ 373.120, found 373.121.

Chiral HPLC: Major Diastereomer: sample preparation: about 2 mg of sample in 1 ml of 80/20 hexane/*i*PrOH.

1. **Column: IA, solvent:** of 80/20 hexane/iPrOH, Flow rate: 0.5 ml/min, t= 12.74/15.14 min.

2. **Column: ODH, solvent:** of 90/10 hexane/iPrOH, Flow rate: 0.5 ml/min t= 21.83/25.91 min.

3. **All Four Diastereomers**: **sample preparation** (product was column purified as a mixture of both diastereomers) about 2 mg of sample in 1 ml of 80/20 hexane/*i*PrOH. **Column: ODH, solvent:** of 90/10 hexane/*i*PrOH, Flow rate: 0.5 ml/min t= 21.68/25.71 min (major diastereomer, 44.4%/44.6%), 19.35/30.38 min (5.4%/5.5%%) (minor).

7.5 General Procedure C for O-P Coupling Reaction under Modified Atherton Todd Reaction conditions using (*S*)-2-(*tert*-butylsulfinyl)phenol :

41a
1 or 1.1 eq
(±)

370
1eq

400a
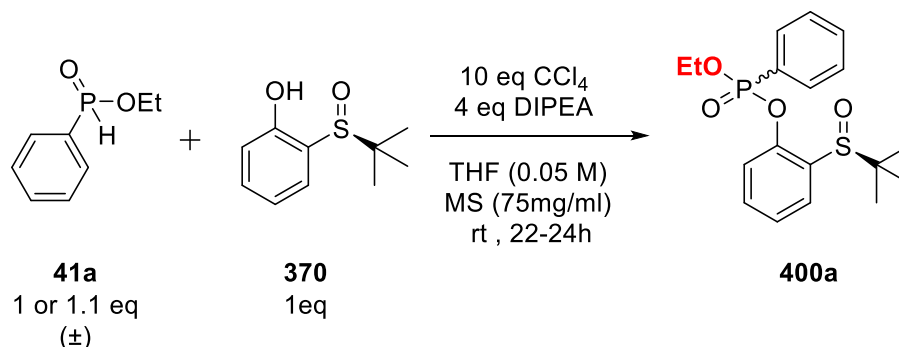
To a flame dried round bottom flask (rb) was added activated molecular sieves (MS) (1200 mg). MS were reactivated by flame (about 2 min flame heating under vacuum and after 10-15 min the process was repeated once more). Then, (*S*)-2-(*tert*-butylsulfinyl)phenol **370** (1 eq., 158 mg, 0.8 mmol) was added, the rb was put on vacuum for few min, then it was filled with argon. It was followed by addition of THF (15.9 mL), ethyl phenylphosphinate **41a** (1 eq., 144 mg, 0.128 mL, 0.8 mmol), CCl_4 (10 eq., 1230 mg, 0.772 mL, 8 mmol) and diisopropylethyl amine (DIPEA) (4 eq., 413 mg, 0.529 mL, 3.2 mmol) under argon while stirring at rt. The reaction mixture was stirred for about 24 h.

The Reaction was quenched with distilled water and was diluted with EtOAc. Organic layer was separated. Aqueous layer was further extracted with EtOAc (2 times). All organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the product was purified as a mixture of both diastereomers of compound **400a** by column chromatography (cyclohexane/ethyl acetate 1/1) in about 80% as light brown oily liquid . ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.00 – 7.90 (m, major diastereomer 2H), 7.90 – 7.77 (m, overlapped signals major-minor diastereomers, 1.54H),7.74-7.70(m,0.23H) 7.67 – 7.55 (m, overlapped signals major-minor diastereomers 1.04H), 7.59 – 7.44 (m, , overlapped signals major-minor diastereomers 4.15H), 7.48 – 7.39 (m, , overlapped signals major-minor diastereomers 0.95H), 7.39 – 7.30 (m, , overlapped signals major-minor diastereomers, 1.28H),729-7.23(m, , overlapped signal with solvent signal) 4.35-4.24(m, minor diastereomer, 0.47H) 4.18 (dq, *J* = 8.5, 7.1 Hz, 2.05H), 1.37 – 1.42 (m, 0.92H),1.27-1.22(t,3.74H) 1.21 – 1.8 (s, overlapped signals major-minor diastereomers 1.5H), 1.12 (s, 9.12H). ^{31}P NMR (CDCl3) (Mixture of two diastereomers, dr: 83.3/16.67, based on P NMR) δ (ppm) 15.59 (minor diastereomer),15.40 (major diastereomer). ^{13}C NMR (126 MHz, Chloroform-*d*) δ (ppm) 148.63, 148.57, 133.28, 133.25, 132.44, 132.40, 132.11, 132.03, 132.00, 131.96, 131.95, 131.88, 128.84, 128.75, 128.71, 128.63, 128.14, 127.83, 127.79, 126.60, 125.03, 124.85, 120.06, 120.04, 63.75, 63.71, 57.91, 22.98, 22.90, 16.31, 16.26. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{24}O_4PS$: 367.1129, found: 302.1127.

7.5.1 2-((S)-tert-butylsulfinyl)phenyl methyl phenylphosphonate 400b
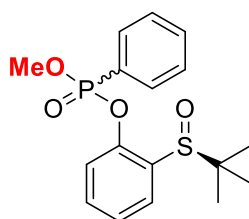
This compound was prepared according to the general procedure C as a colourless oily liquid, total yield 71%, dr: 77/23 (based on P NMR). Recrystallisation in Et$_2$O yielded major diastereomer as a white solid with dr: 95/5 (based on P nmr): ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 16.9 (major diastereomer), 17.14 (minor diastereomer). ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.95 (ddt, J = 14.0, 6.9, 1.3 Hz, 2H), 7.81 (dt, J = 7.7, 1.3 Hz, 1H), 7.68 – 7.59 (m, 1H), 7.58 – 7.41 (m, 4.26H), 7.36 (td, J = 7.5, 1.3 Hz, 1H), 3.80 (d, J = 11.4 Hz, 3H), 1.28 – 1.16 (m, minor diastereomer, 0.44H), 1.13 (s, major diastereomer, 9H).^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 148.54, 148.46, 133.39, 133.36, 132.47, 132.08, 131.97, 128.80, 128.64, 127.87, 127.47, 125.53, 125.10, 120.00, 119.97, 57.94, 53.85, 53.79, 22.87. HRMS (ESI-TOF): m/z calculated for C$_{17}$H$_{21}$NaO$_4$PS: 375.079664, found: 375.079037.

7.5.2 2-((S)-tert-butylsulfinyl)phenyl isopropyl phenylphosphonate 400c
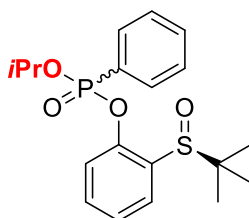
This compound was prepared according to the general procedure C as a colourless oily liquid, total yield 64%, dr: 77/23. Flash chromatography (TLC spots of both the diastereomers are same, while UV profile is different for both, cyclohexene/ethyl acetate 70/30 to 50/50) yielded 28% major diastereomer with dr: 98/2 (based on P nmr). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 16.9 (major diastereomer), 17.14 (minor diastereomer). ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 8.01 – 7.90 (m, 2H), 7.80 (dt, J = 7.9, 1.4 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.57 – 7.46 (m, 3H), 7.44 (td, J = 8.2, 7.8, 1.8 Hz, 1H), 7.38 – 7.29 (m, 1H), 4.81 (dhept, J = 7.9, 6.2 Hz, 1H), 1.27 – 1.18 (m, 6H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 133.05, 133.01, 132.29, 132.00, 131.88, 131.78, 128.63, 128.48, 127.75, 124.88, 120.07, 120.04, 72.92, 72.86, 57.84, 23.81, 23.76, 23.72, 22.86. HRMS (ESI-TOF): m/z calculated for C$_{19}$H$_{26}$O$_4$PS: 381.129513, found 381.1283932.

7.5.2.1 ((S)-tert-butylsulfinyl)phenyl cyclohexyl phenylphosphonate 400d
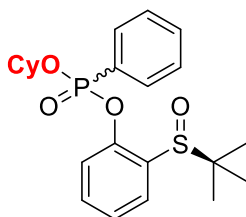
This compound was prepared according to the general procedure C. Crude dr: 64/36. Total yield 67%. Both diastereomers were separated by flash chromatography (cyclohexane/ethyl acetate 80/20 to 50/50). d_1 (major, 41%) dr(d_1/d_2); 97/3 and d_2(minor, 26%) (d_2/d_1); 85/15.

Diastereomer 1 (d_1 major diastereomer): dr (d_1/d_2); 97/3, based on P nmr.

A colourless oily liquid. 41% yield. ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 14.29 (major diastereomer), 14.39 (minor diastereomer). ^1H NMR (400 MHz, Chloroform-d) δ (ppm) 7.95 (ddt, J = 14.0, 6.9, 1.4 Hz, 2H), 7.85 – 7.75 (m, 1H), 7.65 – 7.56 (m, 1H), 7.56 – 7.45 (m, 3H), 7.43 (td, J = 7.7, 1.7 Hz, 1H), 7.37 – 7.28 (m, 1H), 4.53 (dtt, J = 12.7, 8.5, 3.9 Hz, 1H), , 1.74 (s, 2H), 1.68 – 1.58 (m, 2H), 1.52 – 1.41 (m, 3H), 1.32 – 1.14 (m, 3H), 1.10 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 148.65, 133.03, 133.00, 132.27, 131.95, 131.89, 131.78, 128.61, 128.46, 127.72, 127.29, 127.22, 124.88, 120.13, 120.10, 77.52, 77.46, 60.38, 57.83, 33.41, 33.37, 33.35, 33.31, 24.95, 23.37, 22.85, 21.05, 14.20. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{30}O_4PS$: 421.159845, found 421.159693.

Diastereomer 2 (d_2 minor diastereomer): dr (d_2/d_1); 85/15, based on P nmr.

A colourless oily liquid. 26% yield. ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 14.38, 14.29. ^1H NMR (400 MHz, Chloroform-d) δ (ppm) 8-7.89 (m, 0.37H), 7.87 – 7.76 (m, 2.18H), 7.69 (dt, J = 7.8, 1.4 Hz, 1H), 7.61 – 7.37 (m, 5H), 7.37 – 7.27 (m, 1.33H), 7.23 (t, J = 7.5 Hz, 1H), 4.58 (ddtd, J = 44.3, 12.7, 8.4, 3.9 Hz, 1.2H), 1.99 – 1.25 (m, 12H), 1.17 (d, J = 1.0 Hz, 9H), 1.08 (d, J = 0.9 Hz, 1.7H). ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 148.72, 148.67, 133.13, 133.10, 132.35, 132.05, 131.95, 131.84, 131.52, 131.45, 128.77, 128.68, 128.62, 128.42, 127.73, 126.54, 124.95, 124.74, 120.19, 120.19, 119.71, 119.68, 77.29, 77.23, 60.43, 57.94, 33.75, 33.71, 33.63, 33.59, 25.10, 25.02, 23.59, 23.51, 23.43, 22.99, 22.91, 21.10, 14.26. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{30}O_4PS$: 421.159845, found 421.159693.

7.5.3 *tert*-butyl (2-((*S*)-*tert*-butylsulfinyl)phenyl) phenylphosphonate 400e
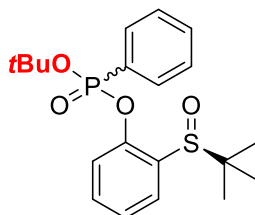
This compound was prepared according to the general procedure with crude dr 60/40. Flash chromatography (cyclohexane/ethyl acetate 80/20 to 50/50) provided about 44 % total yield.

Diastereomer 2 (d2)

A colourless oily liquid, yield = 24%, with dr (d2/d1):89/11: ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.00 – 7.90 (m, 2H), 7.82 – 7.78 (m, 1H), 7.60 – 7.55 (m, 2H), 7.53 – 7.42 (m, 4H), 7.37 – 7.30 (m, 1H), 1.44 (s, 9H), 1.10 (s, 9H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 10.6 (d1), 10.95 (d2) with dr (d2/d1): 89/11. ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 149.13, 147.60, 132.12, 131.90, 131.65, 131.27, 131.17, 127.89, 127.31, 127.08, 126.49, 124.04, 121.09, 57.38, 30.02, 29.98, 29.18, 22.50, 22.31, 13.61. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{27}NaO_4PS$: 417.126566, found 417.125988.

Diastereomer 1 (d1)

^{31}P NMR (crude) (162 MHz, Chloroform-*d*) δ (ppm) 10.6 (d1). could not be isolated (most likely unstable on column chromatography).

7.5.4 Butyl (2-((*S*)-*tert*-butylsulfinyl)phenyl) phenylphosphonate 400f

This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 70/30 to 50/50) provided about 80% yield as an oily liquid and as a mixture of two diastereomers with dr; 84/16 (based on P nmr), (crude nmr

dr: 69/31). ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.95 (ddd, J = 14.0, 8.3, 1.4 Hz, 2H),7.89-7.83(m, 0.34H), 7.83 − 7.77 (m, 1.11H) 7.75-7.69(m, 0.24H), 7.66-7.59 (m, 1.03H), 7.58 − 7.48 (m, 3.48H), 7.48 − 7.40 (m, 1.51H), 7.38 − 7.31 (m, 1.26H), 4.26-4.17(m, 0.4H), 4.11 (m 2H), 1.77-1.67(m,0.42), 1.57 (m 2H), 1.47 − 1.37 (m, 0.4H), 1.34 − 1.22 (m, 2H), 1.21 (s, 1.8H), 1.12 (s, 9H), 0.94 (d, J = 7.4 Hz, 1H),1.96-1.90(t, 0.6H) 0.83 (t, J = 7.4 Hz, 3H). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 15.45(major diastereomer), 15.63(minor diastereomer). ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 148.63, 148.55, 133.21, 133.18, 132.37, 132.11, 131.97, 131.93, 131.86, 128.81, 128.71, 128.66, 128.56, 128.24, 127.80, 127.74, 126.31, 124.96, 124.78, 119.99, 119.96, 67.37, 67.31, 57.89, 32.29, 32.23, 22.94, 22.86, 18.74, 18.59, 13.57, 13.48. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{28}O_4PS$: 395.145246, found 395.144043.

7.5.5 2-((S)-$tert$-butylsulfinyl)-6-methoxyphenyl isopropyl phenylphosphonate 400g

This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 50/50) provided an oily liquid in about 52% yield as a mixture of diastereomers with dr; 78.7/21.3 (based on P nmr ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.89 (dtt, J = 14.1, 7.3, 1.4 Hz, 2.73H), 7.61 − 7.47 (m, 2H), 7.51 − 7.41 (m, 1.93H), 7.37 (ddd, J = 8.0, 1.5, 0.8 Hz, 1H), 7.34 − 7.20 (m, overlapped with solvent signal 1H), 6.99 (d, J = 8.1, 1.5 Hz, 1.3H), 4.99 (ddt, J = 14.6, 12.6, 6.3 Hz, 1.17H), 3.78 (s, 0.81H), 3.61 (s, 3H), 1.43 (d, J = 6.2 Hz, 0.87H), 1.34 (dd, J = 17.2, 6.2 Hz, 7.17H), 1.17 (s, 9H), 1.04 (s, 2.52H).). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 14.22 (major diastereomer), 13.76 (minor diastereomer).^{13}C NMR (101 MHz, Chloroform-d) δ 1(ppm) 34.00, 132.30, 132.27, 132.11, 132.01, 131.66, 131.56, 128.41, 128.29, 128.25, 128.13, 125.49, 125.29, 118.69, 115.35, 115.08, 72.34, 72.28, 58.18, 56.10, 55.91, 24.16, 24.14, 24.10, 23.09, 22.98. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{27}NaO_5PS$: 433.121587, found 433.120902.

7.5.6 2-((*S*)-*tert*-butylsulfinyl)-6-methoxyphenyl methyl phenylphosphonate 400h
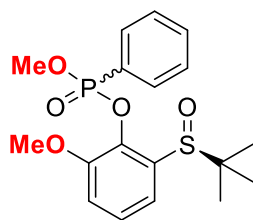
This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 50/50) provided an oily liquid in about 58% yield as a mixture of diastereomers with dr; 79/21 (based on P nmr).

^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.96-7.79 (m, 2.63H), 7.57 (ddq, *J* = 9.0, 4.9, 1.7 Hz, 1.32H), 7.48 (dddt, *J* = 7.1, 5.9, 2.7, 1.3 Hz, 2.73H), 7.40 − 7.26 (m, 1.67H), 7.25 − 7.21 (m, 0.34), 6.98 (dq, *J* = 8.4, 1.9, 1.4 Hz, 1.31H), 4.10 (qd, *J* = 7.2, 1.5 Hz, 0.72H), 3.94 (dd, *J* = 11.6, 1.5 Hz, 3H), 3.76 (d, *J* = 1.2 Hz, 0.81H), 3.57 (d, *J* = 1.9 Hz, 3H), 1.19 (d, *J* = 1.2 Hz, 9H), 1.04 (d, *J* = 1.5 Hz, 2.45H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 17.01 (major diastereomer), 16.29 (minor diastereomer). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 150.45, 138.37, 134.02, 133.98, 132.82, 132.53, 132.50, 132.02, 131.92, 131.61, 131.51, 129.66, 128.47, 128.35, 128.31, 128.20, 127.68, 125.60, 125.40, 125.39, 118.75, 118.70, 115.38, 115.37, 115.12, 60.47, 58.19, 57.96, 56.17, 55.88, 53.56, 53.50, 23.10, 22.91, 21.13, 14.29. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{23}NaO_5PS$: 405.090669, found 405.089602.

7.5.7 Adamantan-1-yl (2-((*S*)-*tert*-butylsulfinyl)phenyl) phenylphosphonate 400i

This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 8/2) provided about 68 % total yield.
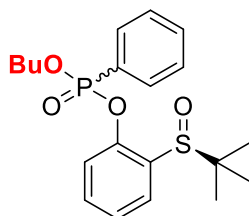
Diastereomer 1 (d$_1$)

A colourless oily liquid, yield = 35%. ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 10.37. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.99 − 7.91 (m, 2H), 7.79 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.57 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.52 − 7.42 (m, 3H), 7.36 − 7.29 (m, 1H), 2.13 − 2.07 (m, 3H), 1.98 (d, *J* = 3.6 Hz, 6H), 1.56 (t, *J* = 3.2 Hz, 6H), 1.09 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm)

132.13, 132.10, 131.61, 131.47, 131.40, 131.34, 131.24, 127.93, 127.77, 127.06, 124.12, 119.77, 119.74, 83.99, 83.91, 57.22, 43.32, 43.28, 43.13, 35.15, 35.08, 35.04, 30.62, 22.35. HRMS (ESI-TOF): m/z calculated for $C_{26}H_{34}O_4PS$ 473.192883, found 473.190994.

Diastereomer 2 (d$_2$)

A colourless oily liquid, yield = 33%. ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 10.72. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.88 – 7.78 (m, 2H), 7.70 (ddd, *J* = 7.8, 1.7, 1.2 Hz, 1H), 7.57 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.45 – 7.33 (m, 3H), 7.26 – 7.20 (m, 1H), 2.21 – 2.13 (m, 9H), 1.63 (t, *J* = 3.0 Hz, 6H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 148.87, 132.79, 132.76, 132.25, 131.96, 131.86, 131.76, 128.66, 128.50, 127.71, 124.62, 120.06, 120.03, 85.01, 84.93, 57.94, 44.25, 44.21, 35.79, 31.37, 23.18. HRMS (ESI-TOF): m/z calculated for $C_{26}H_{34}O_4PS$ 473.192883, found 473.190994.

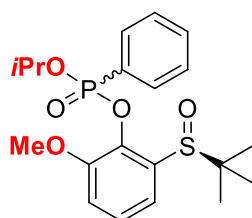### 7.5.8 2-((*S*)-*tert*-butylsulfinyl)phenyl methyl(phenyl)phosphinate 400j
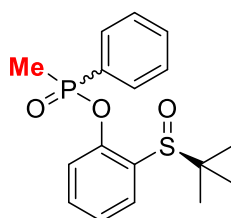
This compound was prepared according to the general procedure C. Flash/Column chromatography (MeOH/CH$_2$Cl$_2$ 98/2 to 5/95) provided about 57% yield with crude dr: 55/45.

Diastereomer 2 (d$_2$):

A colourless oily liquid, 26%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.03 – 7.94 (m, 2H), 7.83 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.60 – 7.53 (m, 3H), 7.47 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 1.80 (d, *J* = 13.9 Hz, 3H), 1.16 (s, 9H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 43.14. ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 148.97, 133.24 and 132.87 (overlapped signals), 131.96, 131.67 and 131.22 (overlapped signals), 130.30, 128.96, 128.12, 125.27, 120.59, 58.40, 23.03, 15.83, 14.89. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{21}O_3PS$: 337.102096 found 337.102179.

Diastereomer 1 (d$_1$):

A colourless oily liquid, 31%. ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.88 – 7.79 (m, 2H), 7.71 – 7.65 (m, 1H), 7.52 – 7.47 (m, 2H), 7.47 – 7.40 (m, 2H), 7.29 – 7.23 (m, 1H), 7.19 (td, J = 7.5, 1.2 Hz, 1H), 1.92 (d, J = 14.7 Hz, 3H), 1.25 (s, 9H). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 43.48. ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 149.33, 133.26, 132.54, 131.60, 130.84, 129.15, 128.86, 127.81, 124.66, 119.80, 58.29, 23.15, 17.22, 16.17. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{21}O_3PS$: 337.102096 found 337.102179.

7.5.9 2-((S)-$tert$-butylsulfinyl)phenyl butyl(phenyl)phosphinate 400k
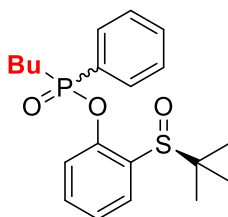
This compound was prepared according to the general procedure C. Flash/Column chromatography (MeOH/CH_2Cl_2 98/2 to 5/95) provided the product in 75% yield.

Diastereomer 1 (d$_1$)

A colourless oily liquid, 34% yield .^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.84 – 7.75 (m, 2H), 7.67 (ddd, J = 7.7, 1.9, 0.9 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.23 (ddd, J = 8.2, 7.3, 1.9 Hz, 1H), 7.16 (td, J = 7.6, 1.2 Hz, 1H), 2.25 – 1.98 (m, 2H), 1.78 – 1.51 (m, 2H), 1.46 – 1.35 (m, 2H), 1.24 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H).). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 36.35(d2), 47.50(d1), dr (d2/d1): 95/5. ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 149.55, 133.09, 132.53, 131.94, 130.75, 129.17, 128.93, 127.98, 124.46, 119.83, 58.17, 30.59, 29.59, 23.94, 23.79, 23.77, 23.76, 23.10, 13.67. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{28}O_3PS$: 379.148832, found 379.149129.

Diastereomer 2 (d$_2$):

 A colourless oily liquid, 41% yield ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.99 – 7.91 (m, 2H), 7.82 (ddd, J = 7.7, 1.7, 0.8 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.59 – 7.52 (m, 3H), 7.44 (ddd, J = 8.2, 7.3, 1.8 Hz, 1H), 7.35 (td, J = 7.5, 1.2 Hz, 1H), 2.18 – 1.95 (m, 2H), 1.49 – 1.35 (m, 2H), 1.34 – 1.24 (m, 2H), 1.18 (s, 9H), 0.80 (t, J = 7.3 Hz, 3H).). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 46.31. ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 149.54, 133.46, 133.11, 131.95, 131.16 129.86, 129.29, 128.39, 125.29, 120.61, 58.65, 29.82, 28.90, 24.41, 24.37, 24.23, 24.06, 23.40, 13.93. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{28}O_3PS$: 379.148832, found 379.149129.
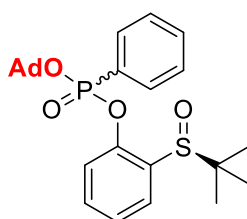
7.5.10 2-((S)-tert-butylsulfinyl)phenyl ethyl naphthalenyl phosphonate 400l
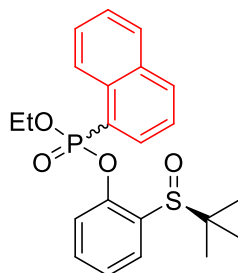
This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 70/30 to 50/50) provided about 72% yield, as an oily liquid and as a mixture of diastereomers with dr; 81/18 (based on P nmr). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.70 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.36 (ddd, *J* = 17.3, 7.1, 1.4 Hz, 1H), 8.15 − 8.08 (m, 1H), 7.94 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.82 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.67 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.58 (dq, *J* = 7.8, 1.4 Hz, 4H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.34 (td, *J* = 7.5, 0.9 Hz, 1H), 4.27 (d, *J* = 7.0 Hz, 2H), 4.11 (d, *J* = 7.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 2H), 1.01 (s, 9H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 16.34(major diastereomer), 15.93(minor diastereomer). ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 148.56, 134.66, 134.26, 133.33, 132.24, 132.12, 131.64, 128.70, 127.60, 126.87, 126.55, 124.68, 120.17,63.67, 63.61, 57.63, 22.70, 22.54, 16.15, 16.09. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{25}NaO_4PS$: 439.110427, found 439.110338.

1.1.1 2-((S)-tert-butylsulfinyl)phenyl ethyl cyclohexylphosphonate 400m
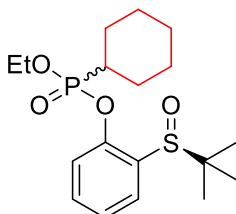
This compound was prepared according to the general procedure C. Flash/Column chromatography provided about 34% yield, as a mixture of diastereomers with dr; 77.5/22.5 (based on P nmr).^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 30.76(major diastereomer), 30.50(minor diastereomer). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.79 (dd, *J* = 7.9, 2.1 Hz, major diastereomers, 1H), 7.70 − 7.50 (m, major diastereomers, 1H), 7.43 (dddd, *J* = 8.3, 6.3, 3.1, 1.3 Hz, major diastereomers, 1H), 7.36 − 7.29 (m, major diastereomers, 1H), overlapped signals in aliphatic region major-minor diastereomers; 4.32 − 3.94 (m, 2.23H), 2.17 − 1.64 (m, 7.2H), 1.61 − 1.38 (m, 2.33H), 1.33 (td, *J* = 7.1, 1.3 Hz, 1.23H), 1.30 − 1.22 (m, 2.97H), 1.22 − 1.18 (s, 9.55H), 1.16 (td, *J* = 7.0, 1.3 Hz, 2.85H). ^{13}C NMR (101 MHz, Chloroform-*d*) (As a mixture of diastereomers δ (ppm) 149.07, 148.98, 132.69, 132.59, 132.17, 132.11, 127.95, 127.91, 125.04, 124.70, 120.84, 120.81, 119.60, 63.69, 63.61, 62.55, 58.08, 57.95, 37.38,

35.96, 26.33, 26.30, 26.16, 26.13, 26.06, 26.04, 26.01, 26.00, 25.89, 23.17, 16.63, 16.57. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{30}O_4PS$ 373.161283, found 373.159693.

7.5.11 (S)-2-(*tert*-butylsulfinyl)phenyl ethyl mesitylphosphonate 400n

This compound was prepared according to the general procedure C. However, attempts to isolate the title product by column chromatography failed. The product **400n** was obtained along with the starting material **41i** left after the reaction, approximate yield is 24%. dr (major diastereomer /minor diastereomer): 72/28.

^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 16.95 (minor), 17.51 (major).,23.96 (starting material **41i**).

7.5.12 2-((S)-*tert*-butylsulfinyl)phenyl ethyl methylphosphonate 400o
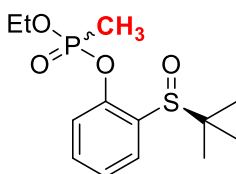
This compound was prepared according to the general procedure C. Flash/column chromatography provided about 80 % yield, and as a mixture of diastereomers with dr; 69.4/30.6 (based on P NMR), ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 27.33 (major diastereomer), 27.68(minor diastereomer). ^{1}H NMR (400 MHz, Chloroform-*d*) (overlapped signals major-minor diastereomers) δ (ppm) 7.83 – 7.77 (m, 1.44H), 7.55 – 7.40 (m, 2.95H), 7.34 (dd, *J* = 1.6, 0.8 Hz, 1.49H), 4.38 – 3.96 (m, 2.28H), 1.64 (t, *J* = 17.6 Hz, 4.32H), 1.36 (s, 1.32H), 1.24 – 1.14 (m, 15.96H). ^{13}C NMR (101 MHz, Chloroform-*d*) (overlapped signals major-minor diastereomers) δ (ppm) 148.41, 148.33, 132.56, 132.43, 131.87, 127.91, 127.87, 125.13, 125.05, 120.15, 120.12, 120.04, 120.01, 63.27, 63.21, 62.53, 57.97, 57.88, 22.88, 16.40, 16.31, 16.25, 12.69, 12.23, 11.23, 10.81. HRMS (ESI-TOF): m/z calculated for $C_{13}H_{21}NaO_4PS$: 327.080051, found 327.079037.

7.5.13 2-((S)-tert-butylsulfinyl)-4-methoxyphenyl ethyl phenylphosphonate 400p
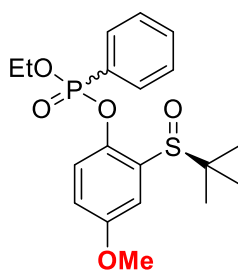
This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 80/20 to 50/50) provided about 64% yield as a colourless oily liquid and as a mixture of diastereomers with dr; 77/23 (based on P nmr).

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.98 – 7.87 (m, 2H),7.87-7.79 (m, 0.6H) 7.60 (dt, J = 7.2, 1.8 Hz, 1H), 7.57 – 7.36 (m, 4.43 H),7.29 (dd, J = 2.5, 1.4 Hz, 1H),7.20 (m, 0.3H) 6.95 (ddd, J = 8.9, 3.1, 1.5 Hz, 1H),6.91-6.83 (m, 0.30H) 4.33-4.22 (m, 0.6H),4.22 – 4.10 (m, 2H), 3.83 (d, J = 1.7 Hz, 3H), 3.77 (d, J = 1.7 Hz, 0.9H), 1.39 (td, J = 7.1, 1.5 Hz, 0.9H), 1.23 (td, J = 7.1, 1.4 Hz, 3H), 1.20 (d, J = 1.6 Hz, 3H) 1.13 (d, J = 1.4 Hz, 9H). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 15.61 (major diastereomer), 15.83 (minor diastereomer). ^{13}C NMR (126 MHz, Chloroform-d) δ (ppm) 156.77, 156.58, 141.99, 141.93, 133.18, 133.13, 133.11, 132.90, 132.84, 132.10, 132.02, 131.92, 131.84, 128.75, 128.66, 128.63, 128.54, 128.24, 126.69, 121.28, 121.25, 118.74, 118.70, 111.14, 111.08, 63.67, 63.62, 58.19, 58.12, 55.94, 55.87, 23.02, 22.94, 16.30, 16.25. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{26}O_5PS$: 397.122137, found 397.123308.

7.5.14 4-bromo-2-((S)-tert-butylsulfinyl)phenyl ethyl phenylphosphonate 400q
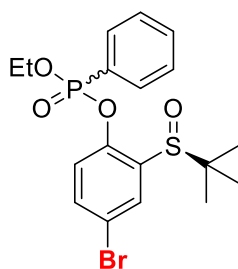
This compound was prepared according to the general procedure C. A colourless oily liquid, 68% yield. dr: 56/44. ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.96 – 7.75 (m, 5H), 7.66 – 7.37 (m, 9H), 4.28 (dqd, J = 7.9, 7.0, 1.0 Hz, 2H), 4.23 – 4.13 (m, 1.52H), 1.42 – 1.36 (m, 2H),

1.26 (t, J = 7.1 Hz, 3H), 1.20 (s, 6.83H), 1.11 (s, 9H).). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 16.04(minor diastereomer), 15.80 (major diastereomer). ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 147.70, 147.62, 135.41, 135.37, 134.33, 134.26, 133.88, 133.80, 133.63, 133.60, 133.54, 133.51, 132.18, 132.07, 132.02, 131.92, 130.55, 130.49, 129.02, 128.92, 128.87, 128.76, 128.64, 128.49, 127.98, 127.15, 126.05, 125.27, 121.84, 121.81, 121.47, 121.45, 118.41, 118.27, 64.02, 63.96, 63.49, 63.43, 62.23, 62.18, 58.58, 58.50, 23.02, 22.94, 16.52, 16.46, 16.40, 16.34. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{22}BrNaO_4PS$: 467.006518, found 467.005200.

1.1.2   2-((S)-$tert$-butylsulfinyl)-6-methoxyphenyl ethyl phenylphosphonate 400r
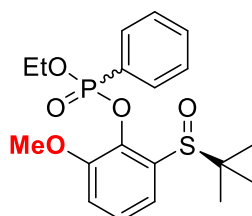
This compound was prepared according to the general procedure C. Flash/Column chromatography (cyclohexane/ethyl acetate 50/50) provided about 78% yield as a colourless oily liquid and as a mixture of diastereomers with dr; 83/17 (based on P nmr).

^{1}H NMR (400 MHz, Chloroform-d) δ (ppm) 7.94 – 7.84 (m, 2.47H), 7.57 (dddd, J = 9.2, 4.0, 2.7, 1.5 Hz, 1.25H), 7.52 – 7.44 (m, 2.53H), 7.37 (ddd, J = 8.0, 1.6, 0.8 Hz, 1H), 7.35(m, 0.25H), 7.30-7.23 (m, overlapped signal with solvent signal, 1.85H), 4.35 (dq, J = 7.8, 7.0 Hz, 2.45H), 3.77 (s, 0.65H), 3.59 (s, 3H), 1.38 (dtd, J = 14.2, 7.1, 0.6 Hz, 3.41H), 1.19 (s, 9H), 1.05 (s, 1.9H). ^{31}P NMR (162 MHz, Chloroform-d) δ (ppm) 15.2 (major diastereomer), 14.81(minor diastereomer). ^{13}C NMR (101 MHz, Chloroform-d) δ (ppm) 150.58, 138.40, 134.05, 134.01, 132.44, 132.41, 132.06, 131.96, 131.65, 131.55, 130.31, 128.34, 128.30, 128.18, 125.56, 125.37, 125.36, 118.72, 115.39, 115.38, 63.28, 63.21, 58.20, 56.16, 55.92, 23.13, 22.97, 16.54, 16.47. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{26}O_5PS$: 397.125124, found 397.123308.

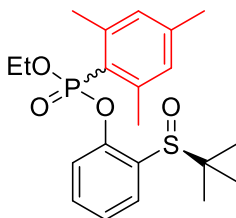## 7.5.15 Adamantan-1-yl (2-((*S*)-*p*-tolylsulfinyl)phenyl) phenylphosphonate
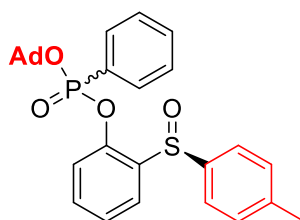
This compound was prepared according to the general procedure C. Flash/Column chromatography provided about 63% yield with crude dr: 55/45

Diastereomer 1 (d$_1$): 25%

^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.98 – 7.90 (m, 1H), 7.70 (ddt, *J* = 14.1, 6.9, 1.4 Hz, 1.94H), 7.61 – 7.51 (m, 1.46H), 7.48 (dt, *J* = 8.1, 1.3 Hz, 1.13H), 7.45 – 7.27 (m, 6.39H), 7.10 (d, *J* = 8.0 Hz, 1.97H), 2.32 (s, 3H), 2.16 (t, *J* = 2.7 Hz, 3H), 2.09 (d, *J* = 2.9 Hz, 6H), 1.64 – 1.58 (m, 6H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 11.05(d2), 10.72(d1). d1/d2= 91/9. HRMS (ESI-TOF): m/z calculated for C$_{29}$H$_{32}$O$_4$PS: 507.175432 found 507.175344.

Diastereomer 1 (d$_1$): 38%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.84 (m, 1.18H), 7.82 – 7.74 (m, 1.92H), 7.53 (dd, *J* = 8.2, 1.7 Hz, 4.12H), 7.48 – 7.37 (m, 2.54H), 7.34 (d, *J* = 1.8 Hz, 1.7H), 7.28 (dd, *J* = 7.6, 1.3 Hz, 0.86H), 7.22 (d, *J* = 8.1 Hz, 1.95H), 2.36 (s, 3H), 2.15 (d, *J* = 4.6 Hz, 3H), 2.08 (d, *J* = 3.0 Hz, 6H), 1.60 (t, *J* = 3.0 Hz, 6H). ^{31}P NMR (162 MHz, Chloroform-*d*) δ (ppm) 11.05(d2), 10.72(d1). d2/d1= 95/5.

7.6 Post Functionalisation: Access to P-stereogenic compounds

7.6.1 Synthesis of PAMPO 40, precursor for the DiPAMP ligand
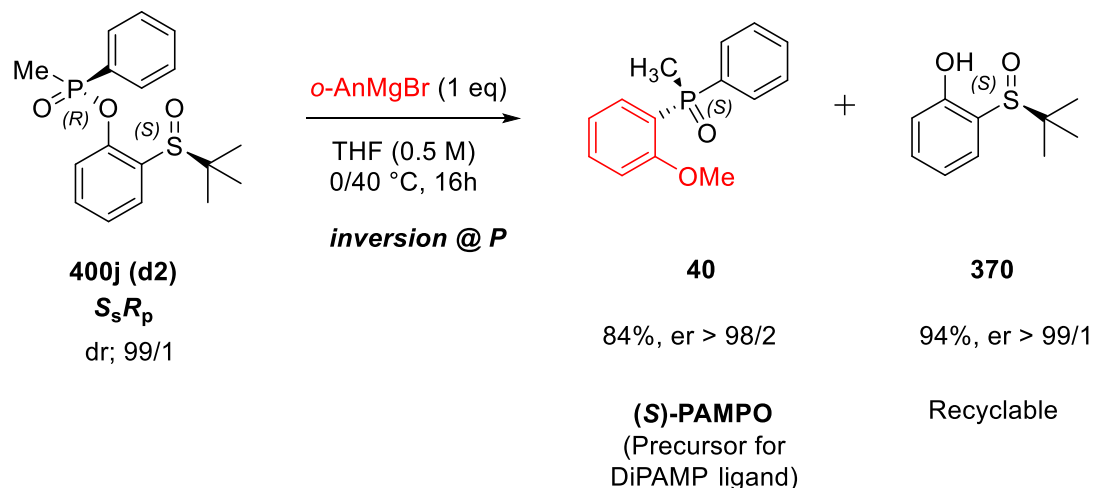
To a cooled solution of 2-((S)-*tert*-butylsulfinyl)phenyl (R)-methyl(phenyl)phosphinate **400r** (P-configuration was determined by comparing x-ray structure of the other enantiomer) (1 eq., 90 mg, 0.268 mmol) in THF (4.9 mL) was added magnesiumbromo(2-methoxyphenyl) (1 eq., 1 M, 0.268 mL, 0.268 mmol) at 0 °C, under an inert atmosphere. After few minutes, the reaction was brought to 40 °C and stirred at this temp for about 16 h.

The reaction mixture was quenched with distilled water at rt. Aqueous phase was extracted with CHCl₃ (2 times). All organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuum. Crude NMR showed presence of the two desired products only. Column chromatography (cyclohexane/ethyl acetate 90/10 to 50/50 provided desired products;

1. PAMPO **40**, ((S)-2-methoxyphenyl)(methyl)(phenyl)phosphine oxide; P-configuration was determined by comparing specific optical rotation value/sign with that of the literature one. White solid, yield = 84%. Analytical data matches with the literature data.[231,266] ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.97 (ddd, *J* = 13.2, 7.6, 1.8 Hz, 1H), 7.74 (ddt, *J* = 12.3, 6.9, 1.5 Hz, 2H), 7.58 − 7.37 (m, 4H), 7.16 − 7.06 (m, 1H), 6.89 (dd, *J* = 8.3, 5.3 Hz, 1H), 3.73 (s, 3H), 2.10 (d, *J* = 13.9 Hz, 3H). ^{31}P NMR (CDCl3) δ (ppm) 29.21. $[\alpha]_D^{20}$. = −9.74 (C = 0.5, CHCl₃). er > 98/2. Chiral HPLC Column: ID, solvent: 80/20 hexane/*i*PrOH, Flow rate: 0.5 ml/min t= 49.64 min (minor enantiomer) / 60.47 min (major enantiomer).

2. (S)-2-(*tert*-butylsulfinyl)phenol; 94% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.95 (s, 1H), 7.36 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.93 − 6.83 (m, 2H), 1.31 (s, 9H). er> 99/1. Chiral HPLC Column IC, solvent: 80/20 hexane/iPrOH, Flow rate: 0.5 ml/min t= 21.02 min (R enantiomer) / 25.48 min (S enantiomer) min.

7.6.2 Post Functionalisation of Adamantyl-Substrate

400i

diastereopure

416

64%
er; 90/10

370

93%
er > 99/1
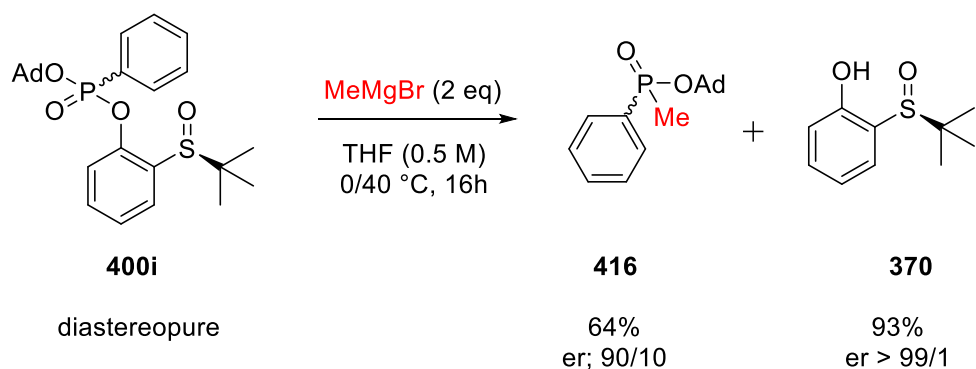
To a cooled solution of adamantan-1-yl 2-[(*R*)-*tert*-butylsulfinyl]phenyl phenylphosphonate **400i** (1 eq., 105 mg, 0.222 mmol) in THF (4.2 mL) was added MeMgBr (2 eq., 1 M, 0.444 mL, 0.444 mmol) at 0 °C, under an inert atmosphere. After few minutes, the reaction was brought to 40°C and stirred at this temp for about 16 h. The reaction mixture was quenched with distilled water at rt. Aqueous phase was extracted with CHCl$_3$ (2 times). All organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuum. Crude NMR showed presence of the two desired products only. Column chromatography (cyclohexane/ethyl acetate 90/10 to 50/50) provided desired products;

(3r)-adamantan-1-yl methyl(phenyl)phosphinate **416**: A colourless oily liquid, 64% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.81 (ddt, *J* = 12.0, 6.8, 1.6 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.45 (ddd, *J* = 8.3, 6.3, 3.2 Hz, 2H), 2.09 (p, *J* = 3.2 Hz, 3H), 2.06 – 1.94 (m, 6H), 1.66 – 1.54 (m, 9H). ^{31}P NMR (CDCl3) δ (ppm) 36.81. ^{13}C NMR (101 MHz, Chloroform-*d*) δ (ppm) 131.69, 131.67, 131.12, 131.02, 128.52, 128.40, 82.40, 44.64, 44.60, 35.88, 31.23, 19.50, 18.46. [α]$_D^{20}$. = +17.78 (C = 0.835, CHCl$_3$). er: 90/10. . Chiral HPLC Column IC, solvent: 80/20 hexane/*i*PrOH, Flow rate: 0.5 ml/min t= 21.8 min (minor) / 23.9 (major) min. HRMS; Calculated 291.1498 for C$_{17}$H$_{24}$O$_2$P and found 291.1508.

(*S*)-2-(*tert*-butylsulfinyl)phenol **370**; 93% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 10.95 (s, 1H), 7.36 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.93 – 6.83 (m, 2H), 1.31 (s, 9H). er> 99/1. Chiral HPLC Column IC, solvent: 80/20 hexane/iPrOH, Flow rate: 0.5 ml/min t= 21.02 min (*R* enantiomer) / 25.48 min (*S* enantiomer) min.

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Résumé

Les composés organiques présentant une chiralité portée par un atome de phosphore sont appelés composés P-chiraux, P-chirogéniques ou P-stéréogéniques. Ces composés trouvent des nombreuses applications dans l'industrie agrochimique et pharmaceutique, en tant qu'outils de coordination, mais surtout en catalyse organométallique asymétrique en tant que ligands privilégiés (Prix Nobel pour W. S. Knowles en 2001). Cependant, la synthèse de composés P-chiraux reste un défi majeur et les méthodes actuellement utilisées sont souvent difficiles à mettre en œuvre et multi-étapes. Au cours de cette thèse nous nous sommes intéressés au développement d'une méthodologie efficace et inédite pour la synthèse de composés P-stéréogeniques. Notre approche est basée sur la réaction d'Atherton-Todd et implique le dédoublement cinétique dynamique lors d'un couplage entre un phénol portant un auxiliaire de chiralité, ie. le sulfoxyde, et un H-phosphinate racémique. De plus, la post-functionalisation des composés diastéréomériques P-chiraux ainsi obtenus est possible dans des conditions douces, permettant ainsi d'accéder à un large panel de composés P-stéréogeniques. Ainsi, cette nouvelle méthodologie permet de synthétiser, via un couplage O-P diastéréosélectif, des précurseurs orignaux de composés P-chiraux variés.

Résumé en anglais

Organic compounds having chirality on phosphorous atom, are called P-stereogenic, P-chirogenic or P-chiral compounds. These compounds are widely used in agrochemistry, pharmacy, coordination chemistry and in organometallic asymmetric catalysis, as one of the most important classes of chiral ligands (Nobel Prize 2001; W. S. Knowles). However, access to these P-stereogenic compounds, is challenging due to the complex, tedious and multi-steps synthetic methodologies. Herein, we report a highly efficient novel methodology to access P-stereogenic compounds, which often involves *dynamic kinetic resolution (DKR)* under modified Atherton-Todd reaction conditions, using a racemic H-phosphinate and an enantiopure phenol bearing a chiral sulfoxide moiety. Furthermore, the newly obtained O-P coupling product can potentially be post-functionalised under mild conditions to obtain various original P-stereogenic scaffolds. Thus, these O-P coupling products can be considered as highly potential precursors to access a variety of original P-stereogenic molecules.

Keywords : P-stereogenic / P-chirogenic / P-chiral compounds, O-P coupling