SYNTHESIS AND REACTIVITY

OF

FUNCTIONALISED TRIARYLPHOSPHINES IN ORGANIC SYNTHESIS

SYNTHESIS AND REACTIVITY OF FUNCTIONALISED TRIARYLPHOSPHINES IN ORGANIC SYNTHESIS

By

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ABBREVIATIONS

$CDCl_3$	Deuterated chloroform.
DCM	Dichloromethane.
THF	Tetrahydrofuran.
Na_2SO_4	Sodium sulphate.
TLC	Thin layer chromatography.
SHOP	Shell higher olefin process.
TMEDA	Tetramethylethylenediamine.
HMPA	Hexamethylphosphoramide.
MeMgCl	Methyl magnesium chloride.
LiCl	Lithium chloride.
*i*PrMgCl	Isopropyl magnesium chloride.
sec-BuLi	*sec*-butyllithium.
n-BuLi	*n*-butyllithium.
DOM	Directed ortho metalation.
NMR	Nuclear magnetic resonance.
HRMS	High Resolution Mass Spectrometry.
OPA	Oxaphosphetane.
$NaNO_2$	Sodium nitrite.
LAH	Lithium aluminium hydride.
HCl	Hydrochloric acid.
HBr	Hydrobromic acid.
KOH	Potassium hydroxide.
PBr_3	Phosphorus tribromide.
TMS	Tetramethylsilane.
PPh_3	Triphenylphosphine.

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ABSTRACT

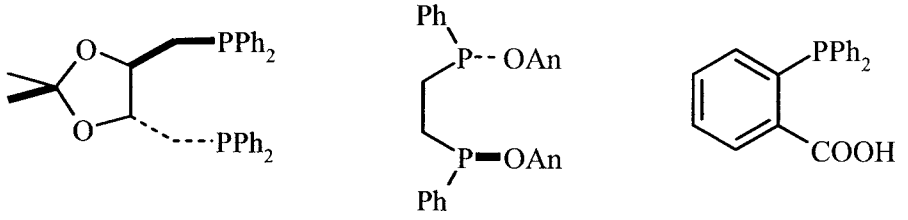
The goal of this research was to develop alternate economic routes for the synthesis of functionalised triarylphosphines. Such species are employed as catalysts ligands in chemical synthesis and can be incorporated into designed-ylides for olefination reactions. The synthesis of the SHOP ligand, the key constituent of the Shell Higher Olefins Process for making linear alpha olefins via ethylene oligomerisation and olefin metathesis, is described using four totally new approaches. These include a Directed Ortho Metalation (DOM) approach, Copper iodide catalyzed cross-coupling, Halogen-Magnesium Exchange reaction and Diazonium salt approaches. The efficiency, in terms of overall yield and mild process conditions, make some of the routes potentially commercialisable. Additionally, a series of ortho-substitued triarylphosphines were derived to probe and modulate the reactivity of the Wittig reaction. We report that non-stabilized ortho-P-alkoxy-substituted ylides react with aromatic and aliphatic aldehydes providing (*E*)-olefins with high stereocontrol employing an intramolecular phenoxy and alkoxy substituent to promote (*E*)-olefination through betaine interconversion. In one particular case; removal of phosphoine oxide was also achieved. Extension of this methodology was also carried out on semi-stabilized benzylic ylides, which are known for producing 1:1 mixtures of (*E*):(*Z*) olefins under classical condition. Potential applications of the methodology are also described.

CHAPTER 1: INTRODUCTION

1.1 Organophosphorus ligands:

Triphenylphosphine (PPh_3) is a common organophosphorus compound. It is widely used in the synthesis of organic and organometallic compounds. The favourable effects of phosphine ligands have been known for over 5 decades. Triphenylphosphine binds to most transition metals[1] in contrast to triphenylamine. Triphenylamine shows little tendency to bind to metals because of greater steric crowding around the nitrogen atom where as in triphenylphosphine steric crowding is less important and a tetrahedral geometry is prefered. The lesser electronegativity of phosphorus is another factor contributing to its electron donating abilities. There are number of interesting early reports in the literature concerning the use of triphenylphosphine as a ligand. Reppe and co-workers used PPh_3 to prepare $NiBr_2(PPh_3)_2$, which was used for the synthesis of acrylate esters from alkynes, carbon monoxide and alcohols.[2] Further, Wilkinson used triphenylphosphine to prepare the novel hydroformylation catalyst $RhH(PPh_3)_2(CO)_2$.[3] There are number of other reports in the literature which makes use of PPh_3, for e.g. the Heck reaction[4] uses tetrakis(triphenylphosphine)palladium(0) to catalyze C-C coupling reactions, Stryker's reagent;[5] $[(PPh_3)CuH]_6$ used as catalyst for conjugate reduction, and Vaska's reagent[6] $IrCl(CO)[P(Ph)_3]_2$ which can undergo oxidative addition.

Phosphorus containing bidentate ligands played an important role in the development of chemistry of organometalic complexes. In late 1950's the synthesis of dppe[7] was reported followed later by several others notably DIOP, DIPAMP and the SHOP ligand.



DIOP DIPAMP The SHOP ligand

Figure 1: Bidentate ligands containing phosphorus.

In the late sixties, Keim and coworkers discovered that certain bidentate ligands containing oxygen and a phosphorous donor atom formed excellent catalyst with nickel for the oligomerisation of ethylene.[8] Examples of such ligands are diphenlphosphinoacetic acid and 2-diphenyl-phosphinobenzoic acid (Figure 1: The SHOP ligand). This discovery led to the Shell Higher Olefins Process[9] that is an important ligand in the industrial scale oligomerisation of alkenes, including ethylene.

The Shell higher olefin process is a chemical process for making linear alpha olefins via ethylene oligomerisation and olefin metathesis. Linear alpha olefins are olefins with the double bond at the primary/alpha position, for e.g. 1-butene, 1-hexene, 1-hexadecene etc. These linear alpha olefins posses a large number of applications.[10] C_4-C_8 linear alpha olefins are used for the production of linear aldehydes, short-chain fatty acids, and linear alcohols whereas C_{10}-C_{14} linear alpha olefins are used for making of detergent formulations, surfactants, linear alkyl benzenes, drilling fluids and these are potential substituent's for diesel or kerosene.[10] C_{16}-C_{30} linear alpha olefins are used for paper sizing, lubricants and many other applications.[10] Looking at the synthetic value of these linear alpha olefins, it is not surprising that various industries have established patented commercialised processes to make linear alpha olefins form ethylene. These processes are Gulf (Chevron Philips Chemical Company), Ethyl Corporation (Ineos) process, Idemitsu Petrochemical process, Alpha-Sablin by Saudi Arabian Basic Industries Company, Sasol Ltd. and the Shell Oil Company (SHOP) process.[10]

In 1972, Keim introduced a homogeneous catalyst system suitable for the oligomerisation of the ethylenes. This novel catalytic system makes use of nickel and a bidentate (P, O) chelator. This process was found to be very efficient in terms of selective production of linear alpha olefins and today forms one of the most important industrial applications of homogeneous catalysis.[11]

1.2 The SHOP ligand catalytic cycle:

The catalyst uses the chelating ability of the (P, O) portion on the SHOP ligand and Ni^{2+} as shown in the figure 2, to form the active catalyst. It is well accepted that the SHOP ligand chelates to nickel and in presence of reducing agent forms ligated nickel hydride; a active species. Ethylene can then react with the Ni-H to generate Ni-alkyl species via insertion with the generation of empty orbital. This process continues until desired alkyl length has achieved. The chain termination occurs with the β-H elimination to regenerate Ni-H species and a desired α-olefin.[12]

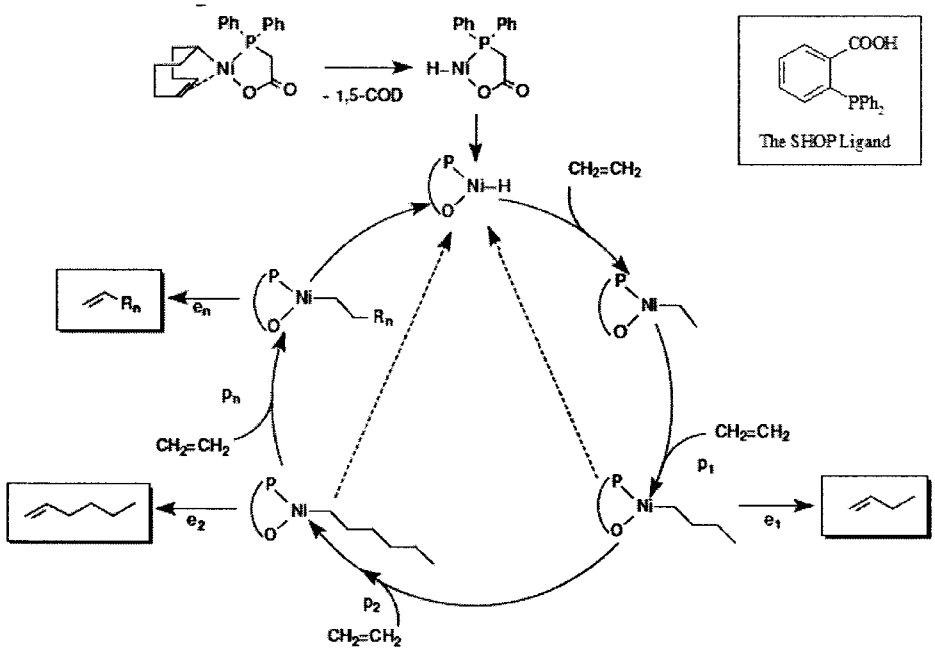


Figure 2: The SHOP type Ligand catalytic cycle. (P_1, P_2, P_3 are propagation steps and e_1, e_2, e_3 are elimination steps)

In last few years several alternatives for the SHOP ligand have been suggested. These modifications helped researchers to understand the catalytic cycle in depth and come up with a conclusion that in addition to (P, O) chelate, monodentate tertiary phosphine plays a crucial role in the catalytic cycle.[12]

There are few reported procedures available for synthesis of the SHOP ligand. These mainly includes nucleophilic displacement of the haloaromatic compounds[13] or use of cross coupling reactions.[14] Trost and coworkers reported the synthesis of the SHOP ligand in 74% yield using 2-chlorobenzoic acid, triphenylphosphine and Na/NH_3 at -60 °C.[13a] Nucleophilic phosphanylation of 2-flurobenzoic acid using Ph_2PH in superbasic medium was reported in poor yields by Hingst and coworkers.[13c] Campbell and Ulrich developed the SHOP ligand synthesis by making use of 2-fluorobenzoic acid, triphenylphosphine and Na/NH_3 at -60 °C.[13d] K. H. Ahn and coworkers make use of $Zn/NiCl_2$, chlorodiphenylphosphine and methyl 2-hydroxybenzoate to synthesise the SHOP ligand,[14a] whereas Kappe used microwave radiation for its synthesis utilising Pd or Ni catalysts.[14b] Some of the above methods face serious problems in terms of yields as well as formation of side products during reactions, for e.g. the crude reaction mixture analysis of 2-chlorobenzoic acid with $NaPPh_2$ at -60 °C showed 3-(diphenylphosphino)benzoic acid as the major impurity, mainly due to reactive benzyne formation.[13d] Poor yields of the SHOP ligand was obtained when Kappe and coworkers used microwave radiations.[14b]

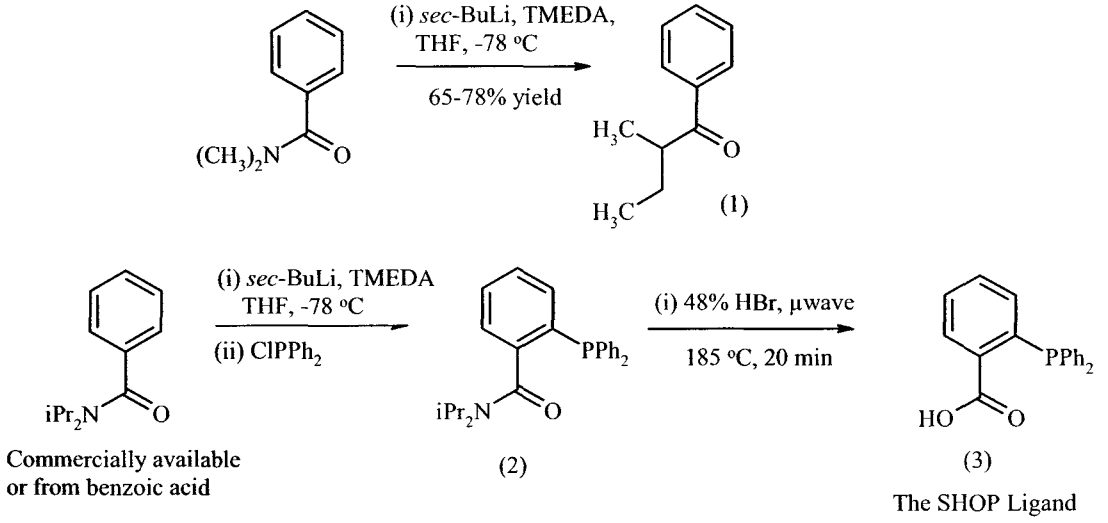
We were interested in the synthesis of the SHOP ligand in order to develop a more efficient and high yielding alternative route in order to improve the efficiency of the overall SHOP process in making alpha-linear olefin. More fundamentally, the synthesis of ortho-substituted triarylphosphines is a general problem that has ramifications in modulating the reactivity of the phosphine component in other reactions, for example in the Wittig olefination reactions. Ortho-substituent effects are known to have an effect on the stereoselectivity of the Wittig olefinations, although interestingly, to our knowledge, the role of ortho-hydroxy substituents has not been previously investigated. Thus, we

decided to explore the synthesis of the SHOP ligand as part of a larger problem of accessing ortho-substituted triarylphosphines in order to develop a viable synthesis of the ligand, and that would also allow us to probe ortho-effects on olefination chemistry. In the next chapter, we describe various experimental strategies that we considered for the synthesis of the SHOP ligand itself and, following this, we extend these studies to more general routes to ortho-substituted triarylphosphines and an investigation of their role in modulating (*E*):(*Z*) selectivity in the Wittig olefination reaction.

CHAPTER 2: SYNTHETIC APPROACHES TO THE SHOP LIGAND

2.1 Directed Ortho Metalation (DOM) approach:

It is well known that tertiary amides provide ortho-lithiated species on treatment with the *sec*-BuLi/TMEDA or *n*-BuLi/TMEDA in THF at -78 °C. Furthermore, lithiation of tertiary amides followed by reaction with different electrophiles gives the expected *ortho* substituted product.[15,16] Bearing in mind the structure of the SHOP ligand, we began the DOM approach starting from *N,N*-dimethylbenzamide as the tertiary amide. Various reaction conditions using *n*-BuLi or *sec*-BuLi at -78 °C or 0 °C in THF gave acylated alkylation product instead of the desired directed ortho metalation.[15,16a] Yields as high as 65-78% were obtained when *sec*-BuLi was used as base at -78 °C in THF. Such results with *N,N*-dimethylbenzamide were not surprising considering nucleophilic addition of *sec*-BuLi or *n*-BuLi to less hindered tertiary amides is known.[15,16a]



Scheme 1: DOM approach towards synthesis of the SHOP ligand.

Next, we used *N,N*-diisopropylbenzamide[17] as the tertiary amide, understanding the fact that it is less prone to undergo nucleophilic addition by such nucleophilic bases. We screened *N,N*-diisopropylbenzamide for the DOM reaction under various conditions (Table 1). The yields of (2) obtained from *sec*-BuLi, THF at -78 °C ranged from 65-69%

whereas with *n*-BuLi, THF gave 32% yield over several runs. We found that the addition of equimolar amount of TMEDA allowed better conversion and high isolated yield of the required phosphine and hence an optimum reaction conditions for DOM reaction was found, which was slow addition of the *sec*-BuLi (1.2 eq.) to a flask containing *N,N*

Sr. No.	Conditions used	% Yield of Phosphine (2)
1.	*sec*-BuLi, -78 °C, THF	65-69
2.	*sec*-BuLi, TMEDA, -78 °C, THF	91-93
3.	*n*-BuLi, -78 °C, THF	32
4.	*n*-BuLi, TMEDA, -78 °C, THF	40
5.	*n*-BuLi Or *sec*-BuLi with or without TMEDA, R.T.	Trace amount of required product (~20%) with too many side products

Table 1: DOM Optimisation using *N,N*-diisopropylbenzamide.

diisopropylbenzamide (1 eq.) in THF at -78 °C, followed by slow addition of TMEDA (1.2 eq.). The resulting reaction mixture was stirred at -78 °C for 30 min and sequentially quenched with chlorodiphenylphosphine (1 eq.). The reaction mixture was stirred additionally for 1 h and then slowly warmed to room temperature. Routine work up procedure afforded yields up to 91% of the *N,N*-diisopropyl-2-(diphenylphosphino)benzamide. The same reaction protocol was followed with *n*-BuLi as base which gave only 40% yield of the *N,N*-diisopropyl-2-(diphenylphosphino)benzamide. Either base, with or without TMEDA at room temperature gave very poor yield (~20%) of the required product. The procedure involving conditions like *sec*-BuLi, TMEDA in THF at -78 °C was more applicable towards the development of the ligand simply because of its ability to give high yield and

spot-to-spot conversion. Thus effect of nitrogen substituents played important role in the planned DOM reaction.

The next task was to hydrolyse the *N,N*-diisopropyl-2-(diphenylphosphino)benzamide to the SHOP ligand. *N,N*-dialkylbenzamides were reported as "stubborn"[15] towards hydrolysis under acidic or basic hydrolysis. The use of tertiary benzamides in DOM study was thus highly questioned in the literature.[18] An extensive study was conducted for the hydrolysis of *N,N*-diisopropyl-2-(diphenylphosphino)benzamide. Conventional heating of the amide under strong acidic conditions like 6N HCl or 48% HBr over 12 h resulted in no conversion of the tertiary amide as indicated by its stubborn nature. Even when 6N HCl was used under microwave radiation, no hydrolysis was observed. Surprisingly when 48% HBr was used under microwave radiation for 20 min at 185 °C, *N,N*-diisopropyl-2-(diphenylphosphino)benzamide readily underwent hydrolysis and gave the SHOP ligand in 85-95% yield. The overall results are summarized in Table 2 .

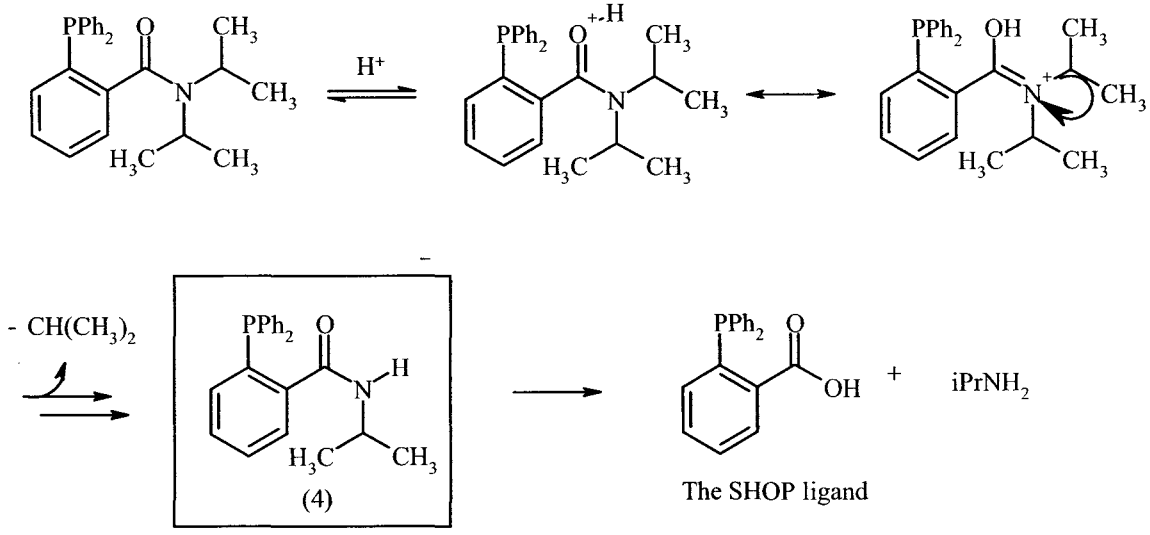
Sr. No.	Conditions used	% Yield obtained of (3)
1.	48% HBr, Microwave heating, 185 °C, 20 min	85-95
2.	48% HBr, conventional heating, overnight	Formation of *N*-isopropyl-2-(diphenylphosphino)benzamide
3.	6N HCl, microwave heating, 185 °C, 20 min	No Conversion Or Formation of *N*-isopropyl-2-(diphenylphosphino)benzamide
4.	6N HCl, conventional heating, overnight	No Conversion

Table 2: Conditions used for the hydrolysis of *N,N*-diisopropylbenzamide.

All the microwave reactions carried out using 48% HBr for inadequate time resulted in formation of *N*-isopropyl-2-(diphenylphosphino)benzamide as intermediate in

good yields. Isolation of this intermediate was of interest simply because it provided us reaction path for the amide hydrolysis under our condition as oppose to generally accepted amide hydrolysis mechanism.[18]

It appeared that under highly acidic condition, carbonyl oxygen of the *N,N*-diisopropyl-2-(diphenylphosphino)benzamide gets protonated followed by loss of the one isopropyl group to yield the secondary amide.[18] This secondary amide now underwent protonation on the carbonyl oxygen and loss of the amine via break down of tetrahedral intermediate to yield acid in excellent yield. The proposed mechanism for the hydrolysis of *N, N*-diisopropyl-2-(diphenylphosphino)benzamide is as shown in scheme 2.



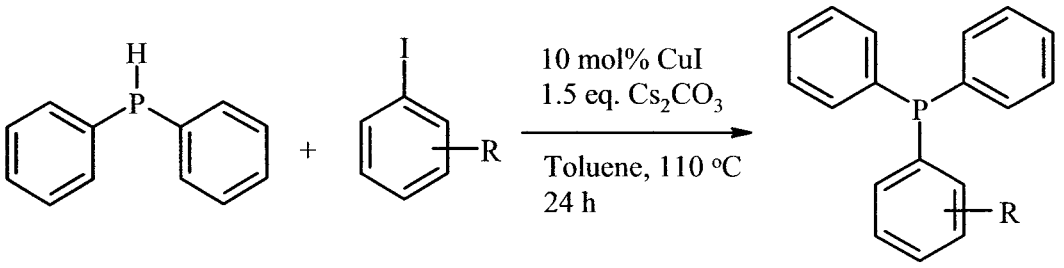
Scheme 2: Proposed mechanism for the amide hydrolysis.

Lastly, we carried out the one pot synthesis of the SHOP ligand starting from *N,N*-diisopropylbenzamide. After carrying out the DOM reaction with *N,N* diisopropylbenzamide, the crude phosphine was mixed with 48% HBr and subjected to microwave radiation for 20 min at 185 °C. The required SHOP ligand was then simply isolated via crystallization using ethyl acetate (5%) and hexane (95%) as solvent in moderate (58-60%) yield.

2.2 Copper catalyzed synthesis of the SHOP ligand:

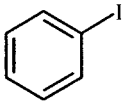
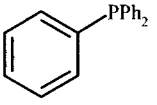
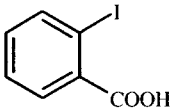
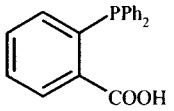
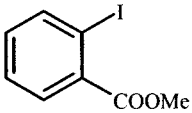
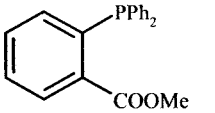
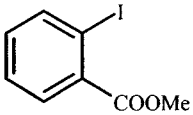
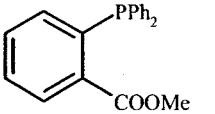
Over the years several synthetic routes emerged for the synthesis of triarylphosphine including the traditional aryl-Grignard and aryl-lithium reagents with phosphine halides[19,20] but these methods suffer major drawbacks in terms of their sensitivity and most often they end up in phosphine oxides as a major product. Advancement of palladium[21]-and nickel[22]-catalyzed cross-coupling reactions helped to improve the functional group tolerance in the synthesis of triarylphosphines. However recently copper-catalyzed Ullmann type cross-coupling reactions[23] attracted major attention because of their increased tolerance towards variety of functional groups and could possibly become industrial solution for making triarylphosphines because it is cheap and can be carried out efficiently at large scales. Recently we were interested in novel protocol developed by D. V. Allen and D. Venkataraman.[24] They developed efficient copper-catalyzed cross-coupling reaction involving different aryl iodides with diphenylphosphine. It was shown that diphenylphosphine was involved as ligand during the reaction course and not triphenylphoshine.[24] This ligand free protocol could be of interest at industrial level as it could lead in great cost reduction if proved efficient in production of the SHOP ligand. Their optimised protocol included use of CuI (10 mol%) as catalyst, Cs_2CO_3 as base in refluxing toluene. Variety of substituted aryl iodides including substitutions like methyl ketone, electron withdrawing groups, electron donating groups, as well as methyl esters were well tolerated in the reaction[24] and yields of corresponding triarylphosphines were obtained in 63-91%.

Surprisingly, D. Venkataraman and coworkers did not handle methyl-2-iodobenzoate as one of the aryl iodide during their studies. Synthesis of triarylphosphine using methyl-2-iodobenzoate and diphenylphosphine followed by hydrolysis of methyl ester could lead to the SHOP ligand.



Scheme 3: CuI protocol for synthesis of Triarylphosphines.

We undertook the task and carried out the CuI catalyzed reaction of 2-iodobenzoic acid with diphenylphosphine. To our notice there was no trace of the required SHOP ligand, when similar protocol was used. The use of methyl-2-iodobenzoate instead of 2-iodobenzoic acid in the reaction at first gave us 60% yield of the methyl 2-(diphenylphosphino)benzoate which was encouraging. We observed that 5-10% of the methyl-2-iodobenzoate remained unreacted after refluxing the reaction mixture in toluene for more than 20 h.

Sr. No.	Aryl Iodide	Product	Base	Isolated Yield %
1			Cs_2CO_3	80
2			Cs_2CO_3	NR
3			Cs_2CO_3	60[a]
4			Cs_2CO_3	68[b]

[a]Reaction carried out with 1.0 eq. of diphenylphosphine[a], 1.2 eq. of diphenylphosphine[b].

Table 3: Optimisation using CuI Chemistry: Methyl 2-(diphenylphosphino)benzoate.

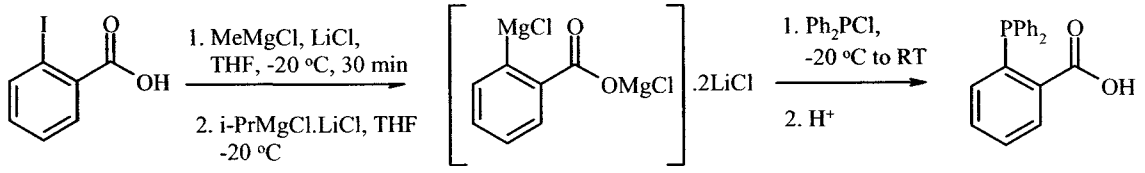
Hence a modified protocol was used using 1.2 eq. of diphenylphosphine as oppose to 1.0 eq. of diphenylphosphine which was used in standard protocol. We obtained isolated yields as high as 68% from the modified protocol. The overall results are summarized in Table 3.

The hydrolysis from the methyl 2-(diphenylphosphino)benzoate was carried out under basic conditions. The SHOP ligand was obtained in as high as 100% yield. Further optimisation of CuI catalysed synthesis of the SHOP ligand is currently under investigation in our laboratories.

2.3 The Halogen-Magnesium exchange reaction:

Recently Knochel and coworkers developed a protocol in which magnesiation of halogenated aromatic or heterocyclic carboxylic acids was achived with MeMgCl in presence of LiCl and subsequent reaction with *i*PrMgCl.LiCl which resulted in double magnesiated species.[25] This double magnesiated species was reacted with variety of electrophiles and yields up to 97% were achieved.[25] It was found that use of LiCl helped to improve the solubility of organometallics as well as increasing the reactivity of the generated Grignard reagent.[26] Such protocol does not require protection of sensitive groups during the reaction. Using the strategy Knochel and coworkers synthesised variety of molecules in good yields.[25]

Once again, it was surprising to find that they did not synthesise the SHOP ligand using their well developed chemistry. We undertook the chemistry and synthesised the SHOP ligand starting from the 2-iodobenzoic acid using their novel approach. The double magnesiated species was generated using the Knochel protocol, i.e. MeMgCl, THF.LiCl and *i*PrMgCl.LiCl at -20 °C. The resultant mixture was quenched with chlorodiphenylphosphine to obtain the SHOP ligand in 40% yield.

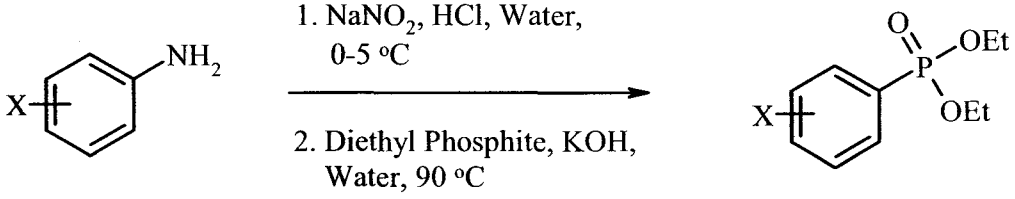


Scheme 4: Synthesis of the SHOP ligand using double-magnesiated species.

Further optimisation of synthesising the SHOP ligand using this novel double magnesiated species is currently underway in our laboratories.

2.4 Use of Diazonium salts:

Aryl diazonium salts are important intermediates in synthetic organic chemistry. These can be prepared in cold aqueous solution (0-5 °C) and generally reacts with the different nucleophiles with loss of thermodynamically stable N_2 group. Some of the useful substitution reactions utilising diazonium salts are Sandmeyer reaction[27] and Schiemann reaction.[28] Using diphenylphosphine as nucleophile, the diazonium salts generated from anthranilic acid can potentially yield the SHOP ligand. Using diethylphosphite as nucleophile, aryl phosphonates can be synthesized. Since diethylphosphites are better nucleophiles than diphenylphosphines, we started the chemistry with diethylphosphite and substituted anilines. Diazonium salts were generated using $NaNO_2$, HCl and water at 0 °C. Excess acid was neutralised with addition of saturated solution of sodium acetate at 0 °C.



Scheme 5: Synthesis of Arylazaphosphonates using diazonium salts.

This freshly prepared solution was added drop wise to the flask containing diethylphosphite and KOH. Resultant mixture was heated on oil bath for 15 min at 90 °C. Following this protocol as many as six substituted anilines were reacted. It was however

surprising to observe that all the reactions proceeded well and gave corresponding arylazaphosphonates instead of desired aryl phosphonates, in excellent yields. As can be seen from the table 4, the reaction preceded efficiently giving high yields. ^{1}H-NMR and HRMS of all the compounds matched with the reported compounds and it was confirmed that these compounds are indeed arylazaphophonates and not aryl phophonates.

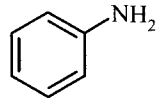
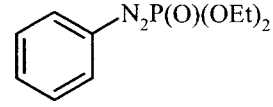
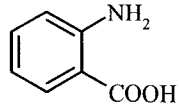
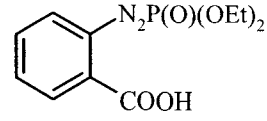
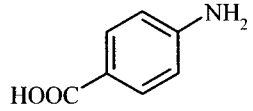
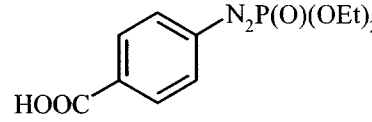
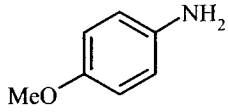
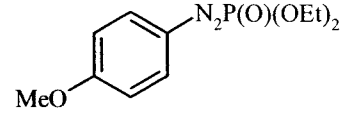
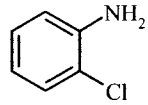
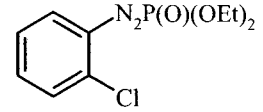
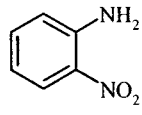
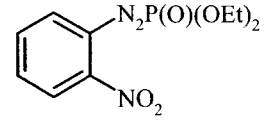
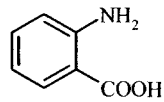
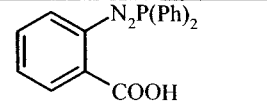
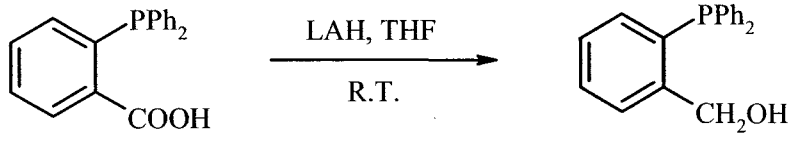
Sr. No.	Anilines	Aryl Phosphonate	% Yield
1			76
2			72
3			70
4			78
5			85
6			80
7		 Used dipheylphosphine instead of diethyphosphite	~30 Not isolated

Table 4: The Diazonium salt approach for synthesis of the SHOP type ligands.

Similar reaction protocol was followed using the diphenylphosphine and anthranilic acid which did not give the required SHOP ligand, instead corresponding dye was obtained in moderate yield.

Resultant reaction failed to provide direct substitution of the phosphorus coming from diethylphosphite or diphenylphosphine on the aryl carbon instead, addition on the electrophilic nitrogen gave us corresponding aryldiazo molecules in good yields.[29]
The SHOP ligand when reduced with LAH gave high yield (80-85% isolated yields) of corresponding primary alcohol, namely-(2-(diphenylphosphino)phenyl)methanol.



Scheme 6: Reduction of the SHOP ligand.

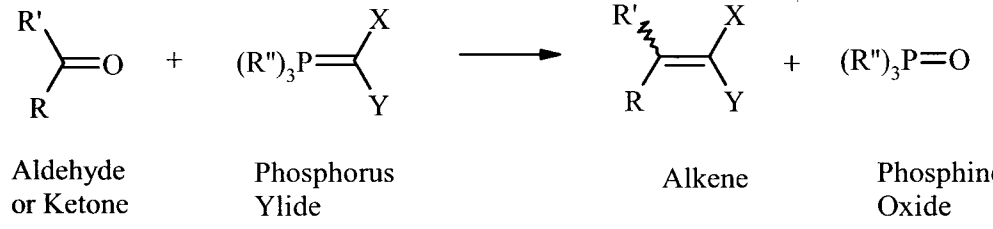
Ortho substituted phosphines may also be of great importance in the Wittig reaction, an important C-C bond forming reaction, especially in order to probe the mechanistic rational of the much debated Wittig reaction. Apart from the (2-(diphenylphosphino)phenyl)methanol where one of the *ortho* proton on the aryl groups attached to phosphorus is replaced by the primary alcoholic group, several other substitutions can be tested, for e.g. substitution by –OH and $-OCH_3$. The use of such phosphines as stereochemical probes of the Wittig reactions is not known till date. In the next chapter, a thorough account of preparation of such ortho substituted phosphines and their effect on the outcome of the Wittig reaction and hence the mechanistic rational will be described.

CHAPTER 3: THE WITTIG RECATION OF ORTHO-SUBSTITUTED YLIDES

3.1 The Wittig reaction:

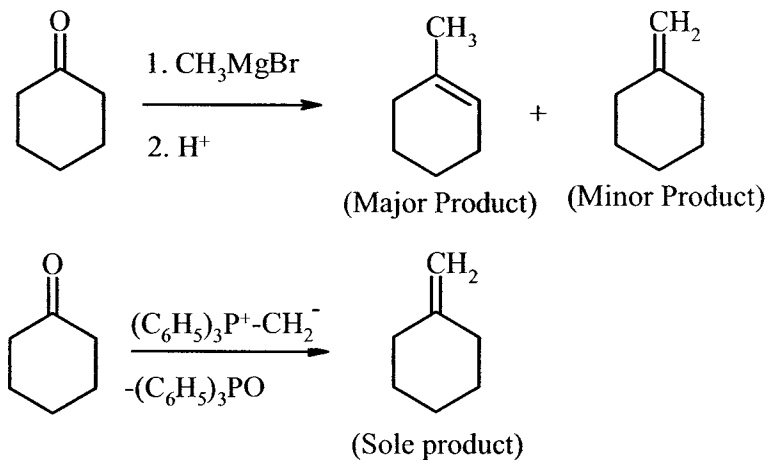
The direct conversion of aldehydes or ketones to olefins was a key fundamental problem for synthetic organic chemist until Wittig and co-workers published their landmark papers in the early 1950s. Only a few years after its discovery, the Wittig reaction started to play a major role in synthetic organic chemistry, thereby changing the course of olefin synthesis for all time. Olefination reactions, including the classic Wittig and later Horner, Horner-Wadsworth-Emmons and Peterson chemistry, are considered highly reliable regio- and stereo- controllable reactions and are now regarded as a strategic C-C bond forming reactions frequently encountered in complex organic synthesis.

A typical Wittig reaction[30] involves the condensation reaction of a phosphorus ylide with an aldehyde or ketone followed by elimination yielding an olefin and phosphine oxide. (Scheme 7)



Scheme 7: General Wittig reaction.

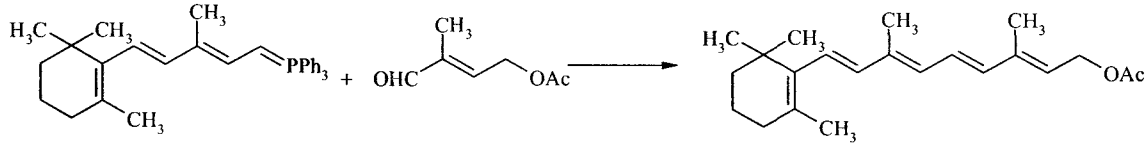
One of the main advantages of the Wittig reaction lies in its complete positional selectivity,[31] for e.g. the addition of the Grignard reagent to carbonyl compound followed



Scheme 8: Structural specificity of the Wittig reaction.

by dehydration yields a mixture of constitutionally isomeric olefins, whereas the new double bond created in the Wittig reaction appears exclusively at the site of formal carbonyl function. (Scheme 8)

Since then, by virtue of its effectiveness and generality, the Wittig reaction has been applied in natural product synthesis and industrial synthesis by scientists. For e.g. the synthesis of vitamin "A" acetate was the first example of the Wittig reaction on industrial scale[32] (Scheme 9). Since then it has been used in many large scale processes in the pharmaceutical industry.



Scheme 9: Vitamin "A" acetate synthesis.

The Wittig reaction also proved useful in economic industrial production of β-Carotene (figure 3) and Citranaxanthin (figure 4) which occurs in citrus fruits and are used as food dye.[32] The sesquiterpenes β-sinensal, is a major constituent in the aroma of orange oil which has also been synthesised with the help of the Wittig reaction.

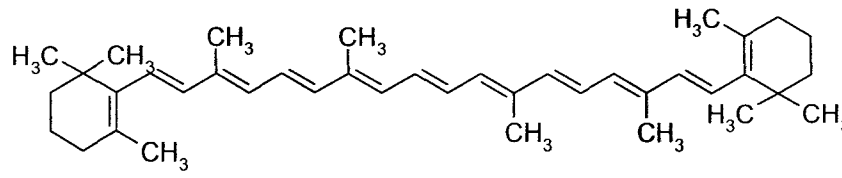


Figure 3: Beta-carotene.

The Wittig reaction is not only useful in the synthesis of terpenoid or pharmaceutical agents but has also been used in the synthesis of industrial chemicals such as the optical brightner- 2, 2'-(p-phenylenedivinylene)dibenzonitrile, also known as "PALANIL Brilliant White R".[32]

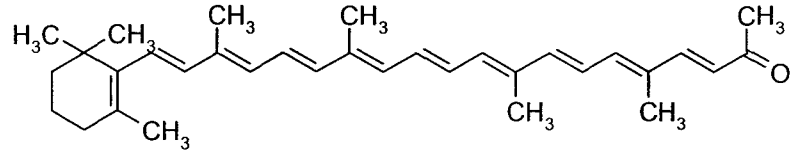


Figure 4: Citranaxanthin.

Among the various applications of the Wittig reaction, industrial production of C-18 Cecropia juvenile hormone (figure 5) remains a classic one.[32] It was believed that selective destruction of the pest could be achieved by synthesising juvenile hormones or analogous structural mimics of the same, which can control the hormonal activity and thereby halt insect development at the larval stage. In 1969 a couple of publications regarding the industrial production of the juvenile hormone using the Wittig reaction brought about a revolution in the control of insect pests.

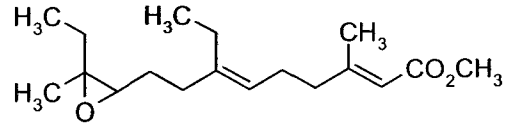


Figure 5: Juvenile hormone.

Thus, the Wittig reaction has proven itself to be one of the most important reactions to date and proved important in synthesis of active compounds having specific effects in medicine, crop protection, insect control etc. The Wittig reaction is one of the

standard reactions to prepare complex unsaturated molecules and its application at industrial level opened new routes to economic synthesis.

3.2 Mechanism of the Wittig Reaction

The Wittig reaction involves phosphorus ylides as the nucleophilic carbon component. The ylides are prepared by deprotonation of the phosphonium salts. These phosphonium salts are usually prepared by reaction of triphenylphosphine and alkyl halide. Alkyltriphenyl phosphonium halides are weakly acidic and therefore strong bases like sodium hydride, organolithium reagents, substituted amide anions like hexamethyldisilylamide (HMDS), etc must be used. The ylides generated are then quenched with the carbonyl compounds.[33]

An ylide is a molecule which has a Lewis structure with opposite charges on adjacent atoms, each of which has an octet of electrons. Phosphorus ylides are stable but quite reactive. These can be represented by the two resonating structures namely ylide and ylene (or phosphorane) form,[33] for e.g. the ylide and ylene form of trimethylphosphonium methylide, as shown in figure 6.

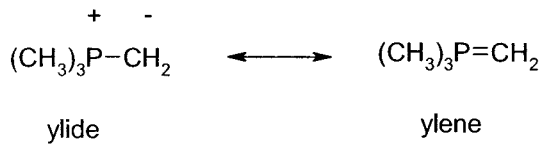
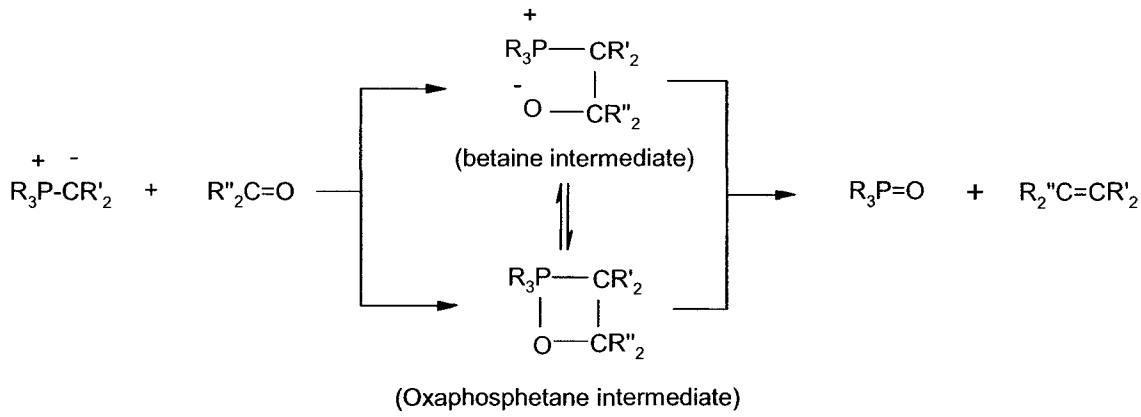


Figure 6: Ylide and Ylene.

Synthetic utility of phosphorus ylides was first developed by the Wittig group. Their reaction with aldehydes or ketones allows carbon-carbon double bond formation with complete positional control. The mechanism proposed initially involved addition of the nucleophilic ylide carbon to the carbonyl group of the aldehyde/ketone to yield a dipolar intermediate termed- a betaine. This was followed by the elimination of phosphine oxide to yield the olefin. This syn-periplanar elimination is believed to occur after formation of a four member oxaphosphetane (OPA) intermediate. Alternatively, the reaction might proceed through initial direct formation of the OPA intermediate (Scheme

10) involving a formal polar [2+2] cycloaddition of the ylide and carbonyl group. Research at the theoretical level has been carried out to study such OPA intermediates. Experimentally low temperature NMR studies have also detected OPA, while betaines have been observed only under special conditions.[34]



Scheme 10: Mechanism of the Wittig reaction.

3.3 Stereochemistry of the Wittig Reaction

The reaction mechanism of the Wittig reaction is one of the most discussed in the literature and is still not completely understood. Wittig developed the concept of the zwitterionic adduct (Figure 7A) which are better[34] described later as (7B); (since that time lithium alkyls have been used for the deprotonation of phosphonium salts)

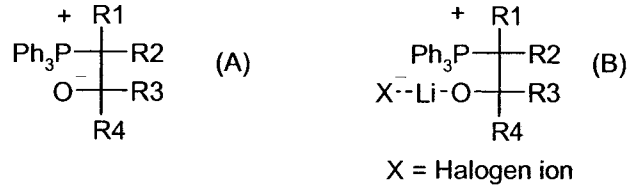


Figure 7: Zwitterionic adduct.

The reversibility of formation of 7(A) and thus *(Z):(E)*-isomer ratios of the olefin have been attributed to the assumption of equilibrium between the diastereomeric betaines. (Scheme 10)

Since then, a lot of discussion about the stereochemistry of the Wittig reaction has arisen; much of this aimed at explaining the stereochemical outcome. Most of the arguments have focussed towards explaining the importance of the intermediate betaine/OPA on the stereochemistry of the Wittig reaction.[34,35]

In general ylides can be classified as non-stabilised (R = alkyl), semi (moderately) stabilised (R = aryl) and stabilised ylide (R = CO_2R, CN) based on the charge delocalization. Of all of these classes, the Wittig reaction of non-stabilised ylides remain the most discussed in the literature due to its high reactivity and ability to provide *(Z)*-olefins. Many attempts were made to explain the high *(Z)*-selectivity of such reactive ylides under "salt free" conditions. It is well understood from the literature that under kinetically controlled conditions *erythro* betaines/OPA should formed from the unstable alkylidenephosphoranes which subsequently gives rise to *(Z)*-olefin through rapid syn-elimination. Use of resonance stabilised ylides or retardation of the elimination step by using complex with lithium salts may lead to *threo* betaine/OPA and thus the *(E)*-olefin. Some of the most discussed proposals regarding mechanism of the Wittig reaction will now be described.

3.4 Proposed mechanism's for the Wittig reaction

3.4.1 Schlosser's proposal[36]

In an attempt to explain the *cis* selective reaction of the "salt free" triphenyl phosphonio ylides and aldehydes, Schlosser put forward "Leeward Approach" of the aldehyde. Schlosser explained his hypothesis in a nice manner in which he states that, at transition state of OPA (Figure 8) all the three stationary phenyl groups are nearly immobilised where in the alkyl group of the ylide (CH_3 here in figure 8) forces neighboring phenyl group out of the plane (phosphorus triagonal) by 50 ^{o} where upon the other phenyl group is only moved out of the plane by 10 ^{o}.

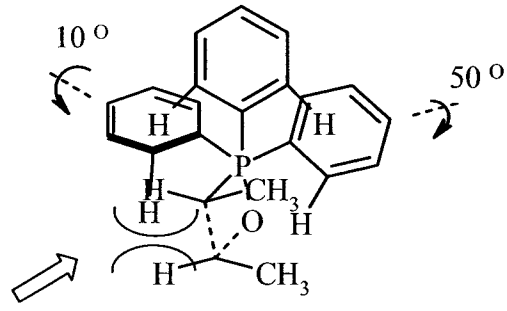


Figure 8: The Leeward approach.

Thus the bulky substituent of the approaching aldehyde (CH_3, here) now may approach in leeward fashion towards ylide which has pushed the neighboring phenyl group by a large distance producing the *(Z)*-olefin. In principle the above approach by Schlosser gives answer to high *(Z)*-selectivity upon structural variation on stationary groups and to high *(E)*-selectivity, when ylide were derived from the trialkyl ethylphosphonium bromide. But assumes that the original *cis/trans* OPA ratio is predominantly conserved on decomposition to olefin.

3.4.2 Schneider's Proposal[37]

Schneider explains his proposal on the basis of steric configuration of substituent on phosphorus as well as coordination of the carbonyl oxygen with the phosphorus before C-C bond formation. The explanation is based on the coordination complex- Triagonal bypyramidal phosphorus with oxygen at the apical position and the ylide carbon equatorial. This model assumes position for aldehyde based on the sterics. Initially the bulky aldehyde alkyl group is away from the equatorial substituent on phosphorus i.e. directed upwards. The aldehyde hydrogen is subsequently placed downwards close to equatorial position (Figure 9, V). In order to form a bond between C^+ and C^-, small anticlockwise rotation around C^+ - O bond should take place resulting in the *erythro* intermediate (R^1 and R^2 are eclipsed) leading to *(Z)*-olefin whereas clockwise rotation brings R^1 and R^2 group to give *threo* intermediate which requires a greater rotation and movement of bonds and serious interaction between R^1 with the equatorial Ph group

(Figure 9, VI). The production of *(E)*-olefin from the stabilised ylide is also explained in which substituent CO_2Et tend to orient the phosphorus coordinated aldehyde in spite of

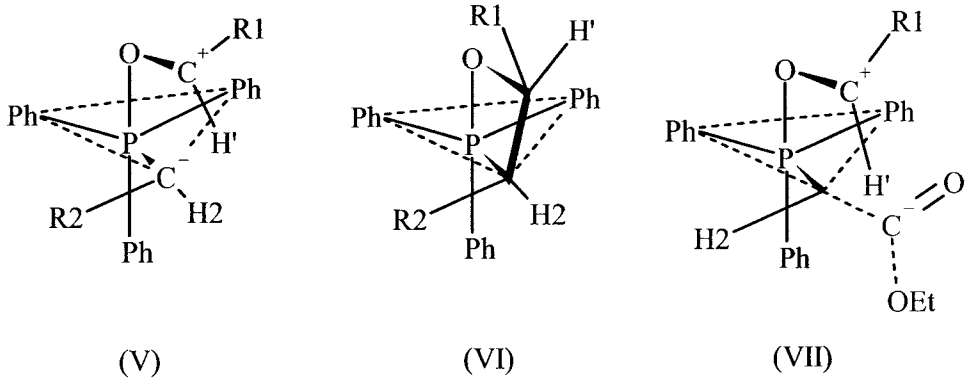
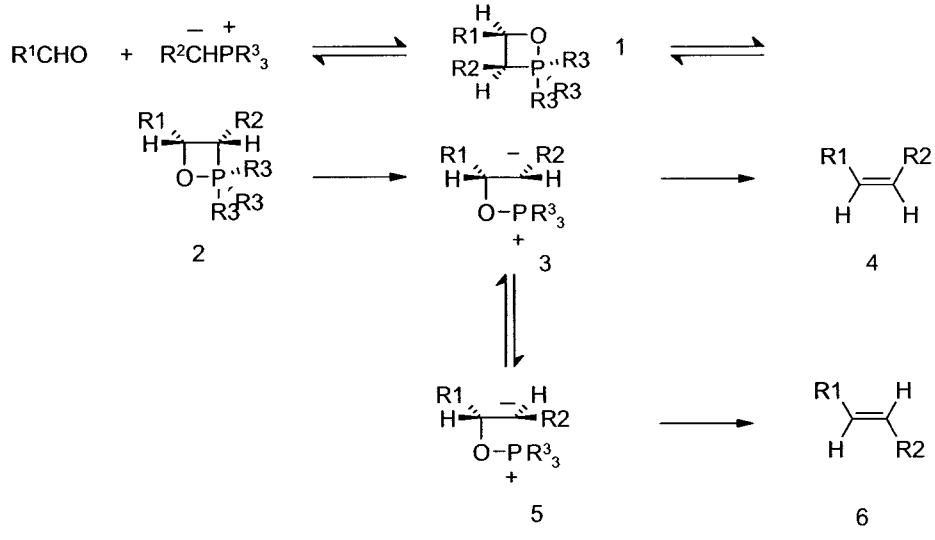


Figure 9: Schneider's Proposal.

the steric hindrance, forms the *threo* intermediate and subsequently the *(E)*-olefin (Figure 9, VII).

3.4.3 Bestmann Proposal[38]

According to Bestmann's mechanism, cycloaddition of ylide and aldehyde takes place to give OPA (1) in which R^1 and R^2 are *cis* to each other. Pseudorotation about the pentacoordinate phosphorus takes place to give (2) in which the departing carbanion center occupies apical position in the phosphorus triagonal bipyramid. Carbon-phosphorus bond ruptures to yield zwitterions (3). If R^2 is unable to stabilise an adjacent carbanion and R^3 is phenyl, a rapid elimination to triphenyl phosphine oxide takes place producing large amount of *(Z)*-olefin (4). However if R^2 is carbanion stabilising group or if R^3 is electron donation group (alkyl), the lifetime of intermediate (3) is extended (Phosphine oxide elimination is slowed). Rotation about C-C bond now takes place resulting in production of thermodynamically stable zwitterion (5). Elimination of phosphine oxide leads to stable *(E)*-olefin (6) as a product.



Scheme 11: Bestmann Proposal.

3.4.4 Vedejs' Proposal

In 1973 Vedejs provided evidence in favour of OPA intermediates based on his low temperature characterisation of the intermediates by NMR studies.[39,40] He proved that 1, 2-OPA could be considered as more important intermediate than betaine. In his study, he observed OPA peaks for various substrates but was unable to detect betaine formation suggesting that the pentavalent OPA would be more stable than the betaine. He also stated clearly the absence of direct evidence of the "true betaine" in non-stabilised ylide reaction.

In order to explain the *(Z)*-selective Wittig reaction in case of non-stabilised salt free ylide, Vedejs proposed *cis* disubstituted OPA as a precursor[40] and OPA dissociation into ylide and aliphatic aldehyde is not a factor (OPA derived from aromatic aldehyde and non stabilised ylide do revert to starting material)

Vedejs proposal involves *cis* selective cycloaddition process having partially rehybridised aldehyde tilted with respect to ylide plane to minimise the nonbonding interaction and also having C=O and ylide C-P bond "criscrossed" to maintain reasonable C---C and P---O bonding distance. Such kind of crisscross transition state geometry gives rise to two

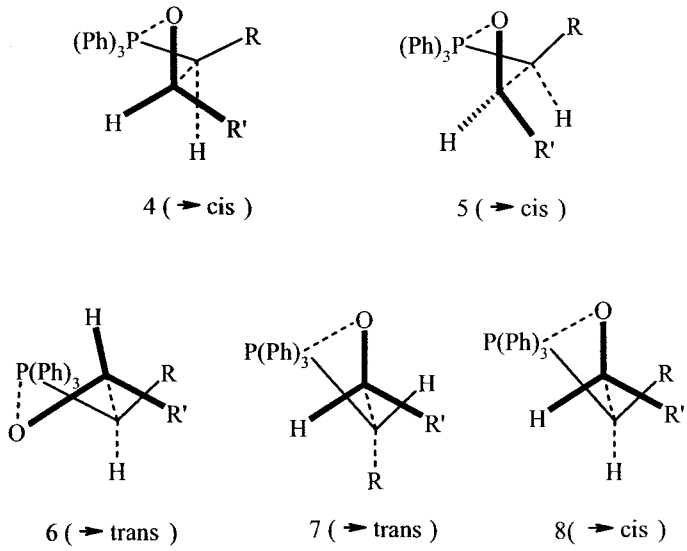
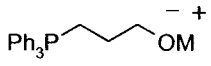
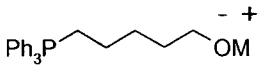
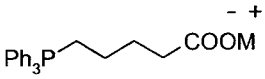
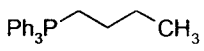


Figure 10: Vedejs' proposal.

situations 4 (parallel plane) and 5 (planes tilted 90 °) which will lead to *cis* disubstituted OPA as bonding proceeds. Alternate arrangements which lead to *trans* disubstituted OPA are as shown in figure 10 (6, 7, 8). Crisscrossed arrangement giving rise to *cis* disubstituted OPA is favoured over 6, later being destabilised by the close interaction of the bulky groups. However there is very little margin for stability when 4 and 7 are considered. In that case 5 which has a tilted plane becomes more important. Competing transition state 6/7 which afford *trans* disubstitued OPA cannot benefit to the same extent by tilting the aldehyde plane. The exact transition state geometry leading to *(Z)*-olefin depends on the angle of tilt and the extent of rehybridisation and the approach of reacting component is largely dependent on the trajectory which maximises the separation between R' and the bulky ylide groups. On the basis of crossover experiment he showed that benzaldehyde derived OPA do revert to the starting material competitively with the alkene formation but intermediates form aliphatic aldehyde and non stabilised aldehydes do not revert to the starting material under typical Wittig reaction.

In 1985, Maryanoff and co-workers wrote about the effects of contributions of nucleophilic group in unstabilised phosphonium ylide on the Wittig reaction outcome. They observed certain surprisingly *(E)*-selective Wittig reaction which largely depended on the chain length of the ylide.[41,42] Abnormal *(E)*-selectivity in the Wittig reaction was

observed when anionic groups are present at a certain optimum distance from the ylide site. Ylides possessing anionic groups at an optimum distance tend to show multitude of unresolved peaks instead of the single sharp ^{31}P shift which explains it as a consequence of various interacting aggregates. Never the less when such ylides (ylides with the anionic group) were allowed to react under typical Wittig condition with benzaldehyde / hexanal, displayed characteristic ^{31}P peaks corresponding to *cis* OPA and *trans* OPA. The ratio of which depends upon the distance of the anionic group from the ylide site.

Ylides bearing anionic group	Ratio of initial *Cis:Trans* Oxaphosphetane at -80°C		Final *Cis:Trans* alkene
 1	1:2.2	(with benzaldehye/ LiHMDS/THF)	1:24
 2	8:1	(with benzaldehyde/ LiHMDS/THF)	1:6
 3	2.2:1	(with benzaldehyde/ NaHMDS/THF)	10:90
	2.7:1	(with aliphatic aldehyde/ LiHMDS/THF)	2.7:1
 4	3:1	(with benzaldehyde/ LiHMDS/THF)	2.4:1.6

* M= Li/ Na

Table 5: Stereochemical drift.

Ylides bearing anionic groups as well as ylides devoid of it gave predominantly *cis* OPA at -80 °C in most of the cases. However "stereochemical drift" was observed in the reaction course to give more *(E)*-alkene in the product than reflected in the OPA. This was more in ylides having the anionic group at optimum distance. Thus such ylides facilitate *(E)*-alkene formation by enhancing the stereochemical drift of the OPA

intermediate more than the ylides devoid of anionic group (Table 5). In an attempt to show thermodynamic control in the Wittig reaction of ylides bearing anionic group, Marynoff and co-workers carried out crossover experiment and showed for the first time that reversible Wittig intermediates derived from the aliphatic aldehydes and the non stabilised triphenylphosphorus ylide having anionic group **do exist.**

This finding supports the view that anamolous *(E)*-stereoselectivity induced by anionic substituents in the phosphonium ylide is associated with reversible dissociation of OPA to ylide and aldehyde, a process which introduces a degree of thermodynamic control.

In 1988 Vedejs made another boosting statement highlighting the importance of 1, 2 and 1, 3 interactions in "salt free" Wittig chemistry.[43] He states that-"Typical non-stabilised or moderated ylides react via early transition state and under kinetic control. The subtle interplay of 1,2 and 1,3 steric interactions is responsible for the *cis* and *trans* selectivity and puckered transition states are increasingly important as the 1,3 interactions associated with the bulk α to the carbonyl group become dominant."

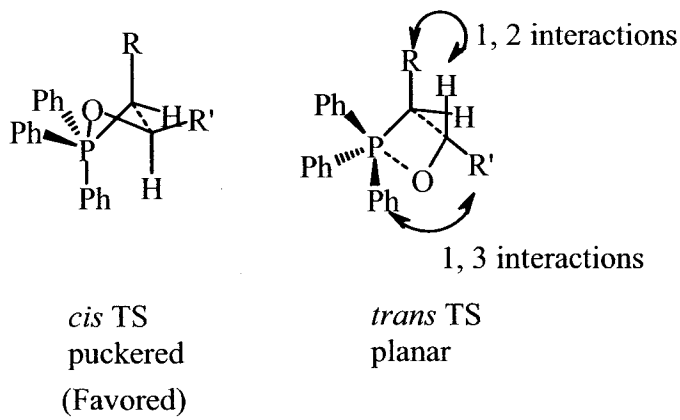
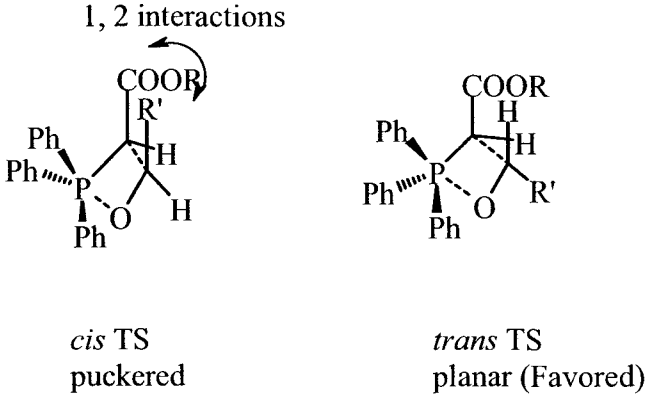


Figure 11: 1, 2 and 1, 3 interactions in non-stabilised ylides.

Thus the non stabilised ylides react via early puckered *cis* TS which minimises 1, 2 and 1, 3 steric interaction while *trans* TS is more planer, although it has unfavourable 1, 3 interaction, subsequent puckering would lead to the increase in 1, 2 interaction. Thus for unstabilised ylides *cis* TS (which leads to *(Z)*-olefin) is favoured over *trans* TS, where

as for stabilised ylides, planer TS is favoured as 1, 2 steric hindrance plays more impotant role in *cis* TS.

Vedejs also gives explanation for the surprising *(E)*-selective Wittig reaction observed by Maryanoff and coworkers. He states that because of the lone-lone pair repulsion caused by heteroatom placed in the side chain, kinetic *trans* selectivity gets increased with respect to the *cis* selective transition state. In further communication Vedejs literally tries to eradicate betaines as major intermediates in the Wittig reaction by conducting "fingerprint" test in which he attempts to prove that all the experimental results are against the betaine as intermediate in the Wittig reaction.[44]

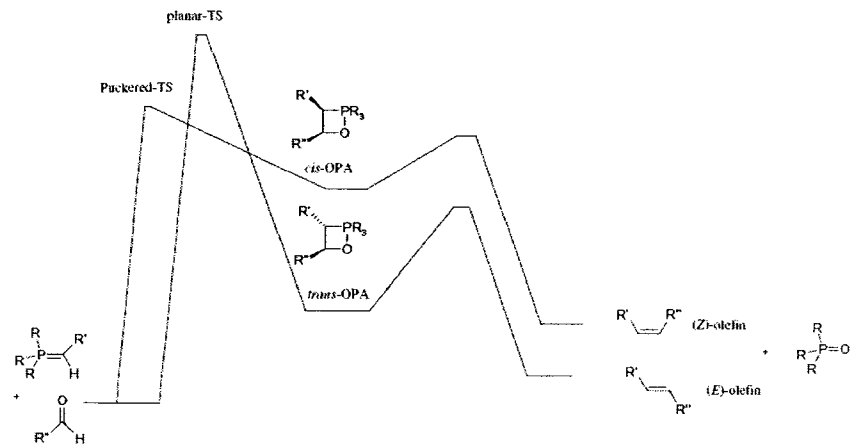


cis TS
puckered

trans TS
planar (Favored)

Figure 12: 1, 2 and 1, 3 interactions in stabilised ylides.

Thus the reaction mechanism qualitatively outlined in Scheme 12, is now believed to involve essentially irreversible, rate-determining addition of the ylide to the carbonyl component yielding either a *cis*- or a *trans*-substituted OPA intermediate. An interplay of 1,2- and 1,3-steric and electronic effects governs the relative transition states leading to either, or both of these intermediates. In general, it is believed that *cis*- to *trans*-OPA equilibration or Wittig reversal does not occur. Stereospecific syn-elimination of the phosphine oxide then leads to the (*Z*)- or (*E*)-olefins, respectively.



Scheme 12: General mechanism of the Wittig olefination reaction.

However, there are few reports where authors report the trapping of the betaine via use of modified stationary groups or use of special aldehydes.[45-47]

Various mechanisms have been put forward till date to explain the "single mechanism" for the Wittig reaction solving the *cis/trans* selectivity problem. But all the results reflect the same thing. The mechanism of the Wittig reaction cannot be generalised in a nut shell. The outcome of reaction largely depends upon the use of solvent, base, aldehyde and substituents on stationary phosphorus during the Wittig reaction. There are special methods to get either *(Z)*-or *(E)*-olefin selectively from reactive ylide. But the outcome of such results should be carefully understood considering all facts and should not be generalised.

3.5 Problems associated with the Wittig reaction:

There are two major problems associated with the Wittig reaction, namely origin and thus control of stereoselectivity and removal of phosphine oxide.

3.5.1 Origin of stereoselectivity:

As one might think the Wittig reaction is not a mere attack of nucleophilic carbon from ylide on a carbonyl group. This does not provide an explanation to the source of

selectivity. One explanation i.e. *erythro* vs. *threo* stereoselectivity, about the C-C bond appears reasonable explanation for the outcome of the stereoselectivity in the Wittig reaction. The Wittig reaction of non-stabilised ylide with aldehyde gives mainly *(Z)*-alkene and there has been several explanations to such stereochemical outcome, (1) substituent steric interactions in a nonsynchronous cycloaddition mechanism,[48] or (2) a steric effect of stationary ligand on phosphorus in a four centered cyclic transition state,[48] or (3) classical anti-betaine arrangement involving anti arrangement of the phosphorous and the oxygen, where the selectivity is determined at the anti-betaine stage.[48] Each of these explanation has its own drawback and advantage. Putting all in nut shell, a clear cut explanation for the *cis*-selective olefination or for its intermediate- betaine/OPA is still waiting.[48]

Going further; semi-stabilised ylides rarely give high stereoselectivity for either *cis* or *trans* olefin, generally they give 50% *cis* and 50% *trans* as a outcome of the Wittig reaction. Stabilised ylides give high >95% *trans* olefination. However special cases show abnormal selectivities like reaction of fluoro-phosphoranium tri-n-butylphosphorous stabilised ylide with aldehydes produce more *(E)*-alkene (94%) than with aromatic aldehyde (13%).[49] Stereochemistry of the Wittig reactions can be affected by the solvent, its concentration, cation, temperature, intermediate reversal and the type of the aldehyde. Thus a concise explanation for the Wittig reaction is still not clear and is most welcome.

3.5.2 Removal of phosphine oxide:

The Wittig reaction is a powerful tool for the preparation of olefins from carbonyl compounds and ylides. These olefins find useful application in various industries, for e.g. in the preparation of perfumes, agricultural chemicals and biologically active substances. However the Wittig reaction has a serious problem of isolation of the required olefin product from the reaction mixture which also consists of phosphine oxide in an equimolar proportion. Isolation of desired olefin in such case is a real challenge.

Phosphine oxide can be removed from the reaction mixture by filtration. However difficulties encountered when such filtration was practiced at industrial scale due to

expensive and special facilities required. Phosphine oxide also proved a potential pollutant and adverse effect of it on the workers are unavoidable.[50]

Various methods have been reported till date to address the problem of phosphine oxide which includes, Use of phosphine having formula PPh_2Ar, where Ar is 4-COOH or 4-NR_2, which facilitates the removal of phosphine oxide after the Wittig reaction by usual washing with base or acid respectively. This method allowed separation of phosphine oxide by solubilising it in aqueous media and thereby getting rid of it.[50] The method described is useful in a way but the disadvantages like lengthy synthetic procedures to prepare the phosphine and further which does not answer the question of stereoselectivity of the Wittig reaction. Another disadvantage is when such water soluble phosphine oxides are produced in large amounts from industries it can potentially produce harmful effects due to acidic or alkaline waste water containing phosphine oxide.[50]

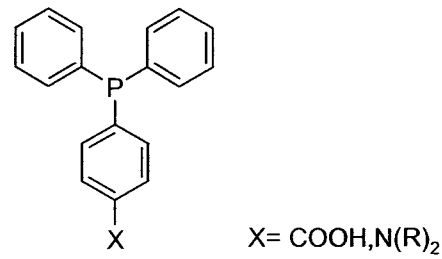


Figure 13: Modified phosphines for the Wittig reaction.

In some cases, it is also possible to distil out[50] the required olefin from a mixture containing phosphine oxide, which makes use of difference in boiling points of the olefin and the phosphine oxide. Elevation of boiling point can be a problem for such kind of method and under such condition stereochemical changes at molecular level like isomerisation, polymerisation of the olefin could potential harm as a result of prolonged heating.

Another method uses lower carboxylic acids containing 1 to 4 carbon atoms (formic acid, acetic acid, propionic acid and butyric acid).[50] This method includes mixing of carboxylic acids to the reaction mixture in hydrocarbon solvent. This method makes use of the preferential solubility of the phosphine oxide in the carboxylic acid forming fluid which is immiscible in a mixture of olefin and hydrocarbon solvent. This fluid can

be separated from a mixture of olefin and the hydrocarbon solvent easily either by distillation or any other routine separation technique.[50]

Schlosser and co-workers utilise the *ortho* position of the stationary phenyl parts of the ylide by substituting it with methoxymethoxy group.[51] Under such condition phosphine oxide by-product can be easily removed from the reaction mixture by acid hydrolysis to trisphenol.[51]

Alternatively phosphine oxide can be isolated and converted back to the phosphine by reduction with alane as shown by Wyatt and co-workers, which doesn't require aqueous work up. [52, 53]

3.6 Reported Methods:

(*E*)-aryl alkenes are highly potent neuroleptic, anti-ulcerogenic, anti-PAF, antifungal and anti platelet agents.[54] Thus synthesis is of such (*E*)-aryl alkenes is of high value. For the synthesis of (*E*)-aryl alkenes several synthetic methods are reported in literature involving Grignard, Wittig-Horner, Aldol-Grob, Fridel-Craft and Photochemical isomerisation. Recent method includes, disodium iron tetracarbonyl, iridium and palladium(II) catalyzed isomerisation of gamma and cis aryl alkenes and ultrasound assisted convenient method as a useful entry in to the (*E*)-aryl alkenes synthesis.[54]

All the above reported methods suffer from serious drawbacks such as,

1. Long reaction time; 2. Tedious work ups and use of expensive and hazardous reagents; 3. Formation of some amount of unwanted *cis*-isomer along with desired *trans*-isomer, and difficulty in separation of such isomers using column chromatography due to resemblance of their R_f values; 4. Unwanted, toxic phosphine oxide formation during the Wittig reaction.

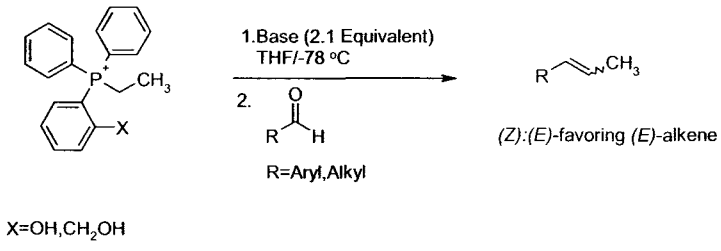
3.7 Proposal for getting high (*E*)-olefination using unstabilised phosphonium salts:

Ylides derived from the unstabilised phosphonium salts undergoes the Wittig reaction with aldehydes, and alkene produced generally contains higher proportion of the *(Z)*-olefin which is a kinetic product of the reaction. The precursor of the *(Z)*-olefin was

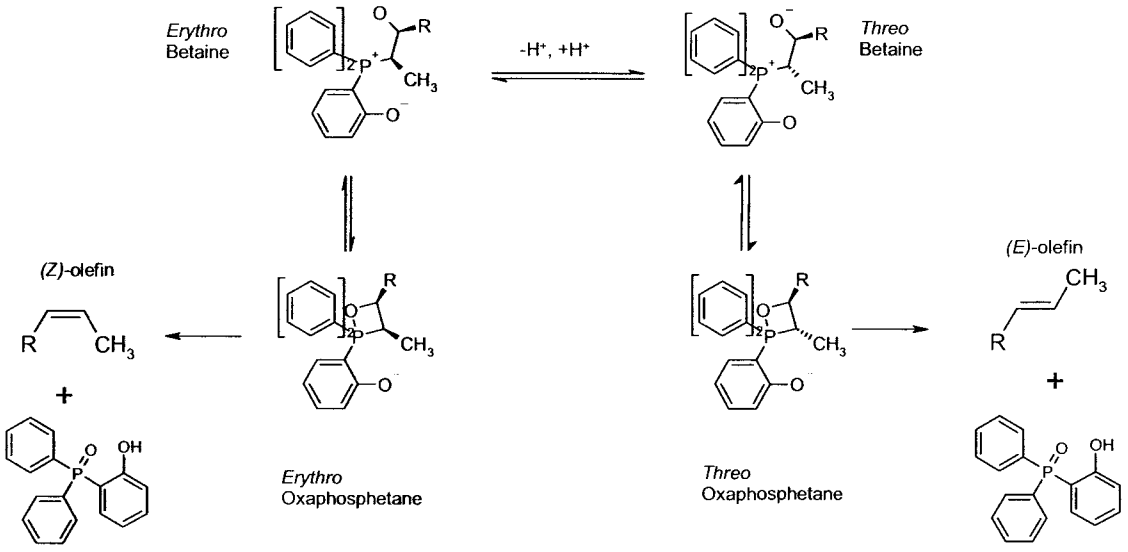
believed to be the *erythro* betaine/OPA. It was clear to our minds that if we can bring about the equilibration at betaine/OPA stage where the kinetically favoured *erythro* intermediate will convert in to *threo* intermediate which on subsequent *syn* elimination should result in thermodynamically more stable (*E*)-olefin.

In 1966 Schlosser and co-workers described a modification[55] for the Wittig reaction wherein they described stereoselective formation of (*E*)-alkenes from unstabilised ylides (when the *(Z)*-isomers would normally be expected to predominate). This method makes use of addition of extra equivalent of butyl or phenyl lithium at low temperature to equilibrate the *erythro* betaine to *threo* betaine via formation of a second ylide. Also, we were attracted to a recent paper that disclosed a fascinating solvent-quench effect on the stereoselectivity of the Wittig reaction, in which protic solvents were shown to increase levels of (*E*)-stereoselection significantly in the reaction with Garner's aldehyde.[56] While an intramolecular stereochemical effect of alkoxy and other nucleophilic groups on the alkylidene portion on ylides has been investigated,[42] also resulting in higher levels of (*E*)-olefin. To our knowledge, the role of related substituents on the aryl portion of the ylide has not been investigated. Although the effect was limited in scope, mechanistically it was attributed to *cis*-OPA protonation and alkoxide-mediated isomerization to the *trans*-OPA. Overall, the combination of the *ortho*-substituent effects and the intriguing intermolecular alkoxide effect prompted us to consider intramolecular *ortho*-aryl alkoxy effects as a possible means of modulating (*E*)-stereocontrol.

The introduction of an *ortho* substitutions (–OH, -CH_2OH) on one of the phenyl groups attached to phosphorus atom in the phosphonium salts which would do the same type of work under basic condition what an extra equivalent of base would do in Schlosser's modification or the methoxide ion or the nucleophilic groups on the alkylidene portion of the ylide. Apart from the expected equilibration from *erythro* to *threo* intermediate via formation of a second ylide, we were sure of getting rid of phosphine oxide-a by product formed during the reaction via normal aqueous workup, as now the phosphine oxide contains phenolic moiety which can be washed off by 10% NaOH wash.



Reaction Mechanism (Assuming X=OH)



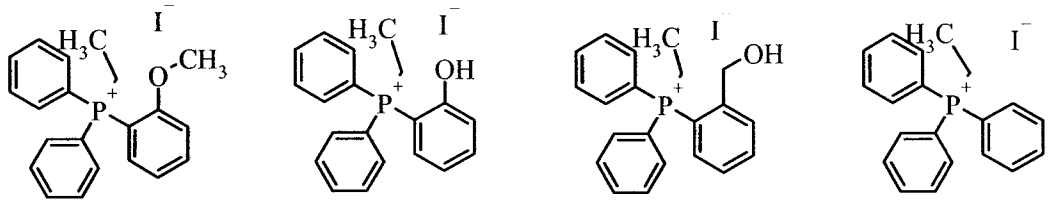
Scheme 13: Proposal for getting high *(E):(Z)*-olefination with non-stabilised ylide.

In order to test this hypothesis, we synthesised four unstabilised phophonium salts and tested them under standard set of conditions. Preparation of these novel unstabilised phosphonium salts and their results along with removal of toxic phosphine oxide in one case are described in the next section. Effect of these substitions on the Wittig reaction of semistaiblied phosphonium salts is also described.

3.8 Results and discussion:

Work towards the proposed goal began with synthesis of the required phosphonium salts in gram scale. Following three new phosphonium salts (A), (B), (C)

were prepared and their applications were studied by carrying out their reactions with different aldehydes. Their results were compared with control set of reaction carried out with triphenyl phosphonium iodide salt (D).

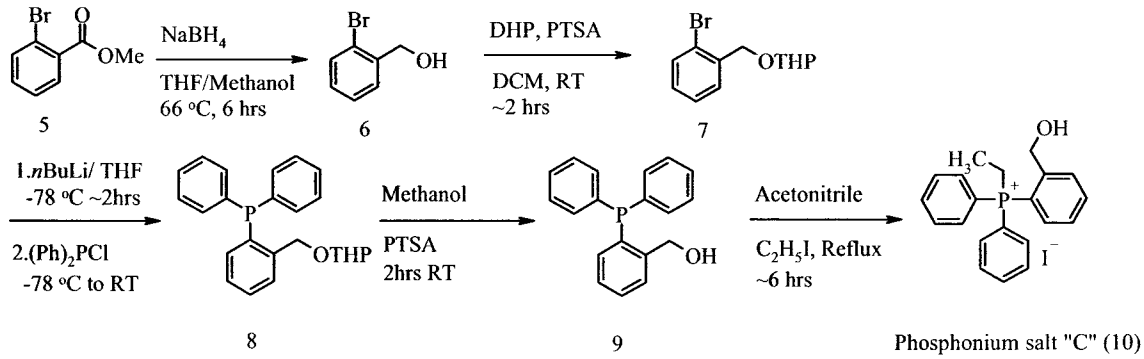


A B C D

Figure 14: "New phosphonium salts".

These phosphonium salts (A-D) bearing *ortho* substitution were synthesized as depicted below,

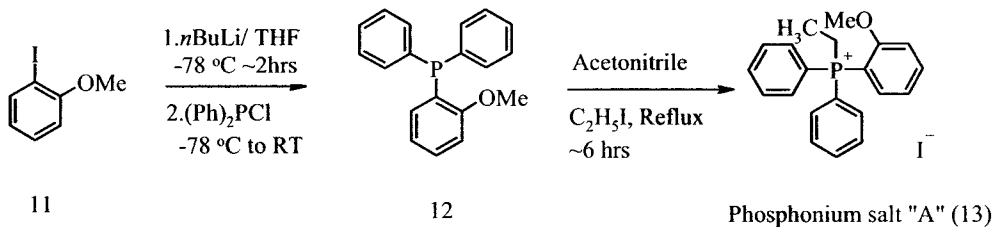
Synthesis of the phosphonium salt C (Scheme 14) was carried out over five steps with excellent (≥ 90%) yields at all stages except the phosphination stage, where yield dropped to 60%. Initially, 2-bromo-benzoic acid methyl ester was reduced with sodium borohydride using co-solvent THF/Methanol[57] at 66 °C to give the corresponding alcohol in quantitative yield. Before displacing the bromine from the compound (6), protection of the primary alcohol with dihydropyran using catalytic amount of PTSA in DCM was carried out, subsequent base catalyzed displacement of this protected bromo compound was carried out using chlorodiphenylphosphine to give compound (8). Deprotection was carried out using aq. methanol with catalytic PTSA. The required phosphine was colorless gummy product which was converted in to its salt by refluxing it with ethyl iodide in acetonitrile to provide good yields of the phosphonium salt "C" (10).



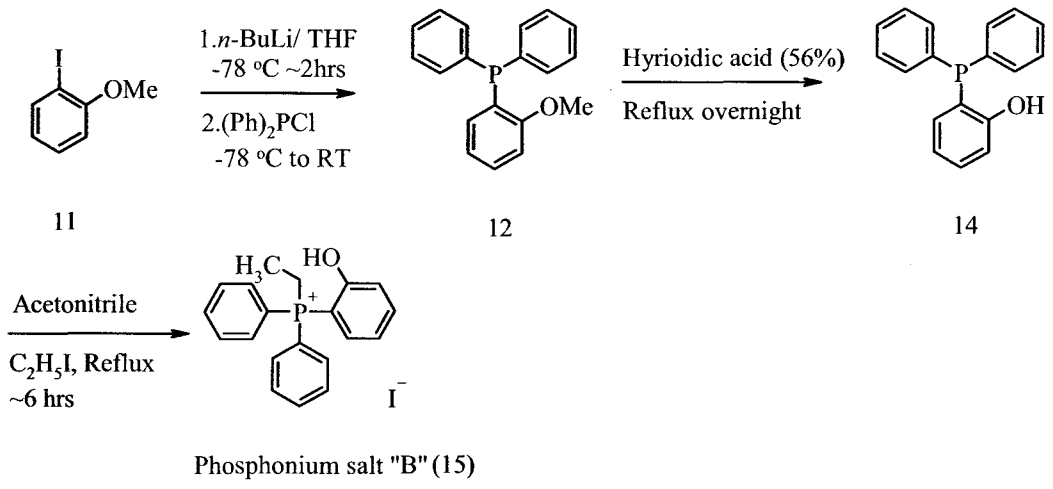
Scheme 14: Preparation of the phosphonium salt "C".

Preparation of the phosphonium salt "A" began with base catalyzed reaction of the 2-iodo anisole (11) with chlorodiphenylphosphine to provide product (12) in good yields. The required phosphine was isolated as white solid which was refluxed with acetonirile using ethyl iodide to provide the phosphonium salt "A" (13) in quantitative yield.

Synthesis of the phosphonium salt "B" (15) began with the same chemistry used for preparation of salt "A". To obtain the phosphine "B", demethylation of phosphine (12) was carried out using various methods like BBr_3,[58] $AlCl_3$-NaI,[59] TMSBr,[60] aq. HBr[61] and aq.HI[61] solution. Use of HI with catalytic amount of hypophosphorus acid (50%) gave required phosphine (14) in low yields. Rest of the methods fail to give required phosphine. Literature survey revealed that there could be other routes for the synthesis of phosphine (B). But we didn't look in to this, as we were not interested in developing synthesis of required phosphine. The primary interest was to see effect of such phosphonium salts on the stereochemical outcome of the Wittig reaction.



Scheme 15: Preparation of the phosphonium salt "A".

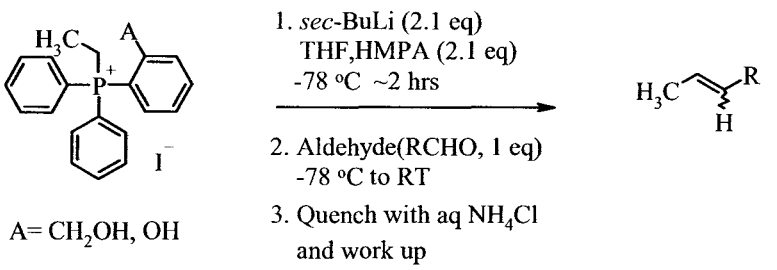


Scheme 16: Preparation of the phosphonium salt "B".

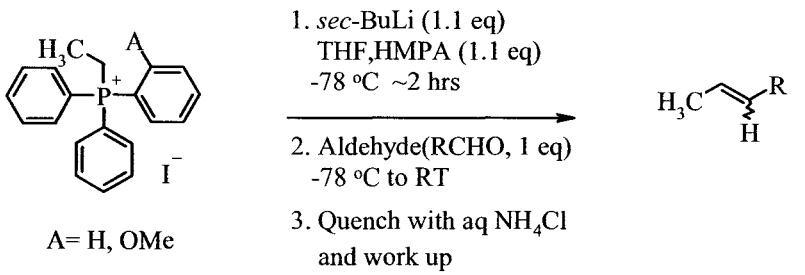
The required phosphine was isolated as white solid which was refluxed with acetonirile using ethyl iodide to provide the phosphonium salt "B" (15) in quantitative yield.

3.9 The Wittig Reaction with modified phosphines:

The phosphonium salts (A-D) were subjected to the Wittig olefination using standard conditions. These conditions kept constant throughout all the experiments owing to fact that slight change in reaction condition could produce dramatic shift in the olefin geometry. For our studies, we carried out all the Wittig reactions (parent and modified phosphonium salts) in THF as solvent. For deprotonation of phosphonium salts *sec*-BuLi was used as base. We also used HMPA in equimolar ratio (with base) and found that yields were better in all the cases. The Wittig reactions with all the phosphonium salts were repeated 4 to 5 times to get reproducible results. The standard conditions are as depicted below,[62]



Scheme 17: Standard reaction condition for phosphonium salts B and C.

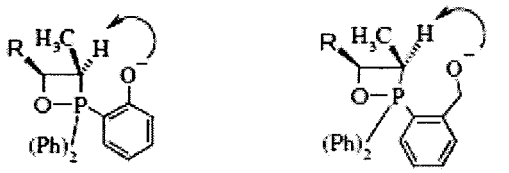


Scheme 18: Standard reaction condition for phosphonium salts A and D.

To begin with, the control ylide derived from phosphonium salt "D" reacted with aromatic aldehydes giving alkenes with good (*Z*)-selectivity as expected[42] and with high selectivity in the case of the aliphatic aldehyde undecanal.[62] The ylide derived from the ortho-methoxy derivative "A" was less selective, but delivered more (*E*)-olefin, similar to the literature data, with the exception of the reaction with the undecanal which provided very high (*Z*)-selectivity. This result appears to indicate an overriding steric effect of the long alkyl chain, possibly due to 1,2-interactions with the ylide substituent, favoring the early *cis*-puckered transition state.[62,63]

More revealing however are, the results with the ylides derived from the *ortho*-hydroxyl and benzyl alcohol-substituted derivatives "B" and "C". In both these cases, the ylides were generated under kinetically controlled conditions using 2.1 eq. of *sec*-BuLi in order to assure the formation of the phenoxide and alkoxide intermediates.[62] A pronounced effect was observed with both of these ylides in their reactions with aromatic aldehydes, yielding olefins with high (*E*)-selectivity, while a moderate increase in (*E*)-selectivity was observed with the aliphatic undecanal.[62]

In comparing the results of the methoxy derivative "A" to the alkoxide containing derivatives "B" and "C", the stereochemical results are not simply due to lone pair interactions or steric factors alone, the involvement of an alkoxide effect is evident. The present intramolecular alkoxide effect does not require initial protonation of the OPA intermediate, and therefore does not appear to involve a β-hydroxy phosphonium intermediate. Furthermore, the similarity of the stereochemical effect in comparing the ylides derived from B and C strongly suggests that the result is not manifested via conjugative or inductive dipolar effects, but it involves a direct through space interaction of the alkoxy oxygen.[62] Figure 15, depicts the expected kinetically produced *cis*-OPA intermediates derived from salts "B" and "C". These species are now set up to participate in an intramolecular variation of the alkoxy effect demonstrated by Kim and co-workers through rapid isomerisation of the *cis*-OPA intermediate, isomerizing to the *trans*-OPA through a 6- or 7-member transition state, and leading to the (*E*)-olefins with high selectivity.[62]



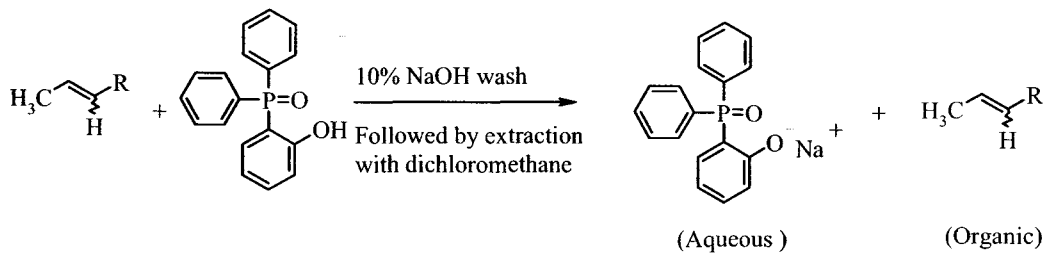
cis-OPA from B *cis*-OPA from C

Figure 15: Transition state comparision: Six and Seven membered ring.

It is not clear if the isomerisation involves initial ionization of the OPA to a betaine, but we do not believe that such ionization is a requirement for the *cis* to *trans* isomerization. Given the dipole moment and polarizability of the O–P bond in the OPA, we believe that the acidity of the alkyl proton α to phosphorus in conjunction with the intramolecular alkoxide is sufficient to allow epimerization.[62] Our present view is therefore the direct epimerization of the OPA intermediates as depicted in Figure 15. These results support the alkoxide-mediated isomerisation pathway postulated by Kim and co-workers, which were limited to the Garner aldehyde. The intramolecular variant

described here expands the scope to aromatic aldehydes, allowing for a significant increase in (*E*)-stereoselectivity in their Wittig reaction with unstabilized ylides.[62]

Finally, in the case of the reactions with the phenoxide reagent "B", in addition to the high (*E*)-olefination observed, we were able to remove the ortho-hydroxyl-triphenylphosphine oxide side product employing a simple base extraction protocol. The reaction mixture was quenched with saturated NH_4Cl, and the olefin partitioned into dichloromethane. The combined organic fractions in dichloromethane were simply shaken with 10% NaOH (aq) which completely removed the phosphine oxide, followed by normal work-up procedures.[62] Thus in case of phosphonium salt "B", we were able to tackle both problems, i.e. stereoselective (*E*)-olefin formation and removal of phosphine oxide. Phosphonium salt "C" gave nearly same selectivity as in salt "B" without solving phosphine oxide problem.[62]



Scheme 19: Protocol for removing phosphine oxide generated during reaction with phosphonium salt "B".

Isolated yields found to be the disadvantage of these Wittig reactions although not particularly in case of phosphonium salt "A" where the yields are moderate to good ranging from 60-66%. Yields obtained from phosphonium salts "B" and "C" (40- 45%) were not great. This can be explained on the basis of reaction course of the Wittig reaction. The Wittig reactions are known to pass through OPA intermediate where upon it eliminates phosphine oxide to generate olefin; the most important aspect of this process is the formation of OPA itself prior to elimination.

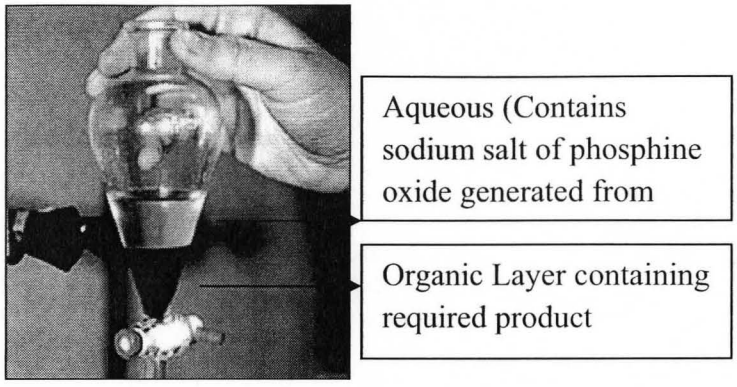


Figure 16: Snapshot of reaction mixture during the work-up of the Wittig reaction with the phosphonium salt "B".

The decreased yields in case of phosphonium salt "B" and "C" can be attributed to the fact that there is restricted formation of the OPA, as ortho phenoxy and benzyl oxy group of these phosphonium salts interfere the normal reaction course of the Wittig reaction.[64]

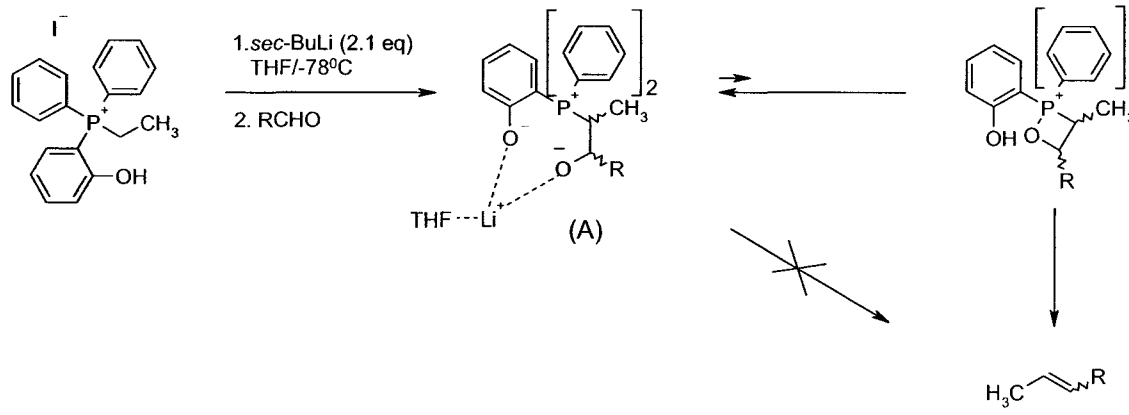
3.10 Effect of HMPA on the Wittig reaction:

During the reaction course, we observed that among four phosphonium salts, only salts "A" and "D" reacted readily with aldehydes, and gave olefins in high yield. Under exactly similar conditions we observed very little or no olefin formation when we used the phosphonium salt "B" or "C". However with the use of HMPA we were able to get the olefins in moderate yield. Looking at these observations, we think that the presence of the "*ortho oxy*" moiety in these phosphonium salts is the culprit.

In the Wittig reaction, OPA is essential for the formation of olefin and any factor which hinders its formation will result in "zero" yield. Initially, the Wittig reaction of the phosphonium salts "B" and "C" were carried out using lithium base alone (devoid of HMPA, as additive). Due to equimolar lithium salts present in the reaction mixture, formation of betaine intermediate (Scheme 20, A) was obvious in the reaction mixture. We think that betaine intermediate (Scheme 20, A) can be formed by stable interactions between "ortho oxy" group, the lithium salt and the carbonyl oxygen of the aldehyde. This intermediate might not convert to the OPA easily from where it can eliminate to

give olefin. If this assumption is correct then addition of HMPA, which is a complexing agent for the lithium ions, should complex lithium and once again the Wittig pathway can be initiated. Experiments carried out with the addition of HMPA were consistent with the proposed mechanism and we were able to get olefin in moderate yield.

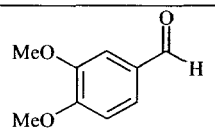
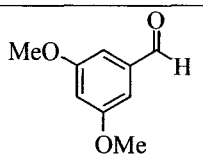
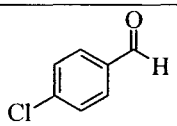
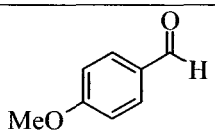
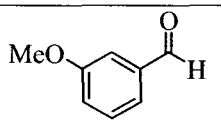
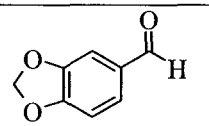
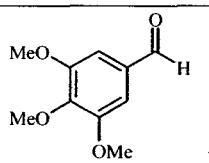
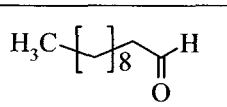
We believe that stabilizing effect of the "*ortho oxy*" group is strong enough to hold the intermediate at the betaine stage.[46-48] Although spectroscopic evidence is unavailable for the same, we strongly believe that detail low temperature NMR studies should reveal betaine as intermediate in our study with phosphonium salts "B" and "C".



Scheme 20: Trapping of betaine intermediate.

We further found that equimolar concentration of the HMPA was just sufficient for optimizing the Wittig reaction and stereochemical ratios were unaffected by 1, 2 or 3 equivalent HMPA addition. Below is the table showing results obtained for the Wittig reaction, when carried out with modified unstabilised phosphonium ylides.

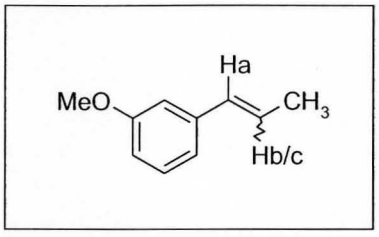
Also, figure 17 shows the comparison of the ^{1}H-NMR spectra's obtained after carrying out the Wittig reaction of phosphonium salts (A-D) with 3-methoxy benzaldehyde.

Aldehyde \ Salt	A	B	C	D
 1	40:60	24:76	25:75	71:29
 2	57:43	25:75	27:73	72:28
 3	39:61	NA	12:88	71:29
 4	23:77	08:92	08:92	63:37
 5	54:46	10:90	17:83	80:20
 6	31:69	08:92	12:88	67:33
 7	45:55	28:72	29:71	62:38
 8	95:05	38:62	38:62	81:19

[a] *(Z): (E)* ratios were determined on the isolated product using ^{1}H-NMR-spectroscopy. [b] Reported ratios are the averaged values of *(Z)*:*(E)* after carrying out individual reaction for at least 3 or 4 times. There was no significant change in the *(Z)*:*(E)* ratios of the crude and purified material.

Table 6: The Wittig reactions of unstabilised ylides with aromatic and aliphatic aldehydes, *(Z)*:*(E)*[a,b].

3.11 An Example - Comparison of spectra's obtained from reaction with 3-Methoxy benzaldehyde



Hb= H is trans to Ha
Hc= H is cis to Ha

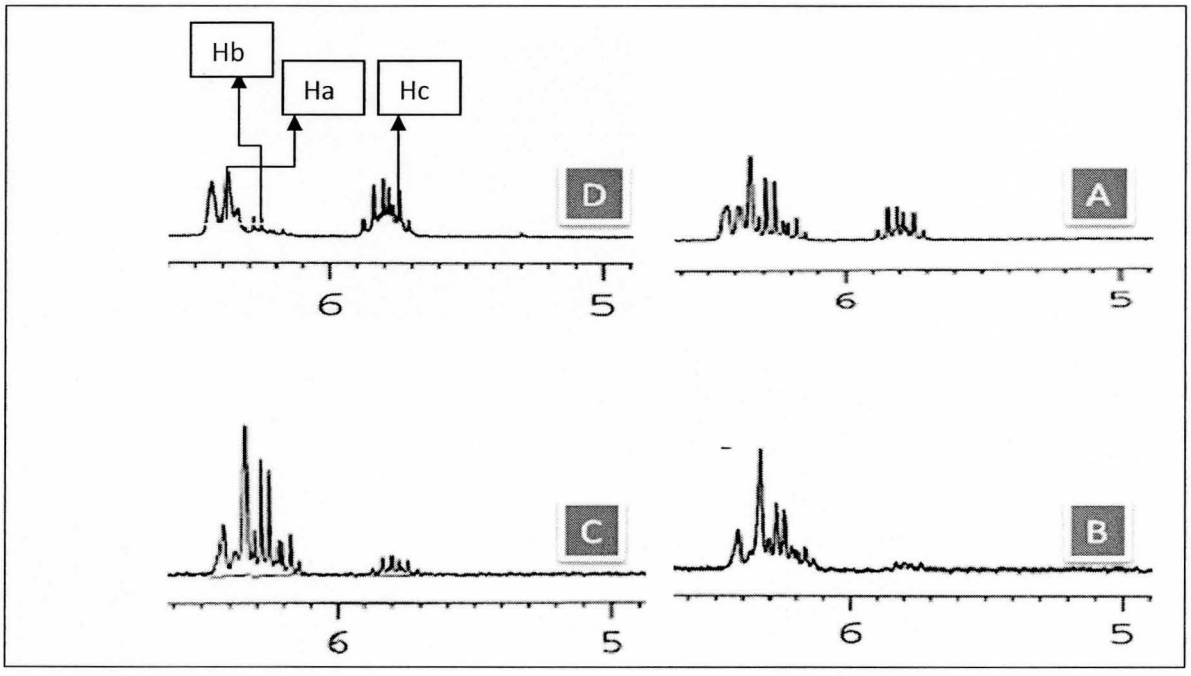
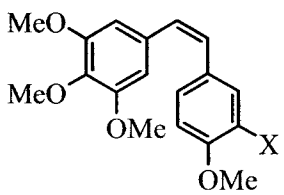


Figure 17: Comparison of ^{1}H-NMR obtained from reaction with 3-Methoxy benzaldehyde

3.12 Extension towards modified benzylic phosphonium salts:

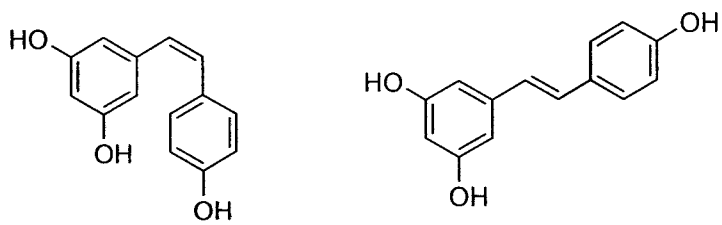
Our interest in extending this methodology to moderate phosphonium salts was mainly due to occurrence of variety of naturally occurring stilbenoid phenols like "Combretastanin family" (*cis*-stilbenes) and "Resveretrol family" (*cis* and *trans*-stilbenes) and their anticancer and other interesting properties. Members of combretastanin family have general structure as in figure 18.



X= NH_2, OH, OCH_3

Figure 18: Combretastanin family.

Combretastanin A-4 (where X= OH) is known to be most potent in tubulin binding activity and cytotoxicity. Members of its family possess ability to cause vascular disruption in tumor cells. Combretastatin binds to the β-subunit of tubulin (colchicine site), Inhibition of tubulin polymerization prevents cancer cells from producing microtubules.[64-66] Microtubules are essential for cytoskeleton production, intercellular movement, cell movement, and formation of the mitotic spindle used in chromosome segregation and cellular division. The anti-cancer activity from this action results from a change in shape in vasculature endothelial cells. Endothelial cells treated with combretastatin rapidly balloon in shape causing a variety of effects which result in necrosis of the tumor core. Resveratrol (figure 19) has been shown to induce apoptosis, which means it kills cancer cells. Resveratrol also possesses antioxidant and anti-angiogenic properties. Recent studies show that resveratrol inhibits production of cytokines which are involved in the development of obesity-related disorders.[67-69]

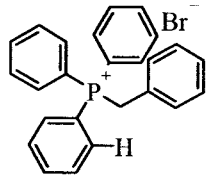


Cis Trans

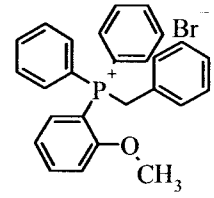
Figure 19: *cis* and *trans* resveratrol.

Classical Wittig reaction produces varying amounts of (*E*)-and (*Z*)-stilbene isomers depending on solvent polarity, temperature, metal cation coordination effects, and the electronic effect of substituents.[42] Synthesis of either *cis*-or *trans*-stilbene alone from the Wittig reaction can be of great value considering its high importance as stated

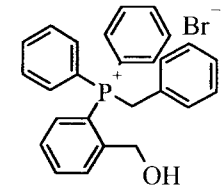
above. It's worthwhile to check the effect of *ortho* hetero atom substitution on one of the phenyl group attached to the phosphorous atom on the selectivity of stilbene synthesis. Extension began with preparation of two new phosphonium salts ("F" and "G") using similar chemistry described previously in order to prepare phosphonium salts "A" and "C". (Corresponding salt B is not prepared owing to its poor yields and has similar effects like salt C, in unstabilised ylides).



E



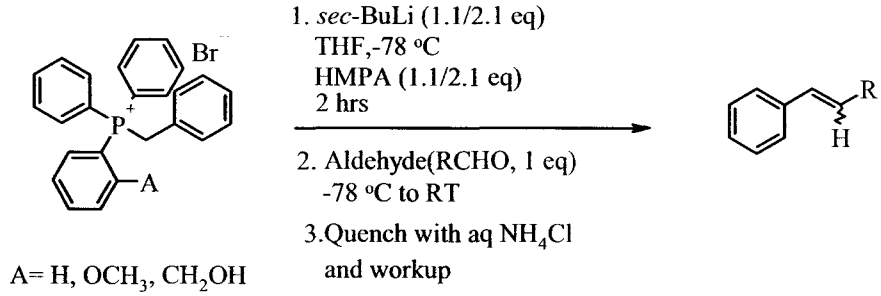
F



G

Figure 20: Modified semistabilized phosphonium salts.

The Wittig reactions of benzylidenetriphenylphosphorane with substituted benzaldehydes are well studied and are reported in huge numbers in literature. The *(Z)*: *(E)*-alkene ratios reported ranges from 68:32 to 47:53 with yields typically in 90's.[70] Our results for the Wittig reactions between modified semistabilised phosphonium salts with different aromatic aldehyde's are shown below. Once again the outcome was compared with control set of reaction carried out with parent phosphonium salt "E".

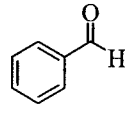
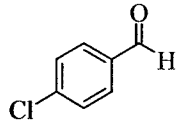
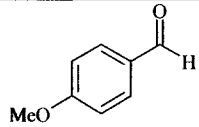
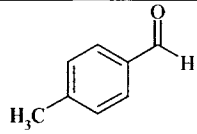
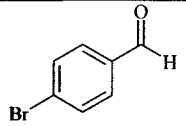


A= H, OCH_3, CH_2OH

Scheme 21: Standard reaction condition for phosphonium salts E, F and G.

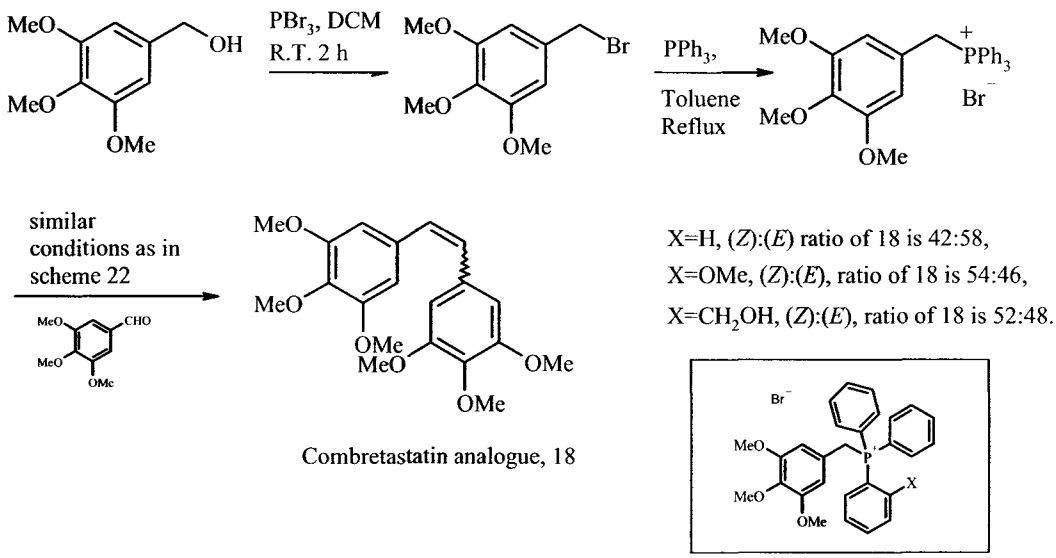
As in earlier case all the reactions were carried out using standard and constant conditions as depicted below. Our result for the control set of reaction with the phosphonium salt "E" is in agreement with the reported values from literature. The stereochemical outcome indicates formation of stilbenes was not specific.

Introduction of the ortho methoxy or benzyl alcohol group dramatically changed the stereochemical outcome of the reaction. When *sec*-BuLi was used as a base along with HMPA, slightly high *(Z)*:*(E)*-stilbene ratios (up to 75:25) were obtained with good yields (75-90%). Synthesis of a combretastatin analogue also showed similar result with slightly higher (*Z*):(*E*)-ratio, when the Wittig reaction was carried out with phosphonium salts "F" and "G".

Salt / Aldehyde	E	F	G
 1	50:50	74:26	73:27
 2	42:58	74:26	75:25
 3	54:46	63:37	60:40
 4	51:49	61:39	57:43
 5	46:54	59:41	56:44

[a] *(Z): (E)* ratios were determined on the isolated product using NMR-spectroscopy. [b] Yields are good ranging from 75-90% (isolated yields).

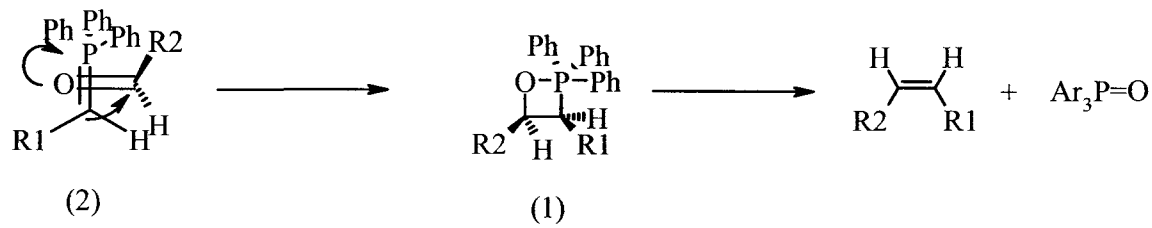
Table 7: The Wittig reactions of semistabilised ylides with aromatic aldehydes, (*Z*):(*E*)[a,b].



Combretastatin analogue, 18

Scheme 22: Synthesis of the combretastatin analogue.

This anomalous behavior can be explained on the basis of the relative stability of the OPA/intermediate at lower temperatures and the steric effects. Generally it has been observed that most OPA's derived from the moderated ylides rapidly decompose at -75 °C to afford olefin and the triphenylphosphine oxide while OPA's generated with the reactive ylides are stable up to at least -25 °C.[71] This means that the intermediate/OPA derived from the moderated ylides have little life time at -78 °C to have the required electronic effects to take place. Our results suggest that steric effects are dominant over the electronic effect and as an outcome of it higher proportion of the *(Z)*-olefin was obtained. It is clear from the results table that increases in steric crowding at phosphorus results in the increase in the *cis* stilbene. One possible explanation provided by the Allen and Ward is the involvement of the cycloaddition mechanism suggested by the Vedejs and Snoble; according to them any increase in steric crowding at phosphorus will favor transition state (2) in scheme 24, in which R_2 is directed away from the phosphorus substituents leading to 1,2 OPA (1) and hence *cis*-alkene.[72]



Scheme 23: Probable mechanism for the formation of *cis*-stilbenes.

Also, according to the recent literature it is widely accepted that semistabilised or unstabilsed ylides react via early transition state which is more reactant like and non planer with dominant 1, 3 interactions, favoring *cis* TS.[73]

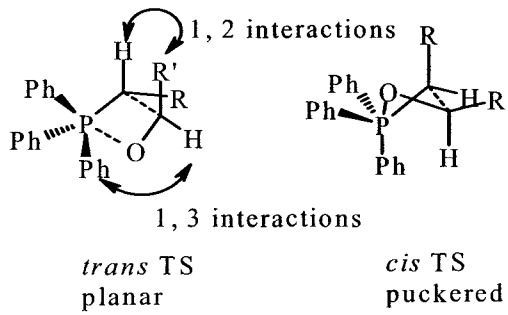


Figure 21: TS models used to account for (*E*):(*Z*) selectivity in semistabilised Wittig reactions.

However, having bulkier groups like OCH_3, CH_2OH on one of the phenyl groups attached to phosphorous atom favors even more *cis* TS resulting in more *cis*-stilbene formation over *trans* stilbene. These kinds of explanations do support the anomalous observation in case of the semistabilised ylides and hence the outcome.

CHAPTER 4: CONCLUSION

4.1 The SHOP ligand:

Synthesis of the SHOP ligand was achieved in different ways, the SHOP ligand can be synthesised with overall yield as high as 90% using directed *ortho* metalation approach. Although this approach requires two steps and subzero temperatures, it presents good overall yields and clean reaction at the outset. This chemistry holds a great deal of potential as an alternative method for the synthesis of the SHOP ligand at the process level. Further, one pot process was developed which was aimed at synthesising the SHOP ligand without column chromatography. The SHOP ligand was obtained in yields ranged from 58-60% using one pot process.

The SHOP ligand can be prepared using methyl 2-(diphenylphosphino)benzoate by D. Venkataraman and co-wokers protocol of CuI catalyzed formation of triarylphosphines. Hydrolysis of the methyl ester gave the SHOP ligand in excellant yield. The major advantage of this method lies in its palladium free approach also it does not require any of the costly ligands for synthesis. Further optimisation of the synthesis of the SHOP ligand using CuI alone is currently under investigation in our laboratories.

The Halogen-Magnesium Exchange reaction reported by Knochel and co-workers gave SHOP ligand in moderate yield (~40%), but it does provide us direct entry to the SHOP ligand from the 2-iodobenzoic acid. Further optimisation of synthesising the SHOP ligand using this novel double magnesiated species is currently underway in our laboratories.

Finally an effort towards synthesizing the SHOP and SHOP type ligand by diazonium salt approach was not successful. Generated diazonium salts from $NaNO_2$, HCl and water at 0 ^{o}C failed to gave direct substitution of the phosphorus coming from diethylphosphite or diphenylphosphine on the aryl carbon, instead addition on the electrophilic nitrogen gave us corresponding aryldiazo molecules in good yields. Never the less it is reported that these aryldiazophosphonates are promising compounds for polymers with application in excimer laser ablation litography.

4.2 The Wittig reaction:

The Wittig reaction of the modified phosphonium salts in which one of the phenyl rings attached to phosphorous was replaced by the *ortho* phenolic / benzyl alcohol / methoxy moiety showed remarkable enhancement in the production of *(E)*-olefins in case of unstabilized ylides. A mechanistic rationale was presented to explain these results.[62]

With the use of the phsphonium salt "B", having an ortho phenolic group attached to the phosphorous, we were successful in removing of the "toxic" and problematic phosphine oxide, employing a simple base extraction protocol.[62]

Extension of the work towards the moderated ylides showed an anomalous enhancement in the *(Z)*-olefins which can be explained based upon the involvement of steric effects at phosphorus. In all the reactions we were able to trap the reaction at betaine stage providing yet another proof of existence of betaines in the Wittig reactions.

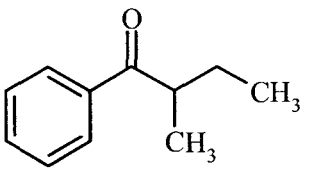
CHAPTER 5: EXPERIMENTAL

5.1 General Information:

All reactions were carried out under argon atmosphere in oven dried glassware. All the Wittig reactions and the DOM reactions were carried out at -78 °C unless specified. All the chemicals were obtained from Aldrich except chlorodiphenylphosphine, which was obtained from Cytec. THF was dried and distilled over sodium metal with benzophenone as indicator. Melting points were recorded in open capillary using Büchi melting point B540 apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel $60F_{254}$ (Merck) and was visualized under 254 nm UV light. HRMS (CI) were performed with a Micromass Q-T of Ultima spectrometer. ^{1}H, ^{13}C and ^{31}P spectra were recorded on a Bruker 200 or AV 600 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (*J*) are expressed in hertz (Hz).

2-methyl-1-phenylbutan-1-one (1)[15,16a]

Into a flame-dried flask, containing a magnetic stirring bar, was weighed *N,N*-dimethylbenzamide (100.0 mg, 0.670 mmol) under argon and anhydrous THF (2 mL) was added. The flask was stirred for 15 min at -78 °C whereupon *sec*-BuLi (0.574 mL, 0.804 mmol, 1.4 M solution in cyclohexane) was added drop wise followed by TMEDA (0.119 mL, 0.804 mmol). Resultant solution stirred at -78 °C for 30 min and then allowed to reach room temperature with continuous stirring. TLC of the reaction mixture showed complete consumption of the starting material. Reaction mixture was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate. The organic phase was washed with water followed by brine, dried over sodium sulphate and the solvent removed *in vacuo*. Purification through chromatography using hexane and ethyl acetate as solvent gave 2-methyl-1-phenylbutan-1-one (1) as oil in 65-78% yield.



1

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.95 (2H, m), 7.51 (3H, m), 3.90 (1H, m), 1.82, 1.51 (2H, 2m), 1.15 (3H, d, J = 6.9 Hz), 0.90 (3H, t, J = 7.4 Hz).

N,N-diisopropyl-2-(diphenylphosphino)benzamide (2)

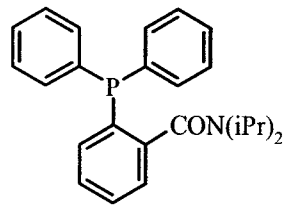
Procedure with the use of TMEDA:

Into a flame-dried flask, containing a magnetic stirring bar, was weighed *N, N*-diisopropylbenzamide (100.0 mg, 0.487 mmol) under argon and anhydrous THF (2 mL) was added. The flask was stirred for 15 min at -78 °C whereupon *sec*-BuLi (0.417 mL, 0.584 mmol, 1.4 M solution in cyclohexane) was added drop wise followed by TMEDA (88 μL, 0.584 mmol). Resultant solution stirred at -78 °C for 30 min. Chlorodiphenylphosphine (90 μL, 0.487 mmol) was added drop wise at -78 °C. Reaction mixture stirred for additional 1 h at -78 °C then allowed to reach room temperature with continuous stirring. Reaction mixture was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate. The organic phase was washed with water followed by brine, dried over sodium sulphate and the solvent removed *in vacuo*. Purification through column chromatography using hexane and ethyl acetate as solvent gave *N,N*-diisopropyl-2-(diphenylphosphino)benzamide (2) as a white solid in 91% yield.

Or, Procedure without use of TMEDA:

Into a flame-dried flask, containing a magnetic stirring bar, was weighed *N, N*-diisopropylbenzamide (100.0 mg, 0.487 mmol) under argon and anhydrous THF (2.0 mL) was added. The flask was stirred for 15 min at -78 °C whereupon *sec*-BuLi (0.417 mL, 0.584 mmol, 1.4 M solution in cyclohexane) was added drop wise. Resultant solution stirred at -78 °C for 30 min. Chlorodiphenylphosphine (90.0 μL, 0.487 mmol) was added drop wise at -78 °C. Reaction mixture stirred for additional 1 h at -78 °C then

allowed to reach room temperature with continuous stirring. Reaction mixture was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate (3 X 15 mL). The organic phase was washed with water followed by brine, dried over sodium sulphate and the solvent removed *in vacuo*. Purification through chromatography gave *N, N*-diisopropyl-2-(diphenylphosphino) benzamide (2) as a white solid in 68% yield.

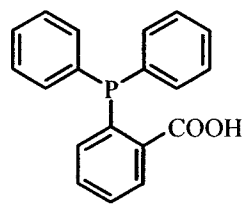


2

White soild, (91% yield, M.P. 95-97 °C);
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (m, 6H), 1.59 (d, 6H), 3.51 (m, 1H), 3.71 (d, 1H), 7.13-7.43 (m, 14H);
^{13}C NMR (200 MHz, $CDCl_3$): δ 20.44, 20.78, 20.86, 45.96, 51.10, 125.18, 125.24, 125.70, 128.29, 128.46, 128.56, 129.28, 133.44, 133.56, 133.77, 134.10, 134.21, 134.98, 137.13, 137.68, 145.65, 145.89, 169.99;
^{31}P (80 MHz, $CDCl_3$): δ -14.13;
HRMS (M^+) calcd. For $C_{25}H_{28}NOP$: 389.1894, found 389.1909.

2-(diphenylphosphino)benzoic acid (3)[13,14]

A mixture of (100.0 mg, 0.257 mmol) of *N, N*-diisopropyl-2-(diphenylphosphino) benzamide (2) and 2.0 mL of a 48% HBr solution in a sealed microwave vial was heated for 20 min/ 185 °C in the microwave oven. Then the solution was cooled and neutralised with saturated sodium bicarbonate solution. The acid was extracted with ethyl acetate (3 X 15 mL), and the extracts dried over anhydrous sodium sulphate and evaporated *in vacuo* to give 2-(diphenylphosphino) benzoic acid (3) in 85% yield as a white solid.



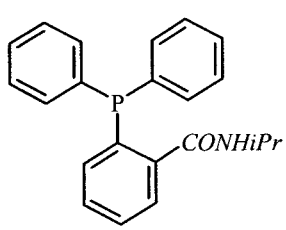
3

White solid, (85-95% yield, M.P. 172-174 °C, Lit. M.P 165-167 °C);
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.00 (m, 1H), 7.30-7.45 (m, 12H), 8.19 (m, 1H);
^{13}C NMR (200 MHz, $CDCl_3$): δ 128.35, 128.59, 128.63, 128.80, 131.82, 132.79, 134.08, 134.22, 134.44, 137.81, 137.88, 141.99, 142.17, 171.03;
^{31}P (80 MHz, $CDCl_3$): δ -4.26;
HRMS (M^+) calcd. For $C_{19}H_{15}O_2P$: 306.0828, found 306.0810.

One pot procedure for making the SHOP ligand (3)

Into a flame-dried flask, containing a magnetic stirring bar, was weighed *N,N*-diisopropylbenzamide (100.0 mg, 0.487 mmol) under argon and anhydrous THF (2.0 mL) was added. The flask was stirred for 15 min at -78 °C whereupon *sec*-BuLi (0.417 mL, 0.584 mmol, 1.4 M solution in cyclohexane) was added drop wise followed by TMEDA (88.0 μL, 0.584 mmol). Resultant solution stirred at -78 °C for 30 min. Chlorodiphenylphosphine (90.0 μl, 0.487 mmol) was added drop wise at -78 °C. Reaction mixture stirred for additional 1 h at -78 °C then allowed to reach room temperature with continuous stirring for another 3 h. THF and volatile impurities are removed *in vacuo*. Resultant crude material was dissolved in 2.0 mL of 48% HBr solution. The mixture was sealed in a microwave vial and was heated for 20 min/ 185 °C in the microwave oven. The acid was extracted with ethyl acetate (3 X 15 mL), and the extracts dried over anhydrous sodium sulphate and evaporated *in vacuo* to give 2-(diphenylphosphino) benzoic acid (3) in 58% yield after crystallisation using ethyl acetate (5%) and hexane (95%) as solvents.

N-isopropyl-2-(diphenylphosphino)benzamide (4)[18c]



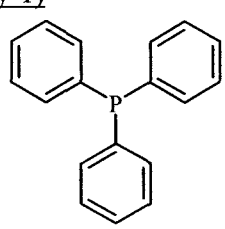
4

White solid, (85-95% yield, M.P. 176 °C; Lit M.P. 177 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.57-7.63 (1H, m), 7.27-7.45 (12H, m), 6.88-6.93 (1H, m), 5.71 (1H, bs), 4.01-4.32 (1H, m), 1.03 (3H, s), 1.0 (3H, s).

Typical procedure for Copper iodide (CuI) catalysed formation of Triarylphosphines[24]

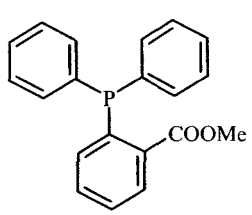
In an 50 mL flame dried pear shaped schlenk flask equipped with a magnetic stir, rubber septum and an argon inlet, cesium carbonate (3.00 mmol) and CuI (10 mol% with respect to diphenylphosphine) were charged and sealed with a rubber septum, toluene (5.0 mL), the aryl halide (2.40 mmol), and diphenylphosphine (2.00 mmol) were injected into the tube through the septum. The rubber septum was replaced with the dry argon flushed reflux condenser. The reaction mixture was then heated at 110 °C for 24 h. The reaction mixture was then cooled to room temperature and filtered with dichloromethane to remove any insoluble residues. The filtrate was concentrated *in vacuo*; the residue was purified by flash chromatography on silica gel to obtain the pure triarylphosphine.

Triphenylphosphine: (Table 3, Entry 1)[24]



White solid, (80% yield);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.33-7.25 (m, 15 H).

Methyl 2-(diphenylphosphino)benzoate: (Table 3, Entry 3 and 4)[74]



White solid, (60% yield, M.P. 97.5-99 °C, Lit. M.P. 96 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 8.10-8.12 (1H, m), 7.32-7.37 (12H, m), 6.96-6.99 (1H, m), 3.78 (3H, s);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -4.41.

Hydrolysis of Methyl 2-(diphenylphosphino)benzoate

A mixture of methyl 2-(diphenylphosphino)benzoate (100.0 mg, 0.312 mmol), lithium hydroxide (0.150 g, 6.243 mol) was suspended in THF-water (2 mL, 1:1) at room

temperature. The resultant mixture was refluxed at 70 °C for overnight. After being cooled to room temperature, the reaction mixture was extracted with ethyl acetate and poured in to saturated citric acid solution. The acid was extracted with ethyl acetate (2 X 15 mL), and the extracts dried over anhydrous sodium sulphate and evaporated *in vacuo* to give (3) 2-(diphenylphosphino) benzoic acid (100%) as white solid.

General procedure for the Halogen-Magnesium exchange reaction[25]

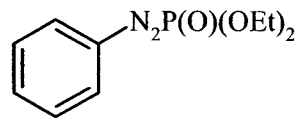
The 2-iodobenzoic acid (2.00 mmol) was placed in a dry and argon-flushed Schlenk tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for 5 min at room temperature., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. The mixture was stirred at -20 °C for further 30 min. *i*-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was then added slowly and the resulting mixture was allowed to warm up to room temperature. After 45 min the resulting slurry was cooled to -20 °C and the chlorodiphenylphopshine (2.00 mmol) was added, reaction mixture was allowed to warm up to room temperature. After the completion of the reaction, the mixture was quenched with saturated NH_4Cl. The clear solution was extracted with dichloromethane (3 X 15 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4. Dichloromethane was removed on rotary evaporator leaving a crude product which was purified with column chromatography to give the SHOP ligand in 40% yield as white solid.

General procedure for diazotisation

Sodium nitrite (0.960 mmol) in 0.40 mL of water was added drop wise to a stirred solution containing (0.800 mmol) of corresponding aniline and 0.100 mL of concentrated hydrochloric acid in 1.00 mL of water cooled in an ice bath, while the temperature was maintained below 5 °C. The solution of the resulting diazonium salt was stirred for 20 min while a solution of basic solution of diethyl phosphite was prepared (diethylphosphite 8.00 mmol/8.00 mmol of KOH aq.). This solution was cooled to 0 °C. The pH of the diazonium salt solution was adjusted to 6.0 with solid sodium acetate and

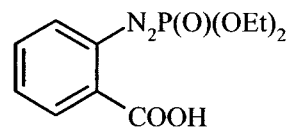
this was then added dropwise to the diethylphosphite solution. The resulting mixture was stirred for 20 min at room temperature, then slowly warmed to 90 °C, cooled to room temperature and the filtrate was acidified with concentrated hydrochloric acid, to give dark red solution floating. The red solution was extracted with ethyl acetate (3 X 15 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4. Dichloromethane was removed on rotary evaporator leaving a crude product which was purified with column chromatography to give corresponding arylazaphosphonate in good yields as red oil.

Table 4, Entry 1[29]



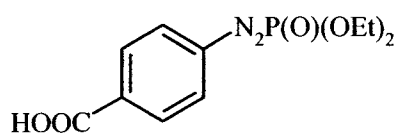
Red oil;
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.91-7.96 (2H, m), 7.48-7.60 (3H, m), 4.28-4.45 (4H, m), 1.38-1.45 (6H, t);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -0.52;
HRMS $(M)^+$ calcd. for: $C_{10}H_{15}N_2O_3P$: 243.0213, found 243.0214.

Table 4, Entry 2[29]



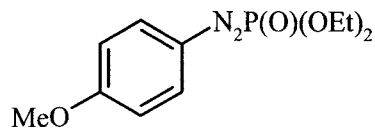
Red oil;
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 8.45 (1H, d, J = 7.6 Hz), 7.66-7.88 (3H, m), 4.36-4.51 (4H, m), 1.42-1.49 (6H, t);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -1.15;
HRMS $(M)^-$ calcd. for: $C_{11}H_{15}N_2O_5P$: 285.0634, found: 285.0632.

Table 4, Entry 3[29]



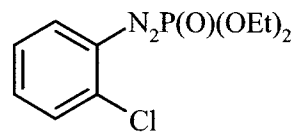
Red oil;
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 8.27 (2H, d, J = 8.6 Hz), 7.99 (2H, d, J = 8.4 Hz), 4.36-4.50 (4H, m), 1.41-1.48 (6H, t);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -1.24;
HRMS $(M)^-$ calcd. for: $C_{11}H_{15}N_2O_5P$: 285.0634, found: 285.0637.

Table 4, Entry 4[29]



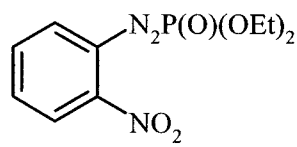
Red oil;
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.94 (2H, d, J = 8.6 Hz), 6.99 (2H, d, J = 8.6 Hz), 4.26-4.41 (4H, m), 3.89 (3H, s), 1.36-1.43 (6H, t);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): 0.46;
HRMS $(M)^+$ calcd. for: $C_{11}H_{17}N_2O_4P$: 273.1003, found: 273.1004.

Table 4. Entry 5[29]



Red oil;
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.47-7.63 (3H, m), 7.26-7.36 (1H, m), 4.34-4.46 (4H, m), 1.40-1.47 (3H, t);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -0.90;
HRMS $(M)^+$ calcd. for: $C_{10}H_{14}ClN_2O_3P$: 277.0519, found: 277.0518.

Table 4, Entry 6[29]

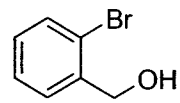


Red oil;
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 8.40 (2H, d, J = 8.8 Hz), 8.06 (2H, d, J = 9 Hz), 4.33-4.95 (4H, m), 1.40-1.47 (6H, t);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -1.50;
HRMS $(M)^+$ calcd. for: $C_{10}H_{14}N_3O_5P$: 288.0741, found: 288.0749.

Preparation of (2-Bromo-phenyl)-methanol (6)[57,75]

Finely powdered sodium borohydride (103.0 mg, 2.79 mmol) was suspended in THF (4.0 mL) with the 2-bromo-benzoic acid methyl ester (100.0 mg, 0.465 mmol). The resulting mixture was stirred for 15 min at 65 °C. Methanol (2.0 mL) was then added drop wise during 0.1 h and effervescence was observed. Stirring at 65 °C was maintained during a further period of 6 h. The reaction was cooled to room temperature, and quenched with saturated aq. NH_4Cl (5.0 mL). Stirring was then continued for 1 h. The

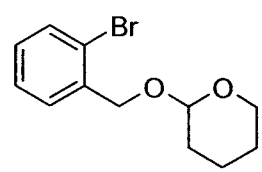
organic layer was separated and the aqueous phase extracted with ethyl acetate (2 X 20 ml). The combined extracts and organic phase were dried over Na_2SO_4 and concentrated to give (2-bromo-phenyl)-methanol (80.0 mg) in 93% yield as white solid.



White solid, (93% yield, M.P. 78 °C, Lit. M.P. 78-80 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.08-7.60 (4H, m, ArH), 4.73 (2H, s), 2.14 (1H, s, -OH).

Preparation of 2-(2-bromobenzyloxy)-tetrahydro-*2H*-pyran (7)[76]

3, 4-Dihydropyran (53.0 mg, 0.641 mmol) was added to a clear solution of (2-bromo-phenyl)-methanol (100 mg, 0.534 mmol) in dichloromethane (4.0 mL). To the resulting solution PTSA (20 mol %) was added slowly and stirred at room temperature for 2 h. The mixture was partitioned between dichloromethane (10.0 mL) and water (5.0 mL). The aqueous layer was further extracted with dichloromethane (10.0 mL) and the organic extracts combined, washed sequentially with water (5.0 mL) and brine (5.0 mL), dried over Na_2SO_4, evaporated *in vacuo* and purified by column chromatography on silica, eluting with dichloromethane to give 2-(2-bromobenzyloxy)-tetrahydro-*2H*-pyran (130 mg, 90%) as colourless oil.

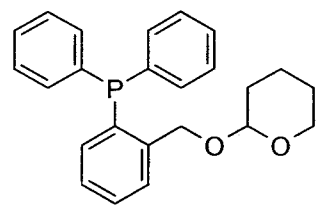


Colourless oil, (90% yield);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.45-7.57 (2H, m, ArH), 7.21-7.36 (1H , m, ArH), 7.04-7.19 (1H, m, ArH), 4.70-4.88 (2H, m), 4.50-4.63 (1H, m), 3.80-4.00 (1H, m), 3.48-3.63 (1H, m), 1.52-1.94 (6H, m).

Preparation of Diphenyl(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)phosphine (8)

To a clear solution of 2-(2-bromobenzyloxy)-tetrahydro-*2H*-pyran (100.0 mg, 0.369 mmol) in THF (5.0 mL) was added *n*-BuLi (0.480 mL, 0.774 mmol, 1.6 M in hexanes) at -78 °C under nitrogen. Resulting solution was stirred at -78 °C for 0.1 h. A

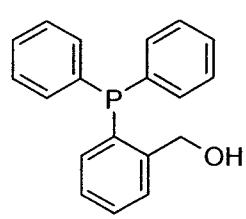
solution of chlorodiphenylphosphine (67.0 μL, 0.369 mmol) in THF (2.0 mL) was added at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Water was added to quench the reaction and the mixture was extracted with ether (3 X 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica to get (83.0 mg, 60%) of diphenyl(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)phosphine as a colourless oil.



Colourless oil, (60% yield);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.49-7.62 (1H, m, ArH), 7.13-7.44 (12H, m, ArH), 6.84-6.97 (1H, m, ArH), 4.89-5.01 (1H, m), 4.53-4.84 (2H, m), 3.75-3.91 (1H, m), 3.39-3.60 (1H, m), 1.19-1.92 (6H, m);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -16.09.

Preparation (2-(diphenylphosphino)phenyl)methanol (9)[77]

To a clear solution of diphenyl(2-((tetrahydro-2H-pyran-2-yloxy)methyl)phenyl)phosphine (100.0 mg, 0.265 mmol) in methanol (5.0 mL) was added PTSA (20 mol %) at room temperature. The resultant mixture was stirred for 2 h. Methanol was evaporated. The crude residue was extracted with ethyl acetate (3 X 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica gel to get 76.0 mg, 98%) (2-(diphenylphosphino)phenyl)methanol as a colourless oil.

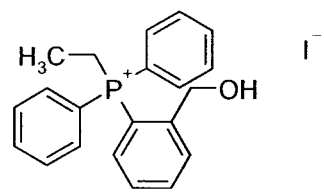


Colourless oil, (98% yield);

^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.46-7.57 (1H, m, ArH), 7.14-7.39 (12H, m, ArH), 6.83-6.95 (1H, m, ArH), 4.82 (1H, s), 2.04(1H, bs, -OH);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -16.29.

Preparation of Ethyl-(2-hydroxymethyl-phenyl)-diphenyl-phosphonium iodide (10)

To a clear solution of 2-(diphenylphosphino)phenyl)methanol (100.0 mg, 0.342 mmol) in acetonitrile (4.0 mL) was added ethyl iodide (56.0 μL, 0.684 mmol). The resultant reaction mixture refluxed at 85 °C overnight. A white precipitate had formed. The precipitate was filtered off, washed with diethyl ether (3 X 10 mL) and dried to give ethyl-(2-hydroxymethyl-phenyl)-diphenyl-phosphonium iodide (135 mg, 88%) as off white solid.

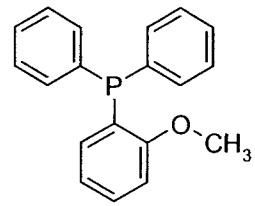


White solid; (88% yield, M.P. 135-137 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.60-7.75 (12H, m, ArH), 7.41-7.43 (1H, m, ArH), 7.29-7.33 (1H, m, ArH), 4.71 (2H, d, J_{PC} = 27.6 Hz), 3.61 (2H, dq, J = 7.2 Hz), 1.36 (3H, td, J = 7.2 Hz, J_{PC} = 21 Hz);
^{13}C NMR (600 HMz, $CDCl_3$); δ (ppm): 148.03 (d, J_{PC} = 30.6 Hz), 136.28 (d, J_{PC} = 42.6 Hz), 135.24, 134.43, 133.05 (d, J_{PC} = 36.3 Hz), 131.59 (d, J_{PC} = 44.4 Hz), 130.37 (d, J_{PC} = 49.2 Hz), 128.40 (d, J_{PC} = 51 Hz), 120.94 (d, J_{PC} = 343.8 Hz), 115.97 (d, J_{PC} = 336.6 Hz), 62.97, 19.13 (d, J_{PC} = 213 Hz), 8.54 (d, J_{PC} = 20.4 Hz);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): 29.48;
HRMS $(M)^+$ calcd. for $C_{21}H_{22}OP$: 320.1339, found 320.1330.

Preparation of (2-methoxyphenyl)diphenylphosphine (12)[24]

To a clear solution 1-iodo-2-methoxybenzene (100.0 mg, 0.427 mmol) in THF (2.0 mL) was added *n*-BuLi (0.530 mL, 0.854 mmol, 1.6 M in hexanes) at -78 °C under nitrogen. The resulting solution was stirred at -78 °C for 1 h. A solution of chlorodiphenylphosphine (76.0 μL, 0.427 mmol) in THF (2.0 mL) was added at -78 °C. Then the mixture was allowed to warm to room temperature and stirred for additional 3 h. Water was added to quench the reaction and the mixture was extracted with diethyl ether (3 X 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4

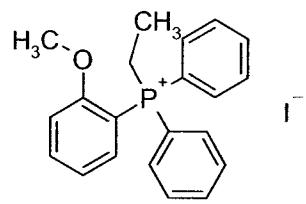
and concentrated. The resulting residue was purified by column chromatography on silica gel to obtain (74.0 mg, 60%) (2-methoxyphenyl)diphenylphosphine as crystalline white solid.



White solid, (60% yield, M.P. 120-122 °C, Lit. M.P. 124-126 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 6.40-7.40 (14H, m, ArH), 3.65 (3H, s, OMe);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -16.74.

Preparation of Ethyl-(2-methoxy-phenyl)-diphenyl-phosphonium iodide (13)

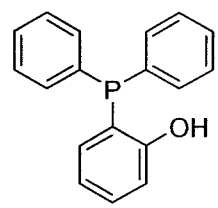
To a clear solution of (2-methoxyphenyl)diphenylphosphine (100.0 mg, 0.342 mmol) in acetonitrile (2.0 mL) was added ethyl iodide (54.0 µL, 0.684 mmol). The resultant reaction mixture refluxed at 85 °C overnight. A white precipitate had formed. The precipitate was filtered off, washed with diethyl ether (3 X 15 mL) and dried to give ethyl-(2-methoxy-phenyl)-diphenyl-phosphonium iodide (137 mg, 90%) as white solid.



White solid, (90 % yield, M.P. 163-165 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.66-7.82 (11H, m, ArH), 7.40-7.44 (1H, m, ArH), 7.18-7.20 (1H, m, ArH), 7.22-7.26 (1H, m, ArH), 3.79 (3H, s, OMe), 3.57 (2H, dq, J = 7.2 Hz), 1.35 (3H, td, J = 7.2 Hz, J_{PC} = 20.4 Hz);
^{13}C-NMR (600 MHz, $CDCl_3$); δ (ppm): 162.10, 138.14, 135.84 (d, J_{PC} = 31.2 Hz), 134.76, 133.34 (d, J_{PC} = 39.6 Hz), 130.39 (d, J_{PC} = 50.4 Hz), 122.91 (d, J_{PC} = 49.8 Hz), 118.67 (d, J_{PC} = 349.8 Hz), 112.97 (d, J_{PC} = 25.2 Hz), 105.53 (d, J_{PC} = 354 Hz), 56.84, 18.31 (d, J_{PC} = 211.2), 7.77 (d, J_{PC} = 18.6 Hz);
^{31}P –NMR (80 MHz, $CDCl_3$); δ (ppm): 25.90;
HRMS $(M)^+$ calcd. for $C_{21}H_{22}OP$: 320.1330, found: 320.1330.

Preparation of 2-(diphenylphosphino)phenol (14)[78]

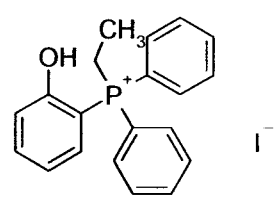
Mixture of 57% hydriodic acid (0.130 mL, 1.712 mmol) and (2-methoxyphenyl)diphenylphosphine (100.0 mg, 0.342 mmol) was heated overnight at 100 °C then cooled to 0 °C. A saturated solution of sodium carbonate was carefully added until the solution was neutral. The resulting mixture was extracted with ethyl acetate (3 X 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated to give 2-(diphenylphosphino) phenol (28.0 mg, 30%) as a white solid.



White solid, (30% yield, M.P. 144-145 °C);
^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): 7.25-7.35 (11H, m, ArH), 6.84-7.08 (3H, m, ArH), 6.21 (1H, bs, OH);
^{31}P NMR (80 MHz, $CDCl_3$); δ (ppm): -29.05.

Preparation of Ethyl-(2-hydroxy-phenyl)-diphenyl-phosphonium iodide (15)

To a clear solution of 2-(diphenylphosphino) phenol (100.0 mg, 0.359 mmol) in acetonitrile (2.0 mL) was added ethyl iodide (57.0 μL, 0.719 mmol). The resultant reaction mixture refluxed at 85 °C overnight. A white precipitate had formed. The precipitate was filtered off, washed with diethyl ether (3 X 15 mL) and dried to yield ethyl-(2-hydroxy-phenyl)-diphenyl-phosphonium iodide (124.0 mg, 80%) as white solid.

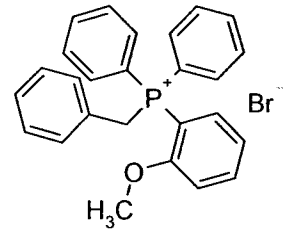


White solid, (80% yield, M.P. 169-171 °C);
^{1}H NMR (600 MHz, CDCl3); δ (ppm): 8.03 (1H, bs, OH), 7.54-7.77 (12H, m, ArH), 6.94-6.97 (1H, m, ArH), 6.87-6.91 (1H, m, ArH), 3.21 (2H, dq, J = 7.8 Hz), 1.34 (3H, td, J = 7.2 Hz, J_{PC} = 20.4 Hz);
^{13}C-NMR (600 MHz, $CDCl_3$); δ (ppm): 162.22, 137.62, 134.75, 134.09 (d, J_{PC} = 32.4 Hz), 133.28 (d, J_{PC} = 38.4 Hz), 130.33 (d, J_{PC} = 49.2 Hz), 120.91 (d, J_{PC} = 49.2 Hz),

119.32, 119.11 (d, J_{PC} = 26.4 Hz), 118.74, 18.03 (d, J_{PC} = 215.4 Hz), 7.74 (d, J_{PC} = 21 Hz);
^{31}P –NMR (80 MHz, $CDCl_3$); δ (ppm): 25.93;
HRMS (H)$^+$ calcd. for: $C_{20}H_{20}OP$): 307.1250, found: 307.1252.

Preparation of Benzyl-(2-methoxy-phenyl)-diphenyl-phosphonium bromide (16)

To a clear solution of (2-methoxyphenyl)diphenylphosphine (100.0 mg, 0.342 mmol) in acetonitrile (2.0 mL) was added ethyl iodide (54.0 µL, 0.684 mmol). The resultant reaction mixture refluxed at 85 °C overnight. A white precipitate had formed. The precipitate was filtered off, washed with diethyl ether (3 X 15 mL) and dried to give benzyl-(2-methoxy-phenyl)-diphenyl-phosphonium bromide (137.0 mg, 90%) as white solid.



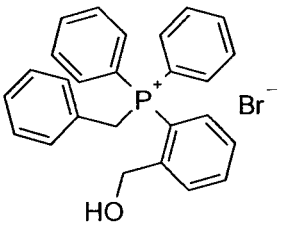
White soild, (90% yield, M.P. 218-220 °C);

^{1}H NMR (600 MHz, $CDCl_3$); δ (ppm): 7.82 (1H, m, ArH), 7.71 (2H, m, ArH), 7.78-7.57 (8H, m, ArH), 7.33 (1H, m, ArH), 7.27 (1H, m, ArH), 7.22 (1H, m, ArH), 7.17 (1H, m, ArH), 7.13 (2H, m, ArH), 7.01 (2H, m, ArH), 5.09 (2H, d, J_{PC} = 15 Hz), 3.79 (3H, s, OMe);
^{13}C-NMR (600 MHz, $CDCl_3$); δ (ppm): 162.08, 138.29, 136.25 (d, J_{PC} = 29.4 Hz), 134.76, 134.52 (d, J_{PC} = 38.4 Hz), 131.25 (d, J_{PC} = 21.6 Hz), 129.94 (d, J_{PC} = 49.8 Hz), 129.03, 128.55, 127.84 (d, J_{PC} = 32.4 Hz), 122.83 (d, J_{PC} = 49.8 Hz), 117.76 (d, J_{PC} = 349.2 Hz), 113.17 (d, J_{PC} = 24 Hz), 105.54 (d, J_{PC} = 348.8 Hz), 56.73, 31.08 (d, J_{PC} = 193.8 Hz);
^{31}P-NMR (80 MHz, $CDCl_3$); δ (ppm): 27.71;
HRMS (M)$^+$ calcd. for $C_{26}H_{24}OP$): 382.1467, found: 382.1487.

Preparation of Benzyl-(2-hydroxymethyl-phenyl)-diphenyl-phosphonium bromide (17)

To a clear solution of 2-(diphenylphosphino)phenyl)methanol (100.0 mg, 0.342 mmol) in acetonitrile (4.0 mL) was added ethyl iodide (56.0 µL, 0.684 mmol). The

resultant reaction mixture refluxed at 85 °C overnight. A white precipitate had formed. The precipitate was filtered off, washed with diethyl ether (3 X 15 mL) and dried to give benzyl-(2-hydroxymethyl-phenyl)-diphenyl-phosphonium bromide (135.0 mg, 88%) as off white solid.



White solid, (88% yield, M.P.186-188 °C);
^{1}H NMR (600 MHz, CDCl3); δ (ppm): 6.90-7.90 (19H, m, ArH), 5.09 (2H, d, J_{PC} = 15 Hz), 4.77 (2H, s);
^{13}C-NMR (600 MHz, $CDCl_3$); δ (ppm): 148.43, 136.32 (d, J_{PC} = 41.4 Hz), 135.21, 134.41, 134.02 (d, J_{PC} = 36.6 Hz), 131.97 (d, J_{PC} = 44.4 Hz), 131.50 (d, J_{PC} = 22.8 Hz), 129.87 (d, J_{PC} = 49.2 Hz), 129.03, 128.57, 128.17 (d, J_{PC} = 50.4 Hz), 127.92 (d, J_{PC} = 34.2 Hz), 120.12 (d, J_{PC} = 342.6 Hz), 116.08 (d, J_{PC} = 330 Hz), 62.94, 32.39 (d, J_{PC} = 193.8 Hz);
^{31}P-NMR (80 MHz, $CDCl_3$); δ (ppm): 25.10;
HRMS $(M)^+$ calcd. for $C_{26}H_{24}OP$: 382.1487, found: 382.1488.

Typical procedure for the Wittig reaction with phosphonium salts A and D:[62]

Phosphonium salt A or D (0.500 mmol), in a 25 mL flame-dried flask equipped with magnetic stir bar, rubber septum and an argon inlet, was suspended in anhydrous THF (2.0 mL), and the suspension was cooled to -78 °C. *Sec*-BuLi (0.550 mmol, 1.4 M in pentane) was added to the reaction mixture to yield a red solution. After 15 min, HMPA (0.550 mmol) was added to the reaction mixture at -78 °C. After 2 h, the corresponding aldehyde (0.500 mmol) was slowly added to the flask at -78 °C. The reaction mixture was stirred for 2 h at -78 °C, and then gradually warmed to room temperature and stirred for an additional 3 h. TLC analysis of the reaction mixture showed complete consumption of the aldehyde. The reaction mixture was quenched with saturated NH_4Cl solution. The clear solution was extracted with (2 X 20 mL) dichloromethane. The combined organic fractions were washed with brine and dried over Na_2SO_4. Dichloromethane was removed

on a rotary evaporator leaving an oily residue which was purified by column chromatography (10:90 ethyl acetate/hexane) to give the alkene as an oil.

Typical procedure for the Wittig reaction with phosphonium salts B and C:[62]

Phosphonium salt B or C (0.500 mmol) was suspended in anhydrous THF (2.00 mL) in a 25 mL flame-dried flask equipped with magnetic stir bar, rubber septum, and an argon inlet, and the suspension was cooled to -78 °C. *Sec*-BuLi (1.050 mmol, 1.4 M in pentane) was added to the reaction mixture to yield a red solution. After 15 min, HMPA (1.050 mmol) was added to the reaction mixture at -78 °C. After 2 h, the corresponding aldehyde (0.500 mmol) was slowly added to the flask at -78 °C and the reaction mixture was stirred for 2 h at -78 °C, and then gradually warmed to room temperature and stirred for an additional 3 h. TLC analysis of the reaction mixture showed complete consumption of the aldehyde. The reaction mixture was quenched with saturated NH_4Cl solution. The clear solution was extracted with (2 X 20 mL) dichloromethane. The combined organic fractions were washed with brine and dried over Na_2SO_4. Dichloromethane was removed on a rotary evaporator leaving an oily residue which was purified by column chromatography (10:90 ethyl acetate/hexane) to give the alkene as an oil.

General protocol for removal of phosphine oxide:[62]

After complete consumption of the corresponding aldehyde in the Wittig reaction employing phosphonium salt "B", the reaction mixture was quenched with saturated NH_4Cl. The reaction mixture containing required olefin and the phosphine oxide by product was partitioned between dichloromethane, and washed successively with (2 X 10 mL) 10% NaOH solution to remove the phhosphine oxide from the reaction mixture.

General procedure for the phosphonium salt "F"

Phosphonium salt F (0.500 mmol), in a 25 mL flame-dried flask equipped with magnetic stir bar, rubber septum and an argon inlet, was suspended in anhydrous THF (2.0 mL), and the suspension was cooled to -78 °C. *Sec*-BuLi (0.550 mmol, 1.4 M in

pentane) was added to the reaction mixture to yield a red solution. After 15 min, HMPA (0.550 mmol) was added to the reaction mixture at -78 °C. After 2 h, the corresponding aldehyde (0.500 mmol) was slowly added to the flask at -78 °C. The reaction mixture was stirred for 2 h at -78 °C, and then gradually warmed to room temperature and stirred for an additional 3 h. TLC analysis of the reaction mixture showed complete consumption of the aldehyde. The reaction mixture was quenched with saturated NH_4Cl solution. The clear solution was extracted with (2 X 20 mL) dichloromethane. The combined organic fractions were washed with brine and dried over Na_2SO_4. Dichloromethane was removed on a rotary evaporator leaving an oily residue which was purified by column chromatography (10:90 ethyl acetate/hexane) to give the stilbene as a solid.

General procedure for the phosphonium salt "G"

Phosphonium salt G (0.500 mmol) was suspended in anhydrous THF (2.00 mL) in a 25 mL flame-dried flask equipped with magnetic stir bar, rubber septum, and an argon inlet, and the suspension was cooled to -78 °C. *sec*-BuLi (1.050 mmol, 1.4 M in pentane) was added to the reaction mixture to yield a red solution. After 15 min, HMPA (1.050 mmol) was added to the reaction mixture at -78 °C. After 2 h, the corresponding aldehyde (0.500 mmol) was slowly added to the flask at -78 °C and the reaction mixture was stirred for 2 h at -78 °C, and then gradually warmed to room temperature and stirred for an additional 3 h. TLC analysis of the reaction mixture showed complete consumption of the aldehyde. The reaction mixture was quenched with saturated NH_4Cl solution. The clear solution was extracted with (2 X 20 mL) dichloromethane. The combined organic fractions were washed with brine and dried over Na_2SO_4. Dichloromethane was removed on a rotary evaporator leaving an oily residue which was purified by column chromatography (10:90 ethyl acetate/hexane) to give the stilbene as a solid.

NMR data for olefins (Table 6: Entry 1-8: ^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): as a mixture of (*Z*)- and (*E*)-isomers,

Table 6, Entry 1
1-(3',4'-Dimethoxyphenyl)prop-1-ene:[54]

δ 6.85-6.93 (3H, m, ArH), 6.34-6.45 (1H_a, br, J = 15.60 Hz, CH_a=CH_bMe), 6.13 (1H_b, dq, J = 6.60 Hz, J = 15.60 Hz, *E* isomer), 5.76 (1H_b, dq, J = 7.2 Hz, J = 11.6 Hz, *Z* isomer), 3.93 (3H, s, OMe, *Z* isomer), 3.91 (3H, s, OMe, *E* isomer), 1.93 (3H, d, J = 7.2 Hz, *Z* isomer and J = 6.6 Hz, *E* isomer)

Table 6, Entry 2
1-(3',5'-Dimethoxyphenyl)prop-1-ene:[79]
δ 6.41-6.54 (3H, m, ArH), 6.40 (1Ha, br, J = 15.60 Hz, CH_a=CH_bMe), 6.31 (1H_b, dq, J = 6.0 Hz, J = 15.60 Hz, *E* isomer), 5.83 (1H_b, dq, J = 7.2 Hz, J = 11.5 Hz, *Z* isomer), 3.40 (6H, OMe), 1.94 (3H, d, J = 7.2 Hz, *Z* isomer and J = 6.0 Hz, *E* isomer).

Table 6, Entry 3
1-(4'-Chlorophenyl)prop-1-ene:[62]
δ 7.29 (2H, d, J = 8.74 Hz, ArH), 7.21 (2H, d, J = 8.52 Hz, ArH), 6.30–6.43 (1H_a, m, J = 16.37 Hz, CH_a=CH_bMe), 6.19 (1H_b, dq, J = 6.12 Hz, J = 15.76 Hz, *E*-isomer), 5.80 (1H*b*, dq, J = 7.18 Hz, J = 11.53 Hz, *Z*-isomer), 1.87 (3H, d, J = 7.2 Hz, *Z*-isomer and J = 6.12 Hz, *E* isomer).

Table 6, Entry 4
1-(4'-Methoxyphenyl)prop-1-ene:[62]
δ 7.26 (2H, d, J = 8.7 Hz, ArH), 6.83 (2H, d, J = 8.7 Hz, ArH), 6.34 (1H_a, m, J = 15.86 Hz, CH_a=CH_bMe), 6.08 (1H_b, dq, J = 6.44 Hz, J = 15.66 Hz, *E*-isomer), 5.70 (1H_b, dq, J = 7.04 Hz, J = 11.37 Hz, *Z*-isomer), 3.81 (3H, s, OMe, *Z*-isomer), 3.79 (3H, s, OMe, *E*-isomer), 1.89 (3H, d, J = 7.04 Hz, *Z*-isomer), 1.85 (3H, d, J = 6.46 Hz, *E*-isomer).

Table 6, Entry 5
1-(3'-Methoxyphenyl)prop-1-ene:[62]
δ 7.16–7.29 (1H, m, ArH), 6.83–6.96 (2H, m, ArH), 6.71–6.80 (1H, m, ArH), 6.33–6.45 (1H_a, m, J = 16.73 Hz, CH_a=CH_bMe), 6.22 (1H_b, dq, J = 6.1 Hz, J = 15.82 Hz, *E*-isomer), 5.79 (1H_a, dq, J = 7.21 Hz, J = 11.60 Hz, *Z*-isomer), 3.81 (3H, s, OMe, *Z*-isomer), 3.80 (3H, s, OMe, *E*-isomer), 1.90 (3H, d, J = 7.21 Hz, Z-isomer), 1.87 (3H, d, J = 6.1 Hz, *E* isomer).

Table 6, Entry 6
1-(3',4'-Dioxymethylenephenyl)prop-1-ene:[62]
δ 6.69–6.90 (3H, m, ArH), 6.31 (1H_a, m, J = 15.75 Hz, CH_a=CH_bMe), 6.05 (1H_b, dq, J = 6.47 Hz, J = 15.65 Hz, *E*-isomer), 5.69 (1H_b, dq, J = 7.12 Hz, J = 11.54 Hz, *Z*-isomer), 5.94 (2H, s, –OCH_2O–, *Z*-isomer), 5.92 (2H, s, –OCH_2O–, *E*-isomer), 1.87 (3H, d, J = 7.12 Hz, *Z*-isomer), 1.84 (3H, d, J = 6.47 Hz, *E*-isomer).

Table 6, Entry 7
1-(3',4', 5'-Trimethoxyphenyl)prop-1-ene:[54]

δ 6.58 (2H, m, ArH), 6.33-6.44 (1Ha, br, J = 15.60 Hz, CH_a=CH_bMe), 6.18 (1H_b, dq, J = 6.0 Hz, J = 15.60 Hz, *E* isomer), 5.80 (1H_b, dq, J = 7.2 Hz, J = 11.60 Hz, *Z* isomer), 3.87-3.90 (9H, OMe), 1.95 (3H, d, J = 7.2 Hz, *Z* isomer and J = 6.0 Hz, *E* isomer).

Table 6, Entry 8
Tridec-2-ene:[62]
^{1}H NMR (600 MHz, $CDCl_3$); δ 5.37–5.45 (2H, m), 1.94–1.97 (2H, m, *E*-isomer), 2.00–2.05 (2H, m, *Z*-isomer), 1.63–1.64 (3H, d, J = 4.2 Hz, *E*-isomer), 1.59–1.60 (3H, d, J = 6.6 Hz, *Z*-isomer), 1.24–1.33 (16H, m), 0.86 (3H, t, J = 7.2 Hz).

NMR data for stilbenes (Table 7: Entry 1-5: ^{1}H NMR (200 MHz, $CDCl_3$); δ (ppm): as a mixture of (*Z*)- and (*E*)-isomers,

Table 7, Entry 1
1,2-diphenylethene:[80]
δ 7.15-7.60 (10H, m, Ar-H), 7.12 (2H, s, *E* isomer), 6.61 (2H, s, *Z* isomer).

Table 7, Entry 2
1-(4-chlorostyryl)benzene:[80a,81]
δ 7.2-7.6 (9H, m, Ar-H), 7.09 (2H, s, *E* isomer), 6.55 (1H, d, J_{HH}12.2Hz), 6.66 (1H, d, 12.2 Hz).

Table 7, Entry 3
1-(4-methoxystyryl)benzene:[80a,82]
(*E*)-isomer: δ 7.52-7.59 (4H, m), 7.43 (2H, t, J = 7.9 Hz), 7.29-7.34 (1H, m), 7.08-7.19 (2H, m), 6.97-7.03 (2H, m), 3.88 (3H, s).
(*Z*)-isomer: δ 7.24-7.36 (7H, m), 7.81 (2H, d, J = 9.7 Hz), 6.59 (2H, s), 3.83 (3H, s).

Table 7, Entry 4
1-(4-methylstyryl)benzene:[80a]
(*E*)-isomer: δ 7.55 (2H, d, J = 7.6 Hz), 7.37-7.47 (4H, m), 7.27-7.32 (1H, m), 7.22 (2H, d, J = 8.3 Hz), 7.12 (2H, s), 2.41 (3H, s).
(*Z*)-isomer: δ 7.19-7.46 (7H, m), 7.07-7.09 (2H, m), 6.61 (2H, s), 2.36 (3H, s).

Table 7, Entry 5
1-(4-bromostyryl)benzene:[80a]
(E)-isomer: δ 7.46-7.60 (4H, m), 7.25-7.41 (5H, m), 7.12 (1H, d, J = 16.2 Hz), 7.04 (1H, d, J = 16 Hz).
(Z)-isomer: δ 7.48 (2H, d, J = 9.7 Hz), 7.21-7.28 (5H, m), 7.15 (2H, d, J = 6.4 Hz), 6.68 (1H, d, J = 12.5 Hz), 6.54 (1H, d, J = 13 Hz)

Scheme23, Entry 17
1,2-bis(3,4,5-trimethoxyphenyl)ethane:[83]

δ 6.95 (2H, s, *E* isomer), 6.74 (4H, s, *E* isomer), 6.52 (6H, s, *Z* isomer), 3.93 (12H, s, *E* isomer), 3.88 (6H, s, *E* isomer), 3.82 (6H, s, *Z* isomer), 3.71 (12H, s, *Z* isomer).

CHAPTER 6: REFERENCES

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