# Design, Synthesis and Applications of Hydroxylmethyl-Aryl Phosphine Oxides in Phosphorus Catalysis

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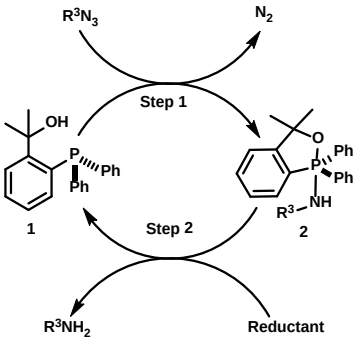
**Thesis submitted to the University of Nottingham**

**for the degree of Doctor of Philosophy**

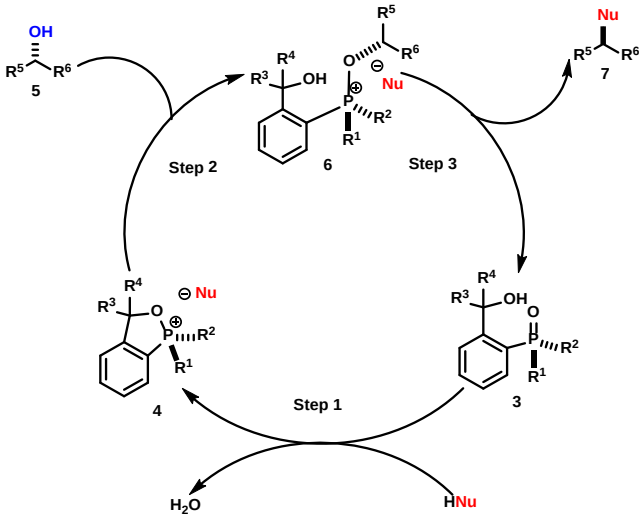
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## Abstract

Organophosphorus-mediated reactions are important tools in organic chemistry and are used in the synthesis of highly desirable drug targets, such as morphine.[1] A major drawback of traditional phosphorus-mediated reactions is the formation of stoichiometric amounts of phosphine oxide by-products; this renders the product purification difficult and reduces the atom efficiency of these transformations. For these reasons, catalytic variants become desirable; there being two potential strategies to achieve the catalysis; i) redox-driven and ii) redox-neutral.[2-4] The redox-driven catalytic cycle requires a reductant for the turnover whilst the redox-neutral system uses a sacrificial reagent to directly turn over the phosphine oxide to the active phosphorus (V) reagent. This thesis will report upon a new class of Hydroxylmethyl-Aryl phosphine **1** and phosphine oxide **3** catalyst for use in a redox-driven catalytic reaction; the Staudinger reduction **Scheme 1**, and routes to a potential redox-neutral catalytic Mitsunobu reaction **Scheme 2**.


**Scheme 1. Redox-driven Staudinger Reduction**




**Scheme 2. Redox-neutral Mitsunobu reaction**

**List of Publications**

1. Development of a redox-free Mitsunobu reaction exploiting phosphine oxides as precursors to dioxyphosphoranes. Xiaoping Tang, Charlotte Chapman, Matthew Whiting and Ross Denton. ***Chem. Commun.***, 2014, **50**, 7340-7343.

**Acknowledgements**

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**Table of Contents**

Abstract ..... 1

List of Publications ..... 2

Acknowledgements ..... 3

List of abbreviations ..... 7

Chapter One: Introduction to Organophosphorus Chemistry ..... 10

1.1 Introduction of Organophosphorus Chemistry ..... 11

1.1.1 The Mitsunobu Reaction; Origins, Mechanism and Modern Interpretations ..... 15

1.1.2 The Wittig Reaction; Origins, Mechanism and Modern Interpretations ..... 24

1.1.3 The Staudinger Reduction and Ligation ..... 29

1.2 Catalysing Phosphorus-Mediated Reactions ..... 31

Chapter Two: Design and Synthesis of New Hydroxylmethyl-Aryl Phosphine Oxides ..... 44

Chapter Three: The Development of Redox-Driven Catalytic Phosphorus (V) - Mediated Reactions ..... 54

3.1 Investigation of the Reduction of Phosphine Oxides using Phenyl Silane ..... 55

3.2 The Development of a Redox-Driven Staudinger Reduction ..... 71

3.3 The Use of Hydroxylmethyl-Aryl Phosphine oxide as a Pre-Catalyst ..... 82

3.4 The Development of a Redox-Driven Staudinger Ligation ..... 85

3.5 The Development of a Redox-Driven Wittig Reaction ..... 88

Chapter Four: The Development of Redox-Neutral Catalytic Phosphorus-Mediated Reactions ..... 92

4.1 The Development of a Redox-Neutral Catalytic Mitsunobu Reaction..... 93

4.2 The Formation of a Dioxyphosphorane – Step Two of the Redox-Neutral Catalytic Mitsunobu Reaction ..... 97

4.3 Nucleophilic Attack of a Dioxyphosphorane – Step Three of the Redox-Neutral Catalytic Mitsunobu Reaction ..... 99

Chapter Five: Conclusions..... 101

Chapter Six: Experimental..... 106

6.1 General Experimental ..... 107

6.2 Synthesis of Hydroxylmethyl-Aryl Phosphine Oxides..... 108

6.3 Synthesis of Alkoxyphosphonium Salt..... 123

6.4 Reductions of the Phosphine Oxides ..... 139

6.5 Reduction of Hydroxylmethyl-Aryl Phosphine Oxides ..... 145

6.6 Reduction of Alkoxyphosphonium Salts ..... 148

6.7 Catalytic Staudinger Reduction ..... 149

6.7.1 Catalytic Staudinger Reduction using Phenyl Silane ..... 151

6.7.2 Catalytic Staudinger Reduction – Screening of Reductions..... 153

6.7.5 General procedure for the catalytic Staudinger reduction ..... 158

6.8 Synthesis of Orangoazides..... 162

6.9 Catalytic Staudinger Reduction with a Pre-catalyst ..... 169

6.9 Catalytic Staudinger Ligation ..... 171

6.10 Catalytic Wittig Reaction ..... 173

6.11 Catalytic Mitsunobu Reaction ..... 175

6.11.1 Formation of Dioxyphosphorane - The formation of the alkene phosphine oxide ..... 175

6.11.2 Nucleophilic Substitution of the Dioxyphosphorane – The nucleophilic attack of Dioxyphosphorane ..... 177

Chapter Seven: References ..... 180

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| Ac | Acetyl |
| Ar | Aryl |
| $CH_2Cl_2$ | Dichloromethane |
| $CHCl_3$ | Chloroform |
| CSA | Camphorsulfonic acid |
| D | Doublet |
| DBAD | Dibenzyl Azodicarboxylate |
| DEAD | Diethyl azodicarboxylate |
| DEBM | Diethyl bromomalonate |
| DIAD | Diisopropyl azodicarboxylate |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DMSO | Dimethyl sulfoxide |
| Equiv. | Equivalent |
| Et | Ethyl |
| $Et_2O$ | Diethyl ether |

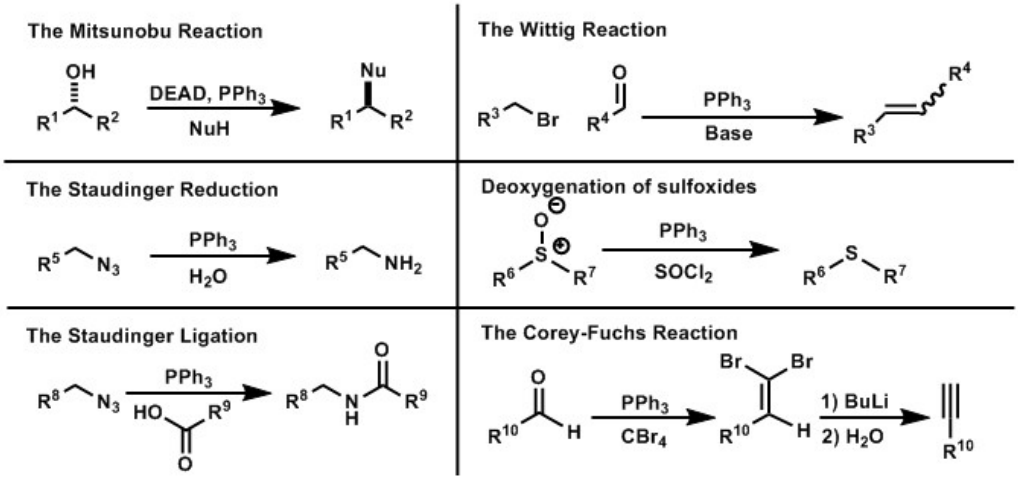
| Abbreviation | Meaning |
|---|---|
| EtOAc | Ethyl acetate |
| hr(s) | Hour(s) |
| Hz | Hertz |
| m | Multiplet |
| Me | Methyl |
| MeCN | Acetonitrile |
| MeOH | Methanol |
| mins | Minutes |
| mol | Mole |
| $^{n}$BuLi | *n*-Butyl lithium |
| NMR | Nuclear magnetic resonance |
| Nu | Nucleophile |
| Ph | Phenyl |
| P-O | Phosphorus-Oxygen bond |
| $PPh_3$ | Triphenyl phosphine |
| ppm | Part per million |

| Abbreviation | Meaning |
|---|---|
| r.t. | Room temperature |
| s | Singlet |
| t | Triplet |
| TBS | *tert*-Butyldimethylsilyl |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| Tol | Toluene |

# Chapter One: Introduction to Organophosphorus Chemistry

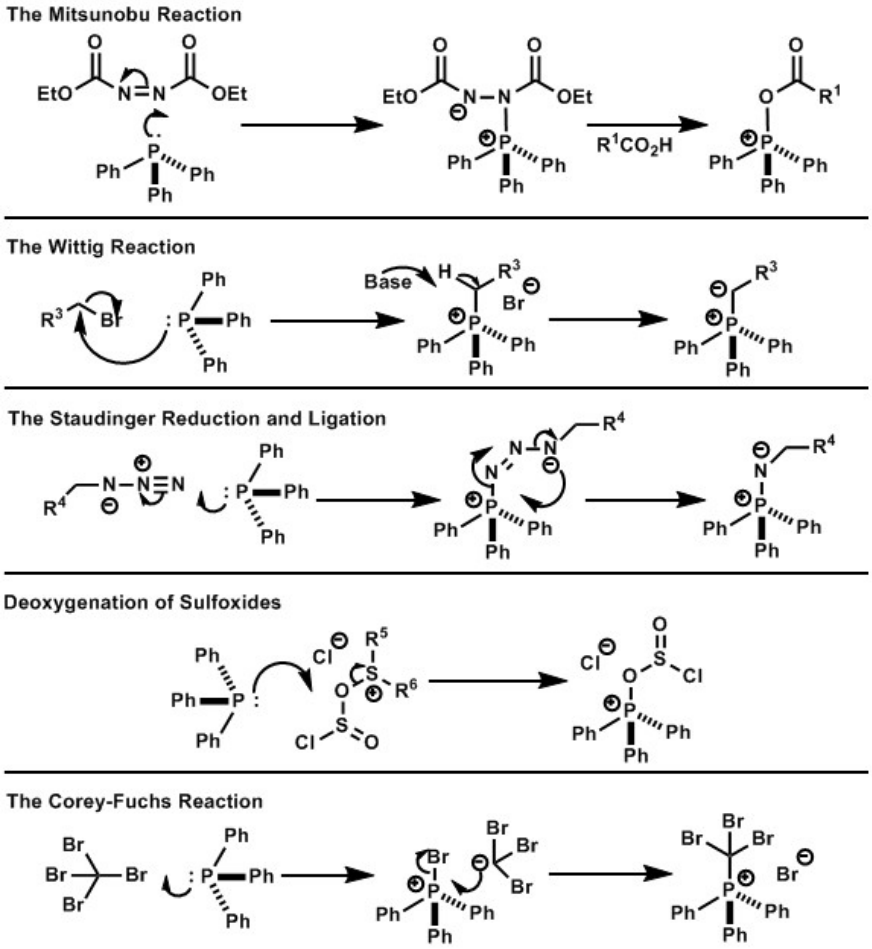
## 1.1 Introduction of Organophosphorus Chemistry

Phosphorus has been used in synthetic chemistry since the turn of the last century to aid in functional group transformations and substitution reactions. These reactions form some of the most important tools in a chemist's arsenal when developing strategies for drug targets or natural product synthesis. Phosphorus mediated reactions can be used to replace alcohols by inversion of their stereocentres and the introduction of new functional groups (Mitsunobu[5, 6] and Appel reactions[7]), to olefinate carbonyl compounds (Wittig reaction[8-10] and Cory-Fuchs Reaction[11]), reduction or ligation of azides (Staudinger reduction and ligation[12-15]) and deoxygenation of sulfoxides[16]. **Scheme 1.**



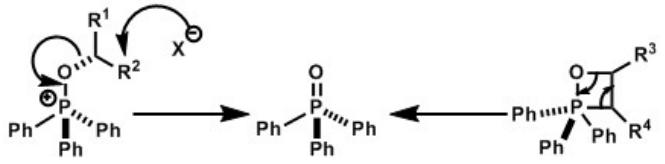

**Scheme 1. Examples of phosphorus mediated reactions.**[6-17]

An inherent feature of these reactions is the in-situ oxidation of the phosphine to yielding reactive ylides, phosphonium salts and phosphorane compounds. This process occurs throughout the each one of these phosphorus-mediated transformations, allowing a variety of interesting phosphorus (V)-intermediates to be formed. **Scheme 2.**




**Scheme 2. Oxidative activation of triphenylphosphine in Phosphorus (V)-mediated reactions.**[8-22]

These intermediates then react further in several reaction mechanisms; the Mitsunobu reaction for example, undergoes nucleophilic attack or the Wittig reaction which undergoes Arbuzov collapse. Though each of these reactions follows a different reaction pathway, each ends with the formation of the same phosphorus product; the phosphine oxide. **Scheme 3.**

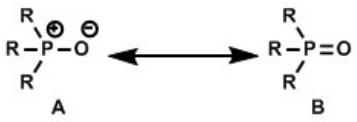


**Scheme 3. General reaction mechanism for the formation of phosphine oxides.**[6-21]

The phosphine oxide is a stable inactive phosphorus (V) compound which is lower in energy than the intermediates formed during the reaction. The nature

of the bonding in phosphine oxides is examined in detail in an excellent review by Gilheany[23] and relevant topics will be summarised in the following paragraphs.

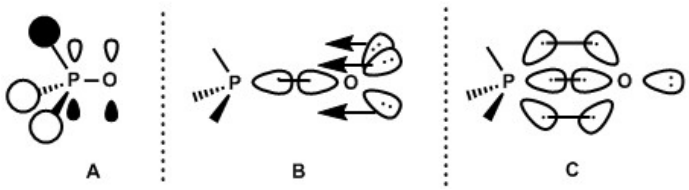
The typical P-O "double" bond is short (147.6-148.9 pm), strong and polarised towards the oxygen atom and has a bond order greater than two. The phosphine oxides are represented by two resonance structures. **Scheme 4.**




**Scheme 4. Resonance Structures for the Phosphine Oxide.**

Both structures are required in order to fully describe the bonding in the phosphine oxides. If the P-O "double" bond is formed by the lone pair of phosphorus donating into the oxygen p orbital in a purely σ bond (which will preserve the octet rule), then the phosphorus will carry a full positive charge and oxygen a full negative one. This will lead to strengthening of the P-O bond due to ionic attraction. This does not however fully explain the phenomena as it implies a single σ bond, whilst studies have shown that the bond has multi-bond character. **(Structure A, Scheme 4).**

Conversely, if the double bond representations are assumed to be correct, then there are three possible bonding explanations for the phosphine oxides. **Scheme 5.**



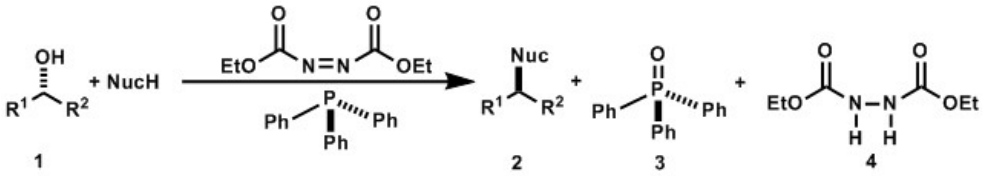

**Scheme 5. Possible Explanations for the Bonding of Phosphine Oxides (P=O).**

Negative hyper-conjugation (**Structure A, Scheme 5**) has one σ bond between the phosphorus and oxygen and two π-type interactions. The lone pairs of the oxygen are donated into the acceptor orbitals (the LUMO of the phosphine moiety) of the phosphorus. These orbitals are the only ones with the correct symmetry and are of p character, thus forming a double bond (partial triple bond). In previous studies it was thought that the acceptor orbitals for the electrons were in fact d orbitals of the correct symmetry, similar to what is seen in the first row transition metal but this has been since shown to be false. **Structure B** is similar to that of **A** except for the polarisation of the opposite charges towards the oxygen, which could be interpreted as back bonding yet is, rather, the polarisation of an ionic bond. An unorthodox view point for the bonding in the phosphine oxides are the banana bonds (or multiple bent bonds **Ω**) (**Structure C, Scheme 5**). These are comprised of 3 electron pairs between phosphorus and oxygen in 3 "banana" bonds (which are curved regions of electron density) dispersed in a symmetrical fashion long the P-O bond at 120° towards each other.

The formation of the phosphine oxide is the major disadvantage in all of the phosphorus (V) mediated reactions as it lowers the atom economy for the reactions and, in practical terms, makes purification of the products difficult. That said, it is the thermodynamic driving force for these reactions and its formation is a critical step in the reaction mechanism. An examination of the three main phosphorus (V) mediated reactions (Mitsunobu, Wittig and Staudinger Reduction) explored within this thesis was undertaken in order to better understand the finer elements of each of the reactions.

### 1.1.1 The Mitsunobu Reaction; Origins, Mechanism and Modern Interpretations

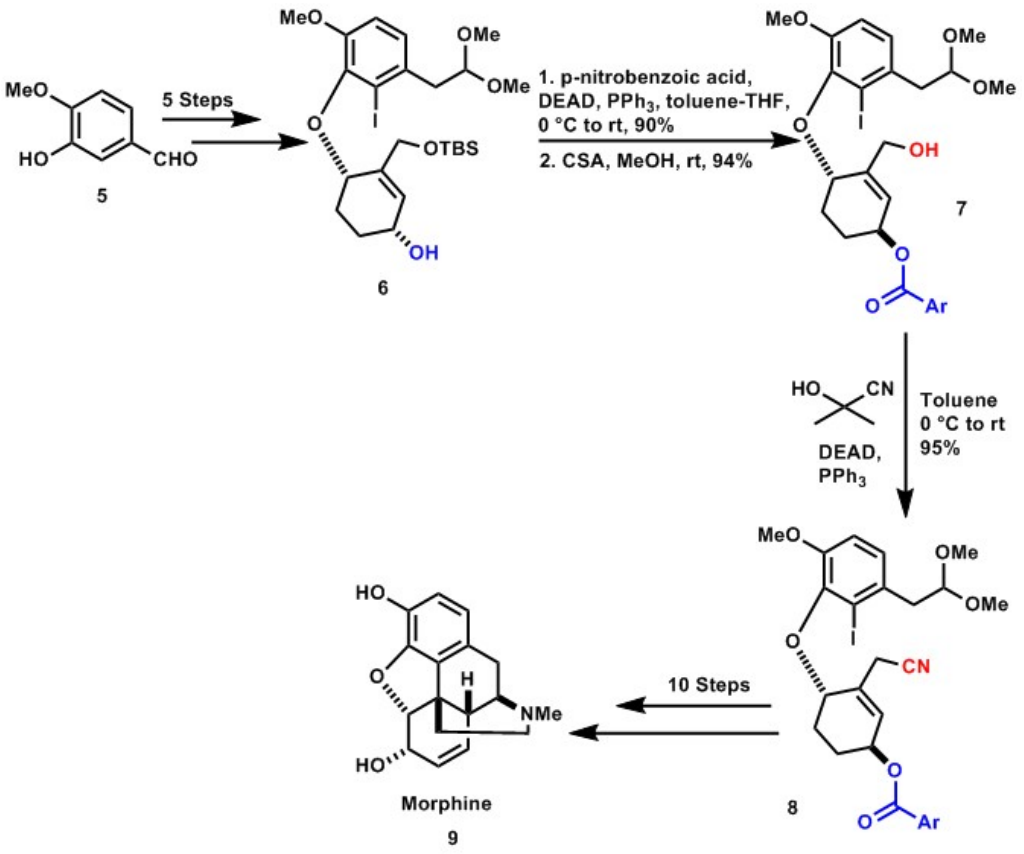
The most widely used nucleophilic substitution reaction used on alcohols is the Mitsunobu reaction. Developed by Oyo Mitsunobu in the early 1980s, the reaction involves a redox dehydration reaction between an alcohol **1** and an acidic nucleophile. **Scheme 6.**[6]




**Scheme 6. The Mitsunobu Reaction.**

The Mitsunobu reaction is synthetically important as the procedure has mild conditions as well as being stereospecific. The thermodynamic driving force for the reaction is the formation of the triphenylphosphine oxide which contains the very strong phosphorus-oxygen double bond. The kinetic element of the reaction, which allows for the mild conditions seen, comes from the charged alkoxyphosphonium salt that is highly reactive with respect to the nucleophilic substitution reaction.[6, 17]

The Mitsunobu reaction has been used in many syntheses to interconvert functional groups or invert the stereochemistry in order to build drug targets or natural products. One such example is Fukuyama and co-workers' synthesis of Morphine. In the 17 step synthesis, the Mitsunobu reaction is used twice. **Scheme 7.**[1]

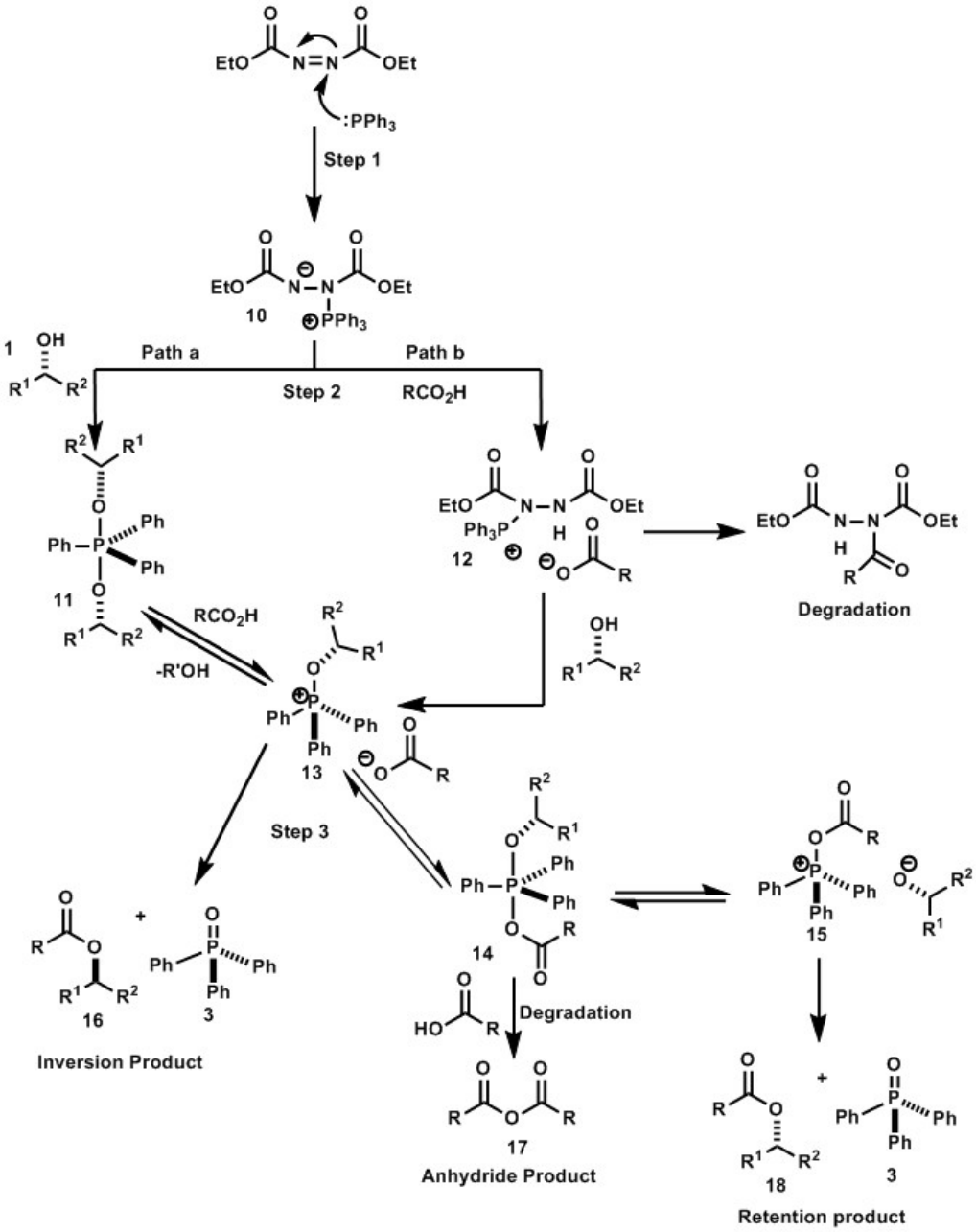



**Scheme 7. Fukuyama and co-workers' synthesis of Morphine.**

The initial Mitsunobu reaction inverts the carbon stereocentre, whilst the second is used for a functional group inter-conversion.

The reaction requires the overall oxidation of triphenylphosphine to the triphenylphosphine oxide **3** and the reduction of azodicarboxylate to hydrazide **4**. The mechanism has been studied in detail and intermediates have been identified *via* phosphorus NMR. **Scheme 8.**[17]

The first step in the reaction involves the nucleophilic addition of the triphenylphosphine to the azodicarboxylate, forming a betaine **10**. This betaine then undergoes one of two pathways; ***Pathway A*** involves the addition of two molecules of the alcohol, forming the dioxyphosphorane **11** intermediate, which, once attacked by the acidic nucleophile, forms the alkoxyphosphonium salt **13**.




**Scheme 8. Plausible reaction pathways in the Mitsunobu Reaction.**

***Pathway B*** involves the deprontonation of the acidic nucleophile, giving rise to a betaine **10** and forming the phosphonium salt **12**. This is then attacked by an alcohol to form the alkoxyphosphonium salt **13**. This alkoxyphosphonium salt **13** is in equilibrium with dioxyphosphorane **11**. This interchange is fast when forming the dioxyphosphorane **11** but slow to decompose to the alkoxyphosphonium salt **13**. The final step is the attack at the carbon centre of

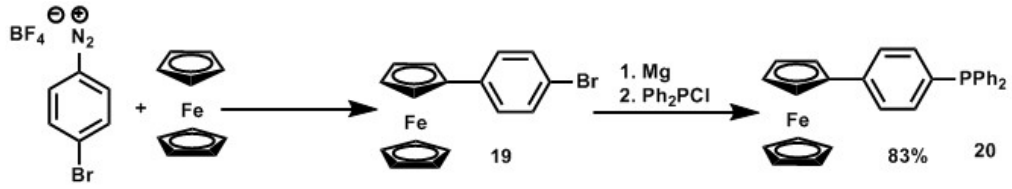
the alkoxyphosphonium salt **13** by the deprotonated nucleophile in order to displace the triphenylphosphine oxide **3** and forms product **16**. There are two other pathways which lead to the unwanted retention product **18** or anhydride **17** formation. These occur as the equilibrium between the dioxyphosphorane **14** and alkoxyphosphonium salt **13** and subsequent decomposition happens at different rates, which can lead to the alternative products. This equilibrium is determined by the pKa of the nucleophile and the sterics of the alcohol substrates, *i.e.* sterically hindered alcohols leading to retention products.

During the Mitsunobu reaction the phosphorus centre is oxidised to the phosphorus (V) species forming the key intermediates; the alkoxyphosphonium salt **13** and the dioxyphosphorane **11**. These intermediates decompose to form the inactive phosphorus (V) species; the triphenylphosphine oxide **3**. In the development of a catalyst, strong phosphorus-oxygen double bond created during the key-bond forming step has to be reduced. These conditions for this transformation are often harsh and would be undesirable for a catalytic Mitsunobu reaction, its most desirable trait being the mild reaction conditions in which the protocol is usually undertaken. For the development of a catalytic variant, the phosphorus species must form the key intermediates under mild reductive conditions.

As demonstrated by the mechanism of the reaction, the product is formed along with two stoichiometric by-products; triphenylphosphine oxide and the hydrazide derived from DEAD, therefore the reaction has a low atom economy. These by-products are hard to remove from the product and, in the case of the hydrazide, are very dangerous in large quantities as they are explosive and very toxic.[17, 24] For these reasons, chemists have tried to find

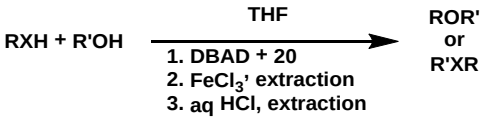
new protocols that alleviate purification difficulties. In some of the first work to improve on the traditional Mitsunobu reaction, polymeric reagents were utilized for easy removal of the by-products.[25, 26] Other reagents have been developed to help purification using phase switching protocols.

The work developed by Plenio and co-workers[17, 27] on redox-switchable phase tags has been applied to phosphines in order to effectively purify the product of a Mitsunobu reaction. The tagged phosphine developed contains a ferrocenium group which can be adjusted so that it is soluble in non-polar solvents. When oxidised to the cationic ferrocenium group it will precipitate out in the non-polar solvent. The ferrocenium groups are easily oxidised under mild conditions. The synthesis of the tagged phosphine **20** is a two-step synthesis which uses cheap commercially available starting materials. **Scheme 9.**[17, 27]



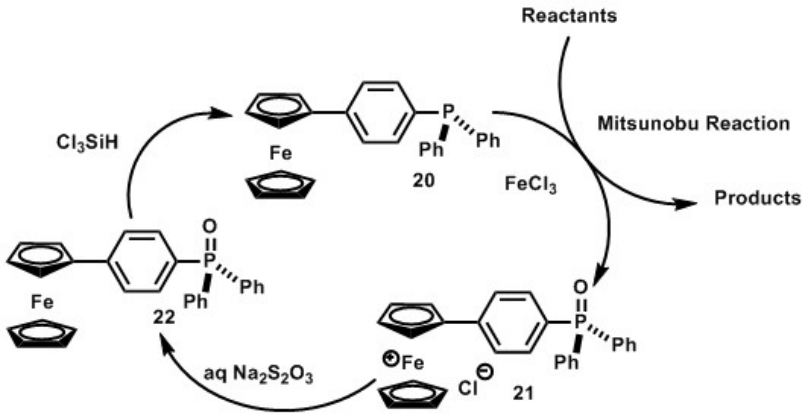

**Scheme 9. Synthesis of ferrocenium tagged phosphines.**

The redox potential of these tagged phosphines **20** can be adjusted to match reaction conditions and substrates.[17, 27] The oxidant required to oxidise the ferrocenium must be mild, cheap, non-toxic and soluble in organic solvents. With this in mind, iron (III) Chloride was chosen for the oxidant. The general procedure for the use of these redox-switchable tagged phase phosphine **20** is depicted in **Scheme 10.**[17, 27]




**Scheme 10. General procedure for the redox-switchable phase-tagged Mitsunobu reaction.**

Once the Mitsunobu reaction has been accomplished, iron (III) chloride is added and the cationic ferrocenium phosphine oxide **21** is washed out with a water-organic extraction. DBAD is the most suitable azodicarboxylate for these Mitsunobu reactions as the hydrazide byproduct can be removed by washing the reaction with 4M hydrochloric acid following the reaction. The ferrocenium phase tagged phosphines **20** will also work with traditional DEAD or DIAD components but this will require further purification once the reaction is complete. Once the phosphine oxide **21** has been isolated from the reaction mixture, it can be reduced using trichlorosilane. In one example, the phosphine oxide **21** was recovered with 80 % isolated yield. **Scheme 11.**[17, 27]

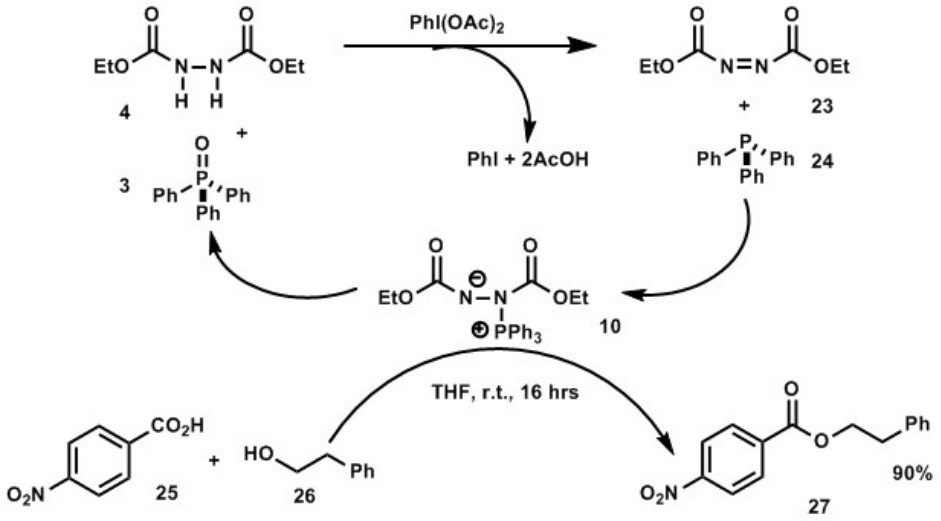



**Scheme 11. Recycling of the redox-switchable phase tagged phosphines 20.**

The yields for the Mitsunobu reaction are greater than 90%, with no need for chromatographic purification if DBAD is used.

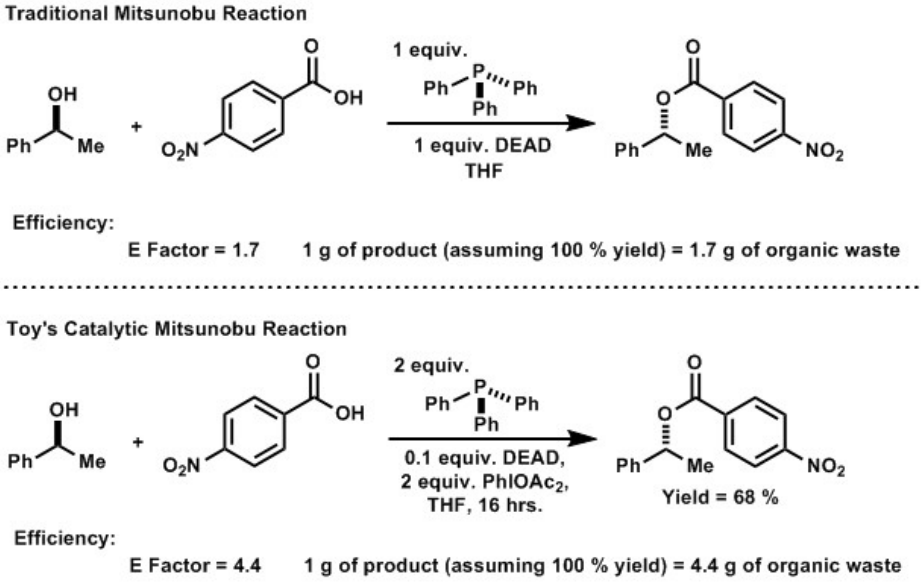
Mitsunobu reactions that are catalytic with respect to the azodicarboxylate component have also been established by two groups; the first protocol was

developed by P. H. Toy and co-workers.[17, 28, 29] The process uses iodo-benzene diacetate to reoxidise the hydrazide to azocarboxylate. This oxidant is used in stoichiometric amounts whilst the DEAD component is reduced to substoichiometric amounts. Though this protocol involves the use of an additional stoichiometric reagent, it results in the reduction of the amount of highly toxic and explosive diazodicarboxylate required. **Scheme 12.**



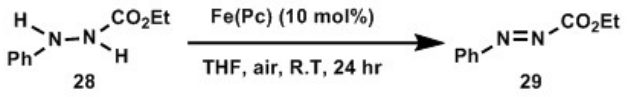

**Scheme 12. Toy and co-workers catalytic Mitsunobu reaction.**

From the initial results, Toy and co-workers developed two new diazo-catalysts to be used instead of DEAD, which were easier to handle and could tolerate a larger group of nucleophiles and alcohols. The by-products are easily removed but the reaction between the iodo-benzene diacetate and triphenylphosphine means that an excess of both reagents has to be used. An analysis of the atom efficiency of the traditional Mitsuonbu reaction compared to that of Toy's catalytic variant illustrates that, although a component is catalytic, it does not decrease waste. The use of secondary reagents can increase the waste generated in a reaction and therefore decrease the atom efficiency. **Scheme 13.**



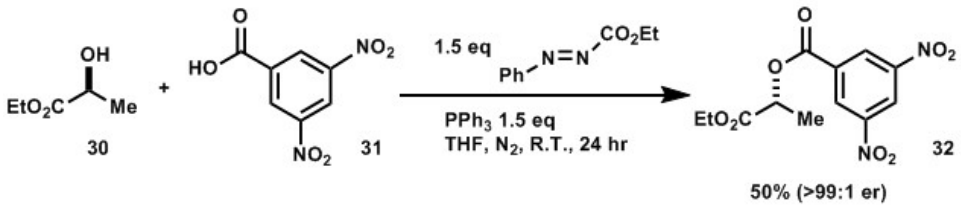

**Scheme 13. Comparison of traditional Mitsunobu and Toy's catalytic variant.**

The most up-to-date and modern Mitsunobu reaction, which is catalytic in the diazo component, was recently developed by Taniguchi and co-workers.[17, 30] The proposed catalytic cycle uses the groups work on reactions of alkoxycarbonyl radicals; these react with iron catalysts to aerobically oxidise hydrazides. **Scheme 14.**



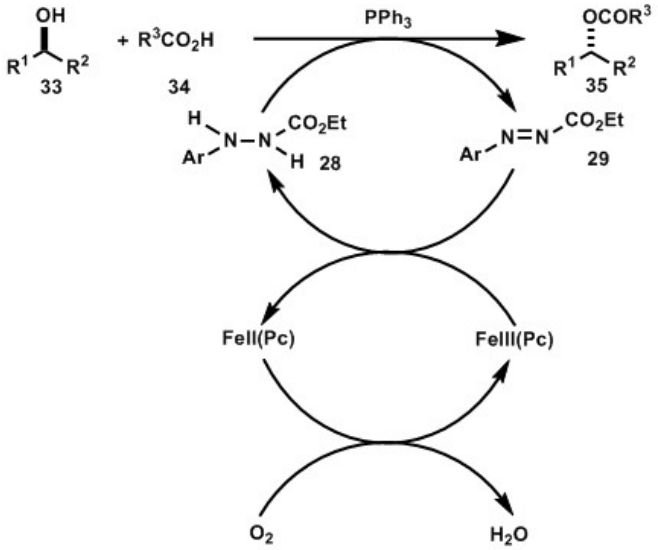

**Scheme 14. Aerobic oxidisation of hydrazide to azocarboxylate.**

For the oxidation to work, the hydrazide was required to have at least one aryl group on at least one of the ester groups. This modification allowed the Mitsunobu reaction to be performed in a stoichiometric sense. **Scheme 15.**




**Scheme 15. Stoichiometric Mitsunobu reaction using the new azocarboxylate.**

Once this was established a catalytic reaction was attempted. Taniguchi and co-workers found that this was not possible in the absence of 4 Å molecular sieves in the reaction. These sieves remove water generated when the hydrazide **28** reacts with oxygen to produce the azocarboxylate **29**. These reaction protocols only lead to a 17% yield with full inversion stereochemistry. Through screening of different analogues of this catalyst it was found that having electron-withdrawing groups on the aryl ring improved the yield and still gave good enantiomeric ratios. **Scheme 15 and 16.**



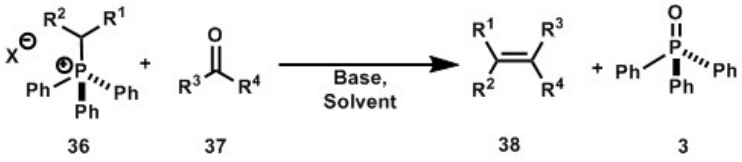

**Scheme 16. Proposed Catalytic Cycle.**

The functional group and reaction scope was still limited and gave low yields for more sterically hindered substrates. This protocol reduces the amount of a "DEAD" component and uses stoichiometric amounts of a cheap readily available oxidising agent.

*To date, there is no catalytic Mitsunobu reaction that is catalytic with respect to the phosphorus element and this remains the major challenge in the development of catalytic reactions.*

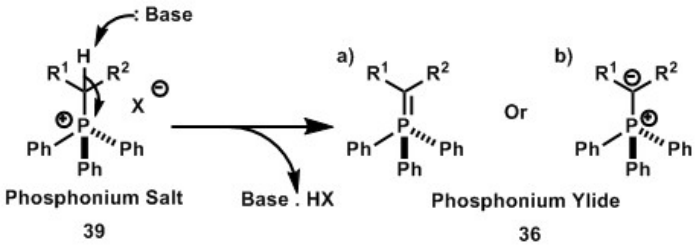
### 1.1.2 The Wittig Reaction; Origins, Mechanism and Modern Interpretations

The most commonly used method for the synthesis of alkenes in organic chemistry is the Wittig reaction. Developed in the 1950s by a German chemist Georg Wittig, it is the reaction between a carbonyl compound **37** and phosphonium ylide **36** to produce the alkene product **38** and the phosphine oxide **3** by-product. The phosphonium ylide **36** is often generated *in situ* from the phosphonium salt **39**. **Scheme 17.**[8, 9]




**Scheme 17. The Wittig reaction developed in the 1950s by Wittig and Geissler.**[8, 9]

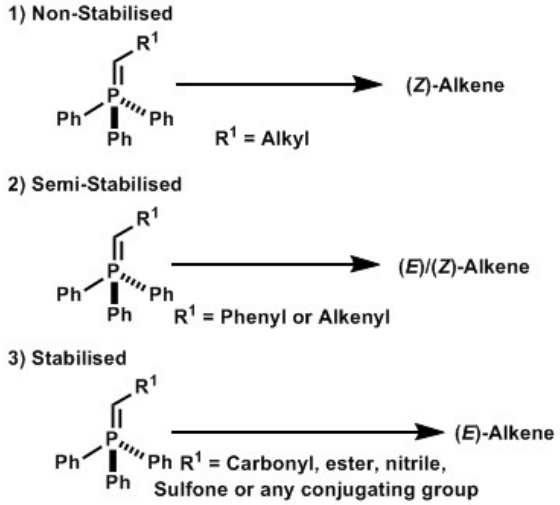
The pKa of the carbon alpha to the phosphorus atom is in the range of 5-20 depending upon the substituents of $R^1$ and $R^2$ and is easily deprotonated with various bases to form the phosphonium ylide **36**. **Scheme 18.**[8, 9, 19, 31]




**Scheme 18. Formation of the Phosphonium salt 39 and Phosphonium Ylide 36 for the use in the Wittig reaction.**[8, 9, 19, 31]

The phosphonium ylide **36** is represented by two structures, which are not classed as resonance forms; a) the alkene phosphonium ylide or b) zwitterionic phosphonium ylide. **Scheme 18**. The carbon-phosphorus bond is polarised towards the α-carbon atom but there is evidence to suggest that there is some stabilisation via negative hyper conjugation of the lone pair into the σ*-orbital

of the phosphorus atom. When discussing of the phosphonium ylides **36** and the mechanism of the Wittig reaction, the phosphonium ylide **36** will be represented by the alkene phosphonium ylide **36** (**Scheme 17, a**). The phosphonium ylides **36** can be organised into three categories depending upon groups attached to the α-carbon; 1) stabilised, 2) semi-stabilised and 3) non-stabilised ylides. **Scheme 19.**

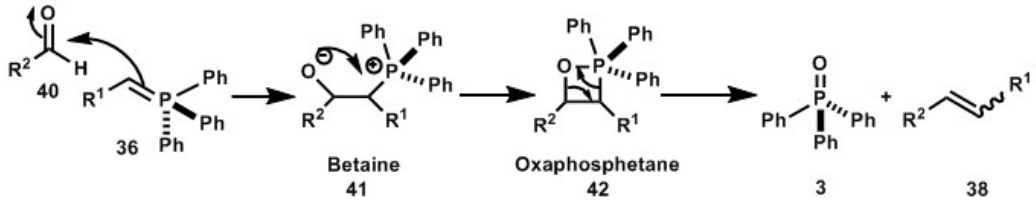



**Scheme 19. The categories for the Phosphonium Ylides 36.**[31]

The non-stabilised or reactive phosphonium ylides **36** are classified as such because they contain no stabilising group (i.e. alkyl) and are often air and moisture sensitive. These phosphonium ylides react instantaneously with the carbonyl compounds and generally give (*Z*)-selectivity. The semi-stabilised phosphonium ylides contain a group which stabilises the ylide via conjugation with an unsaturated group, i.e. phenyl or alkenyl, and are slower to react with carbonyl compounds with no strong selectivity for (*E*) or (*Z*) alkene. The final phosphonium ylide category is the stabilised ylide, which contains electron withdrawing group such as a carbonyl or nitrile group on the α-carbon and is generally (*E*)-alkene selective. The stabilised phosphonium ylide is often stable to air and can be isolated and characterised. With this increased stabilisation, it

is often found that these phosphonium ylides react more slowly than the other categories of the phosphonium ylides and thus require harsher reaction conditions, such as heating.

The reaction mechanism of the phosphonium ylide **36** with carbonyl compounds **37** has been a big area of discussion in the field of organophorphorus reactions. The essential features of the early work on the mechanism for the reaction, developed by Wittig and co-workers, suggests the formation of betaine **41** as the initial intermediate before the ring closure to an oxaphosphetane **42**, which on decomposition forms a phosphine oxide **3** and alkene **38**. **Scheme 20.**[31]




**Scheme 20. Wittig and co-worker's theory for the reaction mechanism for the Wittig reaction.**

When Wittig and co-workers developed this concept for the reaction mechanism there was strong experimental evidence to support the betaine **41** intermediate. Many of the experiments conducted by Wittig to establish the betaine **41** intermediate have since been explained via the use of modern analytical techniques such as phosphorus NMR.

The explanation put forth by Wittig for the stereochemical outcomes of the non-stabilised ylides in the Wittig reaction involves the formation of the kinetic product; the *anti*-betaine (P-C-C-O dihedral angle of 180°). **Figure 1.**

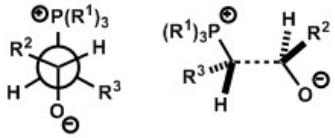


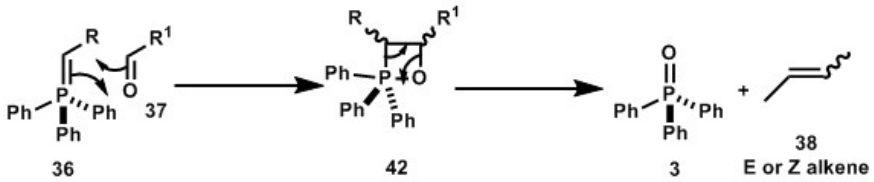
**Figure 1. *Anti*-betaine product.**

Minimisation of steric repulsion in the transition state will also have a dihedral angle of 180° thus an *anti*-*erythro*-betaine which, once it undergoes bond rotation, will irreversibly form the *cis*-oxaphosphetane. The *cis*-oxaphosphetane then decomposes to give the *Z*-alkene. This means that, according to this rationale, all non-stabilising ylides should be irreversible and highly *Z*-selective but reactions of phosphonium ylides, derived from phosphines that are not triphenylphosphine gives, in some cases, very high *E*-selectivity. This means the betaine mechanism cannot justify the *E*-selectivity seen for those non-stabilised ylides under kinetic control in the Wittig reaction.

The stabilised ylides derived from triphenylphosphines are *E*-selective and it has been postulated that an equilibrium is established between either the *threo*-betaine and *erythro*-betaine or the *trans*-oxaphosphetane and *cis*-oxaphosphetane, before irreversible decomposition to the alkene and phosphine oxide. The *threo*-betaine and/or *trans*-oxaphosphetane will ring close and decompose faster than the other isomers, therefore giving high *E*-selectivity. This means the betaine mechanism requires a reversible formation of either the betaine and/or oxaphosphetane in the reaction of stabilised ylides and is unable to explain the *E*-selectivity under kinetic control.

Since Wittig suggested the betaine mechanism there have been several other mechanistic suggestions for the Wittig reaction, which are detailed in a review by P. Byrne and D. Gilheany.[31] The review also details the most modern interpretation of the Wittig reaction and will be summarised in this thesis.

From numerous studies, it has been established that the Li-salt free Wittig reaction progresses irreversibly, therefore implying that the reaction is under kinetic control in all types of phosphonium ylide. The first step of the Li-salt free Wittig reaction is an irreversible [2+2] cycloaddition to form the oxaphosphetane **42**, which has been shown to be the first and only intermediate to be formed from the phosphonium ylide **36** and carbonyl compounds **37**. It is the shape of the transition states of the [2+2] cycloaddition which dictates the stereochemical outcome of the Wittig reaction. The shape is determined by the substituents of the ylide and of the phosphorus centre. **Scheme 21.**

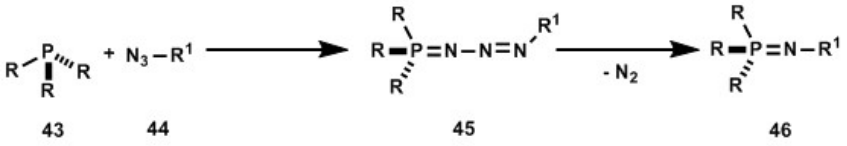



**Scheme 21. [2+2] cycloaddition mechanism for the Wittig reaction.**

There are many alternatives and modifications of the Wittig reaction since its discovery. These alternatives often aid in the purification or help to enable for a specific stereoselectivity. There has also been work done on the catalytic Wittig reaction which will be covered in a later section (*vide infra*).

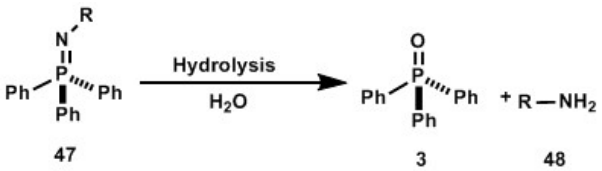
### 1.1.3 The Staudinger Reduction and Ligation

The reduction of azides **44** to form amines has been established since the turn of the century in one of the oldest organophosphorus reactions. It involves the combination of phosphine **43** with an azide **44** to form the nitrogen ylide **46** and the releasing of nitrogen gas, which was discovered by Staudinger and Meyer in the 1920s and described in **Scheme 22.**[15]




**Scheme 22. Reaction between tertiary phosphine and azides.**

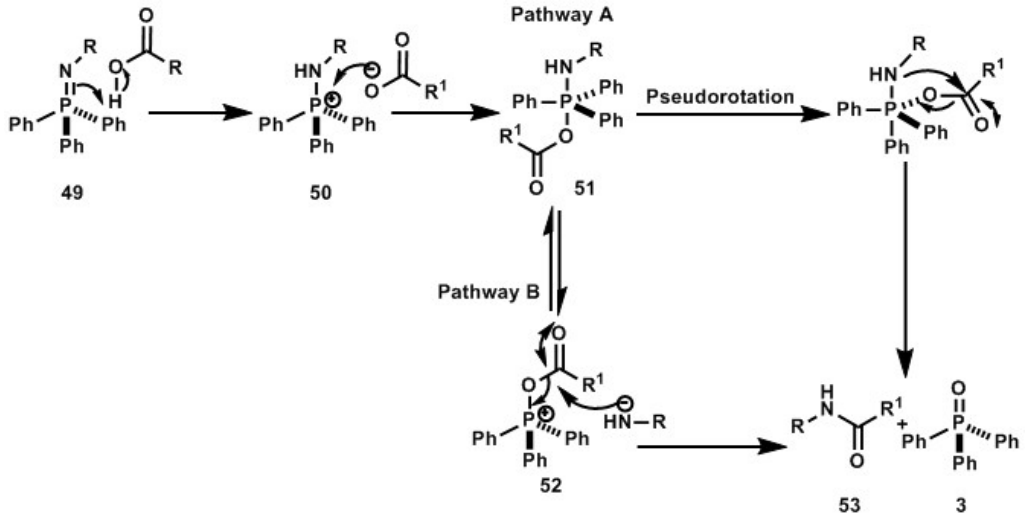
The iminophosphorane **46** intermediate will go on to react under three different pathways depending upon the reaction conditions. If the Staudinger reaction is performed in water then the iminophosphorane **46** is attacked by water, releasing the amine product **48** and phosphine oxide **3**. This is known as the Staudinger Reduction.[12-15] **Scheme 23.**




**Scheme 23. The Staudinger Reduction.[12-15]**

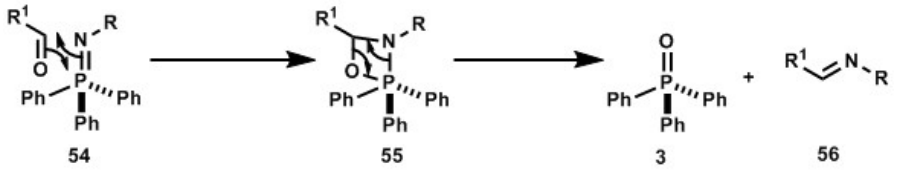
If the Staudinger reaction is performed in an organic solvent in the presence of a carboxylic acid, the Staudinger Ligation will occur. The Staudinger Ligation mechanism involves the addition of the acid to form an amino-oxyphosphorane **51**. This is in equilibrium with the oxyphosphonium salt **52,** which will undergo nucleophilic attack to form the amide. The lone pair of the nitrogen in **51** (**Pathway A**) or negative charge of the amido counter ion in **52** (**Pathway**

**B**) attacks the $\delta^+$ carbon of the carbonyl group of the carboxylic acid, forming the amide **53** and the phosphine oxide **3**.[12-15] **Scheme 24.**




**Scheme 24. The Staudinger Ligation.**[12-15]

An alternative pathway that the iminophosphorane can potentially undergo is the Aza-Wittig reaction. This reaction mechanism is the similar to that of the Wittig reaction; the iminophosphorane **54** reacts with a carbonyl compound and forms an imine **56**.[12-15] **Scheme 25.**

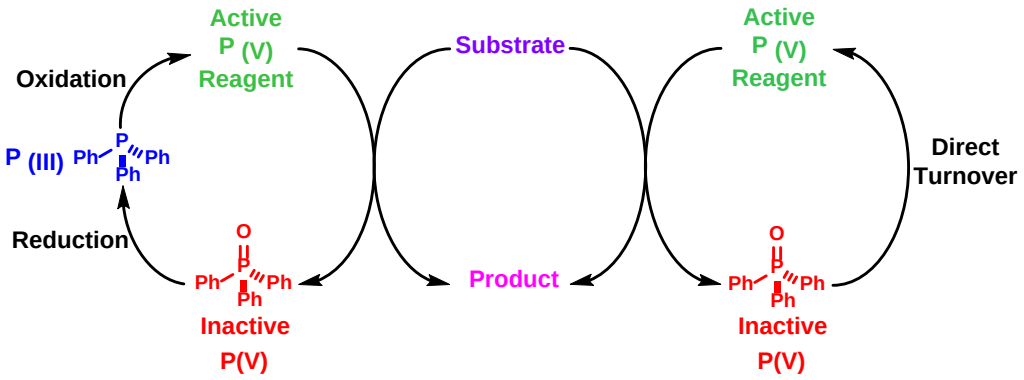



**Scheme 25. The Aza-Wittig Reaction.**[12-15]

Once again the major disadvantage of this transformation is the formation of stoichiometric quantities of triphenylphosphine oxide **3** as a by-product. For industrial purposes, the reduction of azides is usually achieved *via* transition metal catalysed hydrogenation reactions and amide coupling uses other coupling reagents. To date, catalytic variants of the iminophosphorane-based reactions have been developed, which will be discussed in the next section. (*vide infra*).

## 1.2 Catalysing Phosphorus-Mediated Reactions

Development of catalytic variants of the classic phosphorus (V)-mediated reactions is a growing field of chemistry due to possibility of reducing phosphine oxide waste and as a challenge to catalytic reaction development.[2-4, 32] In order to adopt a catalytic manifold, the phosphine oxide must be converted to the active phosphorus (V) reagents e.g. chlorophosphonium salts or phosphonium ylides. This means that the phosphorus-oxygen double bond has to be broken in order to achieve catalytic turnover. With the formation of this bond being the enthalpic driving force and, given the kinetic stability of phosphine oxides, the transformation requires harsh conditions.[33, 34] Theoretically, reactivation of the phosphine oxide bond can occur under two pathways; i) redox-driven and ii) redox-neutral.[2-4] **Scheme 26.**



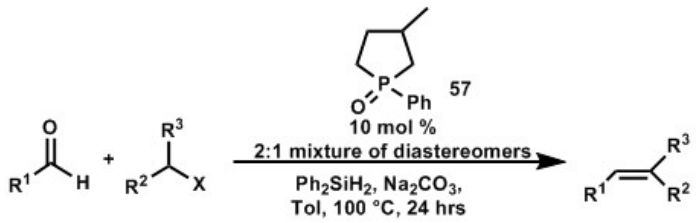

**Scheme 26. Approaches to the catalysation of organophosphorus reactions. i) Redox-driven (left) and ii) Redox-neutral (Right).[2-4]**

The redox-driven approach to the activation of the phosphine oxide (inactive phosphorus (V) compound), requires the reduction of the phosphorus-oxygen double bond to a phosphorus (III) compound (phosphine). The major disadvantage of this approach is the addition of secondary reagents to mediate the reduction and oxidation of the phosphorus centre. Furthermore, the presence of both reductant and formal oxidant renders the reaction

development difficult as a result of the incompatibility of many oxidants and reductants.

In contrast, the redox-neutral approach does not change the oxidation state at phosphorus. This approach involves the cleavage of the phosphorus-oxygen double bond and reconversion of the phosphorus (V) species without formal changes to the oxidation states at the phosphorus centre. This, ideally, could be facilitated by a functional group present within the phosphorus species or by one of the reactants required for the reaction. The clear advantage of this second approach is the absence of additional reagents, making the reaction matrix less complex.

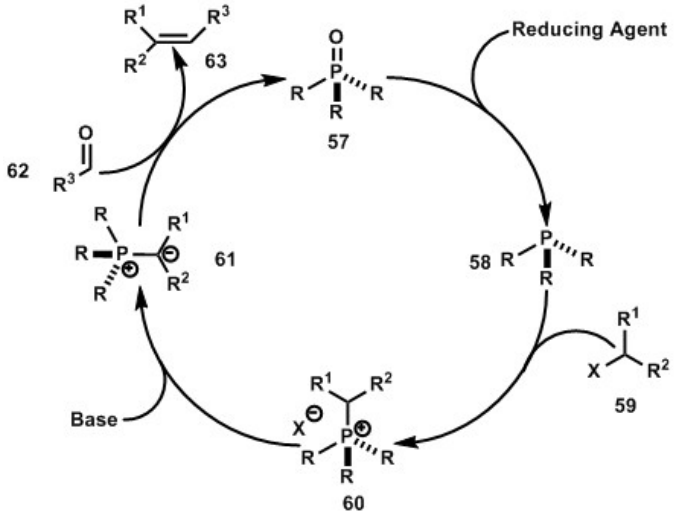
The development of catalytic variants of classic organophosphorus reactions has been undertaken by several groups in the last few years. There have been many examples of the redox-driven catalytic pathway within the literature. The first example was the catalytic Wittig reaction developed by the O'Brien group in 2009,[35] which employs a cyclic phosphine oxide pre-catalyst in conjugation with a hydrosilane terminal reductant to couple the halogenated substrate with an aldehyde in the Wittig manifold. **Scheme 27.**




**Scheme 27. First Generation O'Brien's Catalytic Wittig Reaction.**[35]

The initial step in this reaction is the reduction of phosphine oxide **57** to the phosphine **58**. The phosphine **58** attacks the alkyl halide to afford the alkylphosphonium salt **60.** The phosphonium ylide **61** then is formed *via* deprotonation of the alkylphosphonium salt **60**. This phosphonium ylide **61**

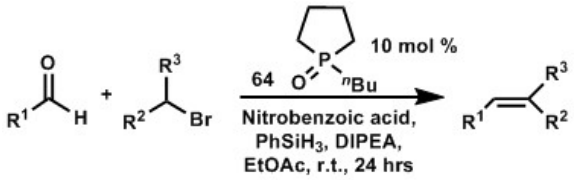
reacts in the traditional Wittig reaction pathway releasing the phosphine oxide **57** and the product **63**. **Scheme 28.**




**Scheme 28. O'Brien's Catalytic Wittig Reaction.**[35]

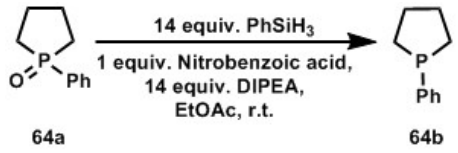
O'Brien utilises hydridosilanes for the reduction of the phosphine oxide to the phosphine without reducing the aldehyde, alkene or alkylhalide. For the cyclic phosphine oxide **57**, it was found that diphenyl silane was the best reagent for the first generation catalyst. This reagent is less harsh than the traditional trichlorosilane or lithium aluminium hydride. The silicon reagent is able to reduce this phosphine oxide **57** more mildly than other phosphine oxides, such as triphenylphosphine oxide **3**, due to the cyclic nature of the phosphine oxide **57**. The angle strain in the 5 membered ring destabilises the ground state of the phosphine oxide, therefore increasing the reactivity towards the reduction.

The second generation catalytic Wittig reaction developed by O'Brien focuses on the reducing the temperature of the reaction. **Scheme 29.**




**Scheme 29. Second Generation O'Brien Catalyst for a Room Temperature Catalytic Wittig Reaction.[36]**

The reduction of the phosphine oxide **64** is the rate determining step of the catalytic cycle. It was noted that the addition of acid and amine to the reduction step allowed the reduction to occur at room temperature. **Scheme 30.**



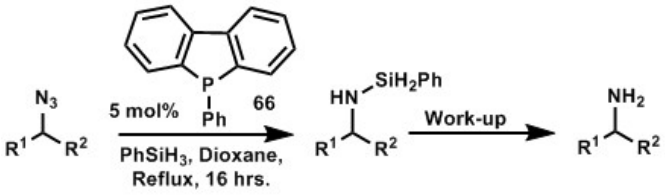

| Entry | Acid | Base | Conversion (%) |
|---|---|---|---|
| 1 | - | 14 equiv. | 6 |
| 2 | 1 equiv. | 14 equiv. | 73 |
| 3 | 1 equiv. | - | 0 |

**Scheme 30. Reduction of O'Brien's Second Generation Catalyst at Room Temperature.[36]**

O'Brien attributed the room temperature reduction to the activation of the phosphine oxide by the Bronsted acid. The reduction of the cyclic phosphine oxide **64a** does not occur without the acid additive over a 10 minute time frame at 100 °C in toluene, whereas, with the acid additive, the conversion is 73%. It is important to note that, in the presence of the acid additive but in the absence of amine base, there is only a 5 % conversion to the phosphine. An alternative rationalisation for this accelerated reduction will be presented in a later chapter **(Chapter 3, Section 3.1, *vide infra*)**, along with alternative reduction conditions.

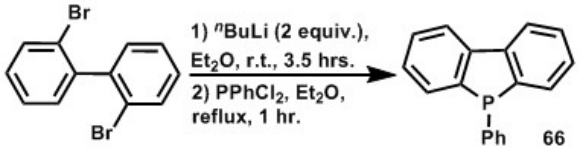
Following O'Brien's catalytic Wittig reaction, there came a series of other redox-driven catalytic phosphorus (V)-mediated reactions, all of which use

hydridosilane reductants to achieve turnover; firstly, Rutjes' catalytic Staudinger reduction, which utilises a different cyclic phosphine as the catalyst. **Scheme 31.**



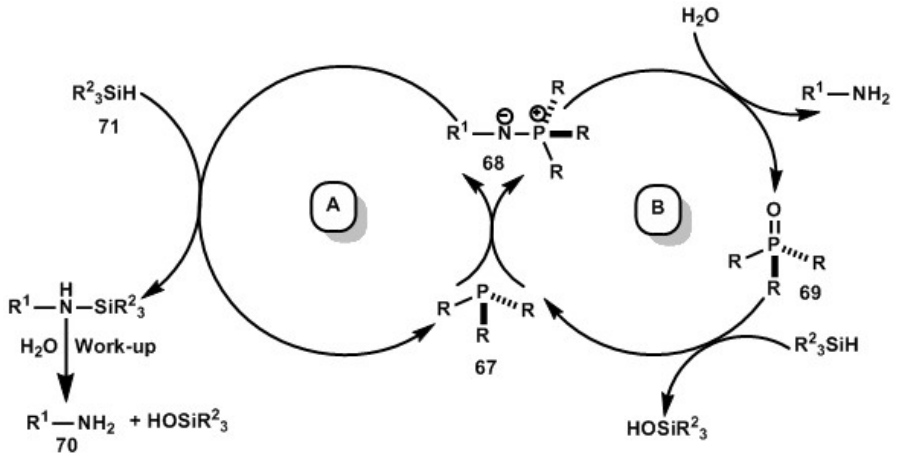

**Scheme 31. Rutjes' Catalytic Staudinger Reduction.**[37]

The catalyst used by the Rutjes group is an aryl cyclic phosphine **66** that is synthesised in one step from the diaryl bromide species.[38] **Scheme 32.**



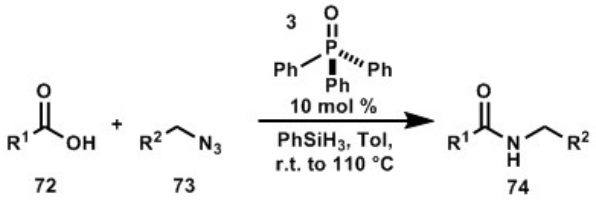

**Scheme 32. Synthesis of the phosphine catalyst.**[38]

The Rutjes catalytic cycle has two parts; **pathway A** and **pathway B**; **pathway A** involves the reduction of the iminophosphorane **68** to the phosphine **67,** releasing a silyl amine which, upon work-up, is hydrolysed to the amine product **71**. Pathway **B** shows the *in situ* hydrolysis of the iminophosphorane **68**, leading to the formation of phosphine oxide **69** which is then reduced to phosphine **67** by hydridosilane **71**. **Scheme 33.**



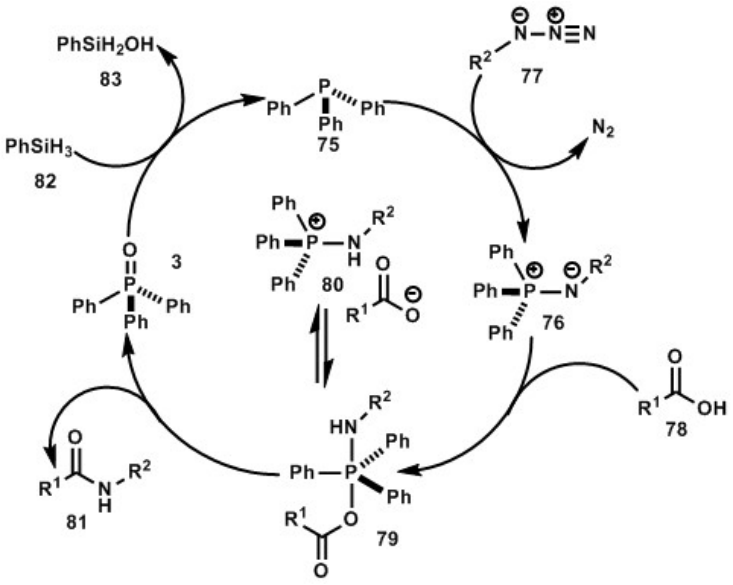

**Scheme 33. Rutjes' Catalytic Staudinger Reduction Catalytic cycle.**[37]

Pathways were determined by the $^{31}P$ NMR and $^{1}H$ NMR experiment which shows that both pathways are present during the catalytic Staudinger reduction. After the development of this catalytic Staudinger reduction, Ashfeld *et al*. published a catalytic Staudinger Ligation (amidation), which was based on work by Garcia and co-workers in 1984.[39, 40] **Scheme 34.**



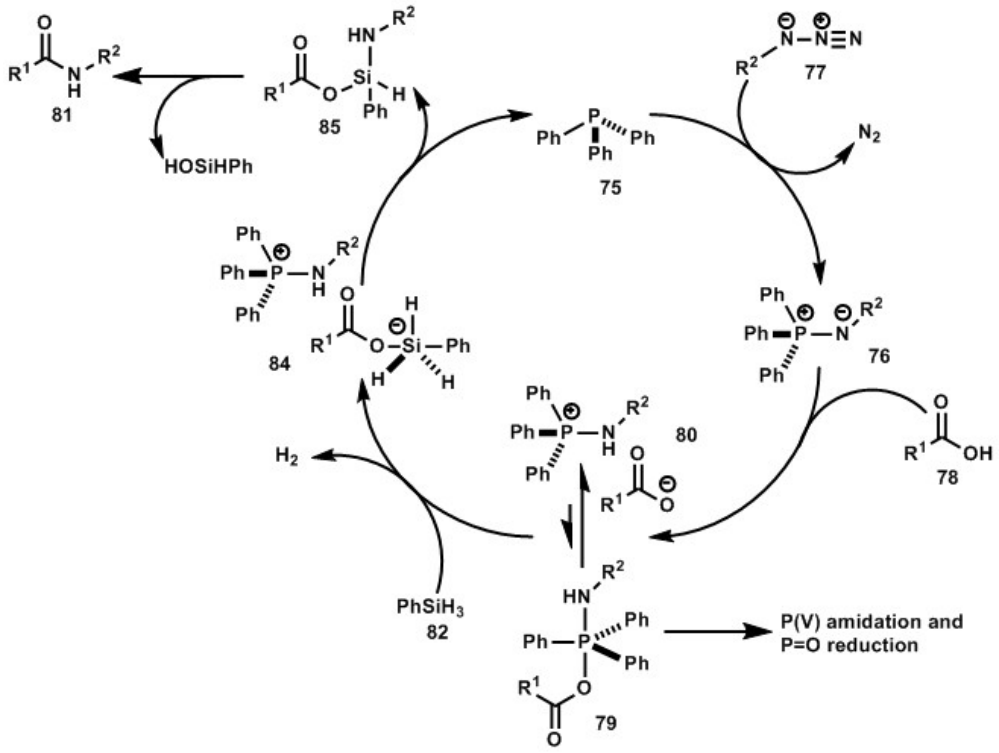

**Scheme 34. Ashfeld's Catalytic Staudinger Ligation.**[39]

Ashfeld hypothesised that the phosphine first reduces the azide **77** to form iminophosphorane **76**, before an attack of the acid forming the amino-oxyphosphorane **79**. It was proposed that the amide product originated from phosphorane **79** with the generation of a triphenylphosphine **3**.[39] **Scheme 35.**




**Scheme 35. Ashfeld's Catalytic Staudinger Ligation.**[39]

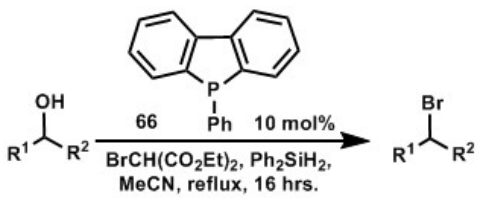
However, there is a possible alternative silicon-mediated pathway that has not been ruled out. **Scheme 36**.[41] The stability of the phosphonium salt **80** to the reduction conditions was investigated and it was shown that the proposed amide precursor was reduced with one equivalent of hydridosilane **82** at room temperature, forming the phosphine **75** and the AMINE product; not the coupled amide product **81**. This is significant as, with the excess hydridosilane **82** and high temperatures conditions; for Ashfeld's catalytic Staudinger Ligation, the phosphonium salt **80** would not be a viable intermediate for this reaction. Therefore the coupling is not mediated *via* the phosphorus centre. The experiments showed that the silyl ester was a key intermediate in the amidation reaction. **Scheme 36.**




**Scheme 36. Diagram of the amide coupling using the catalytic Staudinger reduction.**[41]

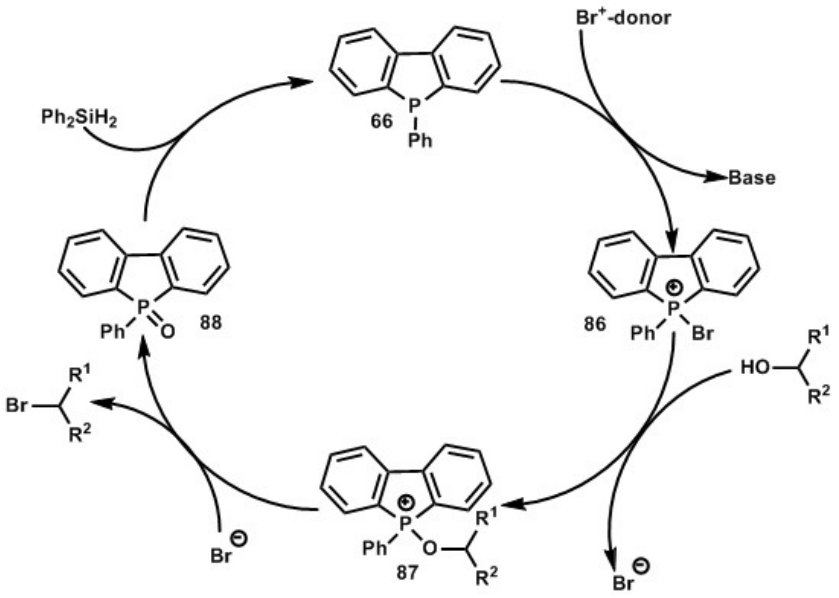
This diagram is an explanation of what is occurring during the catalytic Staudinger ligation developed by Ashfeld and is an example of how complex these redox-driven phosphorus-mediated reactions are. With the reactivity of the hydridosilanes being a relatively unexplored area of chemistry, it can be difficult to predict their involvement in these reactions.

The final redox-driven catalytic organophosphorus reaction is an Appel reaction developed by the Rutjes group. The catalytic Appel reaction uses an unprecedented bromine source for the reaction, diethyl bromomalonate (DEBM).[42] **Scheme 37.**




**Scheme 37. The redox-driven catalytic Appel reaction by Rutjes.**[42]

Primary alcohols were converted to the corresponding alkyl bromines with moderate-to-good isolated yields; a limited number of secondary alcohols also underwent deoxybromination, though no examples were given that took place with inversion of configuration. Sterically hindered alcohols do not undergo the catalytic bromination reaction. The catalytic cycle involves the formation of the bromo phosphonium salt **36** before the key formation of alkoxyphosphonium bromide **87**.[42] **Scheme 38.**

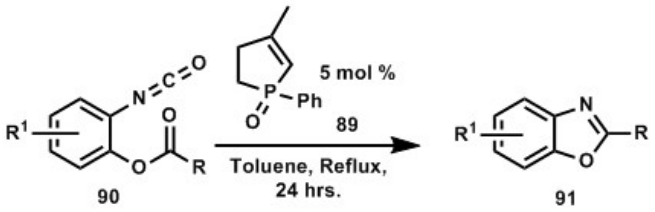



**Scheme 38. Catalytic Appel reaction mechanism.**[42]

The alkoxyphosphonium bromide **87** undergoes nucleophilic attack by the bromide ion to form the product and release the phosphine oxide **88**. The phosphine oxide **88** is then reduced by diphenyl silane. There are no examples of the chloroination reaction as there was no chloride source that was compatible with the reaction conditions.[42]

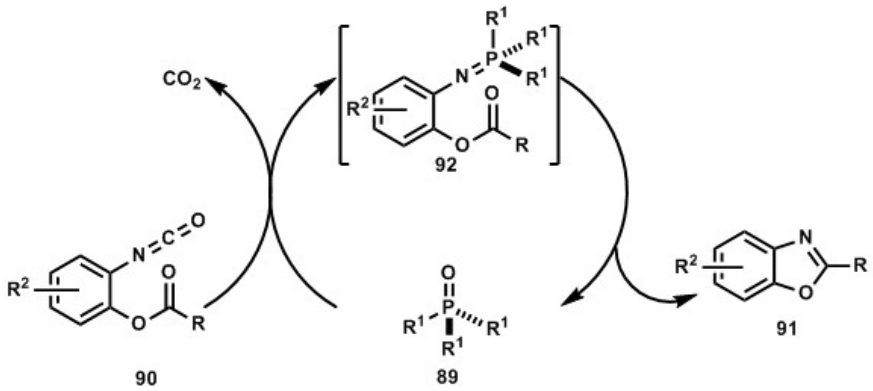
Examples of the redox neutral catalytic cycle include the catalytic aza-Wittig reaction developed by Marsden and co-workers and the catalytic Appel reaction developed by this group. Marsden's catalytic aza-Wittig reaction with

isocyanate **90** and phosphine oxide **89** was the first example of a redox-neutral phosphorus (V) mediated reaction. **Scheme 39.**



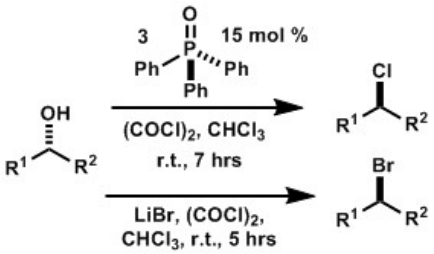

**Scheme 39. Marsden's Catalytic Aza-Wittig Reaction.**[43]

The phosphine oxide **89** reacts with the isocyanate **90**, releasing carbon dioxide and forming iminophosphorane **92**. The iminophosphorane **92** rapidly undergoes aza-Wittig reaction reforming the phosphine oxide **89** and releasing the cyclic imine product **91**. **Scheme 40.**



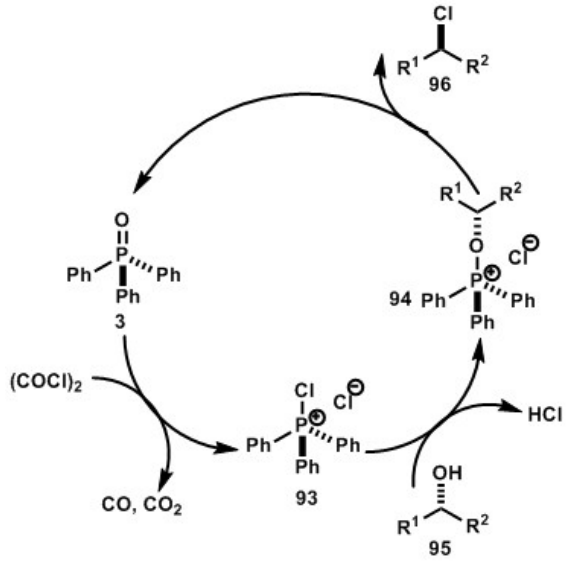

**Scheme 40. Marsden's Catalytic Aza-Wittig Reaction Catalytic Cycle.**[43]

Another example of a redox-neutral phosphorus (V) mediated reaction is the Denton Appel reaction which uses triphenylphosphine oxide **3**, a common by-product of many phosphorus mediated reactions, to convert alcohols into halogens with an inversion of stereochemistry.[2-4] **Scheme 41.**




**Scheme 41. Denton's Catalytic Appel Reaction.**[2-4]

The phosphine oxide **3** is turned over to the chloronium phosphonium salt **93** with oxalyl chloride, which was first established in the 1970s.[44] This chloronium phosphonium salt **93** is attacked by the alcohol to form the alkyloxyphosphonium salt **94** before the attack of the chloride ion, forming the product **96** and the phosphine oxide **3**. **Scheme 42.**



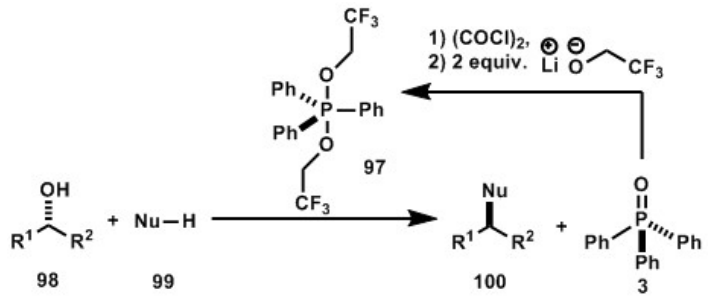

**Scheme 42. Denton's Catalytic Appel Reaction Catalytic Cycle.**[2, 3]

The advantage of this catalytic cycle is that the by-products of the reaction are easily removed as gases. The substrate screening showed moderate to excellent yields for primary and secondary alcohols with inversion of stereochemistry. One exception to this was a steroidal alcohol, which chlorinated with the expected retention of stereochemistry as a result of the participation of the neighbouring alkene. The only disadvantage is a practical one; there is a background reaction between the alcohol and the oxalyl chloride, so therefore the addition of the oxalyl chloride has to be done over a period of time.

For the analogous bromination reaction, an addition source of the bromide ion was required. The alkoxyphosphonium salt is still formed but it is the bromide

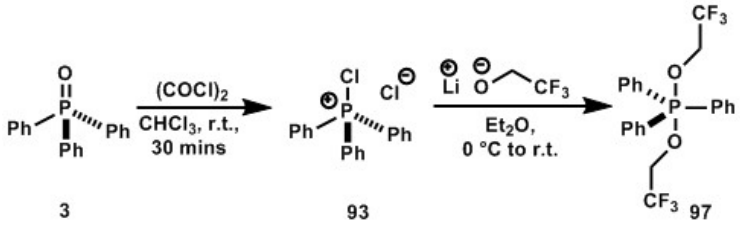
ion which attacks the carbon atom displacing the oxygen atom, forming the alkyl bromide and phosphine oxide.

Despite this progress with the Appel reaction, to date, there have been no reports on the development of a Mitsunobu reaction that is catalytic with respect to phosphorus. However, a redox-free protocol was recently developed by Denton and co-workers that eliminates the need for the reagent DEAD. **Scheme 43.**[45]




**Scheme 43. Preformation of phosphorane intermediate for use in a Mitsunobu Reaction.**

With the triphenylphosphine oxide acting as the source of the active phosphorus reagent in the process, means that the procedure produces no net phosphorus waste. To obtain the reactive dioxyphosphorane **97** from the inactive phosphine oxide it was reacted with oxalyl chloride to form the chlorophosphonium salt **93. Scheme 44.**[45]




**Scheme 44. Synthesis of phosphorane 97 for the Mitsunobu reaction.**

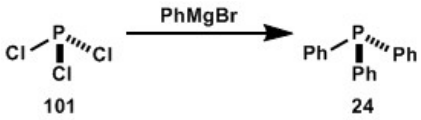
This chlorophosphonium salt **93** was then reacted with a lithium salt of trifluoroethanol, forming the alkoxyphosphorane **97.** Upon addition of the

alcohol and acid, the ligands exchange and the coupling occurs in the traditional Mitsunobu reaction manifold.

To date, no bespoke catalyst has been designed for use as a general catalyst; in the manner that triphenylphosphine is a general reagent for the phosphorus (V) mediated reactions. The common theme in the catalysts used in the literature examples of catalytic phosphorus (V) mediated reactions has been the use of cyclic phosphines and phosphine oxides. The use of these types of phosphine oxides was chosen due to the increased reactivity towards reduction or activation from a selection of known or commercially available compounds. It was the aim of this project to develop a new general catalyst for use in phosphorus (V)-mediated reactions and to understand the mechanisms by which the new catalyst works within the manifolds of the reactions. This catalyst was to contain the same backbone of the triphenylphosphine oxide but also contain some functionalization on one of the aryl rings to aid in catalysis.

# Chapter Two: Design and Synthesis of New Hydroxylmethyl-Aryl Phosphine Oxides

For most of the classical organophosphorus reactions the reagent of choice is triphenylphosphine, which is considered a universal reagent for most of these reactions. It is synthesised from the reaction of phosphorus trichloride with phenyl magnesium bromide. **Scheme 45.**




**Scheme 45. Synthesis of triphenylphosphine.**

Production of phosphorus trichloride is controlled under the chemical weapons convention, and is produced by refluxing white phosphorus with chlorine and continually removing the product to avoid over addition. Triphenylphosphine is able to react with a variety of compounds forming the many different intermediates of the organophosphorus reactions. These intermediates each have characteristic shifts ranges in the $^{31}$P NMR and can be used to determine structures formed during the reactions. **Chart 1.**[2-4, 10, 12, 13, 16, 17, 19, 22, 29, 36-38, 46-52]

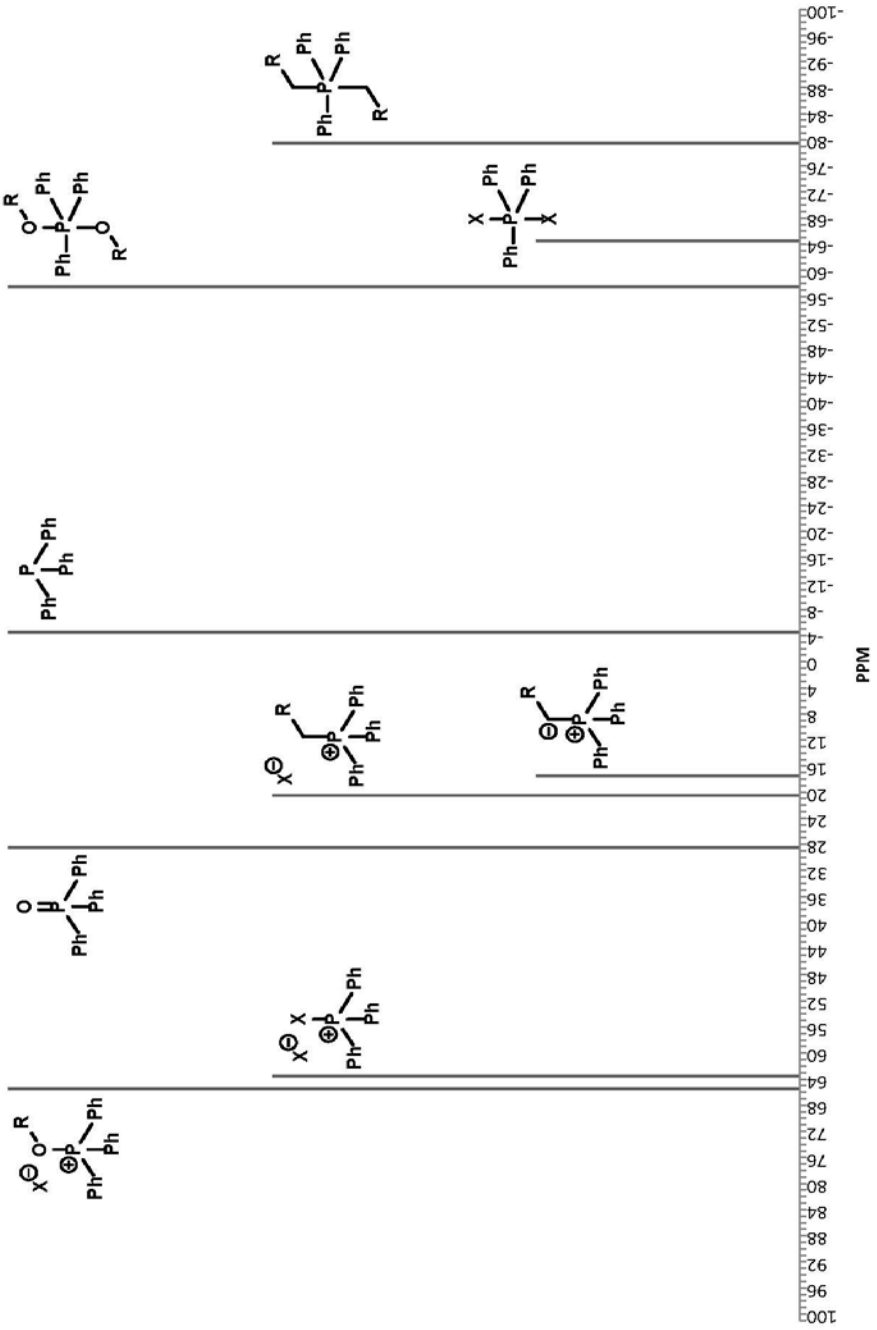



**Chart 1. Common $^{31}$P NMR shifts for Classical Intermediates, Products or Starting materials of Organophosphorus Reactions.**

Previous work has been focused on the reduction of phosphine oxides that are commercially available or contain strained ring systems, but there has been little focus on functionalization in order to render the phosphoryl group more reactive with respect to reduction or activation. The aim of this project has been to functionalise one of the aryl rings in order to; (a) accelerate the

reduction and/or (b) aid in the activation of the oxide to the required organophosphorus intermediates. **Figure 2.**[53]

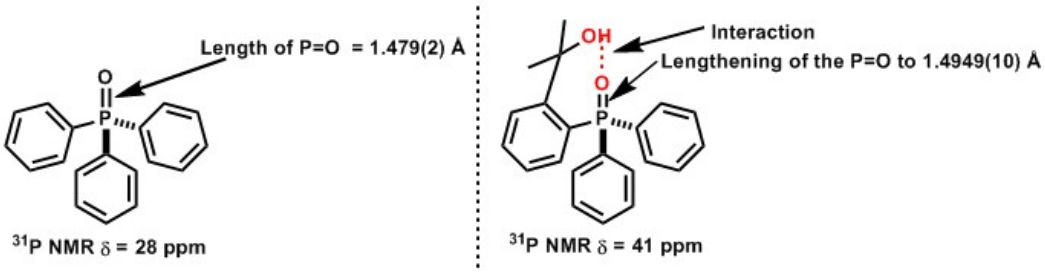
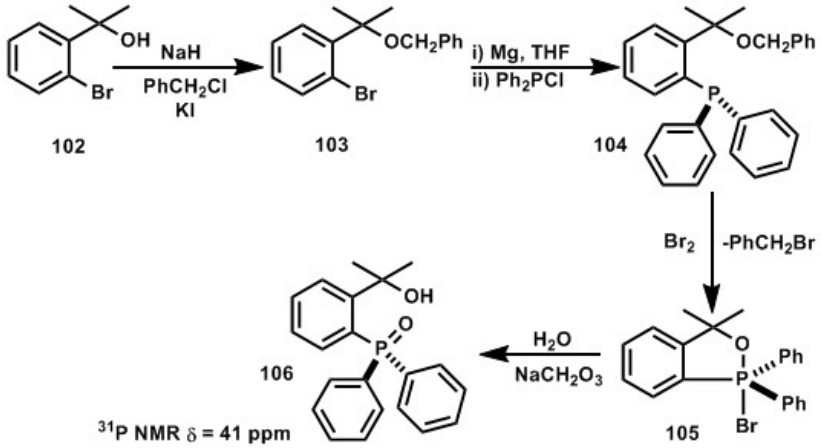



**Figure 2. Proposed functionalised aryl phosphine oxide.**

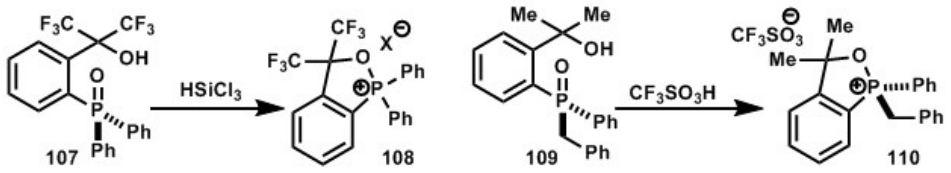
In the early eighties, Granoth and co-workers synthesised an aryl phosphine oxide with a hydroxyl aryl substituent.[54-56] **Scheme 46.**




**Scheme 46. Granoth's synthesis of Hydroxylmethyl-Aryl phosphine oxide.**[54-56]

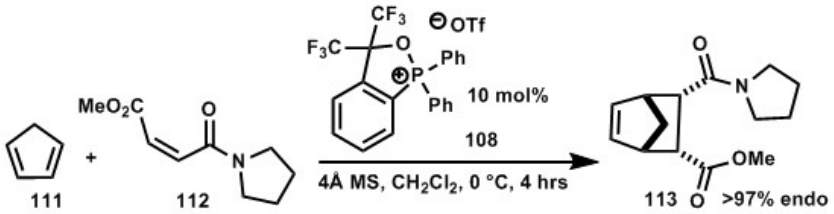
This phosphine oxide **106** had an unusually high downfield shift in the phosphorus NMR ($^{31}$P NMR δ = 41 ppm) compared to tri-aryl phosphine oxides such as tri-phenyl phosphine oxide, which had a $^{31}$P NMR shift of 28 ppm. This shift was caused by a hydrogen bond interaction between the alcohol on the aryl ligand and the oxygen of the P=O. **Figure 2.**

There have been reports that these stable phosphine oxides **106** reacted to form the alkoxyphosphonium salt **108** under various conditions, with different R groups attached. **Scheme 47.**[57]



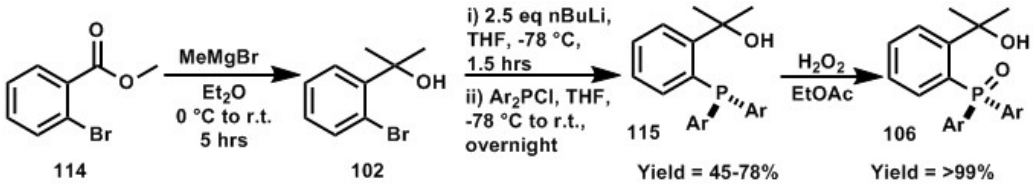

**Scheme 47. Examples of conversion of Hydroxylmethyl-Aryl phosphine oxide 106 into the alkoxyphosphonium salt 108.**

It had also been shown that these alkoxyphosphonium salts **108** can catalyse Diels-Alder reactions, by coordination of the alkoxyphosphonium salt to the carbonyl group present in the dienophile. **Scheme 48.**[57]




**Scheme 48. Lewis-acid catalysed Diels-Alder reaction.**

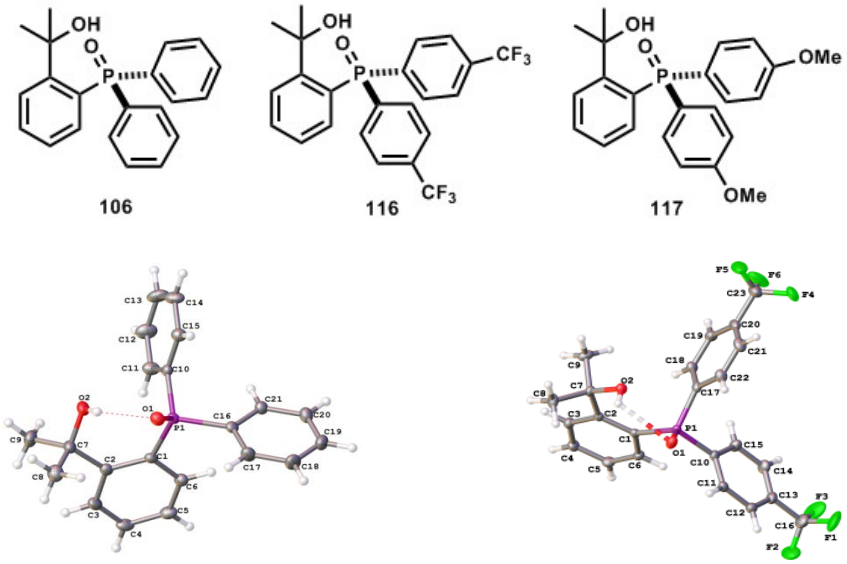
These phosphine oxides contained the functionalization that interacts with the phosphorus-oxygen bond in a way that could potentially increase the reactivity of the oxides towards the reduction to the phosphine. Three different phosphine oxides with various electronic properties and the Hydroxylmethyl-Aryl ligand were synthesised using a new three step protocol developed in the group. **Scheme 49.**




**Scheme 49. Synthesis of the hydroxyl aryl phosphine oxides.**

The reaction was performed at low temperatures as the di-lithium species was very reactive and self-polymerisation was seen at higher temperatures. The

phosphine oxides **106** were all solids, however, yet only two were crystalline and their structures were determined by X-ray crystallography. **Figure 3.**




**106**

$^{31}$P NMR δ = 41 ppm

Distance between P=O and OH = 1.937 Å

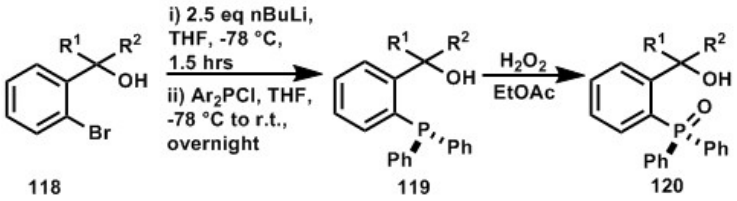
**116**

$^{31}$P NMR δ = 39 ppm

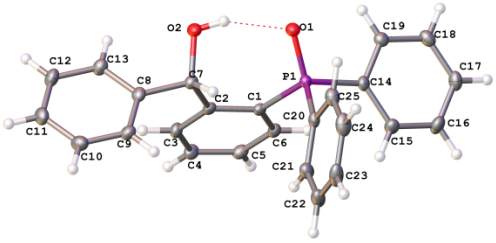
Distance between P=O and OH = 2.408 Å

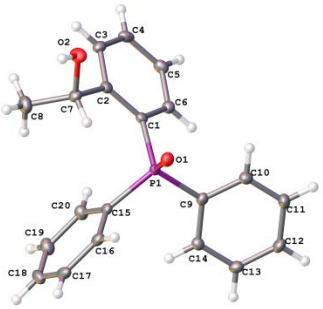
**Figure 3. Synthesised phosphine oxides.**

The hydrogen bond interaction is clearly seen in the crystal structures forming a six-membered ring structure. The effect of the substitution of the hydroxyl group on the hydrogen bond was investigated with the synthesis of two additional phosphine oxides. **Table 1.**




| $R^1$ | $R^2$ | $R^1$ | $R^2$ |
|---|---|---|---|
| Ph | H | Me | H |





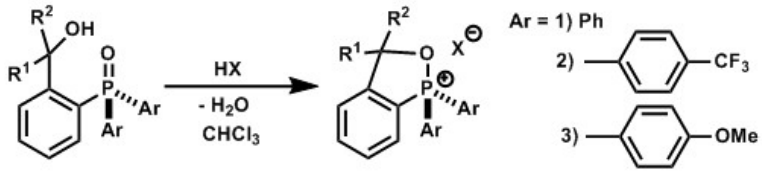
**121**
$^{31}$P NMR δ = 35 ppm
Distance between P=O and OH = 1.855 Å

**122**
$^{31}$P NMR δ = 31 ppm
Distance between P=O and OH = 4.284 Å

**Table 1. X-ray structure of the mono-substituted hydroxyl aryl phosphine oxides.**

The mono-substituted Hydroxylmethyl-Aryl phosphine oxide has a diminished hydrogen interaction between the phosphoryl group and the hydroxyl group. This is seen in the upfield shift of the $^{31}$P NMR shifts towards the triphenyl phosphine oxide shift (δ 28 ppm) and an increase in distance in the X-ray crystal structure. **Table 1**.

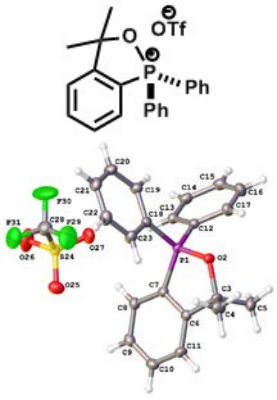
The interaction between the phosphoryl group and the hydroxyl group could lead to the formation of alkoxyphosphonium salt. The formation of the alkoxyphosphonium salt was desirable as a more synthetically useful intermediate than the phosphine oxide. It is also a way to switch between phosphine oxides and alkoxyphosphonium salt. Each of the Hydroxylmethyl-Aryl phosphine oxide was reacted with several acids to ascertain whether the phosphine could be activated for use in catalytic phosphorus (V) mediated reacted. **Table 2.**




| | $R^1$ | $R^2$ | Ar | Acid | Yield (%) | $^{31}$P NMR (ppm) |
|---|---|---|---|---|---|---|
| **1** | Me | Me | 1 | $HBF_4$ | 57 | 74 |
| **2** | Me | Me | 1 | HCl | 100 | 73 |
| **3** | Me | Me | 1 | TfOH | 71 | 73 |
| **4** | Me | Me | 1 | TsOH | 71** | 73 |
| **5** | Me | Me | 1 | Trichloroacetic acid | 76 | 73 |
| **6** | Me | Me | 1 | CSA | 50** | 73 |
| **7** | Me | Me | 1 | TFA | 50** | 73 |
| **8** | Me | H | 1 | $HBF_4$ | 87 | 77 |
| **9** | Ph | H | 1 | $HBF_4$ | 81 | 77 |
| **10*** | Ph | H | 1 | HCl | 52 | 33 |
| **11** | Ph | H | 1 | TsOH | 50** | 77 |
| **12** | Ph | H | 1 | TfOH | 50** | 77 |
| **13** | Me | Me | 2 | $HBF_4$ | 45 | 72 |
| **14** | Me | Me | 3 | HCl | 100** | 72 |

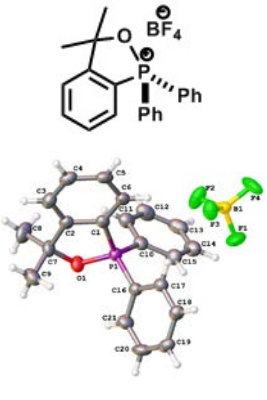
**Table 2. Formation of alkoxyphosphonium salt using various acids. *not isolated as the alkoxyphosphonium salt (*vide infra*). ** Conversion based on $^{31}$P NMR.**

Two of the alkoxyphosphonium salts were crystalline solids and their X-ray crystal structures were determined. **Figure 4.**




**123**

Length of P-O bond = 1.5764(11) Å




**124**

Length of P-O bond = 1.582 (3) Å

**Figure 4. X-ray crystal structures of alkoxyphosphonium salt.**

The formation of the alkoxyphosphonium salt was corroborated by $^{13}$C NMR. **Figure 5.**

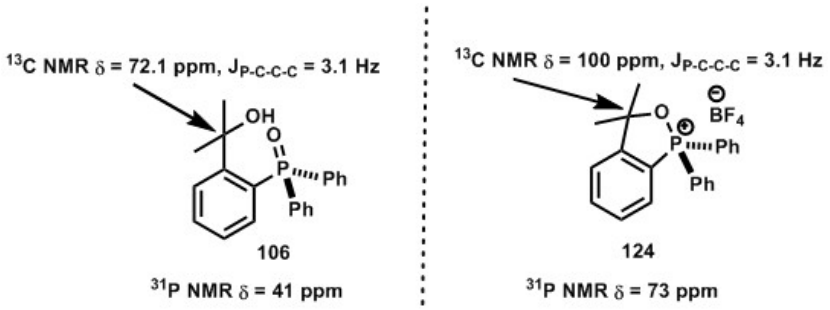



**Figure 5. $^{13}C$ and $^{31}P$ NMR comparison of Hydroxylmethyl-Aryl phosphine oxide and alkoxyphosphonium salt.**

The treatment of the phenyl hydroxyl diphenyl phosphine oxide **(Table 2, entry 10)** with hydrochloric acid resulted in the formation of a new phosphine oxide. In order to determine the structure of this new phosphine oxide, the $^{13}C$ NMR was studied and compared with the original. **Figure 6.**

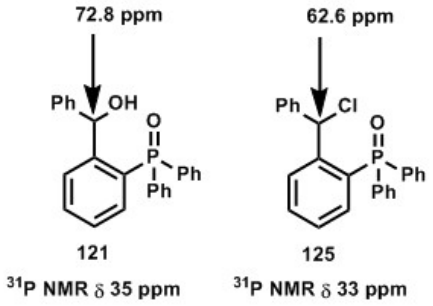
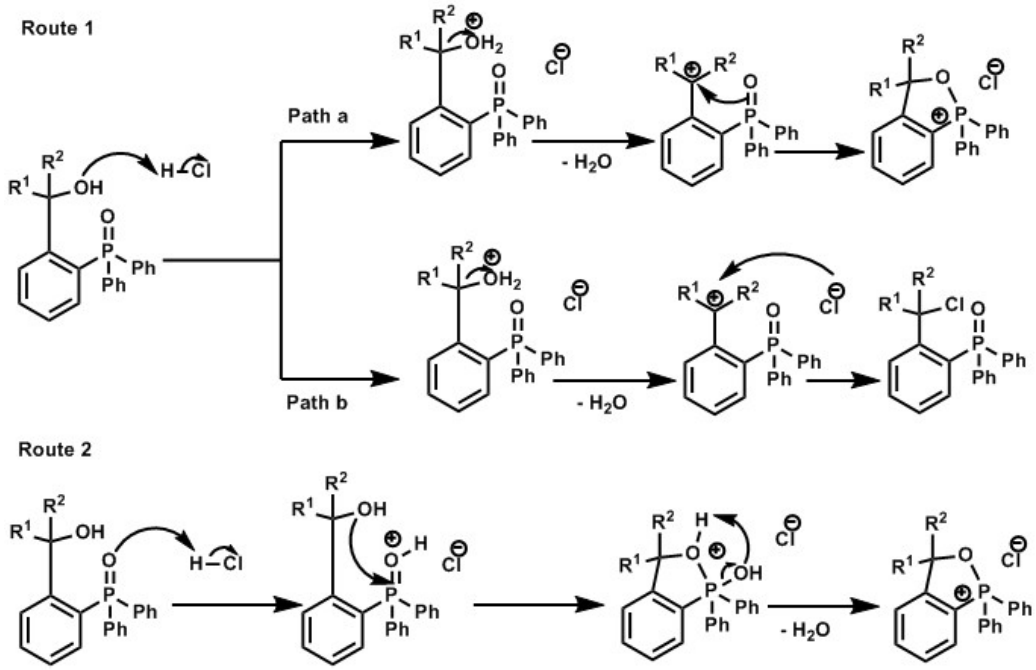



**Figure 6. NMR study of phosphine oxides.**

This suggests a mechanism regarding how the ring closing could hypothetically occur. The oxygen of the phosphoryl group could attack the carbon centre and release the molecule of water, closing the ring, **Route 1. Scheme 50.** The other route of attack was for the hydroxyl group to attack the phosphorus and break the oxide bond, **Route 2. Scheme 50.**




**Scheme 50. Proposed mechanism for the ring closing.**

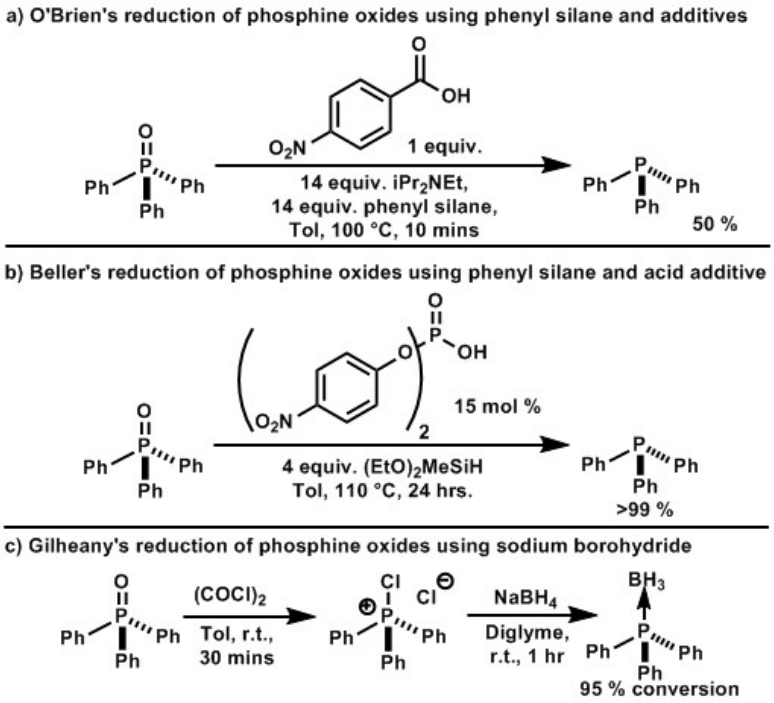
The Hydroxylmethyl-Aryl phosphine oxides and alkoxyphosphonium salts were then used to:

- Investigate the reduction potential of the Hydroxylmethyl-Aryl phosphines compared to that of triphenylphosphine oxides.
- Investigate the reduction of the alkoxyphosphonium salt.
- Investigate the use of the Hydroxylmethyl-Aryl phosphines and alkoxyphosphonium salts in a redox-driven catalytic manifold for phosphorus (V)-mediated reaction.
- Investigate the use of the Hydroxylmethyl-Aryl phosphines and alkoxyphosphonium salts in a redox-neutral catalytic manifold for phosphorus (V)-mediated reaction.

# Chapter Three: The Development of Redox-Driven Catalytic Phosphorus (V) -Mediated Reactions

### 3.1 Investigation of the Reduction of Phosphine Oxides using Phenyl Silane

In order to assess the potential of the Hydroxylmethyl-Aryl phosphine oxide in redox-driven phosphorus (V) mediated reaction, a study into the reduction of triaryl phosphine oxides, such as triphenyl phosphine must be undertaken. With the conditions for the reduction of phosphine oxide usually requiring high temperatures and long reaction times, there have been many studies into milder conditions. The most prominent of these works are by the O'Brien group, the Beller group and the Gilheany groups.[36, 58, 59] **Scheme 51.**

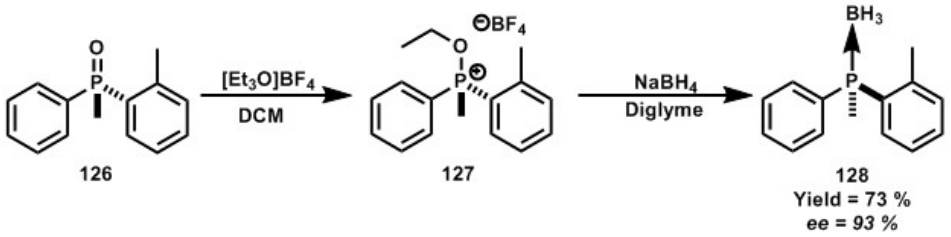



**Scheme 51. Reduction of Phosphine oxides using newly developed protocols.[36, 58, 59]**

Beller and co-workers' work demonstrates an organocatalytic reduction of phosphine oxides to phosohines with an inexpensive hydrosilane reagent ($[EtO]_2MeSiH$) and phosphoric acid ester.[59] The protocol tolerates a range of functional groups with *good-to-very good* yields. It is noted by Beller that the

excellent chemoselectivity protocol has the reduction of only the phosphine oxide in presence of other reducible groups, such as aldehydes and ketones, would make it a methodology for redox-driven catalytic phosphorus (V)-mediated reaction.[59]

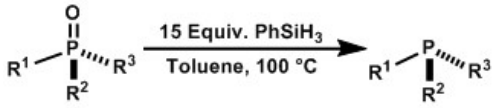
The Gilheany reduction utilises the smooth conversion of phosphine oxides to the corresponding chlorophosphonium salt using oxalyl chloride, before using a mild reductant (sodium borohydride) to form the phosphine-borane complex. These phosphine-boranes are less reactive than phosphine and a common method for storing highly reactive phosphines. The borane is easily removed by stirring with a primary amine to produce the phosphine in high yields.[60] This method can produce the chiral phosphines required as ligands for asymmetric synthesis.[61, 62] This approach eliminates the biggest challenge facing the reduction of the phosphorus-oxygen double bond by transforming the bond into a weaker phosphorus-chlorine bond, which is easier to reduce. This method works well for a range of aryl and alkyl phosphine oxide substrates. For the enantiomerically enriched *P*-stereogenic examples it was found that the oxalyl chloride method resulted in racemisation of the *P*-stereocentre. As an alternative to forming the chlorophosphonium salt, the use of Meerwein's salt results in the formation of an alkoxyphosphonium salt, which can be reduced without degrading the *ee* of the phosphorus centre.[58] **Scheme 52**.

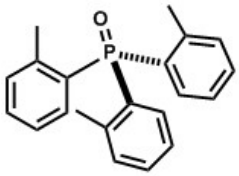
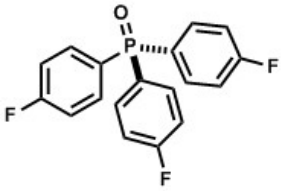
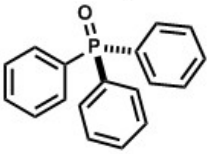



**Scheme 52. Stereospecific Reduction and Boronation of optically active phosphine oxides.**[58]

The work by O'Brien demonstrates that the addition of two additives (acid and amine) can increase the reactivity of the silane toward reductions, decreasing the reaction time or lower reaction temperature.[63] The reduction of phosphine oxides using the method shown by O'Brien was investigated in order to get an understanding into the mechanism and the effect different additives have on the reduction power of the silane involved.

A comparison of Hydroxylmethyl-Aryl and other phosphine oxides was made under uniform reaction conditions. **Table 3.**




| Entry | Phosphine Oxide | 1 hr Conversion (%) | 4 hrs Conversion (%) |
|---|---|---|---|
| **1** |  | 0 | 0 |
| **2** |  | 0 | 9 |
| **3** |  | 4 | 34 |

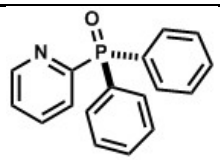
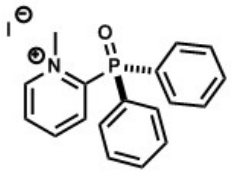
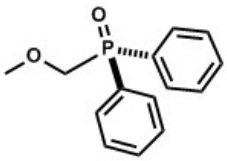
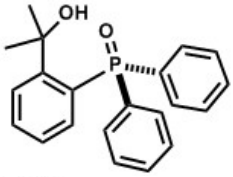
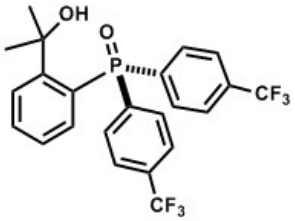
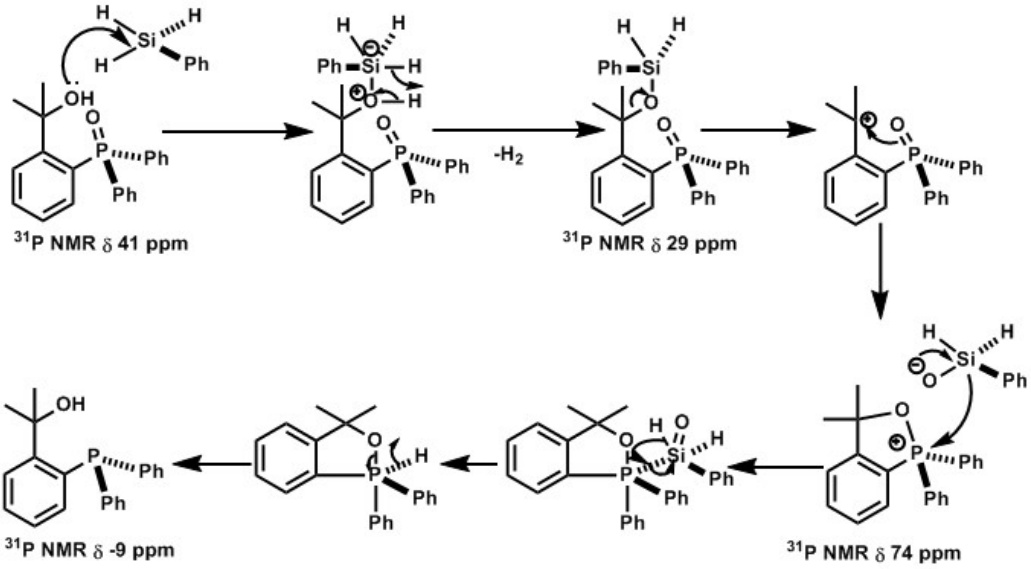
| | | | |
|---|---|---|---|
| **4** |  | 12 | 51 |
| **5** |  | 17 | 58 |
| **6** |  | 11 | 64 |
| **7** |  | 44 | 78 |
| **8** |  | 100 | - |
| **9** |  | 100 | - |

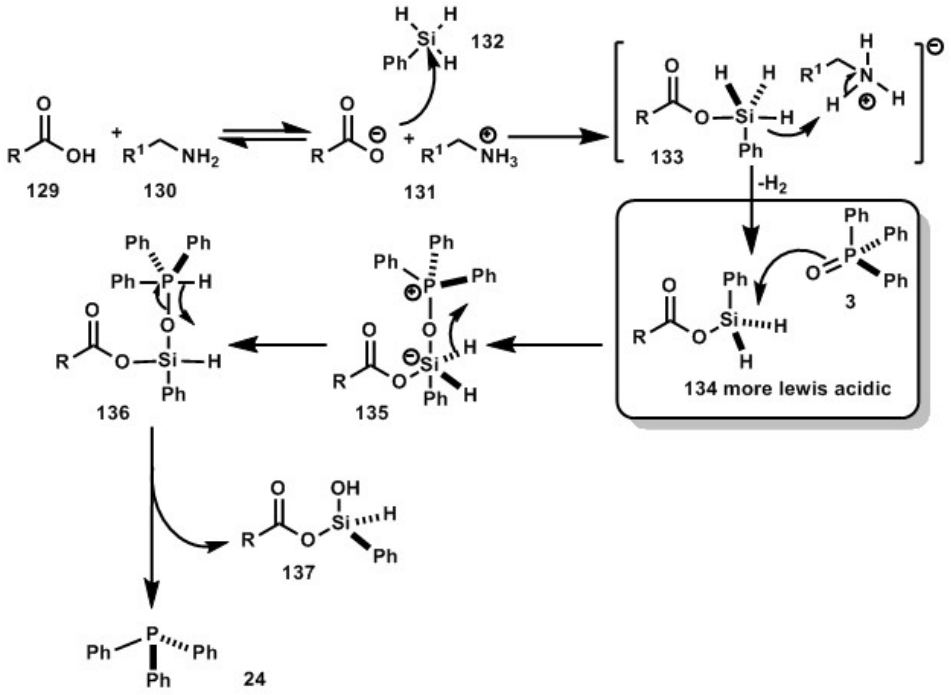
**Table 3. Reduction of a range of phosphine oxides using phenyl silane.**

The inclusion of the Hydroxylmethyl-Aryl substituent has clearly resulted in much faster rates of reduction compared to other aryl and alkyl tertiary phosphine oxides. To understand the mechanism of the reduction of the Hydroxylmethyl-Aryl phosphine oxides, the reaction was monitored over 1 hour. During the reaction, two intermediates were seen in the phosphorus NMR; one at δ 29 ppm and one at δ 74 ppm. The intermediate at δ 29 ppm is indicative of a tertiary aryl phosphine oxide without the hydrogen bond and the peak at δ 74 ppm is known to be the internal alkoxyphosphonium salt of the Hydroxylmethyl-Aryl phosphine oxide.[54-56] The mechanism for the reduction of the Hydroxylmethyl-Aryl phosphine is proposed in **Scheme 53.**




**Scheme 53. Mechanism for the reduction of Hydroxylmethyl-Aryl phosphine oxides with phenyl silane.**

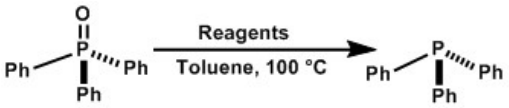
The use of additives has been investigated by O'Brien in the catalytic Wittig reaction in order to aid phosphine oxide reduction and give a room temperature protocol. The investigation of the reduction step conducted by O'Brien and co-workers identified the need for both the amine and acid in the reduction.[36] O'Brien theorises that the acid "activates" the phosphoryl group through proton donation, but in the reduction of the phosphine oxide with the acid; without the presence of the amine base, only 5 % reduction was observed. It is known that amines catalyse the formation of silyl esters and have been used as a protocol for amide coupling.[40] The *in-situ* formation of the more Lewis acidic silyl ester **134** gives the possibility of mild phosphine oxide reduction, which could lead to milder catalytic organophosphorus reactions such as the Wittig reaction. This proposed mechanism can be summarised in **Scheme 54.**

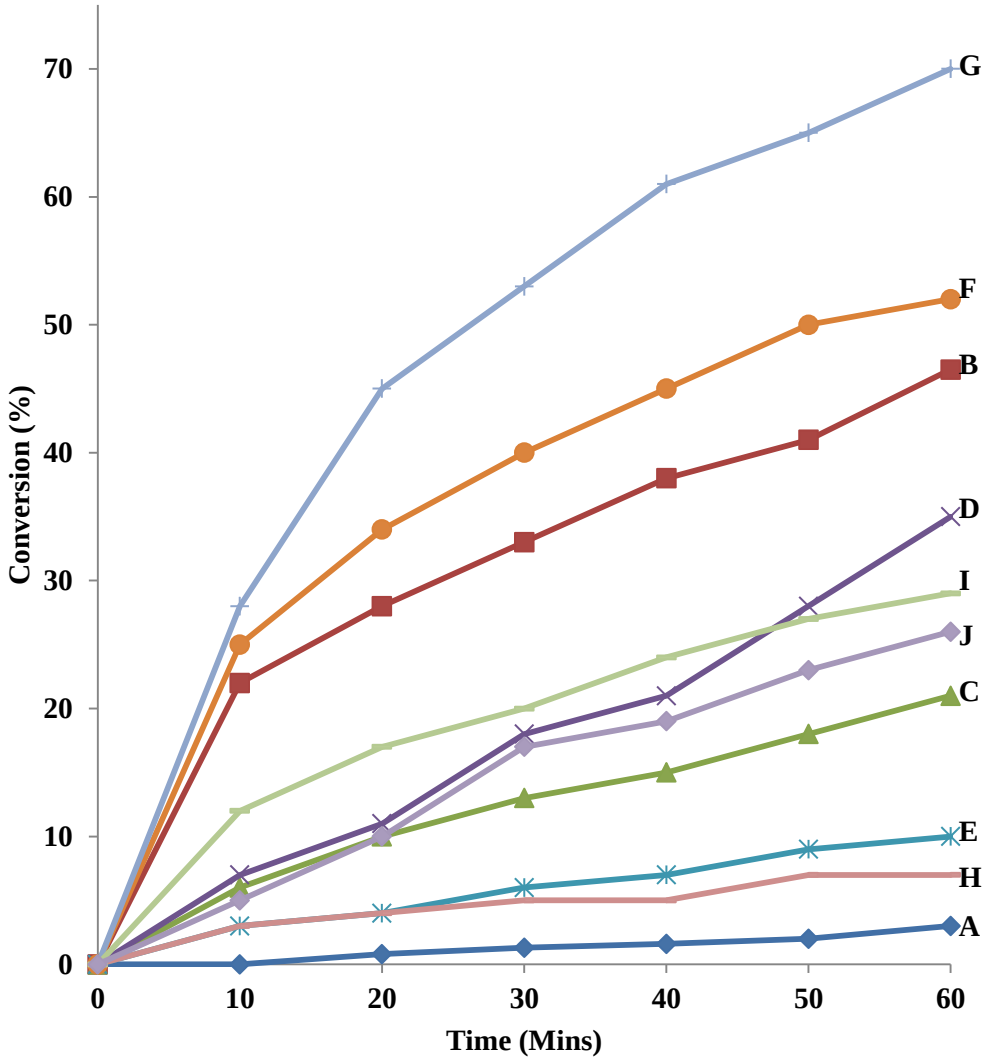



**Scheme 54. Mechanism for the reduction for triphenylphosphine.**

This mechanism is similar to that proposed for the phenyl silane reduction, which, when applied to a chiral phosphine oxide, takes place with retention of stereochemistry. In order to corroborate the proposed mechanism, investigation using a chiral phosphine would need to be undertaken.

Conditions for the reduction of triphenylphosphine oxide were investigated using phenyl silane and a combination of acid and amine. **Graph 1.**




**A** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % DIPEA

**B** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % DIPEA + 10 % TFA

**C** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % DIPEA + 10 % nitrobenzoic acid

**D** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % TFA

**E** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % TFA + 10 % DIPEA + $Bu_4NBr$

**F** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % TFA + 15 equiv. DIPEA

**G** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % TFA + 20 % DIPEA + 10 % HCl

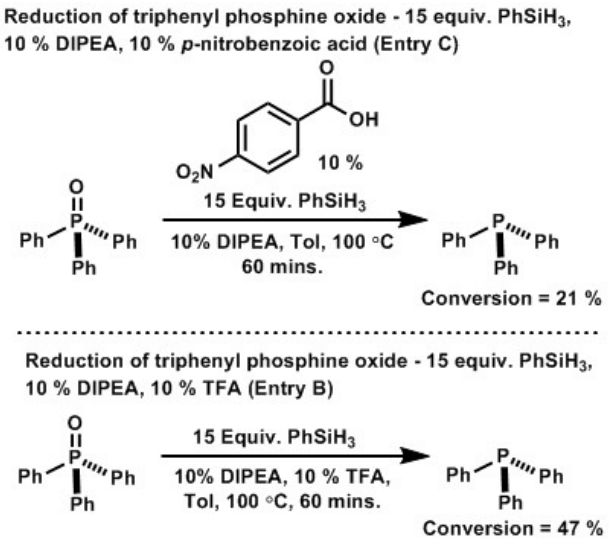
**H** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % TFA + 10 % DIPEA + 15 equiv. $Bu_4NBr$

**I** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 10 % DIPEA + 10 % TFA (EtOAc, 80 °C)

**J** = $(O)PPh_3$ + 15 equiv. $PhSiH_3$ + 20 % DIPEA + 10 % HCl

**Graph 1. Reductions of triphenylphosphine oxide using phenyl silane and a combination of additives.**

The results of this investigation shows that, upon the addition of an amine and acid additive, the rate increases ten-fold, converting 47% of triphenylphosphine oxide in one hour. **Graph 1, entry B**. This gives rise to the mechanistic reasoning, **Scheme 54**, the formation of the more Lewis acidic tetravalent silicon species **134,** leading to the increase in the reactivity of the silicon centre. This is also seen in O'Brien's catalytic Wittig reaction, with the use of benzoic acid as an additive, this allows the reaction to be performed at room temperature with a commercially available cyclic phosphine oxide. A comparison between the use of nitro benzoic acid and trifluoroacetic acid as the additive was studied, **Graph 1, Entry B and C. Scheme 55.**




**Scheme 55. Comparison of trifluoroacetic acid and benzoic acid as additives for the reduction of phosphine oxides.**

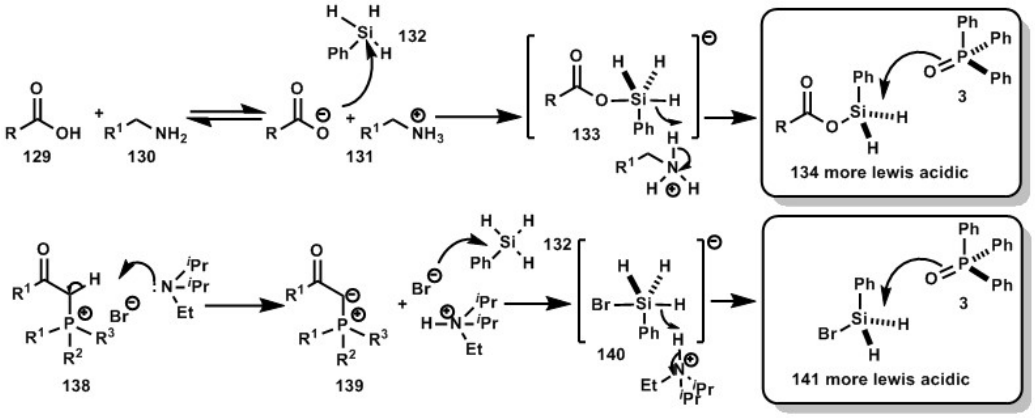
Nitro benzoic acid (*p*Ka 9.1 (DMSO)) is less acidic and reacts more slowly than the stronger acid trifluoroacetic acid (*p*Ka 3.4 (DMSO)), therefore decreasing the rate of reduction of the phosphine oxide.

In the catalytic Wittig reaction, the base removes a proton from the phosphonium salt **138** to form the phosphonium yilde **139** during each iteration of the catalytic cycle. **Scheme 56.**



**Scheme 56. Formation of the phosphonium ylide 139.**

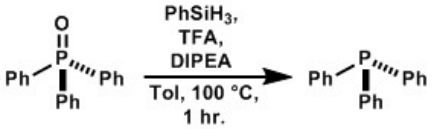
The ammonium salt formed during this process can also activate the silicon species in the same way as the trifluoroacetic acid does, forming the more reactive silicon species. **Scheme 57.**




**Scheme 57. Potential reductant partners of O'Brien's catalytic Wittig reaction.**

The catalytic Wittig reaction contains both of these reductant partners; therefore an experiment using additional protons was undertaken. **Graph 1. Entry G.** The addition of the extra salt increases the rate of the reduction significantly, thus leading to much milder conditions for some phosphines.

The effect of the silyl esters on the reduction was investigated using one equivalent of the silane. **Table 4.**

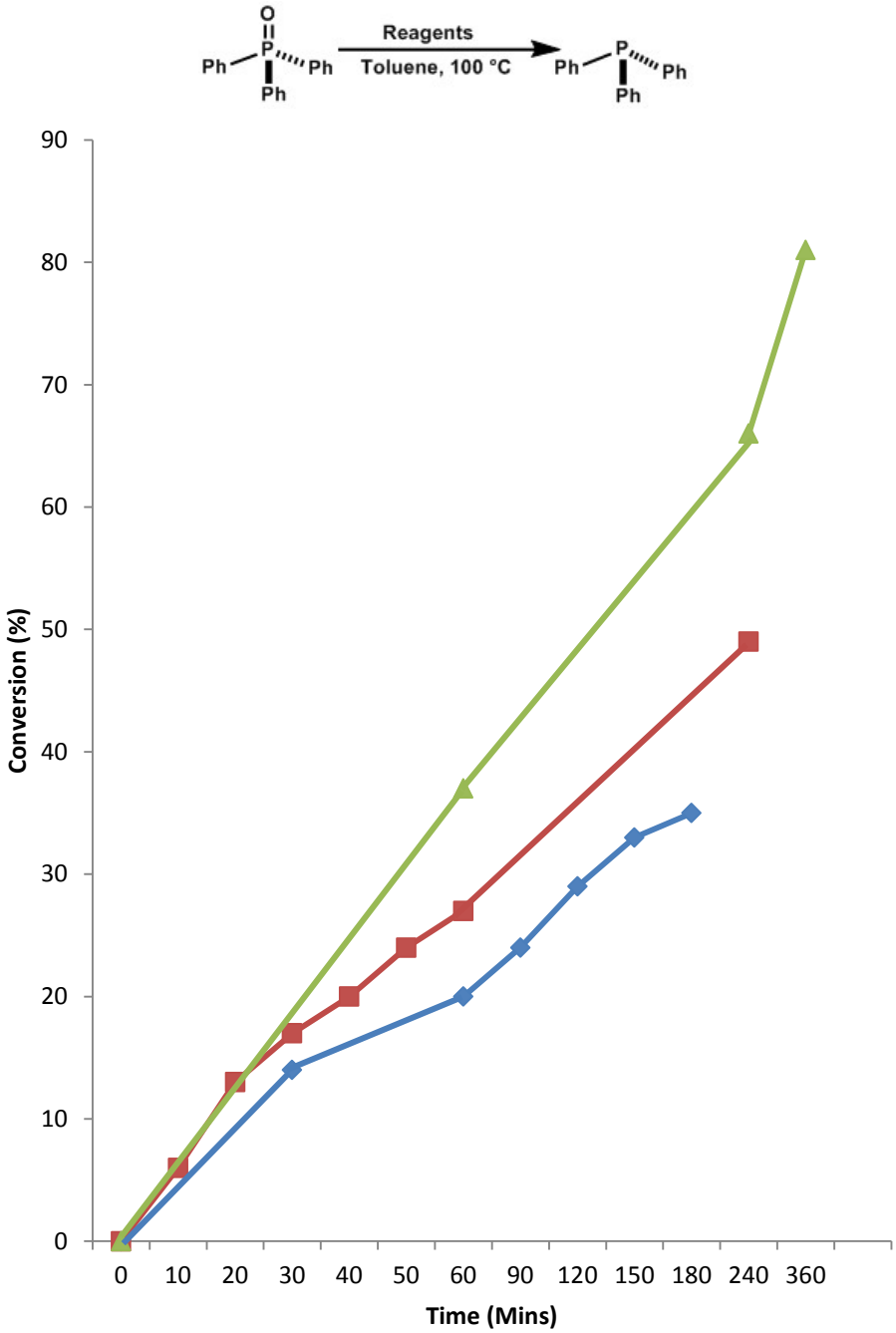



| Entry | Equiv. of $PhSiH_3$ | Equiv. of TFA | Equiv. of DIPEA | 10 mins. (%) | 20 mins. (%) | 30 mins. (%) | 40 mins. (%) | 50 mins. (%) | 1 hr (%) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 1 | 1 | 1 | 22 | 31 | 38 | 43 | 46 | 48 |
| **2** | 1 | 3 | 1 | 3 | 3 | 3 | 4 | 3 | 3 |

**Table 4. Use of the silyl esters to reduce the phosphine oxide.**

The availability of the hydrogens on the silane is important for the reduction to occur. If each site on the silane is block with an ester group, then the reduction will not occur **(Table 4, entry 2).** Even with a 1 : 1 mixture of silane and acid, full reduction was not achieved in a single hour; but it is still an improvement on the traditional reduction using 15 equivalents of silane **(Table 4, entry 1).**

The continual use 15 equivalents of phenyl silane, which is an expensive reductant (£17 per gram), is highly undesirable, so an investigation into using fewer equivalents with the new additive combination was undertaken. **Graph 2.** The optimisation of the reductant showed that three equivalents was the optimal amount of reductant required to reduce the phosphine oxides to phosphine within 6 hours. **Graph 2, Entry C.**



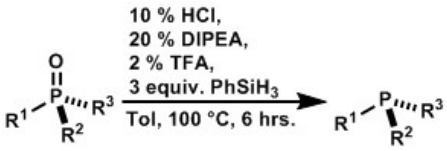

**Blue** = 1.5 equiv. $PhSiH_3$, 10 % DIPEA, 1 % TFA

**Red** = 1.5 equiv. $PhSiH_3$, 10 % HCl, 20 % DIPEA, 1 % TFA

**Green** = 3 equiv. $PhSiH_3$, 10 % HCl, 20 % DIPEA, 2 % TFA

**Graph 2. Optimisation of the reductant required for the formation of phosphine.**

The best conditions (3 equivalents of phenyl silane, 10% hydrochloric acid, 20 % Diisopropylethylamine, 2 % trifluoroacetic acid, 100 °C in toluene for 6 hours) was used to screen phosphine oxide tri-substituted substrates. **Table 5.**



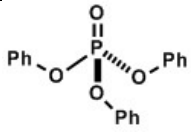
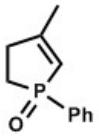
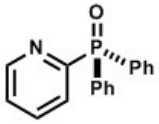
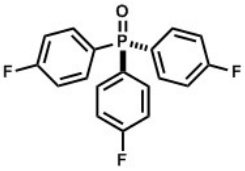
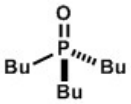
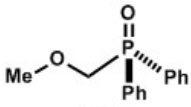
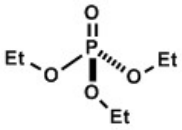
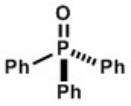
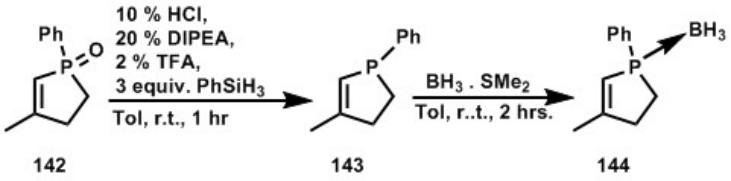

| Entry | Phosphine Oxide | Conversion 1hr (%) | Conversion 4hrs (%) | Conversion 6hrs (%) | Yield (%) |
|---|---|---|---|---|---|
| **1** |  | No reaction | No reaction | No reaction | 0 |
| **2** |  | 100 | - | - | 15* |
| **3** |  | 52 | 89 | 97 | 60* |
| **4** |  | 39 | 68 | 80 | 55 |
| **5** |  | 63 | 100 | - | 40* |
| **6** |  | 100 | - | - | 80* |
| **7** |  | No reaction | No reaction | No reaction | 0 |
| **8** |  | 37 | 66 | 81 | 48* |

**Table 5. Substrate scope for the reduction conditions** *Substrates isolated as the phosphine-borane complex.

From the screening, most tertiary aryl and alkyl phosphine oxides were reduced smoothly under these conditions but, unfortunately, phosphates were not reduced under these conditions. The first generation cyclic phosphine oxide reacted quickly under the initial conditions and reoxidised (**Table 5, Entry 2**) during column chromatography. The cyclic phosphine oxide was subjected to

the amine/acid conditions at room temperature before being subjected to complexation with borane species. **Table 6.**



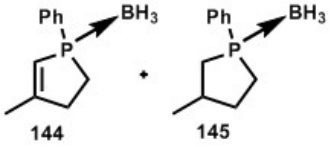
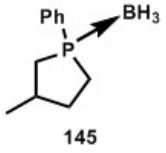

| | Conversion (%) | Equivalents of Borane | Product | Yield (%) |
|---|---|---|---|---|
| **1** | 100 | 1 |  144 + 145 | 20 |
| **2** | 93 | 3 |  145 | 63 |

**Table 6. Room temperature reduction of O'Brien first generation catalyst.**

The alkene in the phosphine oxide **142** is susceptible to hydroboration by the borane complex. With the addition of an excess of the borane the double bond is reduced and the phosphine is complexed.

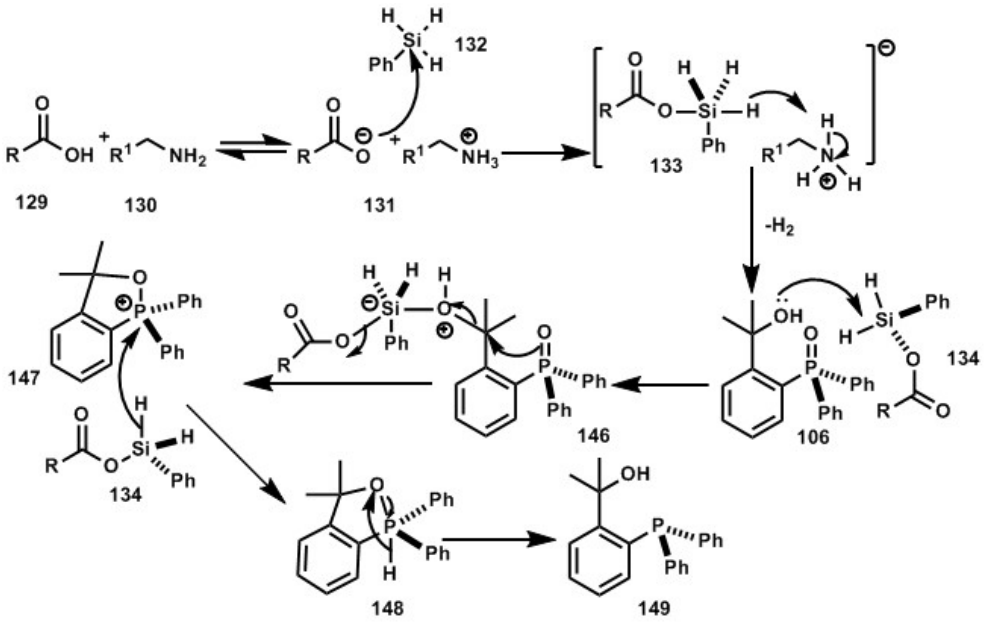
The Hydroxylmethyl-Aryl phosphine oxide **106** reduction was investigated next with the use of the acid and amine additives. **Table 7.**




| Entry | Reduction Conditions | Temperature (°C) | Solvent | Conversion 10 mins (%) |
|---|---|---|---|---|
| **1** | 15 equiv. phenyl silane, 10 % DIPEA, 10 % TFA | 100 | Toluene | 100 |
| **2** | 1.5 equiv. phenyl silane, 10 % HCl, 20 % DIPEA, 1 % TFA | 20 | EtOAc | 20 |
| **3** | 3 equiv. phenyl silane, 10 % HCl, 20 % DIPEA, 2 % TFA | 20 | EtOAc | 100 |

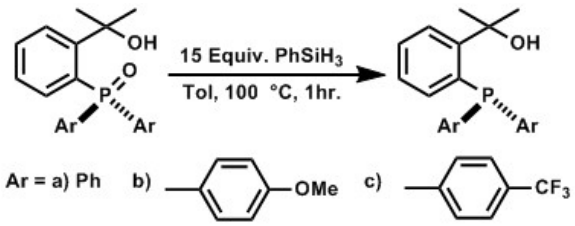
**Table 7. Reduction of the Hydroxylmethyl-Aryl phosphine oxide using amine and acid.**

The reaction proceeds quickly at room temperature, making it ideal as a catalyst for a redox-driven catalytic cycle. The reaction mechanism follows the same pathway as previously seen with the previously seen intermediates seen in the reaction with just phenyl silane. **Scheme 58.**



**Scheme 58. Reaction mechanism with phenyl silane with amine and acid.**

The reduction of the Hydroxylmethyl-Aryl phosphine oxides were compared to establish whether there were any electronic effects. **Table 8.**



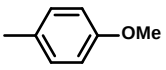
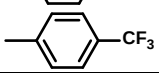
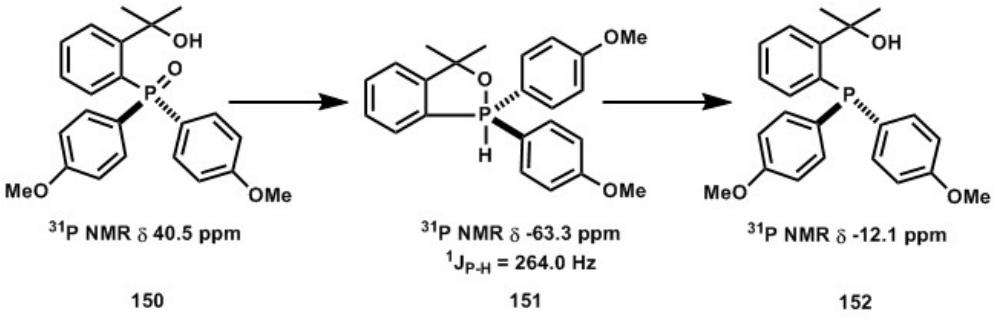

| Entry | Ar | Oxide $^{31}$P NMR shift (ppm) | Phosphine $^{31}$P NMR shift (ppm) | Conversion (%) |
|---|---|---|---|---|
| **1** | Ph | 41 | -11 | 100 |
| **2** |  | 39 | -13 and -63 | 96 (-13 pmm) |
| **3** |  | 40 | -9 | 100 |

**Table 8. Effects of electronics on the reduction of the Hydroyl-aryl Phosphine Oxides 106 to the Hydroxylmethyl-Aryl phosphines 149.**

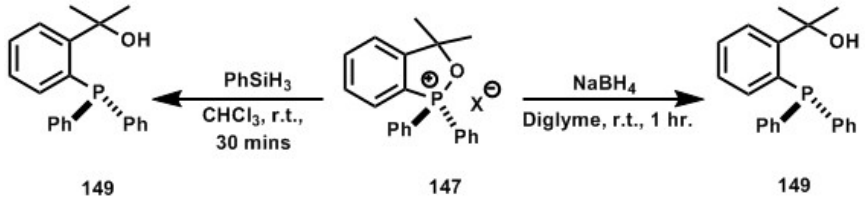
The reduction of methoxy derivative of the Hydroxylmethyl-Aryl phosphine oxide **150** was slower than the other derivatives. In the reduction of this Hydroxylmethyl-Aryl phosphine oxide **150** an intermediary peak is seen in the $^{31}P$ NMR at δ – 63.6 ppm $^{1}J_{P-H}$ = 279.5 Hz. **Scheme 59.**




**Scheme 59. Reduction of the Methoxy derivative Hydroxylmethyl-Aryl phosphine oxide.**

The observation of the phosphorane **151** in the reduction further supports the reduction mechanism for the Hydroxylmethyl-Aryl phosphine oxide proceeding, through the formation of the alkoxyphosphonium salt **147,** followed by the hydride transfer to give **148,** which collapses to form the hydroxyl group and the phosphine **152.**

With the successful reduction of the Hydroxylmethyl-Aryl phosphine oxide **106**, reduction of the alkoxyphosphonium salt **147** was also investigated using both the phenyl silane method and the Gilheany sodium borohydride protocol. **Scheme 60.**



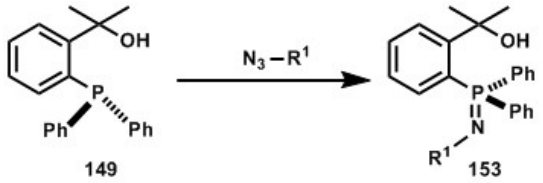

**Scheme 60. Reduction of the alkoxyphosphonium salt.**

The reduction of the alkoxyphosphonium salt **147** is easier than that of the Hydroxylmethyl-Aryl phosphine oxide **106**, which means that just phenyl silane or the milder reductant sodium borohydride, are able to reduce to the Hydroxylmethyl-Aryl phosphine **149** at room temperature within an hour.

With the reduction of this new Hydroxylmethyl-Aryl phosphine oxide **106** taking place under very mild conditions, the modification could lead new and improved phosphine catalysed reactions. The use of the Hydroxylmethyl-Aryl phosphine oxides in redox-driven catalytic phosphorus (V)-mediated reactions was investigated.

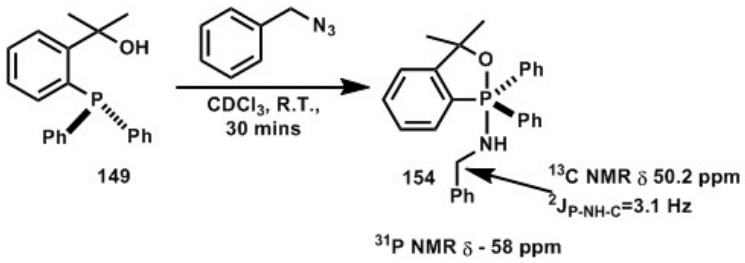
### 3.2 The Development of a Redox-Driven Staudinger Reduction

The Staudinger reduction was the initial reaction to be investigated under the redox-driven manifold. The Hydroxylmethyl-Aryl phosphine **149** was used to investigate the reaction with azides to form the iminophosphorane. **Scheme 61**.



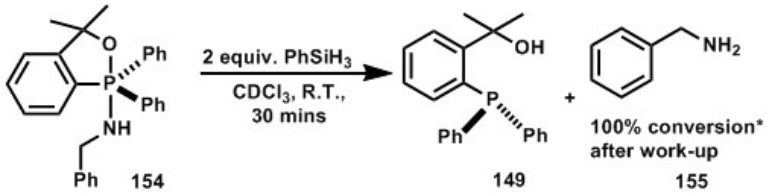

**Scheme 61. Theorised reaction between Hydroxylmethyl-Aryl phosphine and azides.**

The phosphorus NMR of the addition of phosphine **149** and benzyl azide did not produce the expected shift. Instead a new peak was seen in the penta-valent phosphorane region of the $^{31}$P NMR δ -58 ppm. From the $^{13}$C NMR δ 50.2 ppm (d, $^{2}J_{P\text{-}NH\text{-}C}$=3.1 Hz), which showed coupling to phosphorus *via* a heteroatom. It was determined that an amino-oxyphosphorane **154** was formed during the reaction. **Scheme 62**.



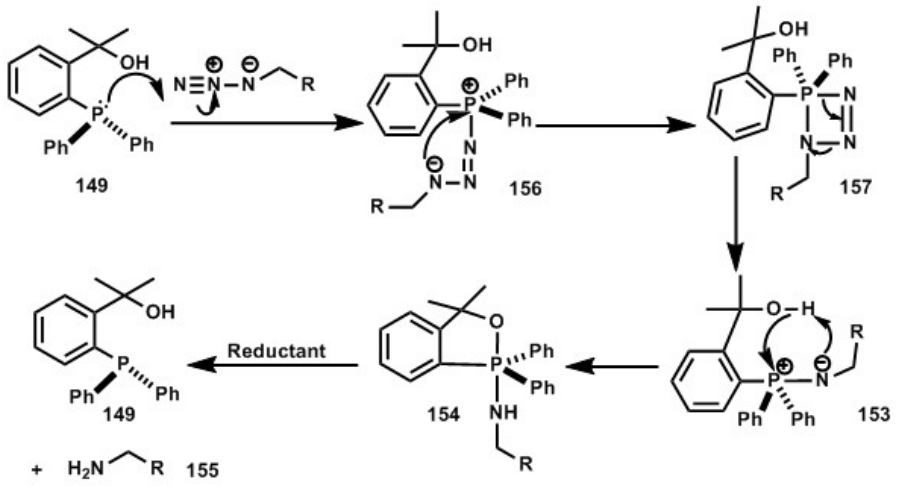

**Scheme 62. Reaction between Hydroxylmethyl-Aryl phosphine and benzyl azide.**

The reduction of this amino-oxyphosphorane **154** with phenylsilane was investigated. **Scheme 63**.




**Scheme 63. Reaction between amino-oxyphosphorane 154 and phenylsilane. *Conversion determined by $^{1}$H NMR.**

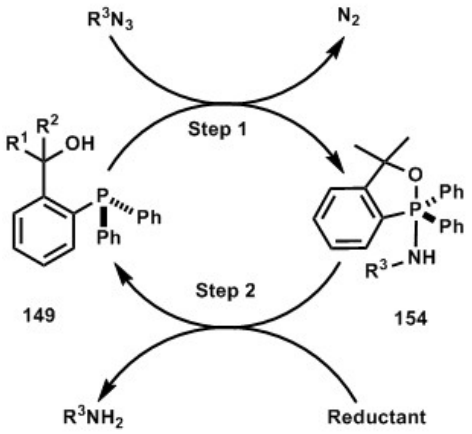
The formation of the amino-oxyphosphorane is rapid as there is an absence of a $^{31}$P NMR shift for the phosphonium ylide and, with the production of nitrogen being seen in the reaction vessel, this leads to the proposed mechanism. **Scheme 64**.




**Scheme 64. Mechanism for the formation of the amino-oxyphosphorane 154**.

The first steps of the mechanism are identical to the classical Staudinger reduction until the formation of the phosphonium ylide **153**. At this point the proton transfer results in the formation of an alkoxide speices and then the amino-oxyphosphorane **154**. The negatively charged oxygen then attacks the positively charged phosphorus, closing the ring and forming the amino-oxyphosphorane **154**.

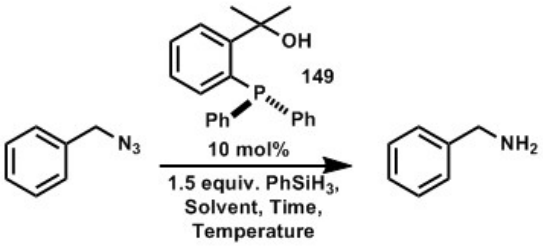
From the stoichiometric investigation of the Staudinger reduction using the new Hydroxylmethyl-Aryl phosphine **149** and phenylsilane, this catalytic cycle was developed. **Scheme 65**.




**Scheme 65**. **Proposed catalytic cycle for the Staudinger reduction using the new Hydroxylmethyl-Aryl phosphine.**

Although it is still redox-driven, as there is a change in oxidation state of the phosphorus atom from phosphorus (III) to phosphorus (V), there is no formation of the inactive phosphine oxide. This unique feature of the catalytic cycle means that milder conditions than those seen in other redox-driven phosphorus mediated reactions can be used.

Investigation into a catalytic Staudinger reduction was undertaken with 10 mol % of the Hydroxylmethyl-Aryl phosphine **149** catalyst. **Table 9**.

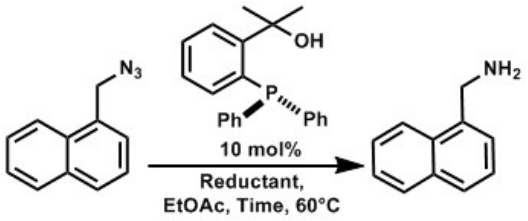



| Entry | Solvent | Time (h) | Temperature (°C) | Conversion* (%) |
|---|---|---|---|---|
| **1** | EtOAc | 1 | 20 | 19 |
| **2** | EtOAc | 5 | 20 | 35 |
| **3** | EtOAc | 16 | 20 | 41 |
| **4** | EtOAc | 3 | 60 | 61 |
| **5** | EtOAc | 5 | 60 | 92 |

**Table 9. Optimisation of the catalytic Staudinger reduction. *Conversion determined by $^{1}$H NMR after work-up.**

Using 1.5 equivalents of phenylsilane reductant, the catalytic Staudinger reduction occurred at room temperature but required a longer reaction time (**entry 1-3**). Once heated to 60 °C in ethyl acetate, the catalytic Staudinger reduction proceeded in 5 hours (**entry 5**). In the absence of the Hydroxylmethyl-Aryl phosphine **149** catalyst, there was no conversion of the azide to the amine. The use of triphenylphosphine as the catalyst, instead of the new Hydroxylmethyl-Aryl phosphine **149**, resulted in only 4 % conversion of the azide to the amine.

With phenylsilane being an expensive and very hygroscopic reductant, an investigation into alternatives was undertaken **Table 10**.

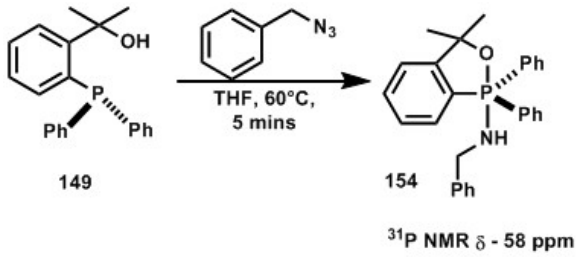



| Entry | Reductant | Time (h) | Conversion* (%) |
|---|---|---|---|
| **1** | $Et_3SiH$ | 5 | 6 |
| **2** | PMHS | 24 | 0 |
| **3** | $NaBH_4$ | 5 | 26 |

**Table 10. Screening of reductants for the catalytic Staudinger reduction. *Conversion determined by $^1$H NMR after work-up.**

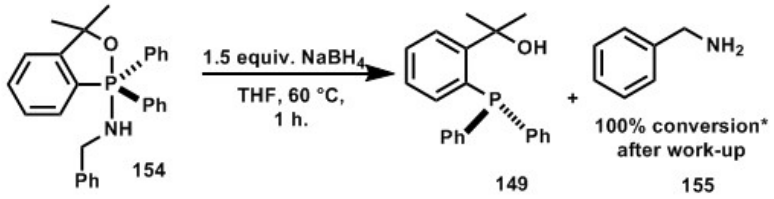
The cheaper and less reactive hydridosilanes were ineffective as reductants for the catalytic Staudinger reductant. Sodium borohydride showed some reactivity and was taken forward in a stoichiometric investigation.

In order to investigate the stoichiometric Staudinger reduction using sodium borohydride, the formation of the amino-oxyphosphorane **154** in a new solvent must be established. **Scheme 66**.




**Scheme 66. Formation of the amino-oxyphosphorane 154 in THF.**

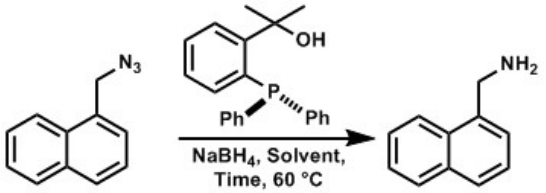
Sodium borohydride was added to the reaction mixture. **Scheme 67**. The reduction of the amino-oxyphosphorane is slower with sodium borohydride, as the solubility of the reductant is lower in organic solvents.




**Scheme 67. Reduction of the amino-oxyphosphorane 154 using sodium borohydride. *Conversion determined by $^{1}$H NMR after work-up.**

The boron NMR was taken during the reaction without any addition of water. The $^{11}$B NMR gave rise to two peaks; sodium borohydride (δ -37.13 ppm) and amine-borane complex (δ -18.22 ppm). This supports the mechanistic view that the reductant ligand exchanges a hydride for the amine. The hydrogen-phosphorane then collapsed to form the phosphine.

The use of sodium borohydride as a reductant is unprecedented for catalytic organophosphorus reactions and conditions for its use were optimised using the Hydroxylmethyl-Aryl phosphine **149**. **Table 11**.

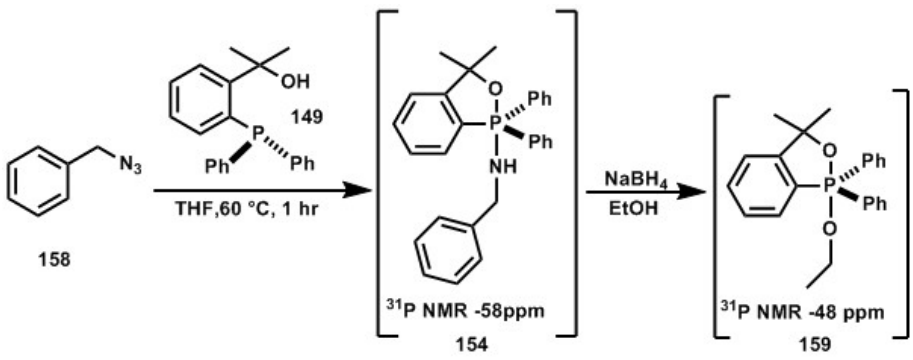



| Entry | Catalyst amount (mol %) | Equivalents of reductant | Solvent | Time (h) | Conversion* (%) |
|---|---|---|---|---|---|
| **1** | 10 | 1.5 | THF | 24 | 48 |
| **2** | 20 | 1.5 | THF | 24 | 76 |
| **3** | 20 | 3 | THF | 24 | 89 |
| **4** | 20 | 1.5 | THF/Methanol (1:1) | 24 | 100 |
| **5** | 20 | 1.5 | THF/Propan-2-ol (1:1) | 24 | 50 |
| **6** | 20 | 1.5 | THF/Butanol (1:1) | 24 | 100 |
| **7** | 20 | 1.5 | THF/Ethanol (1:1) | 5 | 100 |
| **8** | 0 | 1.5 | THF/Ethanol (1:1) | 5 | 18 |

**Table 11. Optimisation of the catalytic Staudinger reduction using sodium borohydride as the reductant. *Conversion determined by $^{1}$H NMR after work-up.**

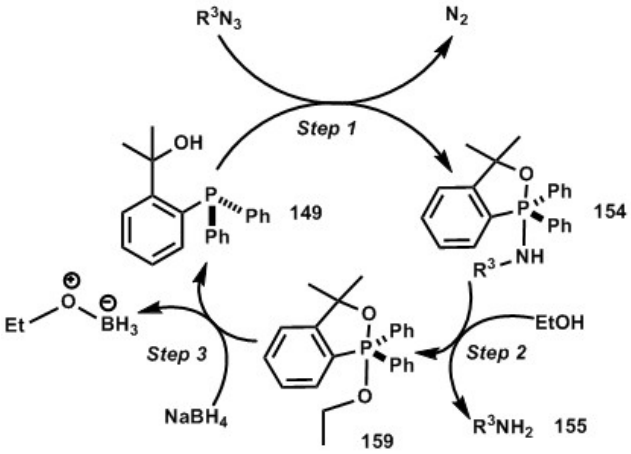
The initial catalytic Staudinger reduction, using 10 mol % of the Hydroxylmethyl-Aryl phosphine and 1.5 equivalents of sodium borohydride with THF as the solvent yielded 48 % conversion of azide to amine (**entry 1**). On the increase of phosphine catalyst or the equivalents of sodium borohydride, there is an increase in the conversion from azide to amine (**entry 2-3**). Sodium borohydride reductions traditionally use an alcohol as a solvent so, for the use of sodium borohydride as the reductant, a screening of alcohols as co-solvents was undertaken (**Entries 4-7**). The optimal condition for the Staudinger reduction using sodium borohydride uses ethanol as the co-solvent and gives 100 % conversion to the amine after 5 hours (**entry 7**). In the absence of the phosphine catalyst, there is a small background reaction between sodium borohydride and the azide (**entry 8**). This reduction is slow and is thought to occur through a radical pathway.

With the optimal solvent system established for the catalytic Staudinger reduction, the stoichiometric reaction was performed to see the effect the solvent has on the process. **Scheme 68.**



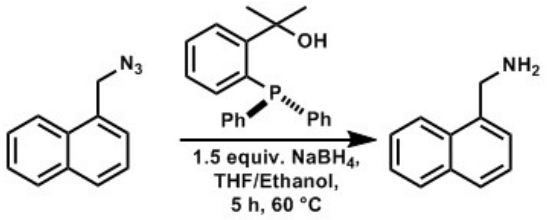

**Scheme 68. Use of alcohol solvents in the catalytic Staudinger reduction.**

The presence of an alcohol in the reaction meant that the amine ligand of the amino-oxyphosphorane **154** could be exchanged for the alcohol to form the dioxyphosphorane **159** intermediate. This was then reduced by the sodium borohydride. Investigating and reinvestigating the stoichiometric reaction alongside the development of the catalytic cycle allowed for the establishment of a true catalytic cycle. **Scheme 69.**




**Scheme 69. The newly proposed catalytic cycle for the reduction of azides using the Hydroxylmethyl-Aryl phosphine 149.**

The amount of catalyst was optimised with the solvents conditions required. **Table 12**.

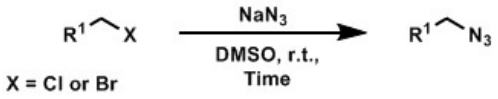



| Entry | Amount of phosphine catalyst (mol %) | Conversion* (%) |
|---|---|---|
| **1** | 3 | 59 |
| **2** | 6 | 54 |
| **3** | 9 | 65 |
| **4** | 10 | 86 |
| **5** | 20 | 100 |

**Table 12. Optimisation of catalyst amount needed for the catalytic Staudinger Reduction. *Conversion determined by $^{1}$H NMR after work-up.**

The catalytic Staudinger reduction can use as little as 3 mol % Hydroxylmethyl-Aryl phosphine catalysts and still yield a moderate conversion of the azide to the amine (**entry 1**).

For the scope of the reaction, a sample of azide substrates were synthesised from the halogen parent substrate and sodium azide. **Table 13**.



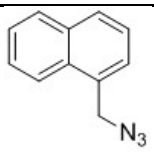
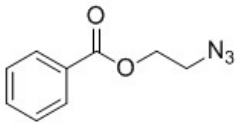
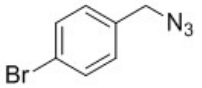
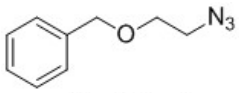
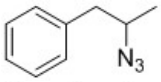
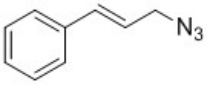
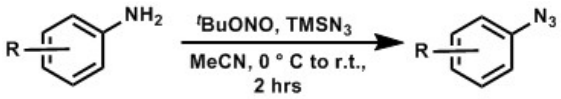

| Entry | Product | Time (h) | Yield (%) |
|---|---|---|---|
| **1** |  | 24 | 97 |
| **2** |  | 24 | 98 |
| **3** |  | 24 | 82 |
| **4** |  | 24 | 52 |
| **5** |  | 24 | 90 |
| **6** |  | 24 | 94 |

**Table 13. Synthesis of Azide Substrates using nucleophilic substation reaction.**

The aryl substrates were synthesis using the method developed by the Moses group. **Table 14.**[64]



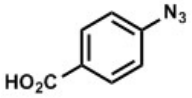
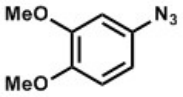
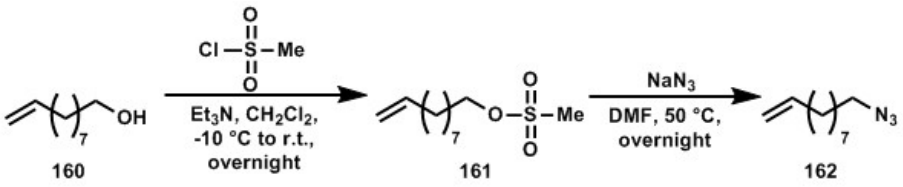

| Entry | Product | Yield (%) |
|---|---|---|
| **1** |  | 98 |
| **2** |  | 60 |

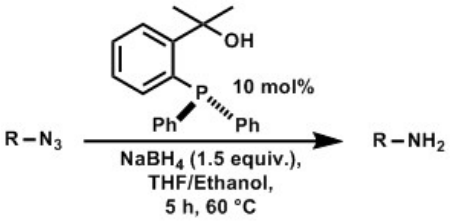
**Table 14. Synthesis of Azide Substrates using the diazo-method.**

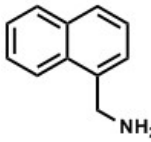
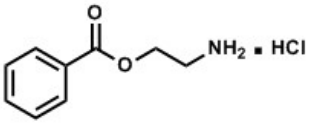
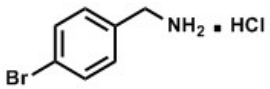
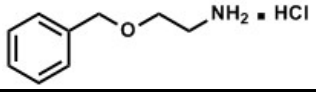
A single substrate was synthesised individually according to literature preparation from the parent alcohol. **Scheme 70.**




**Scheme 70. Synthesis of Azide synthesised by individual procedure.**

These substrates were treated to the catalytic Staudinger reduction conditions using the Hydroxylmethyl-Aryl phosphine **149** as the catalyst. **Table 15.**




| Entry | Product | Yield (%)* |
|---|---|---|
| **1** |  | 72 |
| **2** |  | 80 |
| **3** |  | 71 |
| **4** |  | 53 |

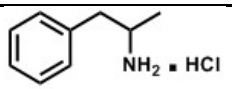
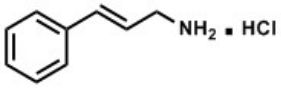
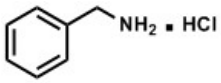
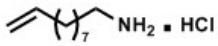
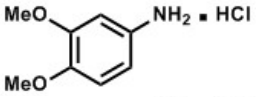
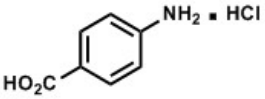
| | | |
|---|---|---|
| **5** |  | 92 |
| **6** |  | 54 |
| **7** |  | 54 |
| **8** |  | 55 |
| **9** |  | 60 |
| **10** |  | 85 |

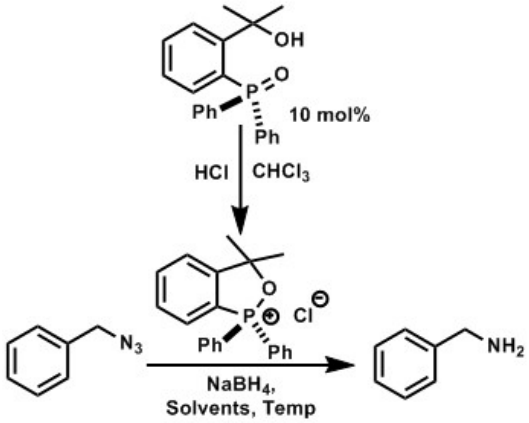
**Table 15. Screening of azides in the catalytic Staudinger reduction using Hydroxylmethyl-Aryl phosphine catalyst. *Isolated as the hydrogen chloride salt.**

The screening of this azide shows that the catalytic procedure with the Hydroxylmethyl-Aryl phosphine was tolerant of a range of functional groups. These substrates include those that are sensitive to reduction via hydrogenation reactions **(Entries 3, 4 and 8, Table 15).**

The Hydroxylmethyl-Aryl phosphine **149** showed excellent scope in the catalytic Staudinger reduction, tolerating a range of substrates with moderate to good yields. Unfortunately, the Hydroxylmethyl-Aryl phosphine **149** was not bench stable and slowly oxidised to the Hydroxylmethyl-Aryl phosphine oxide **106** over time, therefore an investigation into the use of the Hydroxylmethyl-Aryl phosphine oxide **106** as a pre-catalyst was carried out.

### 3.3 The Use of Hydroxylmethyl-Aryl Phosphine oxide as a Pre-Catalyst

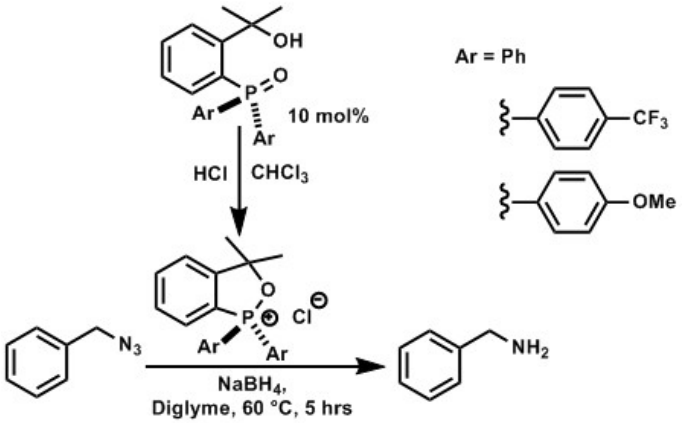
The Hydroxylmethyl-Aryl phosphine slowly oxidises over a period of a month and therefore is not a viable bench stable reagent. With this in mind, the Hydroxylmethyl-Aryl phosphine oxide was then screen for use in the reduction of azides. **Table 16.**




| Entry | Solvent | Temperature (° C) | Time (hrs) | Conversion (%)* |
|---|---|---|---|---|
| **1** | THF/EtOH | 60 | 5 | 46 |
| **2** | Diglyme | 60 | 5 | 73 |

**Table 16. Catalytic Staudinger reduction of azides using Hydroxylmethyl-Aryl phosphine oxide. *Conversion determined by $^{1}$H NMR after work-up.**

The use of the Hydroxylmethyl-Aryl phosphine oxide **106** as the pre-catalyst requires the use of the diglyme in order for the reduction to proceed smoothly in similar yield to the catalytic Staudinger reduction using the Hydroxylmethyl-Aryl phosphine **106**. The electronic effect of the aryl groups on the reactivity of the catalyst was investigated. **Table 17.**



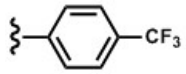
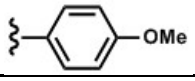
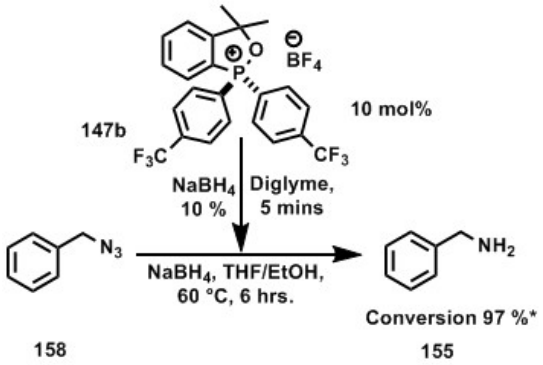

| Entry | Ar | Conversion (%)* |
|---|---|---|
| **a** | Ph | 73 |
| **b** |  | 91 |
| **c** |  | 57 |

**Table 17. Screening of Hydroxylmethyl-Aryl Phosphine Oxides as a pre-catalyst for the Staudinger Reduction. *Conversion determined by $^{1}$H NMR after work-up.**

The best conversion was obtained for the electron deficient alkoxyphosphonium salt **(Table 17, Entry b)**. The screening of substrates using the new alkoxyphosphonium salt catalyst **147b** showed low isolated yields, although crude $^{1}$H NMR studies showed high conversions. This is due to the procedure for the removal of the diglyme from the reaction. Diglyme is a high boiling solvent (162 °C) and difficult to remove under vacuum, and is normally removed from the reaction by washing repeatedly with water while products are extracted with ethyl acetate. In the case of amines, the addition water washings also remove some of the product as many of the amines are water soluble or volatile. That said, the reduction of the alkoxyphosphonium salt **147** using sodium borohydride is only possible with diglyme as the solvent. In order to use the minimum amount of diglyme, the alkoxyphosphonium salt

**147b** was dissolved in a small amount of the solvent before 10 % of the 1.5 equivalents of sodium borohydride were added. **Scheme 71.**



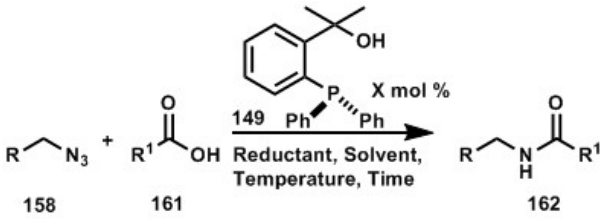

**Scheme 71. Staudinger reduction using alkoxyphosphonium salt as a pre-catalyst. *Conversion determined by $^{1}$H NMR after work-up.**

This method requires less washing with water to remove the lower volume of diglyme solvent than previously used; therefore more of the product can be isolated from the reaction.

A new catalytic variant of the Staudinger reduction established, we next sought to investigate the utility of the Hydroxylmethyl-Aryl phosphines in a range of further phosphorus (V)-mediated reactions.

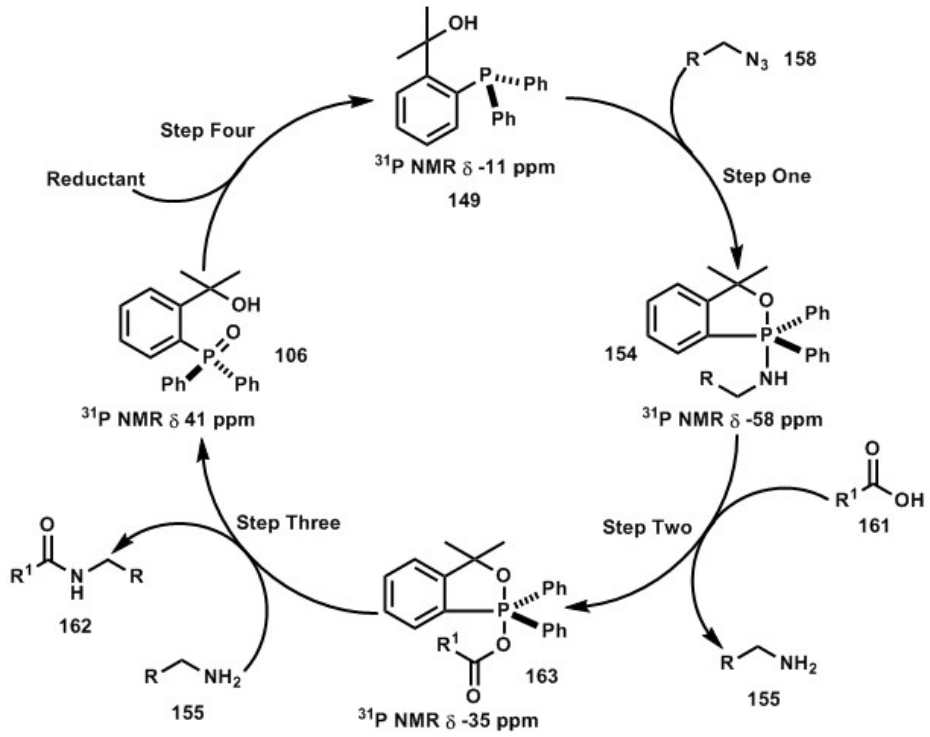
### 3.4 The Development of a Redox-Driven Staudinger Ligation

Having successfully implemented a catalytic variant of the Staudinger reduction, an investigation into the use of the Hydroxylmethyl-Aryl phosphine catalyst in the Staudinger ligation was then undertaken. **Scheme 72.**




**Scheme 72. Proposed investigation of the Catalytic Staudinger Ligation.**

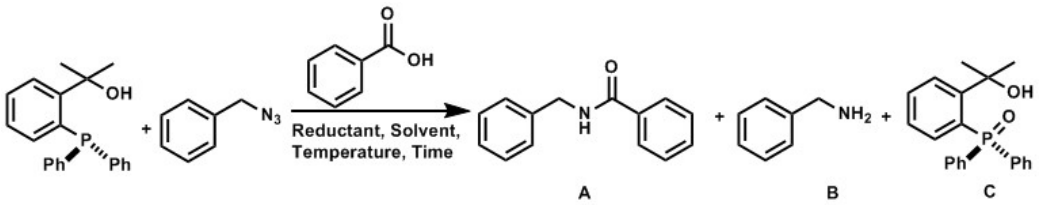
The initial investigation into the ligation was done in a stoichiometric sense, with the acid added after the formation of the amino-oxyphosphorane **154** has occurred. **Scheme 73.**




**Scheme 73. Proposed Catalytic Cycle for the Staudinger ligation using the Hydroxylmethyl-Aryl Phosphine.**

The initial step **(Step one)** proceeds as in the catalytic Staudinger reduction **(Chapter 3, Section 3.2)**. The exchange of the nitrogen ligand with the acid

**(Step Two)** was also covered in the previous section with the exchange of the ligand with the ethanol solvent. At room temperature, the nucleophilic attack on the carbonyl by the amine **(Step Three)** did not occur, although the reduction of the dioxyphosphorane did, when phenyl silane was used as the reductant. So an investigation into solvent, temperature and time was undertaken. **Table 18.**




| Entry | Solvent | Temperature (° C) | Phosphine (Mol %) | Reductant | Time (Hrs) | Product |
|---|---|---|---|---|---|---|
| **1** | Toluene | 60 | 100 | - | 72 | B |
| **2** | Toluene | 100 | 100 | - | 1 | B |
| **3** | EtOAc | 60 | 100 | - | 24 | A + B |
| **4** | EtOAc | 60 | 10* | $NaBH_4$ | 24 | B |
| **5** | THF/EtOH | 60 | 10 | $NaBH_4$ | 24 | B |

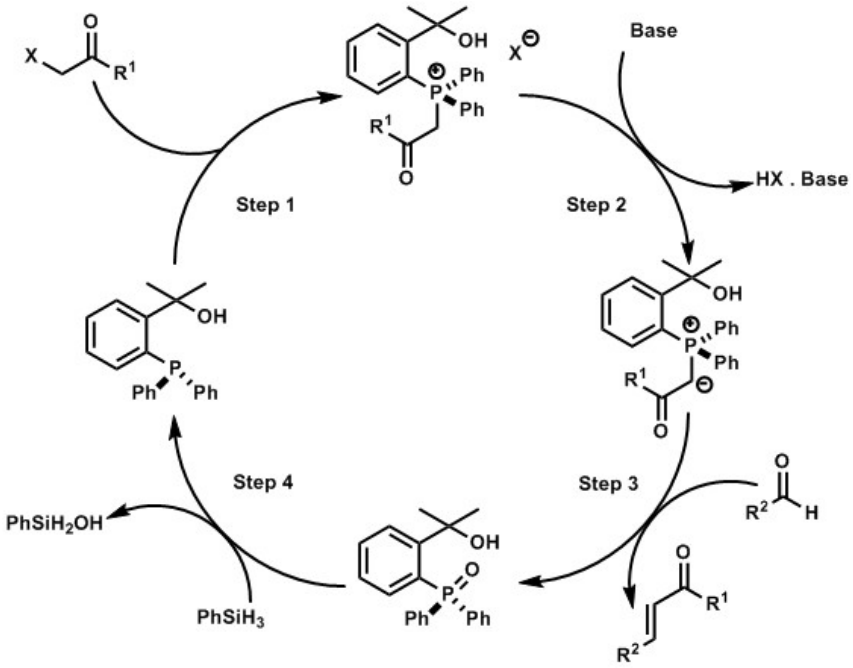
**Table 18. Screening of the conditions of the Catalytic Staudinger Ligation. *Use of the Hydroxylmethyl-Aryl phosphine oxide.**

For the coupling the best solvent was ethyl acetate over the use of toluene **(Table 18, Entry 1-3)** as the coupling only occurred in this high boiling solvent. When the catalytic Staudinger Ligation was attempted using this set of conditions, only the amine was observed **(Table 18, Entry 4 – 5)**. This means that the intermediate in the reaction, *i.e.* the dioxyphosphorane, was too reactive which was seen in the stoichiometric cycle **(Scheme 73)** when phenyl silane was used. The rate for the reduction of dioxyphosphorane is faster than the coupling of the acid and amine, as the reduction will occur at room temperature but the coupling is a thermal process; therefore the catalysing this reaction using the Hydroxylmethyl-Aryl phosphine is not possible.

The new functionalization of the catalyst means that the catalytic Staudinger reduction is possible under mild conditions but the intermediates of the reaction, i.e. dioxyphosphorane and amino-oxyphosphorane, are too sensitive for even these mild reduction conditions. With this information development of a catalytic Staudinger ligation was abandoned, and an investigation into a Wittig reaction based on the Hydroxylmethyl-Aryl phosphine oxide was undertaken.

### 3.5 The Development of a Redox-Driven Wittig Reaction

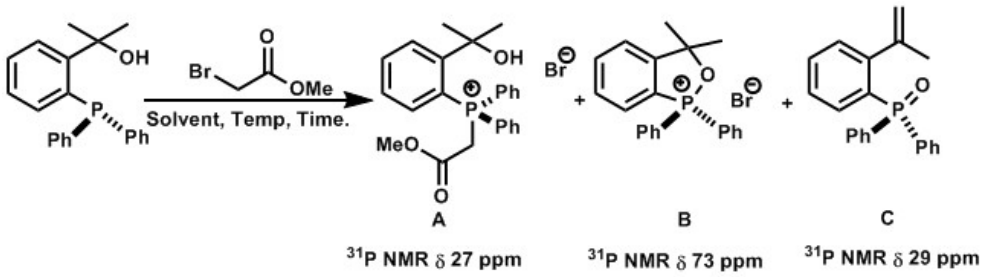
The room temperature catalytic Wittig reaction by the O'Brien group has demonstrated the possibility of using the new Hydroxylmethyl-Aryl phosphine oxide as a catalyst. **Scheme 74.**




**Scheme 74. Possible catalytic cycle for the Wittig reaction using Hydroxylmethyl-Aryl Phosphine oxide.**

The reduction step in the proposed catalytic cycle has already been established in a previous chapter **(Chapter 3, Section 1)** and, comparing this step to the reduction of the O'Brien second-generation catalyst, both phosphine oxide reduced easily at room temperature and at similar rates. With this in mind, the use of the Hydroxylmethyl-Aryl phosphine oxide in the Wittig reaction should proceed under similar conditions to those published by O'Brien.

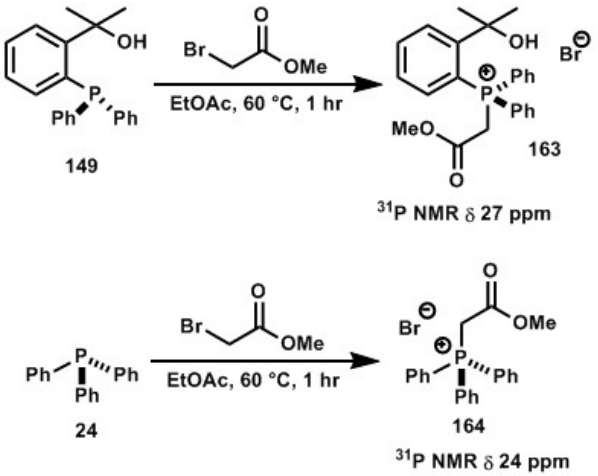
The investigation into the Wittig was under taken stoichiometrically so that each intermediate of the reaction could be characterised fully. The investigation began with the formation of the phosphonium salt **(Step 1)** using methyl bromoacetate. **Table 19.**




| Entry | Solvent | Temperature (° C) | Time (hr) | Major Product |
|---|---|---|---|---|
| **1** | Toluene | 100 | 1 | C |
| **2** | EtOAc | 60 | 1 | A |
| **3** | EtOAc | 20 | 1 | B |
| **4** | Toluene | 60 | 0.5 | A |

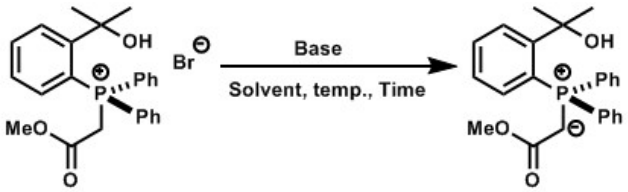
**Table 19. Formation of the phosphonium salt using methyl bromoacetate.**

The formation of the phosphonium salt only occurs at a specific temperature, if the temperature is too low, *i.e.* room temperature, only the alkoxyphosphonium salt **147** is formed. If the temperature is too high however, the eliminated alkene phosphine oxide is formed. The formation of the phosphonium salt **163** occurs at 60 °C in both ethyl acetate and toluene. The formation of the phosphonium salt **163** with the Hydroxylmethyl-Aryl phosphine **149** is similar to that of the formation of the phosphonium salt **164** with triphenyl phosphine **24**. **Scheme 75.**[65-67]




**Scheme 75. Reaction of Hydroxylmethyl-Aryl phosphine 149 compared to triphenyl phosphine 24.**

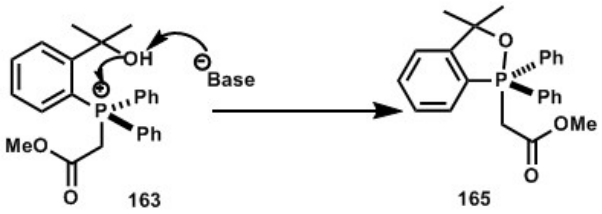
The formation of the phosphonium salt **163** did not occur at room temperature, therefore any catalytic variant using the Hydroxylmethyl-Aryl would require heating in order to proceed. The next step in the cycle was the formation of the ylide. In the room-temperature catalytic Wittig reaction developed by O'Brien, this ylide is very reactive and was not observed during the reaction when monitored *via* $^{31}$P NMR.[35] The phosphonium ylide derived from the triphenyl phosphonium salt **164** could be isolated as a crystalline solid, therefore one could predict that the Hydroxylmethyl-Aryl phosphine would yield a stable ylide similar to this. An investigation into the formation of the ylide for the catalytic reaction was undertaken. **Table 20.**




| Entry | Base | Solvent | Temperature (° C) | Time (hr) | $^{31}$P NMR Shift |
|---|---|---|---|---|---|
| **1** | $Et_3N$ | EtOAc | 60 | 0.5 | 27 ppm |
| **2** | Di-$^t$Butyl-Pyridine | EtOAc | 60 | 0.5 | 27 ppm |
| **3** | Lutidine | EtOAc | 60 | 0.5 | 27 ppm |
| **4** | NaOH | DCM | 20 | 2 | 28 ppm & 17 ppm |
| **5** | NaOH | Toluene | 100 | 1 | 28 ppm |
| **6** | NaOH | EtOAc | 60 | 1 | 41 ppm |
| **7** | $Et_3N$ | EtOAc | 60 | 20 | 27 ppm |
| **8** | DBU | EtOAc | 60 | 20 | 27 ppm |
| **9** | $Cs_2CO_3$ | EtOAc | 60 | 20 | 27 ppm |

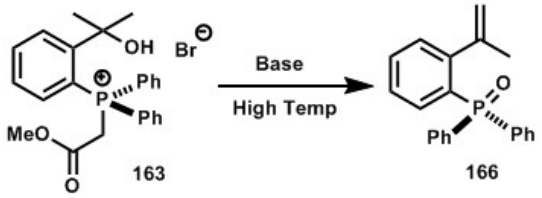
**Table 18. Formation of the Phosphonium Ylide.**

The attempts to form the phosphonium ylide of the Hydroxylmethyl-Aryl phosphonium salt were fruitless. It was possible for the base to deprotonate the hydroxyl group of the phosphonium salt **163** to potentially form the phosphorane **165**. **Scheme 76.**




**Scheme 76. Possible formation of the phosphorane.**

The $^{31}$P NMR showed no peaks in any of the experiments that could account for this, nor was there a peak to represent the ylide. When excess base or high temperature was used, this caused rapid degradation to the alkene phosphine oxide **166**. **Scheme 77.**




**Scheme 77. The formation of degradation product 166.**

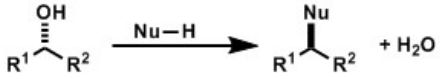
The inability to form the ylide in a stoichiometric cycle means that the Hydroxylmethyl-Aryl phosphine oxide **106** will not work as a catalyst for the Wittig reaction.

To this point the Hydroxylmethyl-Aryl phosphine oxide **106** has only been explored in redox-driven catalytic cycles. The use of the Hydroxylmethyl-Aryl phosphine oxides **106** in redox-neutral catalytic cycles was also investigated for the Mitsunobu reaction.

# Chapter Four: The Development of Redox-Neutral Catalytic Phosphorus-Mediated Reactions

### 4.1 The Development of a Redox-Neutral Catalytic Mitsunobu Reaction

The nucleophilic substitution reaction of alcohols is an important tool within synthetic organic chemistry. The ideal nucleophilic substitution would involve the direct attack of the nucleophile with inversion of the stereochemistry and the releasing of water as the only by-product.[32] **Scheme 78.**

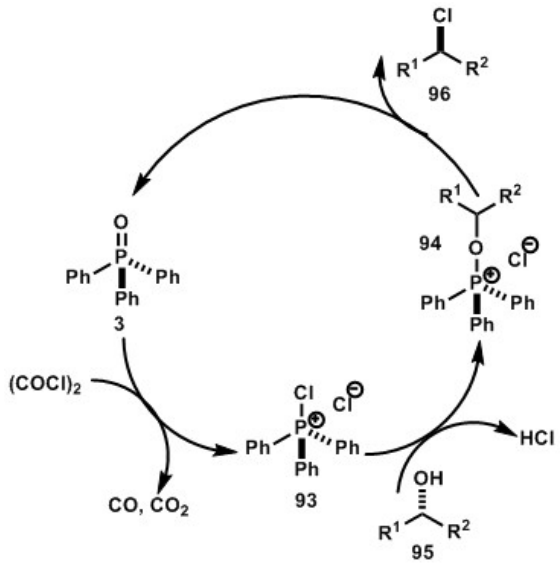



**Scheme 78. The "Ideal" nucleophilic substitution reaction.[ref]**

Unfortunately, this ideal reaction has high thermodynamic and kinetic barriers to overcome for this to be possible. The thermodynamic barrier concerns the replacement of the C-O bond with a weaker C-Nu bond, giving the product of the reaction which is higher in energy than the starting material, with the energy difference not being satisfied by the formation of water by-product. The reactivity of the different nucleophiles will vary, but the hydroxyl group is known to be a poor leaving group that greatly effects the kinetics of the reaction. In order to overcome these factors, many chemists have used stoichiometric activating agents in order to cleave the C-O bond. Although this strategy has been widely employed, it has a significant disadvantage in terms of the generation of additional stoichiometric products, lowering the atom efficiency of the reactions. The call for catalytic methods of nucleophilic substitution of alcohols has been a demanded from the industrial sector (particularly within pharmaceuticals) for many years. The main challenges for the development of catalytic nucleophilic substitution reactions are i) potential unwanted interactions between catalyst, nucleophile and product, and ii) the turnover of the catalyst, i.e. cleavage of the oxygen-catalyst bond that will be generated from the nucleophilic substitution reaction. In terms of phosphorus

(V) mediated reactions, the Mitsunobu reaction and the Appel reaction are examples of activated nucleophilic substitution reaction of alcohols.

The redox-neutral pathway for the catalysis of phosphorus mediated reactions only requires one reagent to promote the phosphine oxide catalyst to the active phosphorus (V) complex. An example of a catalytic cycle that is redox-neutral with respect to phosphorus is the work on the Appel reaction by the Denton group. **Scheme 79.**[2, 4]

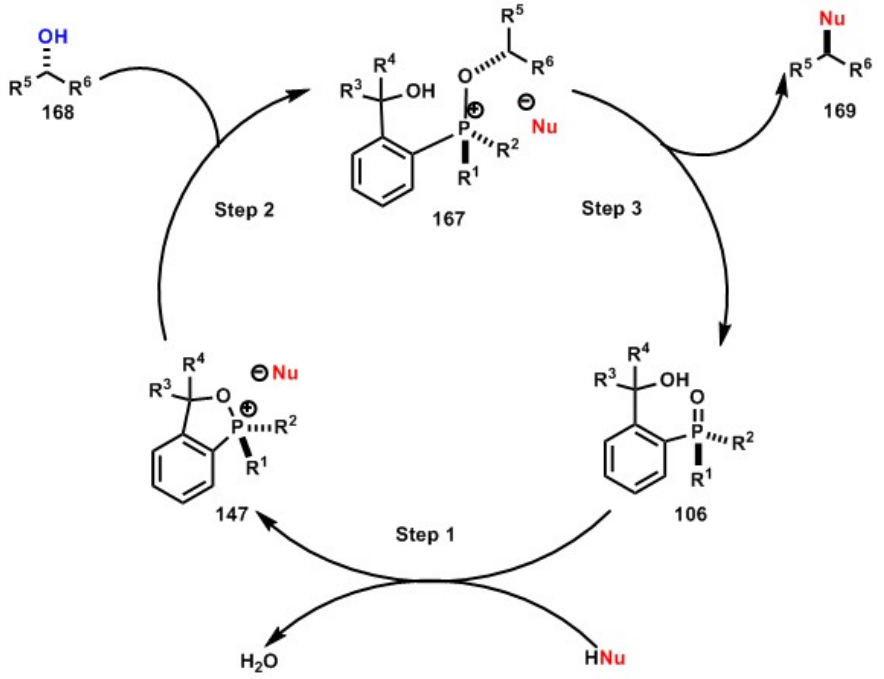



**Scheme 79. Denton and co-workers' catalytic Appel Reaction.**

The triphenylphosphine oxide **3** catalyst was activated by oxalyl chloride to the chlorophosphonium salt **93** which was then attacked by the alcohol **95,** to form an alkoxyphosphonium salt with a chloride anion. The carbon centre of the alcohol was attacked by the chloride anion, the chlorinated product **96** released and the catalyst **3** regenerated. A disadvantage of this catalytic cycle is the side reaction between oxalyl chloride and the alcohol **95**. This side reaction means that the oxalyl chloride and alcohol **95** have to be added slowly over several hours to minimise the effects of the subsequent side reaction. An improvement

on this would be to find a catalyst that can be promoted to the active phosphorus (V) complex within the reaction conditions.

Inspired by this process, a new catalytic cycle for the Mitsunobu reaction was developed based upon a new type of phosphine oxide containing a hydroxyl group. **Scheme 80.**




**Scheme 80. Proposed catalytic cycle for the Mitsunobu reaction.**

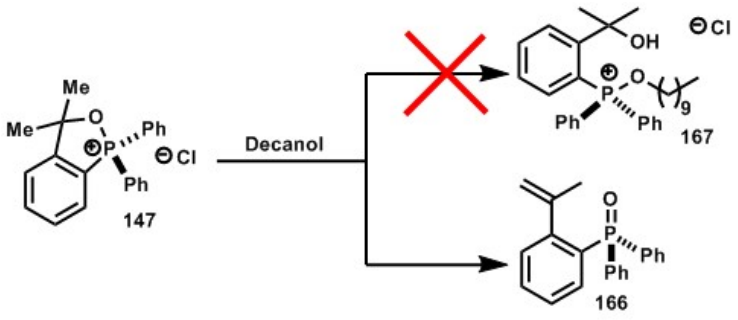
The hydroxyl group present within phosphine oxide **106** plays a critical role in the proposed catalytic cycle and allows the key turnover to the alkoxyphosphonium salt **147** to occur under mild conditions using acids, the only by-product of the cycle being water. The first step of the cycle is to generate the alkoxyphosphonium salt **147** under acidic conditions. This is then attacked by the alcohol **168** for one of two possible intermediates; a new alkoxyphosphonium salt **167,** which is ring opened, and a dioxyphosphorane, which is ring closed. The nucleophile can be a secondary reagent that is added in, or the counter anion of the acid used in the first step. This nucleophile attacks the carbon centre of the alkoxyphosphonium salt **167** or the

dioxyphosphorane, releasing the product **169** and regenerating the oxide catalyst **106**.

Each step of the catalytic cycle was investigated individually in a stoichiometric reaction therefore identifying each of the phosphorus intermediates for the cycle. The first step of the catalytic cycle (formation of the alkoxyphosphonium salt) has already been established. (**Chapter 2**). Therefore the analysis will begin with step two of the catalytic cycle.

## 4.2 The Formation of a Dioxyphosphorane – Step Two of the Redox-Neutral Catalytic Mitsunobu Reaction

With **step 1** of the proposed catalytic cycle established, **step 2** was investigated. The hydrochloride salt **(Table 21, entry 2)** was taken and decanol was added and the reaction mixture was heated under various conditions. **Table 21.**

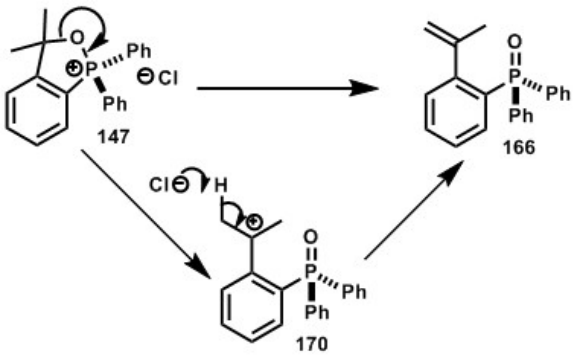



| | Equivalents of Decanol | Solvent | Temperature (°C) |
|---|---|---|---|
| **1** | 3 | Tol | 100 |
| **2** | 3 | Xylene | 150 |
| **3** | 3 | EtOAc | 70 |
| **4** | 30 | MeCN | 70 |
| **5** | 5 | DMF | 150 |

**Table 21. Results of Step 2: addition of decanol to alkoxyphosphonium salt 147.**

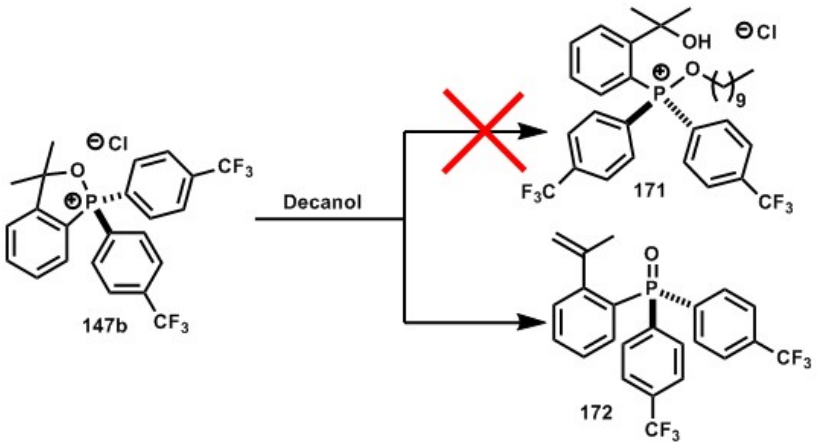
The results of the reaction showed that the formation of the desired alkoxyphosphonium salt **167** did not occur under any condition. Competitive unwanted elimination occurred via the attack of one of the methyl groups upon the ring, causing it to open and forming the phosphine oxide **166.** The identification of the phosphine can be determined in both $^{31}P$ NMR and $^{1}H$ NMR. A new phosphorus peak can be seen at δ 27 ppm, which shows the loss of the hydroxyl group and the hydrogen bond as it is up-field in the $^{31}P$ NMR.

In the $^{1}H$ NMR, alkene peaks can be clearly seen as a doublet of doublets. The mechanism of this reaction is described in **Scheme 81.**




**Scheme 81. The mechanism for the formation of the alkene phosphine oxide.**

To resolve this problem, a blocking group such a phenyl was used to replace the dimethyl groups upon the Hydroxylmethyl-Aryl ligand. This only led to the slow hydrolysis of the salt back to the phosphine oxide. The more reactive alkoxyphosphonium salts **147b,** derived from the Hydroxylmethyl-Aryl phosphine oxide **116**, also eliminated to the alkene phosphine oxides **172. Scheme 82.**

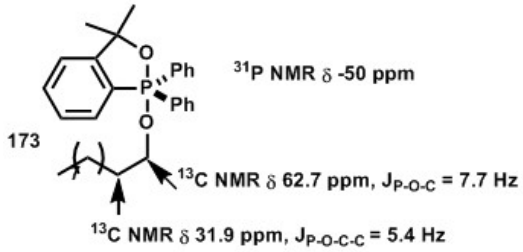



**Scheme 82. Reaction of Decanol with alkoxyphosphonium salt 147b.**

With the inability of the alkoxyphosphonium salt **147** to form the desired intermediate required for the catalytic cycle, the nucleophilic attack of the alkoxyphosphonium salt or the Dioxyphosphorane will be studied using a preformed intermediated.

### 4.3 Nucleophilic Attack of a Dioxyphosphorane – Step Three of the Redox-Neutral Catalytic Mitsunobu Reaction

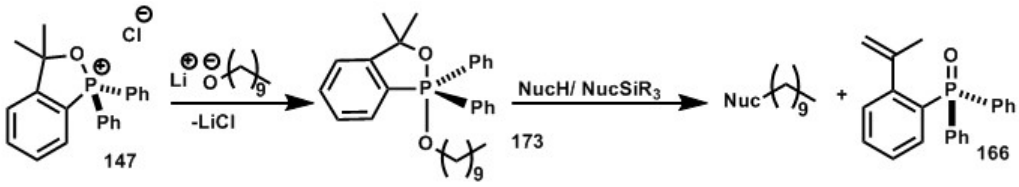
To establish the premise of the catalytic cycle, the deprotonated alcohol was added into the phosphonium salt **147**. Dioxyphosphorane **173** was formed and fully characterised. **Scheme 83.**




**Scheme 83. NMR data for the dioxyphosphorane.**

The $^{31}$P NMR spectrum exhibited a single peak in the typical cyclic dioxyphosphorane region; δ -50 ppm. Studies into the NMR of dioxyphosphoranes by Evans and co-workers[46] showed that the typical $^{2}J_{POC}$ value is ~ 7 Hz and the $^{3}J_{POCC}$ is ~5.5 Hz in the $^{13}$C NMR. In the experimental $^{13}$C NMR for this dioxyphosphorane the J values are δ 62.7 ppm $^{2}J_{POC}$ = 7.7 Hz and δ 31.9 ppm $^{3}J_{POCC}$ = 5.4 Hz, matching those observed by Evans and co-workers.[47]

With the phosphorane **173** in hand, reaction with an acidic nucleophile was then carried out in an attempt to access key intermediate **167** and turnover the cycle to establish **step 3**. The addition of standard nucleophile used for the Mitsunobu reaction, **(Table 22),** lead to the formation of the alkene phosphine oxide **166** and the release of the reprotonated alcohol or the silyl product.



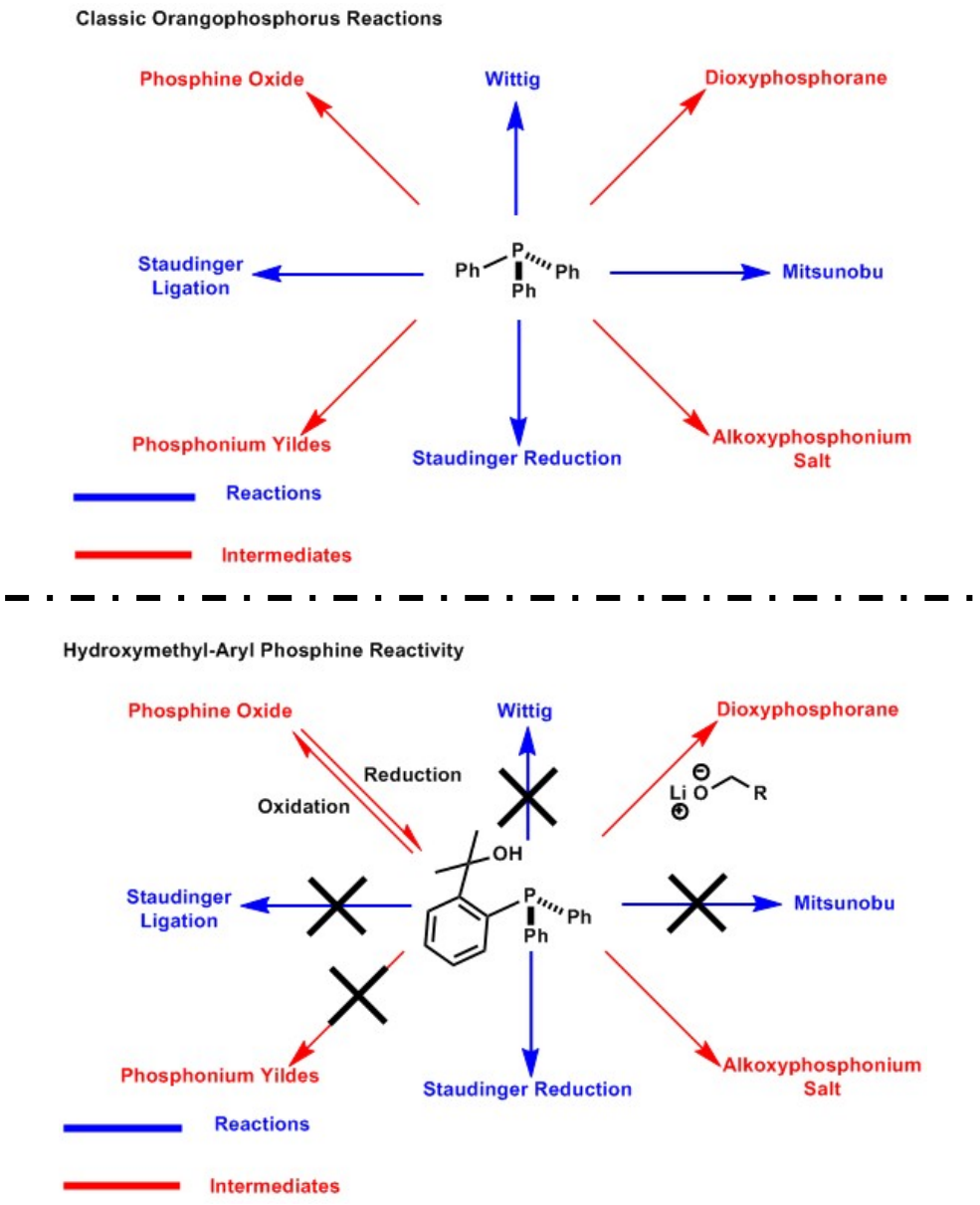

| | Nucleophile | Solvent | Temperature (°C) | Product |
|---|---|---|---|---|
| **1** | nitro benzoic acid | THF | 50 | **166** |
| **2** | benzoic acid | THF | 50 | **166** |
| **3** | $TMSN_3$ | THF | 25 | **166 + silyl alcohol** |

**Table 22. Step 3: Reaction of the dioxyphosphorane 173.**

Again, the reactivity of the phosphorus centre only leads to the elimination of the alkene, showing that the modification greatly affects the reactivity of the phosphorus.

# Chapter Five: Conclusions

The use of a functionalised phosphine oxide in various classical organophosphorus reactions has been demonstrated throughout this thesis. It has shown that a small change to the triaryl phosphine oxide backbone can greatly impact the reactivity of the phosphorus centre. **Scheme 84**.

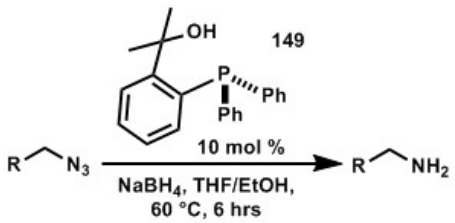



**Scheme 84. The Classic Triphenylphosphine reactions and intermediates compared to the new Hydroxylmethyl-Aryl phosphine.**

These changes to the ligand of the tri-aryl phosphorus moiety have not only increased the reduction ability of the phosphine oxide, but it also affected the

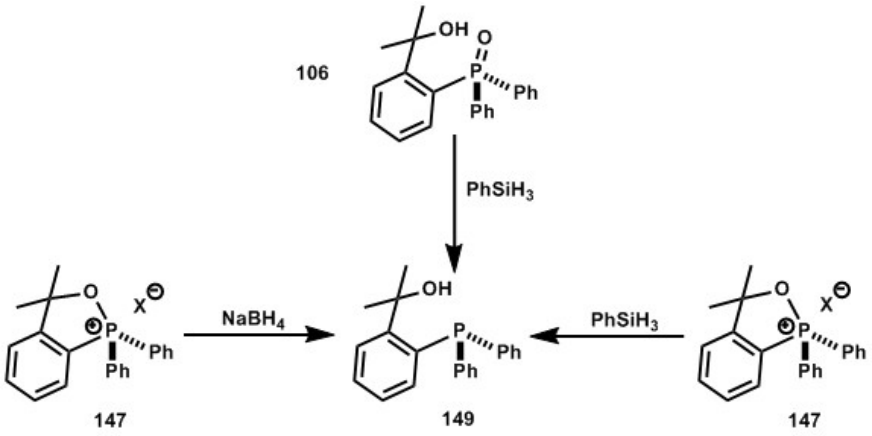
core reactivity. This altered reactivity has meant that the standard phosphorus mediated reactions, such as the Wittig reaction, are unable to be catalysed by these Hydroxylmethyl-Aryl phosphines and phosphine oxides, as some of the reaction intermediate cannot be formed or are too sensitive to the conditions to mediate the reactions.

Although the Hydroxylmethyl-Aryl phosphine **149** was unable to catalyse all of the desired phosphorus mediated reactions, it did show great reactivity in a mild Staudinger reduction and presented the formation of the amino-oxyphosphorane intermediates. **Scheme 85.**




**Scheme 85. Catalytic Staudinger Reduction.**

But what these Hydroxylmethyl-Aryl phosphine oxides demonstrate best are their ability to be easily reduced to the hydroxylmethyl-aryl phosphine. **Scheme 86.**




**Scheme 86. Reduction of the Hydroxylmethyl-Aryl Phosphine 149 and Alkoxyphosphonium salt 147.**

This work represents the possibility for a general catalyst, which is functionalised in a way to balance the ability to promote the desired reactions and the easy turnover of the phosphine oxide. The change in reactivity can be observed in the $^{31}P$ NMR shifts for the new Hydroxylmethyl-Aryl phosphine oxides and its intermediates compared to that of the triphenylphosphine oxide. **Chart 2.**

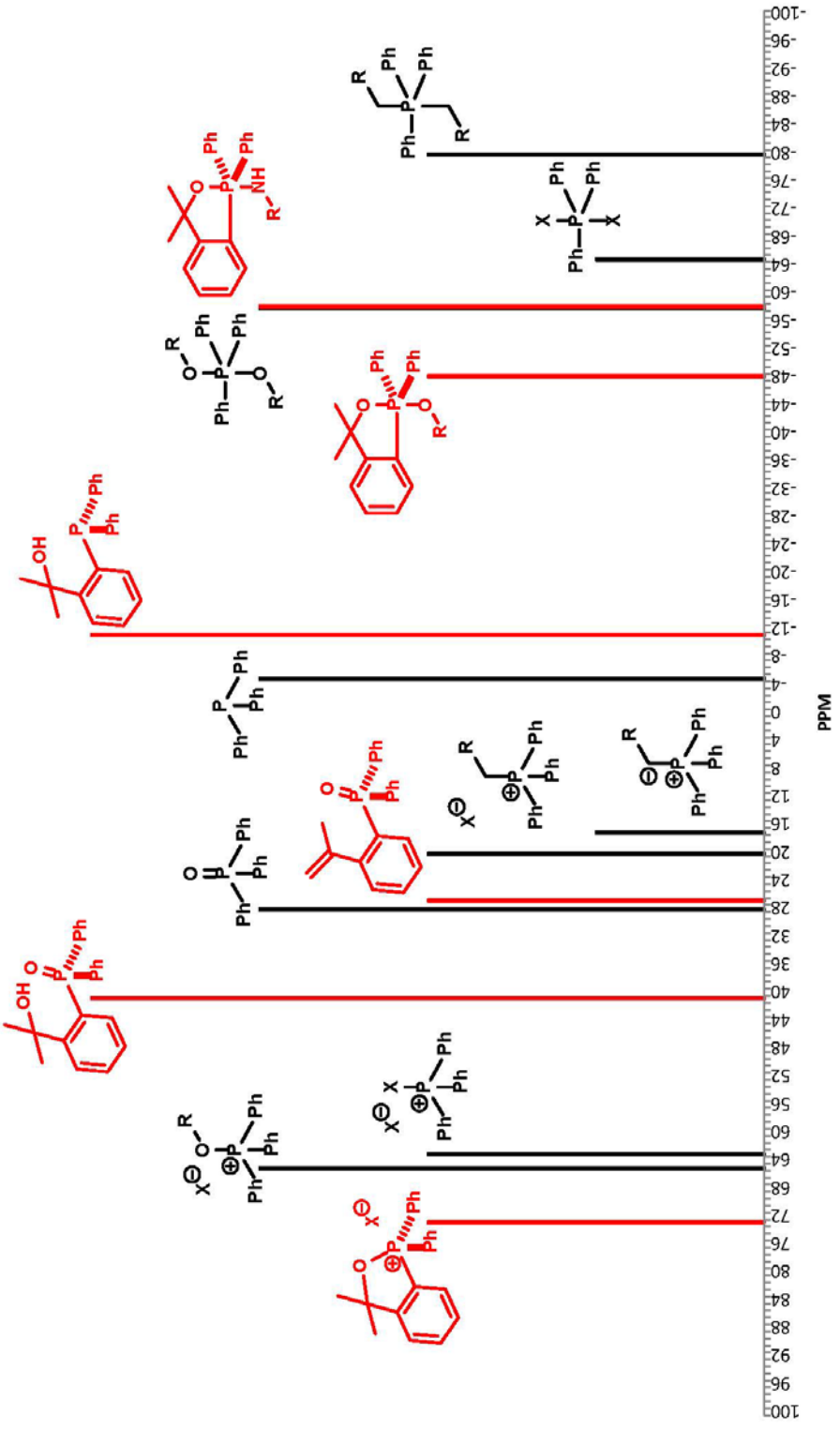



**Chart 2. Comparison of $^{31}$P NMR shifts of the Hydroxylmethyl-Aryl phosphine compounds and the triphenyl phosphine.**

# Chapter Six: Experimental

## 6.1 General Experimental

All commercially available chemicals were purchased from Sigma Aldrich and solvents were dried according to standard procedures. $^{1}H$, $^{31}P$ and $^{13}C$ NMR spectra were recorded with Bruker (400 MHz) spectrometer. $^{1}H$ NMR spectra were referenced to residual $CDCl_3$ (7.26 ppm) and are reported as follows; chemical shift, multiplicity (s = singlet, d =doublet, t = triplet, q = quartet, quint = quintet, m = multiplet) and J-coupling (Hz). Chemical shifts of $^{13}C$ NMR spectra were measured relative to $CDCl_3$ (77.23 ppm) and are $^{1}H$ decoupled, and $^{19}F$ and $^{31}P$ coupled. $^{19}F$ and $^{31}P$ NMR spectra were recorded with $^{1}H$ decoupling unless stated otherwise. All reactions were performed using dry solvents, inert atmosphere and glassware that were flame dried under vacuum. The mass spectroscopic was collected using a Bruker MircoTOF machine. X-ray crystal structures were collected and determined by a Bruker Apex CCD or a SuperNova Atlas CCD. The infra-red spectra was collected via a Bruker Tensor$^{TM}$ 27.

## 6.2 Synthesis of Hydroxylmethyl-Aryl Phosphine Oxides

### Preparation of 2(2-bromophenyl)propan-2-ol 102[68]




114 102

A solution of methyl-2 bromobenzoate (4.20 g, 19.5 mmol) in dry diethyl ether (30 mL) was cooled to 0 °C, before methyl magnesium bromide (16.2 mL, 48.7 mmol of 3M in diethyl ether) was added. The reaction mixture was stirred for 5 hours at room temperature. The reaction mixture was quenched with aqueous ammonium chloride (20 mL) and stirred for a further 15 minutes before being extracted using diethyl ether (30 mL) and washed with water (3 x 30 mL). The organic layer was dried with magnesium sulfate and the solvent was removed under vacuum. This gave a colourless oil in quantitative yield. (>99%).

NMR data matches known data on compound.

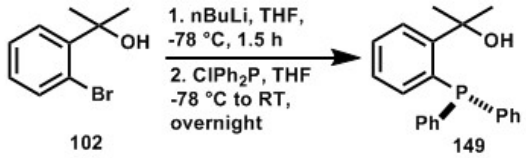
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.70 (dd, *J*=7.9, 1.8 Hz, 1 H, C**H$_{Ar}$**) 7.59 (dd, *J*=7.9, 1.3 Hz, 1 H, C**H$_{Ar}$**) 7.31 (dd, *J*=8.0, 1.6 Hz, 1 H, C**H$_{Ar}$**) 7.11 (dd, *J*=8.6, 1.3 Hz, 1 H, C**H$_{Ar}$**) 2.90 - 3.07 (m, 1 H, O**H**) 1.77 (s, 6 H, 2 x C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.0 (s, $C_q$) 134.9 (s, $CH_{Ar}$) 128.4 (s, $CH_{Ar}$) 127.4 (s, $CH_{Ar}$) 127.1 (s, $CH_{Ar}$) 120.3 (s, $C_q$) 73.4 (s, $C_q$) 29.4 (s, 2 x $CH_3$)

**IR υ/ cm$^{-1}$:** 3597 (-OH), 3006 (-$CH_3$), 951(-$CH_{Ar}$).

**MS (EI, m/z, rel. intensity):** 236.98 ($M^+$Na).

**Preparation of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine 149[69]**




102 149

A solution of 2(2-bromophenyl) propan-2-ol (3.90 g, 18.0 mmol) in tetrahydrofuran (25 mL) was cooled to -78 °C, before *n*-butyl lithium (1.6 M solution in hexanes, 28.0 mL, 45.0 mmol) was added drop-wise over 20 minutes. The reaction mixture was then stirred for 1.5 hours at -78 °C. After this time, a solution of chlorodiphenylphosphine (3.90 mL, 22.0 mmol) in tetrahydrofuran (20 mL) was added drop-wise over 30 minutes to the reaction mixture at -78 °C. The reaction mixture was stirred overnight and allowed to warm up from -78 °C to room temperature. The reaction mixture was washed with water (3 x 30 mL) and the product extracted using ethyl acetate (2 x 30 mL). The organic was dried with magnesium sulfate and solvent removed under vacuum to yield a bright yellow crude solid. The solid was purified using flash chromatography; hexane:ethyl acetate (9:1), to yield a white-yellow solid 3.90 g (68%). M.P. 117 – 120 °C (97 – 101 °C).

NMR Data matches known data on compound.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.60 (ddd, *J*=7.9, 4.9, 0.9 Hz, 1 H, C**H$_{Ar}$**) 7.30 - 7.41 (m, 11 H, C**H$_{Ar}$**) 7.27 (ddd, *J*=7.6, 4.9, 1.4 Hz, 1 H, C**H$_{Ar}$**) 7.13 - 7.20 (m, 1 H, C**H$_{Ar}$**) 1.83 (s, 6 H, 2 x C**H$_3$**) 1.72 (s, 1 H, O**H**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 153.8 (s, *J*=20.7 Hz, $CH_{Ar}$) 143.1 (d, *J*=418.7 Hz, $C_q$) 137.5 (s, *J*=9.2 Hz, $CH_{Ar}$) 137.0 (s, $CH_{Ar}$) 134.6 (s, *J*=13.8 Hz, $CH_{Ar}$) 133.1 (d, *J*=19.9 Hz, $CH_{Ar}$) 128.2 (d, *J*=4.6 Hz, $CH_{Ar}$) 127.7 (d, *J*=15.3 Hz,

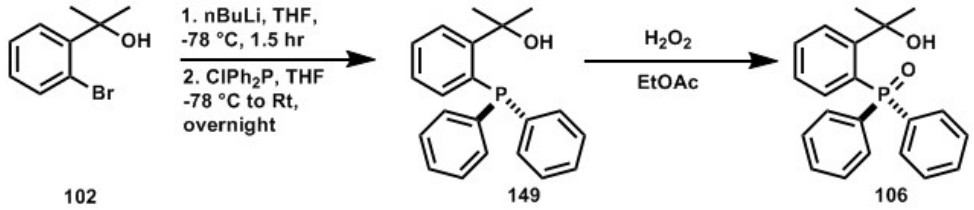
$CH_{Ar}$) 127.3 (d, *J*=219.3 Hz, $C_q$) 125.2 (d, *J*=6.9 Hz, $CH_{Ar}$) 125.0 (d, *J*=3.8 Hz, $CH_{Ar}$) 74.3 (s, $C_q$) 32.1 (d, *J*=7.7 Hz, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ -12.2 (1P, s, P(III)).

**IR υ/cm$^{-1}$:** 3400 (-OH), 3000 (-$CH_3$), 1450 (-$CH_{Ar}$).

**MS (EI, m/z, rel. intensity):** 321.14 ($M^+H$).

**Preparation (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide 106[55, 56]**




102 149 106

A solution of 2-2(bromophenyl)propan-2-ol (4.01 g, 18.7 mmol) in tetrahydrofuran (20 mL) was cooled to -78 °C, before *n*-butyl lithium (25.70 mL, 41.14 mmol of a 1.6M solution in hexanes) was added drop wise over 20 minutes. The mixture was stirred for 1.5 hours at -78 °C. After this time, chlorodiphenylphosphine (5.00 mL, 28.05 mmol) in tetrahydrofuran (20 mL) was added over 30 minutes. The reaction mixture was stirred for 24 hours and warmed from -78 °C to room temperature. It was then extracted with ethyl acetate (2 x 30 mL) and washed with water (3 x 30 mL). The organic layers were combined and hydrogen peroxide (23.0 ml, 80.0 mmol of a 12% solution in water) was added and stirred for 2 hours. It was then extracted by ethyl acetate (2 x 10 mL) and washed with water (3 x 30 mL). The organic layers were combined and dried with magnesium sulfate. The mixture was filtered and solvent was removed under vacuum. Recrystallized with ethyl acetate to yield a white crystalline solid 4.03 g. (64%). M.P. 154 °C. (147-149 °C).

NMR data matches known data for the compound.

**$^{1}$H (400 MHz, $CDCl_3$):** δ 7.42 - 7.61 (m, 12 H, C**$H_{Ar}$**) 7.16 (d, *J*=3.9 Hz, 2 H, C**$H_{Ar}$**) 1.66 (s, 6 H, 2 x C**$H_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 156.4 (d, *J*=6.1 Hz, $C_q$) 135.1 (d, *J*=13.8 Hz, $CH_{Ar}$) 133.4 (d, *J*=106.6 Hz, $C_q$) 131.6 (d, *J*=9.2 Hz, $CH_{Ar}$) 131.4 (d, *J*=2.3 Hz, $CH_{Ar}$) 131.2 (d, *J*=10.0 Hz, $CH_{Ar}$) 128.1 (d, *J*=12.3 Hz, $CH_{Ar}$) 127.6 (d, *J*=10.0

Hz, $CH_{Ar}$) 127.3 (d, *J*=99.7 Hz, $C_q$) 125.2 (s, *J*=13.8 Hz, $CH_{Ar}$) 72.7 (d, *J*=3.1 Hz, $C_q$) 32.1 (2 x $CH_3$).

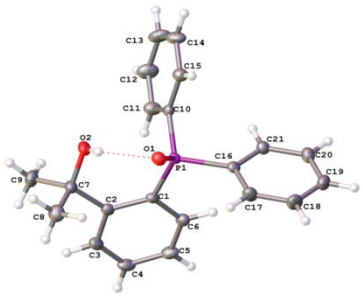
**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 41 (1P, P(V)).

**IR υ/cm$^{-1}$:** 3248 (-OH), 3066 (-$CH_3$), 1119 (P=O)

**MS (EI, m/z, rel. intensity):** 359 ($M^+$Na).

**CHN (ELEMENTAL ANALYSIS):** Predicted C 74.99, H 6.29, N 0. Actual C 74.54, H 6.28, N 0.

**Crystal Data**




Formula: C21 H21 O2 P *M* = 336.35 gmol-1

Crystal System: Monoclinic Space Group: *P*21/*n*

Unitcell: *a* = 9.1117(2), *b* = 12.6467(4) *c* = 15.5296(4) Å

a = 90.00, b = 98.112(3), g = 90.00 °, *V* = 1771.62(8) Å3

Refined using 5488 reflections, 6.98 £ 2q £ 148.26 ° Radiation: Cu*K*a (l 1.54184 Å) Z = 4 *D*calc = 1.261 gcm-3 *T* = 90(2)K m = 1.443 mm-1 *F*(000) = 712

Crystal colour: colourless Shape: block Size: 0.7480 x 0.5302 x 0.3435 mm3

SuperNova, Single source at offset), Atlas, Cu*K*a radiation, *T* = 90(2)K, scan mode w, frame width 1.0000°, frame time 3.0000s, 8500 data collected, 2qmax 148.6°, *h* -11 ® 10, *k* -15 ® 13, *l* -19 ® 19, Unique data 3518, *R* int

= 0.0190, Collection program: CrysAlisPro, Agilent Technologies, Version 1.171.35.11

Reduction program(s): CrysAlisPro, Agilent Technologies, Version 1.171.35.11, Crystal decay: 0

Absorption correction type: gaussian, *TF* range: 0.528 - 1.883, Program(s) used: CrysAlisPro, Agilent

Technologies, Version 1.171.35.11 (release 16-05-2011 CrysAlis171 .NET) (compiled May 16 2011,17:55:39)

Numerical absorption correction based on gaussian integration over a multifaceted crystal model

**Structure Analysis and Refinement**

The hydroxy-alkyl group is disordered rotationally over two positions. The occupancies of these were refined competitively, converging at a ratio of 0.58:0.42. Chemically equivalent 1,2- and 1,3- distances of the disordered group were restrained to be approxiamtely equal, and rigid bond restraints were applied to the whole molecule. The OH group of the minor component rotated away from any possible hydrogen bond acceptors when freely refined, so the H2A-O1 distance was restrained to 1.9 Å to give a sensible hydrogen bond interaction.

Method of structure solution: iterative and difmap, Program(s) used: Olex2 1.1

Method(s) of location of H atoms: mixed, Refinement details for H atoms: constr *RF* = 0.0366, *wRF* 2 = 0.0939 for 3391 data with *F* ³ 4s(*F*), Restraints: 87 *RF*= 0.0376, *wRF* 2 = 0.0945, *S* = 1.089 for all 3518 data, Parameters 251

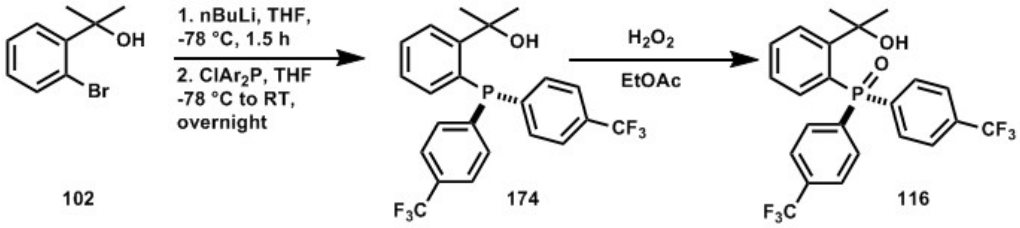
Final D*F* synthesis: Maximum peak 0.524, Minimum trough -0.378 eÅ-3

Weighting scheme: 1/[\s2(Fo2)+(0.0441P)2+1.0742P] whereP = (Fo2+2Fc2)/3

Secondary extintion parameter: 251, Final (D/smax) 0.000

Completeness (all data): 97.3%, Completeness (2q = 135.0°): 99.9%

**Preparation of (2-(2-hydroxypropan-2-yl)phenyl) bis(4-(trifluoromethyl) phenyl) phosphine oxide 116**




To a solution of 2-(2-bromophenyl)propan-2-ol (1.0 g, 4.6 mmol) in tetrahydrofuran (10 mL) was cooled to -78 °C, before *n*-butyl lithium (4.0 mL, 10 mmol of a 2.5M solution in hexanes) was added drop-wise over 20 minutes. The reaction mixture was stirred at -78 °C for 1.5 hours, before a solution of chlorobis[4-(trifluoromethyl)phenyl]phosphine (1.9 g, 5.5 mmol) in tetrahydrofuran (8 mL), was added drop-wise over 30 minutes. The solution was then allowed to warm from -78 °C to room temperature overnight. The reaction mixture was washed with water (3 x 20 mL) and the product was extracted by ethyl acetate (2 x 20 mL). The organic layers were combined and hydrogen peroxide (12% w/w in water, 15 mL, 50 mmol) was added at room temperature. The reaction mixture was stirred for 2 hours before being washed with water (3 x 20 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum to yield crude yellow oil. The crude mixture was recrystallized by ethyl acetate yielding a white crystalline solid 0.95 g (45 %). M.P. 156 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.65 - 7.77 (m, 8 H, C**H**$_{Ar}$) 7.54 - 7.59 (m, 2 H, C**H**$_{Ar}$) 7.17 - 7.23 (m, 1 H, C**H**$_{Ar}$) 7.04 (dd, *J*=16.4, 7.7 Hz, 1 H, C**H**$_{Ar}$) 5.79 - 6.49 (m, 1 H, O**H**) 1.65 (s, 6 H, 2 x C**H**$_3$)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 157.1 (d, *J*=6.1 Hz, $CH_{Ar}$) 138.0 (d, *J*=105.0 Hz, $C_q$) 134.8 (d, *J*=14.6 Hz, $CH_{Ar}$) 133.5 (d, *J*=3.1 Hz, $C_q$) 132.6 (d, *J*=3.1

Hz, $C_{Ar}$) 132.2 (d, *J*=10.0 Hz, $CH_{Ar}$) 128.5 (d, *J*=10.7 Hz, $CH_{Ar}$) 125.8 (d, *J*=13.8 Hz, $CH_{Ar}$) 125.5 (dd, *J*=12.3, 3.8 Hz, $C_q$) 124.8 (d, *J*=103.0 Hz, $C_q$) 122.9 (d, *J*=85.9 Hz $CF_3$) 73.6 (d, *J*=2.3 Hz, $C_q$) 32.6 (s, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 39.8 (1P, s, P (V))

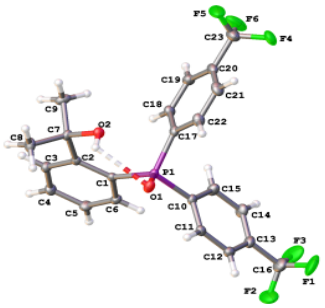
**$^{19}$F NMR (376 MHz, $CDCl_3$)**: δ -63.18 (d, *J*=0.6 Hz, C**$F_3$**)

**IR υ/ cm$^{-1}$:** 3011(OH), 1323(CF), 1174(P=O), 1017(P=O), 837($CH_{Ar}$).

**MS (EI, m/z, rel. intensity):** 473.10 ($M^+H$) and 495.09 ($M^+Na$).

**CHN (ELEMENTAL ANALYSIS):** Predicted C 58.48, H 4.05, N 0. Actual C 58.27, H 4.02, N 0.

**Crystal Data**




Bond precision: C-C = 0.0021 A Wavelength=1.54184

Cell: a=15.4442(7) b=10.3367(5) c=13.2681(7)

alpha=90 beta=99.734(5) gamma=90

Temperature: 120 K

Calculated Reported

Volume 2087.65(18) 2087.65(18)

Space group P 21/c P 1 21/c 1

Hall group -P 2ybc -P 2ybc

Moiety formula C23 H19 F6 O2 P C23 H19 F6 O2 P

Sum formula C23 H19 F6 O2 P C23 H19 F6 O2 P

Mr 472.41 472.35

Dx,g cm-3 1.503 1.503

Z 4 4

Mu (mm-1) 1.831 1.831

F000 968.1 968.0

F000’ 973.00

h,k,lmax 19,12,16 19,12,16

Nref 4271 4131

Tmin,Tmax 0.363,0.576 0.450,0.642

Tmin’ 0.274

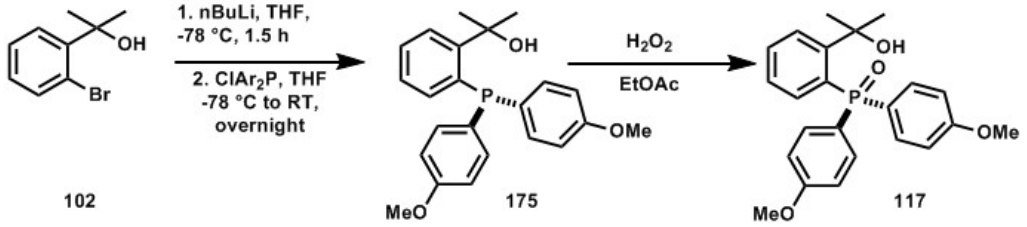
Correction method= GAUSSIAN

Data completeness= 0.967 Theta(max)= 74.440

R(reflections)= 0.0411( 3780) wR2(reflections)= 0.1129( 4131)

S = 1.037 Npar= Npar = 409

**Preparation of (2-(2-hydroxypropan-2-yl)phenyl) bis(4-methoxyphenyl) phosphine oxide 117**




To a solution of 2-(2-bromophenyl)propan-2-ol (3.3 g, 15 mmol) in tetrahydrofuran (15 mL) was cooled to -78 °C, before *n*-butyl lithium (24 mL, 38 mmol of a 1.6M solution in hexanes) was added drop-wise over 20 minutes. The reaction mixture was stirred at -78 °C for 1.5 hours before a solution of chlorobis(4-methoxyphenyl)phosphine (5.0 g, 18 mmol) in tetrahydrofuran (20 mL), was added drop-wise over 30 minutes. The solution was then allowed to warm from -78 °C to room temperature overnight. The reaction mixture was washed with water (3 x 20 mL) and the product was extracted by ethyl acetate (2 x 30 mL). The organic layers were combined and hydrogen peroxide (21 mL, 50 mmol of a 12 % solution in water) was added at room temperature. The reaction mixture was stirred for 2 hours before being washed with water (3 x 20 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum to yield crude yellow oil. The crude mixture was purified by column chromatography (Ethyl acetate : Petrol 1:1) to yield a white solid 1.4 g. (24 %).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.53 - 7.58 (m, 1 H, C**H**$_{Ar}$) 7.44 - 7.52 (m, 5 H, C**H**$_{Ar}$) 7.37 - 7.42 (s (br.), 1 H, O**H**) 7.14 (d, *J*=12.1 Hz, 2 H, C**H**$_{Ar}$) 6.95 (dd, *J*=8.8, 2.3 Hz, 4 H, C**H**$_{Ar}$) 3.84 (s, 6 H, 2 x OC**H**$_3$) 1.66 (s, 6 H, 2 x C**H**$_3$)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 162.2 (d, *J*=3.1 Hz, $CH_{Ar}$) 156.5 (d, *J*=6.1 Hz, $C_q$) 135.4 (s, *J*=14.6 Hz, $C_q$) 133.8 (d, *J*=11.5 Hz, $CH_{Ar}$) 131.5 (d, *J*=3.1 Hz,

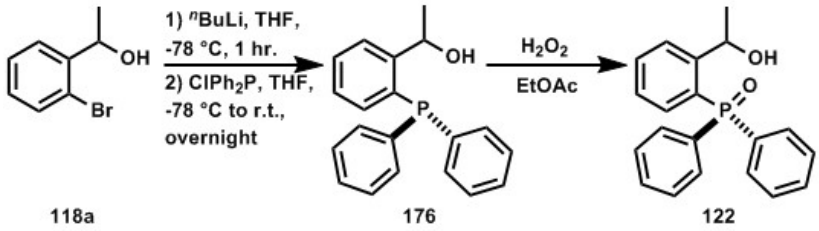
$CH_{Ar}$) 128.6 (s, $C_q$) 127.7 (d, *J*=10.0 Hz, $CH_{Ar}$) 125.2 (d, *J*=13.8 Hz, $CH_{Ar}$) 125.2 (d, *J*=113.5 Hz, $C_q$) 113.9 (d, *J*=13.0 Hz, $CH_{Ar}$) 72.9 (s, *J*=3.1 Hz, $C_q$) 55.2 (s, 2 x $OCH_3$) 32.3 (s, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 40.6 (1P, s, P(V))

**IR υ/ $cm^{-1}$:** 3011(OH), 1598, 1504, 1256(P=O), 1162(P=O), 861($CH_{Ar}$).

**MS (EI, m/z, rel. intensity):** 397.15 ($M^+H$) and 419.13 ($M^+Na$).

**Preparation of (2-(1-hydroxyethyl) phenyl) diphenylphosphine oxide 122[70, 71]**



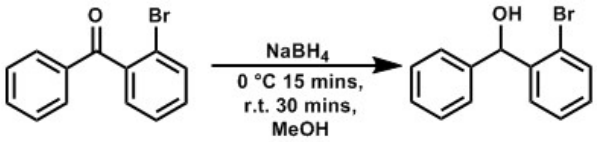

To a solution of 1-(2-bromophenyl) ethan-1-ol (0.50 g, 2.50 mmol) in tetrahydrofuran (5 mL), *n*-butyl lithium (2.50 mL, 6.25 mmol of a 2.5M solution in hexanes) was added over 10 minutes at -78 °C before being stirred for 1 hour. At -78 °C, a solution of chlorodiphenylphosphine (0.45 mL, 2.5 mmol) in tetrahydrofuran (5 mL) was added over 30 minutes before the reaction mixture was allowed to warm from -78 °C to room temperature overnight. The reaction mixture was washed with water (3 x 20 mL) and the product was extracted by ethyl acetate (2 x 30 mL). The organic layers were combined and hydrogen peroxide (2.83 mL, 10.0 mmol of a 12 % w/w solution in water) was added at room temperature. The reaction mixture was stirred for 2 hours before being washed with water (3 x 20 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum to yield crude yellow oil. The crude mixture was purified by column chromatography (Ethyl acetate) to yield a white solid 0.21g. (27%).

Data matches known NMR data for the compound.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.42 (d, *J*=2.6 Hz, 2 H, C**H**$_{Ar}$) 7.35 (d, *J*=2.5 Hz, 2 H, C**H**$_{Ar}$) 7.33 (d, *J*=2.6 Hz, 2 H, C**H**$_{Ar}$) 7.27 (dt, *J*=8.0, 0.6 Hz, 2 H, C**H**$_{Ar}$) 7.08 - 7.11 (m, 1 H, C**H**$_{Ar}$) 6.94 (dd, *J*=6.9, 0.9 Hz, 1 H, C**H**$_{Ar}$) 6.89 (s, 1 H, C**H**$_{Ar}$) 6.77 - 6.81 (m, 1 H, C**H**$_{Ar}$) 6.71 (d, *J*=8.6 Hz, 1 H, C**H**$_{Ar}$) 4.68 (s, 1 H, C**H**$CH_3$) 4.62 (s, 1 H, O**H**) 3.79 (s, 3 H, C**H**$_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 39.8 (s, 1 P (V))

**Preparation of (2-bromophenyl) (phenyl) methanol 118b**[72]




To a solution of 2-bromobenzophenone (1.09 mL, 6.00 mmol) in methanol (30 mL), sodium borohydride (0.23 g, 6.00 mmol) was added at 0 °C and was stirred for 30 minutes, before being warmed to room temperature for 30 minutes. The reaction mixture was quenched with water (15.0 mL) and stirred for 30 minutes. The product was extracted with ethyl acetate (2 x 20 mL) and the organic layer was dried with magnesium sulfate before the solvent was removed to yield crude yellow oil. The product was purified using column chromatography (Petrol : Ethyl acetate, 9 : 1) yielding colourless oil 0.95 g (60 %).

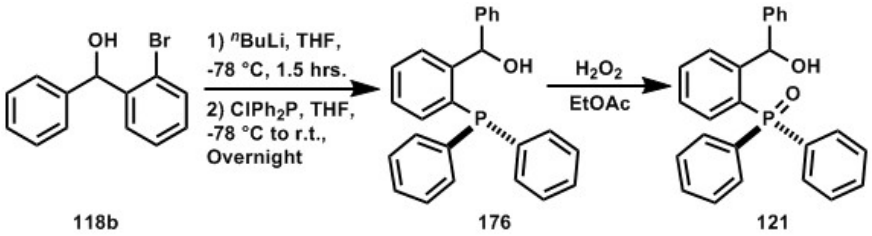
Data matches known NMR data for the compound.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.62 (ddd, *J*=11.0, 7.9, 1.3 Hz, 2 H, C**H$_{Ar}$**) 7.31 - 7.47 (m, 6 H, C**H$_{Ar}$**) 7.19 (td, *J*=7.6, 1.7 Hz, 1 H, C**H$_{Ar}$**) 6.18 (s, 1 H, C**H**OH) 3.22 (br. s., 1 H, O**H**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 142.3 ($C_q$) 142.0 ($C_q$) 132.6 ($CH_{Ar}$) 128.9 ($CH_{Ar}$) 128.2 ($CH_{Ar}$) 127.5 ($CH_{Ar}$) 126.9 ($CH_{Ar}$) 122.6 ($C_q$) 74.4 (CHOH)

**MS (EI, m/z, rel. intensity):** 284.98 ($M^+$Na).

**Preparation of (2-(hydroxyl (phenyl) methyl) phenyl) diphenyl phosphine oxide 121[70]**




To a solution of (2-bromophenyl) (phenyl) methanol (0.7 g, 2.7 mmol) in tetrahydrofuran (10 mL), *n*-butyl lithium (3.4 mL, 5.4 mmol of a 1.6 M solution in hexanes) was added over 20 minutes at -78 °C before being stirred at that temperature for 2 hours. At – 78 °C, a solution chlorodiphenylphosphine (0.96 mL, 5.40 mmol) in tetrahydrofuran (10 mL) was added over 1 hour, before being allowed to warm to room temperature overnight. The reaction mixture was washed with water (3 x 10 mL) and the product was extracted by ethyl acetate (2 x 10 mL). The organic layers were combined and hydrogen peroxide (12% w/w in water, 7.00 mL, 16.0 mmol) was added at room temperature. The reaction mixture was stirred for 2 hours before being washed with water (3 x 10 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum to yield crude yellow oil. The crude mixture was purified by column chromatography (Ethyl acetate : Petrol 1 : 1) to yield a white solid 0.62g. (60%). M P 167-169 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.67 - 7.73 (m, 2 H, C**H**$_{Ar}$) 7.39 - 7.65 (m, 9 H, C**H**$_{Ar}$) 7.16 - 7.25 (m, 6 H, C**H**$_{Ar}$) 7.00 - 7.12 (m, 2 H, C**H**$_{Ar}$) 6.25 (br. s., 1 H, O**H**) 6.21 (s, 1 H, C**H**).

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 150.31 (d, *J*=7.7 Hz, $C_q$) 141.38 (s, $C_q$) 133.71 (d, *J*=13.0 Hz, $CH_{Ar}$) 133.04 (d, *J*= 104.1 Hz, $C_q$) 132.44 (dd, *J*=18.8, 2.7 Hz, $CH_{Ar}$) 132.24 (s, $CH_{Ar}$) 132.15 (s, $CH_{Ar}$) 131.78 (d, *J*=10.0 Hz, $CH_{Ar}$)

130.43 (d, *J*=100.0 Hz, $C_q$) 130.24 (d, *J*=9.2 Hz, $CH_{Ar}$) 128.74 (d, *J*=12.3 Hz, $CH_{Ar}$) 128.56 (d, *J*=12.3 Hz, $CH_{Ar}$) 127.84 (s, $CH_{Ar}$) 126.91 (s, $CH_{Ar}$) 126.77 (s, $CH_{Ar}$) 126.64 (s, $CH_{Ar}$) 72.80 (d, *J*=5.4 Hz, CH).

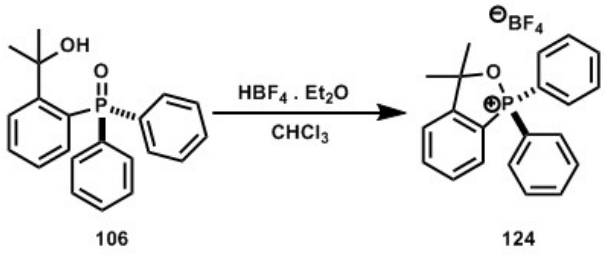
**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 35.25 (s, 1 P, P=O)

**IR υ/ $cm^{-1}$:** 3266 (OH), 3066 (CH), 1438 (C-O), 1162 (P=O)

**MS (EI, m/z, rel. intensity):** 385.13 ($M^+H$) and 407.11 ($M^+Na$)

### 6.3 Synthesis of Alkoxyphosphonium Salt

**Preparation of diphenyl alkoxyphosphonium salt 124** [54-56, 70]




106 124

To solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.33 g, 1 mmol) in dry chloroform (5 mL), tetrafluoroboric acid (0.14 mL, 1 mmol) was added at room temperature, and the reaction mixture was stirred for 2 hours. The reaction mixture was dried with magnesium sulfate then filtered before the solvent was removed. Recrystallised in $CHCl_3/Et_2O$ to yield a white crystalline solid in 51% yield. M.P. 165 °C. (158 °C).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.16 (t, *J*=8.5 Hz, 1 H, C**H**$_{Ar}$) 7.96 (t, *J*=1.3 Hz, 1 H, C**H**$_{Ar}$) 7.94 (s, 2 H, C**H**$_{Ar}$) 7.92 (t, *J*=1.3 Hz, 1 H, C**H**$_{Ar}$) 7.88 (q, *J*=1.5 Hz, 2 H, C**H**$_{Ar}$) 7.85 - 7.87 (m, 1 H, C**H**$_{Ar}$) 7.84 (q, *J*=1.5 Hz, 1 H, C**H**$_{Ar}$) 7.82 (d, *J*=1.2 Hz, 1 H, C**H**$_{Ar}$) 7.80 - 7.81 (m, 1 H, C**H**$_{Ar}$) 7.78 - 7.80 (m, 1 H, C**H**$_{Ar}$) 7.76 - 7.78 (m, 1 H, C**H**$_{Ar}$) 7.69 - 7.76 (m, 1 H, C**H**$_{Ar}$) 1.76 - 2.10 (m, 6 H, 2 x C**H**$_3$)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 152.8 (d, *J*=15.3 Hz, $CH_{Ar}$) 136.8 (d, *J*=3.1 Hz, $CH_{Ar}$) 136.6 (d, *J*=3.1 Hz, $CH_{Ar}$) 132.7 (d, *J*=13.0 Hz, $CH_{Ar}$) 131.7 (d, *J*=13.0 Hz, $CH_{Ar}$) 131.1 (s, *J*=10.0 Hz, $CH_{Ar}$) 130.5 (d, *J*=14.6 Hz, $CH_{Ar}$) 130.0 (d, *J*=13.0 Hz, $CH_{Ar}$) 128.3 (d, *J*=13.0 Hz, $CH_{Ar}$) 123.4 (d, *J*=11.5 Hz, $CH_{Ar}$) 120.3 (d, *J*=105.8 Hz, $C_q$) 117.1 (d, *J*=99.7 Hz, $C_q$) 100.4 (s, *J*=2.3 Hz, $C_q$) 30.0 (d, *J*=1.5 Hz, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.7 (1P, s, P(v))

**$^{19}$F NMR (376 MHz, $CDCl_3$):** δ -153.2 (dd, *J*=1.7, 0.9 Hz, B**F$_4$**)

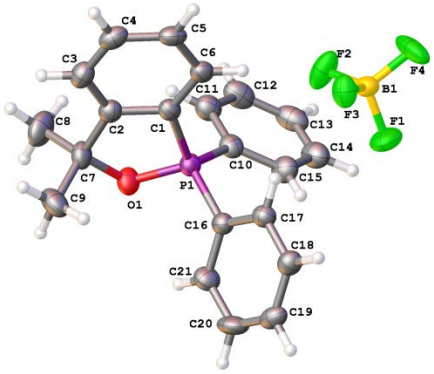
**$^{11}$B NMR (128 MHz, $CDCl_3$):** δ -0.93 (s, **B**$F_4$)

**IR υ/cm$^{-1}$:** 3009 (CH), 1439 (C-O), 1269 (P-O), 1030 ($CH_{Ar}$)

**MS (EI, m/z, rel. intensity):** 342 ($M^+Na$) and 319 ($M^+$).

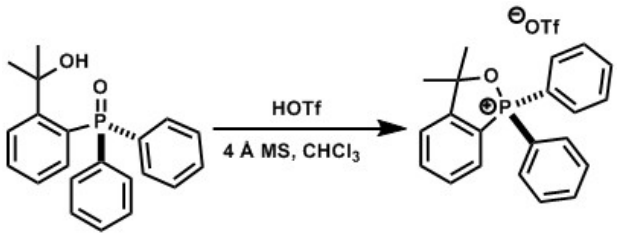
**CHN (ELEMENTAL ANALYSIS):** Predicted C 62.10, H 4.96, N 0. Actual C 62.14, H 4.99, N 0.

**Crystallography Data:**




| | |
|---|---|
| Identification code | CCRDCA |
| Empirical formula | $C_{21}H_{20}BOF_4P$ |
| Formula weight | 406.15 |
| Temperature/K | 120(2) |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| a/Å | 14.9293(11) |
| b/Å | 18.5401(9) |
| c/Å | 14.5158(8) |
| α/° | 90 |
| β/° | 91.228(5) |

| | |
|---|---|
| γ/° | 90 |
| Volume/Å$^3$ | 4016.9(4) |
| Z | 8 |
| $\rho_{calc}$mg/mm$^3$ | 1.343 |
| m/mm$^{-1}$ | 1.617 |
| F(000) | 1680.0 |
| Crystal size/mm$^3$ | 0.3443 × 0.1519 × 0.0395 |
| 2Θ range for data collection | 7.604 to 149.412° |
| Index ranges | -18 ≤ h ≤ 18, -17 ≤ k ≤ 22, -18 ≤ l ≤ 17 |
| Reflections collected | 28479 |
| Independent reflections | 8021[R(int) = 0.0773] |
| Data/restraints/parameters | 8021/476/543 |
| Goodness-of-fit on $F^2$ | 1.089 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0968, $wR_2$ = 0.2825 |
| Final R indexes [all data] | $R_1$ = 0.1072, $wR_2$ = 0.2909 |
| Largest diff. peak/hole / e Å$^{-3}$ | 1.29/-0.54 |




106 123

A solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.1 g, 0.3 mmol) in dry chloroform (5 mL), was stirred with 4 Å molecular sieves for 30 minutes. At room temperature, triflic acid (0.03 mL, 0.30 mmol) was added and the reaction mixture was stirred for 2 hours. The sieves were filtered off and the solvent was removed. Recrystallised in $CHCl_3/Et_2O$ to yield a white crystalline solid in 71% yield.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.12 (m, 1 H, C**H$_{Ar}$**) 7.92 (m, 1 H, C**H$_{Ar}$**) 7.82 (dd, *J*=7.3, 1.4 Hz, 2 H, C**H$_{Ar}$**) 7.66 - 7.80 (m, 10 H, C**H$_{Ar}$**) 1.90 (s, 6 H, 2 x C**H$_3$**)

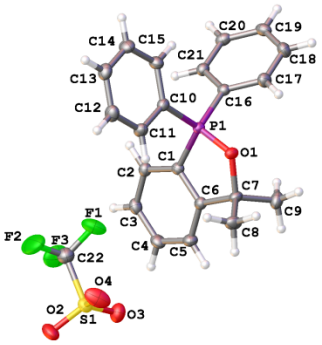
**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 153.0 (d, *J*=16.1 Hz, $C_q$) 137.1 (d, *J*=3.1 Hz, $CH_{Ar}$) 136.8 (d, *J*=3.1 Hz, $CH_{Ar}$) 132.9 (d, *J*=13.0 Hz, $CH_{Ar}$) 132.0 (d, *J*=13.8 Hz, $CH_{Ar}$) 130.3 (d, *J*=11.5 Hz, $CH_{Ar}$) 128.7 (d, *J*=12.3 Hz, $CH_{Ar}$) 123.7 (d, *J*=11.5 Hz, $CH_{Ar}$) 120.5 (d, *J*=106.6 Hz, Cq) 117.3 (d, *J*=98.9 Hz, $C_q$) 100.6 (d, *J*=3.1 Hz, $C_q$) 30.2 (d, *J*=1.5 Hz, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ ppm 73.56 (s, 1 P)

**IR υ/cm$^{-1}$:** 3009($CH_3$), 1439(C-O), 1269(P-O), 1030($CH_{Ar}$)

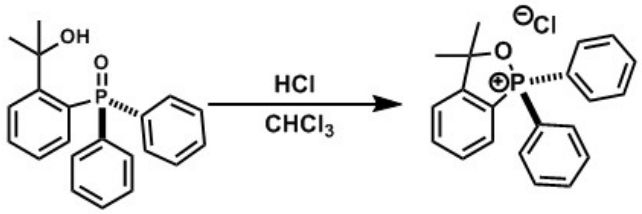
**MS (EI, m/z, rel. intensity):** 342 ($M^+Na$) and 319 ($M^+$).

**Crystallography Data:**




| | |
|---|---|
| Identification code | CCRDCB |
| Empirical formula | $C_{22}H_{20}O_4F_3PS$ |
| Formula weight | 468.41 |
| Temperature/K | 120(2) |
| Crystal system | monoclinic |
| Space group | $P2_1/n$ |
| a/Å | 11.3172(3) |
| b/Å | 14.0130(3) |
| c/Å | 14.7642(5) |
| α/° | 90 |
| β/° | 108.686(3) |
| γ/° | 90 |
| Volume/Å$^3$ | 2218.01(12) |
| Z | 4 |
| $\rho_{calc}$mg/mm$^3$ | 1.403 |
| m/mm$^{-1}$ | 2.444 |
| F(000) | 968.0 |
| Crystal size/mm$^3$ | 0.1221 × 0.1068 × 0.0493 |

| | |
|---|---|
| 2Θ range for data collection | 8.636 to 148.912° |
| Index ranges | $-13 \leq h \leq 13$, $-11 \leq k \leq 17$, $-18 \leq l \leq 17$ |
| Reflections collected | 14617 |
| Independent reflections | 4423[R(int) = 0.0200] |
| Data/restraints/parameters | 4423/0/282 |
| Goodness-of-fit on $F^2$ | 1.033 |
| Final R indexes [I>=2σ (I)] | $R_1 = 0.0335$, $wR_2 = 0.0831$ |
| Final R indexes [all data] | $R_1 = 0.0378$, $wR_2 = 0.0859$ |
| Largest diff. peak/hole / e $Å^{-3}$ | 0.58/-0.42 |




106 147

To solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenyl phosphine oxide (1.00 g, 3.00 mmol) in dry chloroform (35 mL), hydrochloric acid (6.00 mL, 6.00 mmol of a 1M solution in diethyl ether) was added at room temperature and the reaction mixture was stirred for 30 minutes before magnesium sulfate was added. The solvent was removed to yield crude white solid. The solid was purified by recrystallisation ($MeCN/Et_2O$) to yield white foam 0.76 g (72%).

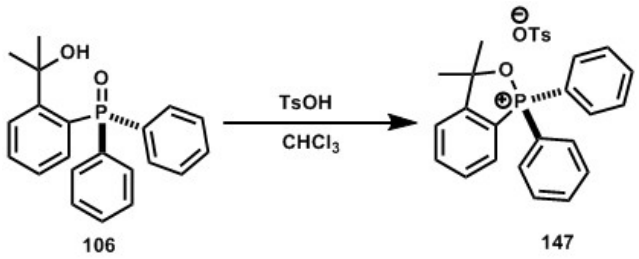
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.09 (t, *J*=8.3 Hz, 1 H, C**H$_{Ar}$**) 7.73 - 7.81 (m, 1 H, C**H$_{Ar}$**) 7.49 - 7.72 (m, 10 H, C**H$_{Ar}$**) 7.43 (td, *J*=8.7, 3.1 Hz, 1 H, C**H$_{Ar}$**) 7.16 - 7.24 (m, 1 H) 1.65 - 1.84 (s, 6 H, 2 x C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 152.3 (d, *J*=15.3 Hz, $C_q$) 136.4 (d, *J*=2.3 Hz, $CH_{Ar}$) 136.1 (d, *J*=2.3 Hz, $CH_{Ar}$) 132.2 (d, *J*=13.0 Hz, $CH_{Ar}$) 131.3 (dd, *J*=8.4, 2.3 Hz, $CH_{Ar}$) 130.0 (d, *J*=14.6 Hz, $CH_{Ar}$) 129.5 (d, *J*=13.0 Hz, $CH_{Ar}$) 127.7 (d, *J*=12.3 Hz, $CH_{Ar}$) 123.3 (d, *J*=11.5 Hz, $CH_{Ar}$) 119.8 (d, *J*=105.8 Hz, $C_q$) 116.3 (d, *J*=98.9 Hz, $C_q$) 100.0 (d, *J*=2.3 Hz, $C_q$) 29.7 (d, *J*=1.5 Hz, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.3 (s, 1 P)

**IR υ/cm$^{-1}$:** 2940 (CH), 1140 (C-O), 959 (P-O)

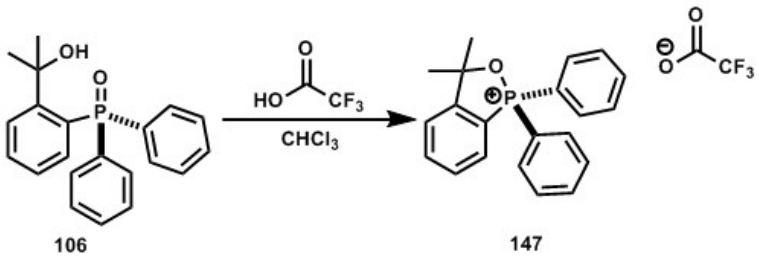
**MS (EI, m/z, rel. intensity):** 342 ($M^+Na$) and 319 ($M^+$)




106 147

To solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.1 g, 0.3 mmol) in dry chloroform (3 mL), tosylic acid (0.39 mL, 0.30 mmol) was added at room temperature, and the reaction mixture was stirred for 2 hours. The solvent was removed yielding colourless crude oil, conversion 71% determined by $^{31}$P NMR. The product was not isolated.

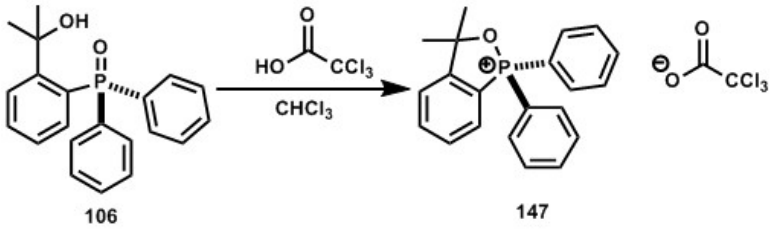
**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.86 (s, 1 P, P-O).




106 147

To a solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.10 g, 0.3 mmol) in dry chloroform (1 mL), trifluoroacetic acid (0.03 mL, 0.3 mmol) was added at room temperature, and the reaction mixture was stirred for 30 minutes. The solvent was removed yielding colourless oil, conversion to the salt was at 51% and was determined by $^{31}$P NMR. The product was not isolated.

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.81 (s, 1 P)




106 147

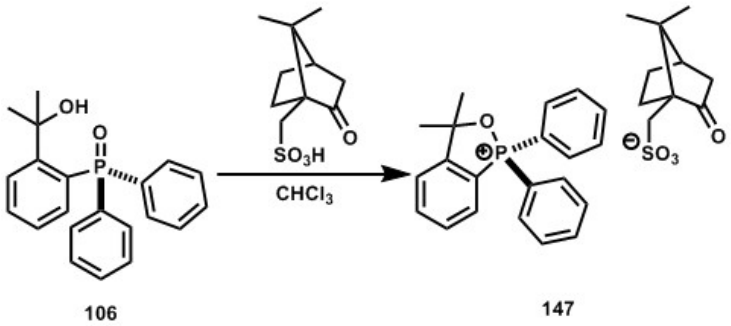
A solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.10 g, 0.30 mmol) in dry chloroform (5 mL), was stirred with 4 Å molecular sieves. At room temperature, trichloroacetic acid (0.04 g, 0.30 mmol) was added and the reaction mixture was stirred for 2 hours. The sieves were filtered off and the solvent was removed to yield crude white solid. The solid was purified via recrystallisation ($MeCN/Et_2O$) to yield white foam 0.11 g (77 %).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.14 (t, *J*=8.5 Hz, 1 H, C**H$_{Ar}$**) 7.97 (d, *J*=8.0 Hz, 1 H, C**H$_{Ar}$**) 7.85 - 7.92 (m, 2 H, C**H$_{Ar}$**) 7.72 - 7.84 (m, 8 H, C**H$_{Ar}$**) 7.68 (dd, *J*=7.9, 2.0 Hz, 1 H, C**H$_{Ar}$**) 7.41 - 7.59 (m, 1 H, C**H$_{Ar}$**) 1.94 (s, 6 H, 2 x C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 163.3 (s, $C_q$) 152.8 (d, *J*=15.4 Hz, $C_q$) 137.0 (d, *J*=2.2 Hz, $CH_{Ar}$) 136.8 (d, *J*=2.9 Hz, $CH_{Ar}$) 132.8 (d, *J*=13.2 Hz, $CH_{Ar}$) 131.8 (d, *J*=13.2 Hz, $CH_{Ar}$) 131.5 (d, *J*=11.0 Hz, $CH_{Ar}$) 130.5 (d, *J*=13.9 Hz, $CH_{Ar}$) 129.9 (d, *J*=13.2 Hz, $CH_{Ar}$) 128.7 (d, *J*=13.9 Hz, $CH_{Ar}$) 123.3 (d, *J*=11.7 Hz, $CH_{Ar}$) 120.2 (d, *J*=106.1 Hz, $C_q$) 117.0 (d, *J*=99.5 Hz, $C_q$) 100.3 (d, *J*=2.2 Hz, $C_q$) 30.1 (d, *J*=2.2 Hz, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.82 (br. s., 1 P)

**MS (EI, m/z, rel. intensity):** 342 ($M^+Na$) and 319 ($M^+$)




106 147

To a solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.10 g, 0.3 mmol) in dry chloroform (1 mL), camphor sulfonic acid (0.069 mL, 0.3 mmol) was added at room temperature, and the reaction mixture was stirred for 30 minutes. The solvent was removed yielding colourless oil, conversion to salt was 85% determined by $^{31}$P NMR.

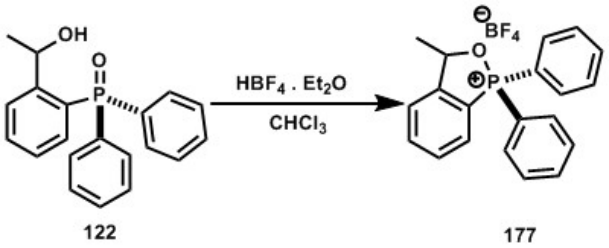
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.23 (t, *J*=8.3 Hz, 1 H, C**H$_{Ar}$**) 7.91 (t, *J*=7.3 Hz, 1 H, C**H$_{Ar}$**) 7.64 - 7.83 (m, 10 H, C**H$_{Ar}$**) 7.41 - 7.50 (m, 1 H, C**H$_{Ar}$**) 7.32 - 7.40 (m, 1 H, C**H$_{Ar}$**) 3.34 (d, *J*=14.9 Hz, 1 H, C**H$_2$**) 2.88 (d, *J*=14.9 Hz, 1 H, C**H$_2$**) 2.65 - 2.76 (m, 1 H, C**H**) 1.81 - 1.93 (m, 6 H, 2 x C**H$_3$**) 1.72 (m, 2 H, C**H$_2$**) 1.55 (s, 1 H, C**H$_2$**) 1.15 - 1.25 (m, 1 H, C**H$_2$**) 1.07 (s, 3 H, C**H$_3$**) 0.74 (s, 3 H, C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 216.17 (s, $C_q$) 152.53 (d, *J*=15.3 Hz, $C_q$) 136.72 (d, *J*=3.1 Hz, $CH_{Ar}$) 136.34 (d, *J*=3.1 Hz, $CH_{Ar}$) 132.54 (d, *J*=13.0 Hz, $CH_{Ar}$) 131.62 (dd, *J*=6.1, 2.3 Hz, $CH_{Ar}$) 130.28 (d, *J*=13.8 Hz, $CH_{Ar}$) 128.21 (d, *J*=12.3 Hz, $CH_{Ar}$) 123.35 (d, *J*=11.5 Hz, $CH_{Ar}$) 120.25 (d, *J*=105.8 Hz, $C_q$) 116.76 (d, *J*=98.9 Hz, $C_q$) 100.22 (d, *J*=2.3 Hz, $C_q$) 77.20 (s, $CH_2SO_3$) 58.28 (s, $C_q$) 47.41 (s, CH) 46.95 (s, $CH_2$) 42.48 (d, *J*=6.1 Hz, 2 x $CH_3$) 29.93 (s, $C_q$) 26.75 (s, $CH_2$) 24.33 (s, $CH_2$) 20.04 (s, $CH_3$) 19.53 (s, $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.54 (s, 1 P)

**MS (EI, m/z, rel. intensity):** 342 ($M^+Na$) and 319 ($M^+$)

**Preparation of 3-methyl-1,1-diphenyl-1,3-dihydrobenzo [c][1,2] oxaphosphol-1-ium tetrafluoroborate 177[70]**




122 177

To a solution of (2-(1-hydroxyethyl) phenyl) diphenyl phosphine oxide (0.10 g, 0.30 mmol) in dry chloroform (3 mL), tetrafluoroboric acid (0.04 mL, 0.30 mmol) was added at room temperature, and the reaction mixture was stirred for 2 hours. The reaction mixture was dried with magnesium sulfate then filtered before the solvent was removed to yield crude white solid. The product was purified by recrystallisation ($CHCl_3/Et_2O$) to yield a white solid in 0.10 g (87%) yield.

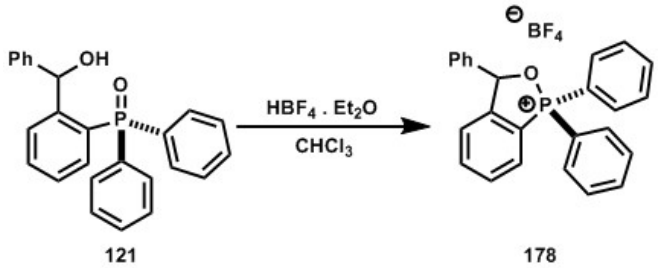
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.14 (t, *J*=8.4 Hz, 4 H, C**H$_{Ar}$**) 7.68 - 7.94 (m, 10 H, C**H$_{Ar}$**) 6.42 (t, *J*=6.2 Hz, 1 H, C**H**) 1.91 (d, *J*=6.6 Hz, 3 H, C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 136.6 - 136.7 (m, $CH_{Ar}$) 136.5 - 136.8 (m,$CH_{Ar}$) 136.5 - 136.8 (m, $CH_{Ar}$) 133.0 (d, *J*=3.7 Hz, $CH_{Ar}$) 132.9 (d, *J*=3.7 Hz, $CH_{Ar}$) 131.6 (d, *J*=12.4 Hz, $CH_{Ar}$) 130.5 (d, *J*=6.6 Hz, $CH_{Ar}$) 130.4 (d, *J*=5.9 Hz, $CH_{Ar}$) 129.8 (d, *J*=13.2 Hz, $CH_{Ar}$) 124.0 (d, *J*=11.0 Hz, $CH_{Ar}$) 120.0 (d, *J*=161.0 Hz, $C_q$) 89.8 (s, *J*=2.2 Hz, $C_q$) 22.9 (s, *J*=2.2 Hz, $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 77.56 (s, 1 P)

**MS (EI, m/z, rel. intensity):** 305 ($M^+$)

**Preparation of 1,1,3-triphenyl-1,3-dihydrobenzo [c][1,2] oxaphosphol-1-ium tetrafluoroborate 178[70]**




121 178

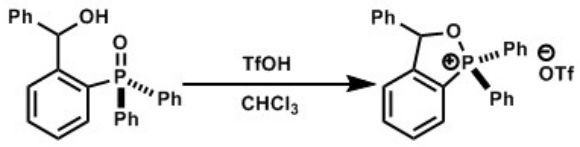
To a solution of (2-(hydroxy(phenyl) methyl) phenyl) diphenyl phosphine oxide (0.73 g, 1.90 mmol) in dry chloroform (5 mL), tetrafluoroboric acid (0.25 mL, 1.90 mmol) was added at room temperature and the reaction mixture was stirred for 2 hours. The reaction mixture was dried with magnesium sulfate then filtered before the solvent was removed to yield crude white solid. The product was purified by recrystallisation ($CHCl_3/Et_2O$) to yield a white solid in 0.79 g (81%) yield.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.16 (t, *J*=6.9 Hz, 4 H, C**H$_{Ar}$**) 7.72 - 7.89 (m, 8 H, C**H$_{Ar}$**) 7.67 (d, *J*=3.5 Hz, 2 H, C**H$_{Ar}$**) 7.32 - 7.45 (m, 10 H, C**H$_{Ar}$**) 7.23 - 7.31 (m, 1 H, C**H**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 147.14 (d, *J*=16.1 Hz, $C_q$) 136.61 (dd, *J*=13.0, 3.8 Hz, $CH_{Ar}$) 136.18 (d, *J*=3.1 Hz, $CH_{Ar}$) 135.51 (s, *J*=2.3 Hz, $CH_{Ar}$) 132.93 (d, *J*=13.8 Hz, $CH_{Ar}$) 132.77 (d, *J*=13.0 Hz, $CH_{Ar}$) 131.76 (s, $C_q$) 130.55 (s, $CH_{Ar}$) 130.31 (dd, *J*=16.9, 3.1 Hz, $CH_{Ar}$) 129.44 (d, *J*=13.0 Hz, $CH_{Ar}$) 129.19 (s, $CH_{Ar}$) 128.46 (s, $CH_{Ar}$) 119.55 (dd, *J*=108.9, 3.1 Hz, $C_q$) 117.99 (d, *J*=102.0 Hz, $C_q$) 93.55 (d, *J*=2.3 Hz, CH)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 77.59 (s, 1 P)

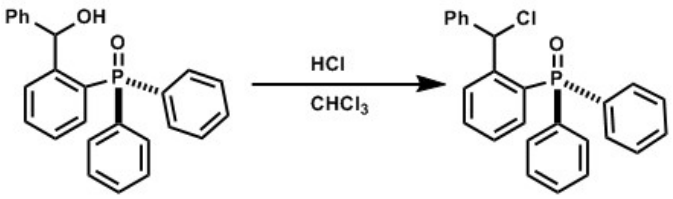
**MS (EI, m/z, rel. intensity):** 366 ($M^+$)




To a solution of (2-(hydroxy(phenyl) methyl) phenyl) diphenyl phosphine oxide (0.10 g, 0.26 mmol) in dry chloroform (1 mL), triflic acid (0.02 mL, 0.26 mmol) was added at room temperature and the reaction mixture was stirred for 30 minutes. The solvent was removed yielding colourless oil with a conversion of 54% to the salt (conversion determined by $^{31}$P NMR). The product was not isolated.

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 77.61 (s, 1 P)

**MS (EI, m/z, rel. intensity):** 366 ($M^+$)




121 125

To a solution of (2-(hydroxy(phenyl) methyl) phenyl) diphenyl phosphine oxide (0.10 g, 0.26 mmol) in dry chloroform (3 mL), hydrochloric acid 2M in diethyl ether (0.13 mL, 0.26 mmol) was added at room temperature and the reaction mixture was stirred for 2 hours. The reaction mixture was dried in magnesium sulfate then filter before the solvent was removed, yielding a colourless oil with a 76 % conversion to the chlorophenyl diphenyl phosphine oxide (Conversion was determined by $^{31}$P NMR).

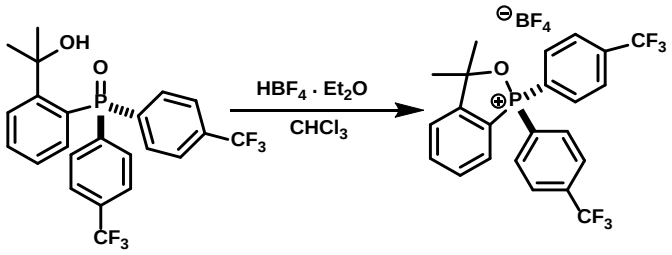
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.81 (dd, *J*=7.7, 3.9 Hz, 4 H, C**H$_{Ar}$**) 7.70 (dd, *J*=12.1, 7.5 Hz, 2 H, C**H$_{Ar}$**) 7.35 - 7.65 (m, 7 H, C**H$_{Ar}$**) 6.99 - 7.25 (m, 7 H, C**H$_{Ar}$**) 6.23 (s, 1 H, C**H**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.77 (d, *J*=6.9 Hz, $C_q$) 141.26 (s, $C_q$) 140.32 (s, $CH_{Ar}$) 133.57 (d, *J*=13.0 Hz, $CH_{Ar}$) 132.36 (d, *J*=2.3 Hz, $CH_{Ar}$) 131.86 (dd, *J*=13.8, 6.1 Hz, $CH_{Ar}$) 131.60 (d, *J*=10.0 Hz, $CH_{Ar}$) 131.25 (d, *J*=9.2 Hz, $CH_{Ar}$) 129.60 (d, *J*=85.1 Hz, $C_q$) 128.60 (d, *J*=12.3 Hz, $CH_{Ar}$) 128.38 (t, *J*=12.7 Hz, $CH_{Ar}$) 127.95 (s, $CH_{Ar}$) 127.55 (s, $CH_{Ar}$) 127.08 (d, *J*=12.3 Hz, $CH_{Ar}$) 126.80 (d, *J*=82.8 Hz, $C_q$) 59.42 (d, *J*=4.6 Hz, CH)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 32.28 (d, *J*=10.0 Hz, 1 P)

**MS (EI, m/z, rel. intensity):** 376 ($M^+H$)

**Preparation of bis(4-(trifluoromethyl) phenyl) alkoxyphosphonium salt 179**




116 179

To solution of (2-(2-hydroxypropan-2-yl) phenyl) bis(4-(trifluoromethyl) phenyl) phosphine oxide (0.1 g, 0.2 mmol) in chloroform (0.6 mL), tetrafluoroboronic acid complex with diethyl ether (0.1mL, 1 mmol) was added at room temperature. The reaction mixture was stirred for 30 minutes before the solvent was removed. Recrystallised in MeCN/$Et_2O$ to yield a white crystalline solid 100 % conversion determined by $^{31}$P NMR. M.P. 167 °C.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.21 (t, *J*=8.6 Hz, 1 H, C**H$_{Ar}$**) 7.95 - 8.05 (m, 9 H, C**H$_{Ar}$**) 7.80 - 7.87 (m, 1 H, C**H$_{Ar}$**) 7.68 (dd, *J*=7.8, 1.8 Hz, 1 H, C**H$_{Ar}$**) 1.95 (s, 6 H, 2 x C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 139.7 (s, *J*=6.9 Hz, $CH_{Ar}$) 137.6 (s, *J*=3.1 Hz, $C_q$) 133.5 (d, *J*=13.0 Hz, $CH_{Ar}$) 132.1 (d, *J*=13.0 Hz, $CH_{Ar}$) 130.8 (d, *J*=118.8 Hz, $C_q$) 127.4 (d, *J*=3.8 Hz, $CH_{Ar}$) 127.3 (s, *J*=3.8 Hz, $CH_{Ar}$) 124.3 (d, *J*=106.6 Hz, $C_q$) 84.1 (s, $C_q$) 29.9 (s, 2 x $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 72.7 (s, 1 P (V))

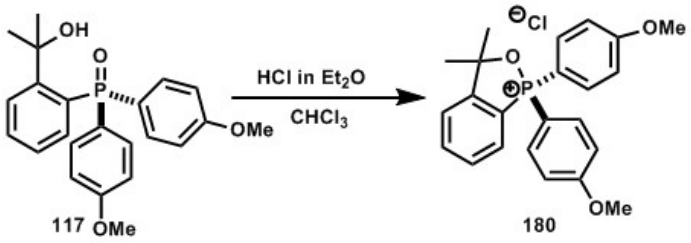
**$^{19}$F NMR (377 MHz, $CDCl_3$):** δ -63.9 (s, 6 F, $CF_3$)

**IR υ/cm$^{-1}$:** 3045 (CH), 1400 (C-O), 1323 (P-O), 1064 (CF), 951 ($CH_{Ar}$)

**MS (EI, m/z, rel. intensity):** 455.09 ($M^+$).

**CHN (ELEMENTAL ANALYSIS):** Predicted C 50.95, H 3.35, N 0. Actual C 50.46, H 3.29, N 0.

**Preparation of bis(4-methoxyphenyl) alkoxyphosphonium salt 180**




To solution of (2-(2-hydroxypropan-2-yl)phenyl) bis(4-methoxyphenyl) phosphine oxide (0.4 g, 1 mmol) in chloroform (2 mL), hydrochloric acid 1M in diethyl ether (1 mL, 1 mmol) was added at room temperature. The reaction mixture was stirred for 30 minutes. The reaction mixture was dried with magnesium sulfate then filtered before the solvent was removed to yield yellow oil. 100 % conversion to the salt determined by $^{31}$P NMR.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.06 - 8.26 (m, 12 H, C**H**$_3$) 3.94 (br. s., 6 H, 2 x OC**H**$_3$) 1.76 - 2.01 (s, 6 H, 2 x C**H**$_3$)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 162.4 (d, *J*=3.1 Hz, $C_q$) 149.6 (d, *J*=9.2 Hz, $CH_{Ar}$) 144.2 (d, *J*=4.6 Hz, $C_q$) 134.1 (d, *J*=10.7 Hz, $CH_{Ar}$) 132.1 (d, *J*=3.1 Hz, $CH_{Ar}$) 129.9 (d, *J*=10.7 Hz, $CH_{Ar}$) 129.2 (d, *J*=105.8 Hz, $C_q$) 126.3 (d, *J*=13.0 Hz, $CH_{Ar}$) 123.4 (d, *J*=111.9 Hz, Cq) 117.0 (s, *J*=15.3 Hz, $CH_{Ar}$) 114.0 (d, *J*=13.8 Hz, $C_q$) 57.2 (s, 2 x –$OCH_3$) 31.0 (s, 2 x $CH_3$)

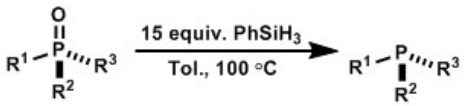
**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 72.6 (1P, S, P(v))

**IR υ/cm$^{-1}$:** 3691 ($CH_3$), 1270 (C-O), 1124 (P-O), 949 ($CH_{Ar}$)

**MS (EI, m/z, rel. intensity):** 379.14 ($M^+$)

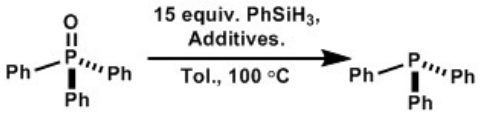
## 6.4 Reductions of the Phosphine Oxides

### Reductions of phosphine oxides using phenyl silane




To a solution of phosphine oxide (1 equivalent) in toluene (0.3 M), phenyl silane (15 equivalents) was added before heating to 100 °C. $^{31}$P NMRs were taken after 1 hour and 4 hours.

### Reductions of phosphine oxides using phenyl silane and additives




To a solution of triphenylphosphine oxide (0.2 g, 0.7 mmol) in toluene (0.6 mL), before phenyl silane (1.4 mL, 10.5 mmol), diisopropylethylamine (0.01 mL, 0.07 mmol) and trifluoroacetic acid (0.005mL, 0.07 mmol). $^{31}$P NMRs were taken every 10 minutes.

| | 10 mins | 20 mins | 30 mins | 40 mins | 50 mins | 60 mins |
|---|---|---|---|---|---|---|
| **A** | 0 | 0.8 | 1.3 | 1.6 | 2 | 3 |
| **B** | 22 | 28 | 33 | 38 | 41 | 47 |
| **C** | 6 | 10 | 13 | 15 | 18 | 21 |
| **D** | 7 | 11 | 18 | 21 | 28 | 35 |
| **E** | 3 | 4 | 6 | 7 | 9 | 10 |
| **F** | 25 | 34 | 40 | 45 | 50 | 52 |
| **G** | 28 | 45 | 53 | 61 | 65 | 70 |
| **H** | 3 | 4 | 5 | 5 | 7 | 7 |
| **I** | 12 | 17 | 20 | 24 | 27 | 29 |

**A** = 15 equivalents phenyl silane, 10 % diisopropylethylamine.

**B** = 15 equivalents phenyl silane, 10 % diisopropylethylamine, 10 % trifluoroacetic acid.

**C** = 15 equivalents phenyl silane, 10 % diisopropylethylamine, 10 % nitrobenzoic acid.

**D** = 15 equivalents phenyl silane, 10 % trifluoroacetic acid.

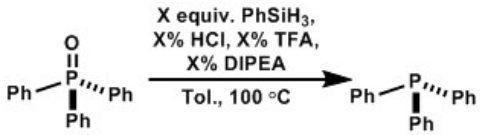
**E** = 15 equivalents phenyl silane, 20 % diisopropylethylamine, 10 % trifluoroacetic acid, 10 % tetraphenylphosphonium bromide.

**F** = 15 equivalents phenyl silane, 15 equivalents diisopropylethylamine, 10 % trifluoroacetic acid.

**G** = 15 equivalents phenyl silane, 10 % hydrochloric acid, 20 % diisopropylethylamine, 10 % trifluoroacetic acid.

**H** = 15 equivalents phenyl silane, 20 % diisopropylethylamine, 10 % trifluoroacetic acid, 10 % tetraphenylphosphonium bromide.

**I** = 15 equivalents phenyl silane, 10 % hydrochloric acid, 20 % diisopropylethylamine, 10 % trifluoroacetic acid. Solvent = ethyl acetate. Temperature = 80 °C.



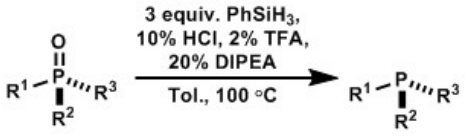

To a solution of triphenylphosphine oxide (0.2 g, 0.7 mmol) in toluene (1.8 mL), phenyl silane (0.14 mL, 1.05 mmol), diisopropylethylamine (0.02 mL, 0.1 mmol) and trifluoroacetic acid (0.001 mL, 0.01 mmol) were added. The reaction was heated to 100 °C and $^{31}P$ NMRs were taken to monitor the conversion.

| | 10 mins | 20 mins | 30 mins | 40 mins | 50 mins | 60 mins | 4 hrs | 24 hrs |
|---|---|---|---|---|---|---|---|---|
| **A** | - | - | 14 | - | - | 20 | 35 | 71 |
| **B** | 6 | 13 | 17 | 20 | 24 | 27 | 49 | 94 |
| **C** | - | - | - | - | - | 37 | 66 | 81 |

**A** = 1.5 equivalents phenyl silane, 10 % diisopropylethylamine, 1 % trifluoroacetic acid.

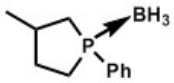
**B** = 1.5 equivalents phenyl silane, 10 % hydrochloric acid, 20 % diisopropylethylamine, 1 % trifluoroacetic acid.

**C** = 3 equivalents phenyl silane, 10 % hydrochloric acid, 20 % diisopropylethylamine, 2 % trifluoroacetic acid.




To a solution of phosphine oxide (1 mmol) in toluene (2 mL), phenyl silane (0.4 mL, 3 mmol), diisopropylethylamine (0.035 mL, 0.2 mmol), hydrochloric acid (1M in diethyl ether, 0.1 mL, 0.1 mmol) and trifluoroacetic acid (0.002 mL, 0.02 mmol) were added before the reaction mixture was heated to 100 °C. $^{31}$P NMRs were taken after 1 hr, 4 hrs and 6 hrs. The reaction mixture was allowed to cooled to room temperature before borane dimethyl sulphide complex (1M in dichloromethane, 1 mL, 1 mmol) was added and stirred overnight. The reaction mixture was quenched with water (5 mL) before being extracted with ethyl acetate (2 x 10 mL) and washed with water (2 x 5 mL). The organic layers were combined and dried with magnesium sulfate before the solvent was removed under vacuum to yield clear oil. The phosphine-borane complex was purified using column chromatography (Petrol : Ethyl acetate 9 : 1).

**3-methyl-1-phenylphospholane Borane 181**[35]



**Yield:** 63 %

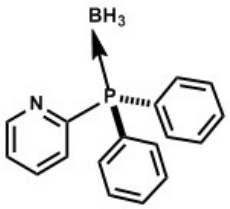
NMR data matches known NMR data for the compound

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.60 - 7.66 (m, 1 H, C**H**$_{Ar}$) 7.34 - 7.47 (m, 2 H, C**H**$_{Ar}$) 7.18 - 7.29 (m, 2 H, C**H**$_{Ar}$) 4.25 (s, 2 H, C, C**H**$_2$) 4.16 (q, *J*=7.1 Hz, 1

H, C**H**$CH_3$) 2.08 (s, 3 H, C$\mathbf{H_3}$) 1.40 (d, *J*=6.7 Hz, 1 H, C**H**) 1.33 (d, *J*=6.7 Hz, 1 H, C**H**) 1.30 (t, *J*=7.2 Hz, 1 H, C**H**) 1.20 - 1.25 (m, 1 H, C**H**)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ ppm 38.5 - 50.7 (m, 1 P (P-$BH_3$))

**Diphenyl-2-pyridine phosphine borane 182[58]**




**Yield:** 60 %

NMR data matches known NMR data for the compound

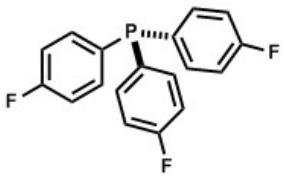
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.79 (d, *J*=4.7 Hz, 2 H, C$\mathbf{H_{Ar}}$) 8.08 (t, *J*=6.9 Hz, 3 H, C$\mathbf{H_{Ar}}$) 7.70 - 7.85 (m, 3 H, C$\mathbf{H_{Ar}}$) 7.39 - 7.55 (m, 4 H, C$\mathbf{H_{Ar}}$) 7.32 - 7.38 (m, 2 H, C$\mathbf{H_{Ar}}$) 0.79 - 2.03 (m, 3 H, C$\mathbf{H_{Ar}}$)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 154.2 (d, *J*=76.7 Hz, $C_q$) 150.5 (d, *J*=13.0 Hz, $CH_{Ar}$) 136.1 (d, *J*=10.0 Hz, $CH_{Ar}$) 133.2 (d, *J*=9.2 Hz, $CH_{Ar}$) 131.2 (d, *J*=2.3 Hz, $CH_{Ar}$) 129.7 (d, *J*=26.8 Hz, $CH_{Ar}$) 128.5 (d, *J*=10.7 Hz, $CH_{Ar}$) 128.5 (d, *J*=59.8 Hz, $C_q$) 124.8 (d, *J*=2.3 Hz, $CH_{Ar}$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 18.4 (d, *J*=71.3 Hz, 1 P)

**$^{11}$B NMR (128 MHz, $CDCl_3$):** δ -38.4 (d, *J*=46.0 Hz, 1 B)

**Tris(4-fluorophenyl)phosphine 183[73]**




**Yield:** 55 %

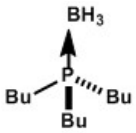
NMR data matches known NMR data for the compound

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.32 (dd, *J*=10.5, 7.3 Hz, 6 H, C**H$_{Ar}$**) 7.10 (dd, *J*=9.2, 0.9 Hz, 6 H, C**H$_{Ar}$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 163.49 (d, *J*=249.2 Hz, $C_q$) 135.51 (dd, *J*=13.8, 7.7 Hz, $CH_{Ar}$) 132.57 (dd, *J*=11.1, 3.4 Hz, $CH_{Ar}$) 115.97 (dd, *J*=16.1, 7.7 Hz, $CH_{Ar}$)

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -9.05 (1 P(III))

**Tributylphosphine borane 184[58]**




**Yield:** 40 %

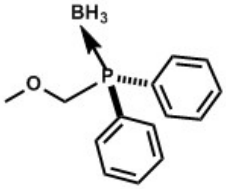
NMR data matches known NMR data for the compound

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 1.30 - 1.59 (m, 18 H, 9 x C**H$_2$**) 0.85 - 0.95 (m, 9 H, 3 x C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 24.6 (d, *J*=2.3 Hz, $CH_2$) 24.2 (d, *J*=12.3 Hz, $CH_2$) 22.7 (d, *J*=34.5 Hz, $CH_2$) 13.5 (s, $CH_3$)

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ 14.4 (q, *J*=51.2 Hz, 1 P)

**(Methoxymethyl)diphenylphosphine borane 185[74]**




**Yield:** 80 %

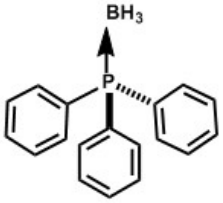
NMR data matches known NMR data for the compound

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.76 - 7.84 (m, 4 H, C**H$_{Ar}$**) 7.42 - 7.55 (m, 6 H, C**H$_{Ar}$**) 4.29 (s, 2 H, C**H$_2$**) 3.41 (s, 3 H, C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 132.7 (d, *J*=8.4 Hz, $CH_{Ar}$) 131.3 (d, *J*=2.3 Hz, $CH_{Ar}$) 128.5 (d, *J*=9.2 Hz, $CH_{Ar}$) 127.2 (d, *J*=56.7 Hz, $C_q$) 69.9 (d, *J*=44.5 Hz, $CH_2$) 61.6 (d, *J*=8.4 Hz, $OCH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 15.3 (d, *J*=62.4 Hz, 1 P)

**Triphenylphosphine borane 186[58]**




**Yield:** 48 %

NMR data matches known NMR data for the compound

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ ppm 7.56 - 7.63 (m, 6 H, C**$H_{Ar}$**) 7.48 - 7.54 (m, 3 H, C**$H_{Ar}$**) 7.41 - 7.48 (m, 6 H, C**$H_{Ar}$**) 0.82 - 0.94 (m, 3 H, B**$H_3$**)

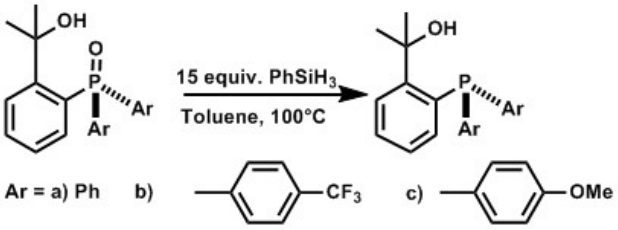
**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 133.16 (d, *J*=10.0 Hz, $CH_{Ar}$) 131.21 (d, *J*=2.3 Hz, $CH_{Ar}$) 129.14 (d, *J*=58.3 Hz, $C_q$) 128.74 (d, *J*=10.0 Hz, $CH_{Ar}$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 15.26 - 23.81 (m, 1 P, P-$BH_3$)

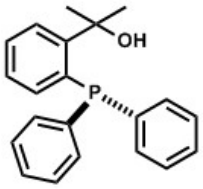
**$^{11}$B NMR (128 MHz, $CDCl_3$):** δ -37.92 (d, *J*=49.9 Hz, 1 B, P-$BH_3$)

## 6.5 Reduction of Hydroxylmethyl-Aryl Phosphine Oxides

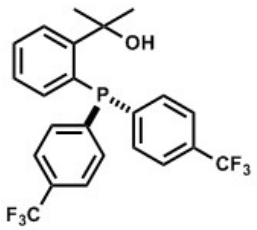
**Reductions of hydroxyl aryl phosphine oxides with phenyl silane**



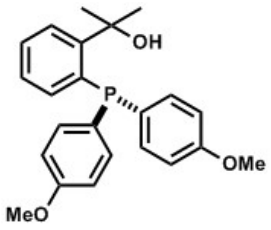

To a solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine oxide (0.2 g, 0.6 mmol) in toluene (2 mL), phenyl silane (0.2 mL, 1.5 mmol) was added at 100°C and stirred for 6 hours.



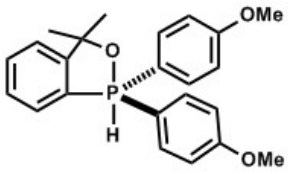

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ -12.2 (1P, s, P(III)).




**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -9.52 (1 P, s, P(III)).

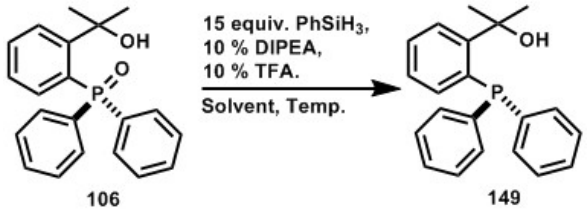



**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -12.14 (1 P, s, p(III)).




**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -63.3 (d, $J_{P-H}$=264.0 Hz, 1 P (V)) (Phosphorus NMR coupled to hydrogen).

**Reductions of the hydroxyl aryl phosphine oxide using phenyl silane and additives**




106 149

To a solution of (2-(2-hydroxypropan-2-yl)phenyl) diphenylphosphine oxide (0.12 g, 0.35 mmol) in toluene (0.3 mL), phenyl silane (0.70 mL, 5.25 mmol), diisopropylethylamine (0.006 mL, 0.03 mmol) and trifluoroacetic acid (0.003 mL, 0.03 mmol) were added. The reaction mixture was heated to 100 °C and $^{31}$P NMRs were taken every 10 mins.

| Entry | Solvent | Temperature (°C) | Conversion after 10 mins (%) |
|---|---|---|---|
| **A** | Tol | 100 | 100 |
| **B** | EtOAc | 80 | 100 |
| **C** | EtOAc | 20 | 20 |
| **D** | THF | 20 | 0 |
| **E** | THF | 20 | 68 |

**A** = 15 equivalents phenyl silane, 10 % diisopropylethylamine, 10 % trifluoroacetic acid, toluene, 100 °C.

**B** = 15 equivalents phenyl silane, 20 % diisopropylethylamine, 10 % hydrochloric acid, 10 % trifluoroacetic acid, ethyl acetate, 80 °C.

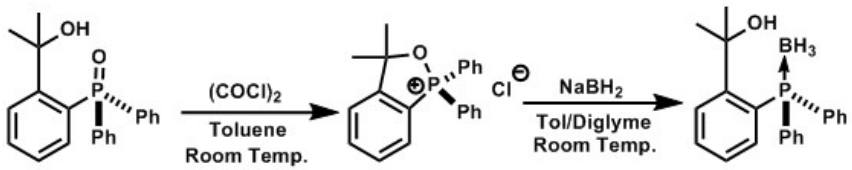
**C** = 1.5 equivalents phenyl silane, 20 % diisopropylethylamine, 10 % hydrochloric acid, 10 % trifluoroacetic acid, ethyl acetate, room temperature.

**D** = 1.5 equivalents phenyl silane, 1 % trifluoroacetic acid, 20 % diisopropylethylamine, 10 % hydrochloric acid, tetrahydrofuran, room temperature.

**E** = 3 equivalents phenyl silane, 1 % trifluoroacetic acid, 20 % diisopropylethylamine, 10 % hydrochloric acid, tetrahydrofuran, room temperature.

## 6.6 Reduction of Alkoxyphosphonium Salts

**Reductions of the Alkyoxyphosphonium salt 147 using sodium borohydride**



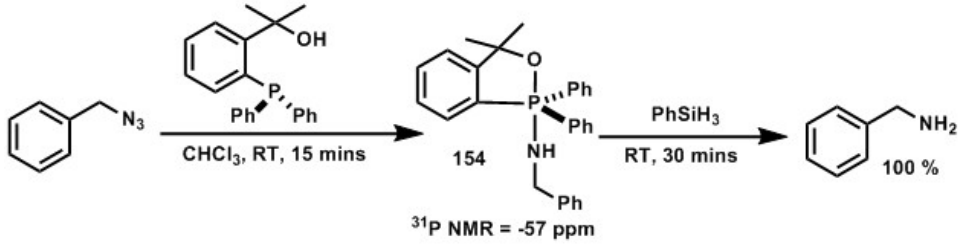

To a solution of (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine oxide (0.10 g, 0.30 mmol) in toluene (1 mL), oxalyl chloride (0.03 mL, 0.30 mmol) was added at room temperature. The reaction was stirred for 30 minutes before a solution of sodium borohydride (0.02 g, 0.63 mmol) in diglyme (1 mL) was added. The reaction was stirred for an hour before a sample was taken for $^{31}$P NMR.

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ 28 ($R_3P$-$BH_3$ complex, 1 P, br. S.).

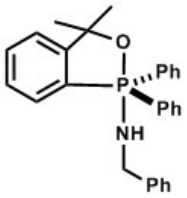
The reaction was quenched with water (5 mL) and the product was extracted with DCM. Mixture of Phosphine and phosphine oxide was produced.

### 6.7 Catalytic Staudinger Reduction

**Stoichiometric Staudinger Reductions using phenyl silane – Formation of the amino-oxyphosphorane 154.**




To a solution of (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.5 g, 1.5 mmol) in chloroform-d (5 mL), benzyl azide (0.19 g, 1.5 mmol) was added and stirred until nitrogen ceased to be released.




**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ ppm 7.81 - 7.94 (m, 1 H, C**H$_{Ar}$**) 7.66 - 7.80 (m, 1 H, C**H$_{Ar}$**) 7.28 - 7.63 (m, 10 H, C**H$_{Ar}$**) 7.06 - 7.26 (m, 8 H, C**H$_{Ar}$**) 4.50 (d, *J*=7.9 Hz, 2 H, C**H**NH) 4.14 (d, *J*=7.2 Hz, 1 H, N**H**) 1.65 - 1.72 (m, 6 H, 2 x C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 157.8 (d, *J*=23.0 Hz, $CH_{Ar}$) 157.0 (d, *J*=6.9 Hz, $C_q$) 142.3 (d, *J*=6.9 Hz, $CH_{Ar}$) 135.6 (d, *J*=5.4 Hz, $CH_{Ar}$) 135.1 (d, *J*=13.8 Hz, $CH_{Ar}$) 133.6 (d, *J*=18.4 Hz, $CH_{Ar}$) 133.3 (d, *J*=16.1 Hz, $CH_{Ar}$) 132.4 (d, *J*=13.0 Hz, $CH_{Ar}$) 132.2 (d, *J*=10.0 Hz, $CH_{Ar}$) 132.0 (q, *J*=3.1 Hz, $CH_{Ar}$) 130.2 (d, *J*=16.1 Hz, $CH_{Ar}$) 129.8 (d, *J*=9.2 Hz, $CH_{Ar}$) 128.8 (d, *J*=31.4 Hz, $CH_{Ar}$) 128.6 (dd, *J*=23.8, 3.8 Hz, $CH_{Ar}$) 128.2 (d, *J*=56.0 Hz, $C_q$) 127.5 (dd, *J*=46.0, 8.4 Hz, $C_q$) 126.9 (d, *J*=8.4 Hz, $CH_{Ar}$) 126.4 (d, *J*=13.0 Hz, $CH_{Ar}$) 125.6 (d,

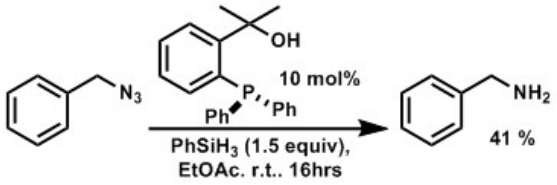
*J*=13.8 Hz, $CH_{Ar}$) 122.3 (d, *J*=15.3 Hz, $CH_{Ar}$) 73.2 (s, *J*=2.3 Hz, $C_q$) 50.4 (d, *J*=3.1 Hz, $CH_2$) 32.6 (s, 2 x $CH_3$)

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -57.4 (br. s., 1 P(V))

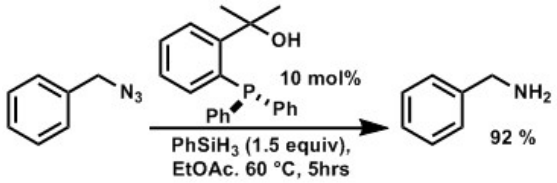
To a solution of **154** (0.6 g, 1.5 mmol) in chloroform-d (4.5 mL), phenyl silane (0.4 mL, 3 mmol) was added at room temperature and stirred for 30 minutes.

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -9.5 (br. s., 1 P).

### 6.7.1 Catalytic Staudinger Reduction using Phenyl Silane

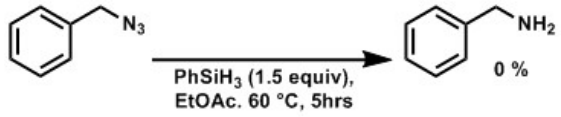



To a solution of benzyl azide (0.09 mL, 0.7 mmol) in ethyl acetate (2 mL), (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.02 g, 10 mol%, 0.07 mmol) and phenyl silane (0.14 mL, 1 mmol) were added at room temperature. The reaction mixture was stirred for 16 hours before water (3 mL) was added to quench the reaction. The product was extracted with ethyl acetate, dried with magnesium sulfate and the solvent removed under vacuum. The crude $^{1}$H NMR showed a 41% conversion of the azide to the amine.



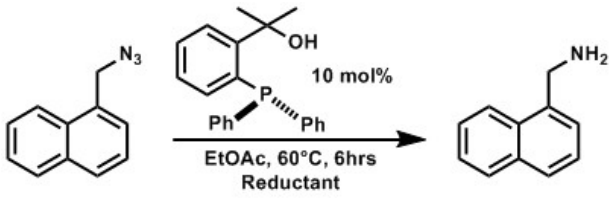

To a solution of benzyl azide (0.09 mL, 0.7 mmol) in ethyl acetate (2 mL), (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.02 g, 10 mol%, 0.07 mmol) and phenyl silane (0.14 mL, 1 mmol) were added at 60°C. The reaction mixture was stirred for 5 hours before water (3 mL) was added to quench the reaction. The product was extracted with ethyl acetate, dried with magnesium sulfate and the solvent removed under vacuum. The crude $^{1}$H NMR showed a 92% conversion of the azide to the amine.

**Control reaction for Catalytic Staudinger Reduction using phenyl silane**




To a solution of benzyl azide (0.09 mL, 0.7 mmol) in ethyl acetate (2 mL), phenyl silane (0.14 mL, 1 mmol) was added at 60°C. The reaction mixture was stirred for 5 hours before water (3 mL) was added to quench the reaction. The product was extracted with ethyl acetate, dried with magnesium sulfate and the solvent removed under vacuum. The crude $^{1}$H NMR showed a 0% conversion of the azide to the amine.

### 6.7.2 Catalytic Staudinger Reduction – Screening of Reductions



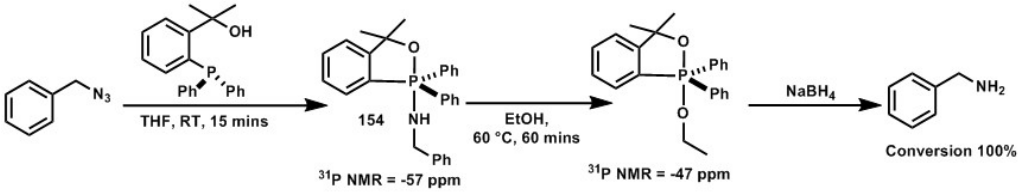

To a solution of azomethylnaphthalene (0.18 g, 1 mmol) and (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.03 g, 10 mol%, 0.1 mmol) in ethyl acetate (3 mL), a reductant (1.5 equivalents) was added at 60°C. The reaction mixture was stirred for 6 hours before water (5 mL) was added to quench the reaction. The product was extracted with ethyl acetate, dried with magnesium sulfate and the solvent removed under vacuum.

| Reductant | Equivalents of Reductant | Conversion* |
|---|---|---|
| **$PhSiH_3$** | 1.5 | 100 |
| **$Et_3SiH$** | 1.5 | 6 |
| **$NaBH_4$** | 1.5 | 24 |
| **PMHS**** | 1.5 | 0 |

* Conversion based on $^1$H NMR

** Reaction time = 24 hours

### 6.7.3 Stoichiometric Staudinger Reduction using Sodium Borohydride




To a solution of (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.10 g, 0.30 mmol) in chloroform-d (0.5 mL), benzyl azide (0.04 mL , 0.30 mmol) was added and stirred until nitrogen ceased to be released.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ ppm 7.81 - 7.94 (m, 1 H, C**H$_{Ar}$**) 7.66 - 7.80 (m, 1 H, C**H$_{Ar}$**) 7.28 - 7.63 (m, 10 H, C**H$_{Ar}$**) 7.06 - 7.26 (m, 8 H, C**H$_{Ar}$**) 4.50 (d, *J*=7.9 Hz, 2 H, C**H**NH) 4.14 (d, *J*=7.2 Hz, 1 H, N**H**) 1.65 - 1.72 (m, 6 H, 2 x C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 153.9 - 154.1 (m, $C_q$) 153.8 - 154.2 (m, $CH_{Ar}$) 137.5 (d, *J*=8.4 Hz, $CH_{Ar}$) 137.2 (s, $CH_{Ar}$) 135.3 (d, *J*=14.6 Hz, $CH_{Ar}$) 134.7 (d, *J*=13.8 Hz, $CH_{Ar}$) 134.2 - 134.3 (m, $CH_{Ar}$) 133.2 - 133.4 (m, $CH_{Ar}$) 133.1 - 133.3 (m, $CH_{Ar}$) 133.0 - 133.5 (m, $CH_{Ar}$) 131.8 (d, *J*=10.0 Hz, $CH_{Ar}$) 131.6 (d, *J*=2.3 Hz, $CH_{Ar}$) 131.4 (s, $CH_{Ar}$) 129.0 (s, $C_q$) 128.2 - 128.5 (m, $C_q$) 127.9 (d, *J*=10.7 Hz, $CH_{Ar}$) 127.3 (t, *J*=10.7 Hz, $CH_{Ar}$) 126.8 - 127.0 (m, $CH_{Ar}$) 126.6 (s, $CH_{Ar}$) 125.4 (d, *J*=7.7 Hz, $CH_{Ar}$) 125.2 (d, *J*=6.1 Hz, $CH_{Ar}$) 77.2 (s, $C_q$) 72.9 - 73.0 (m, $CH_2$) 32.3 (d, *J*=7.7 Hz, 2 x $CH_3$)

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ ppm -58.49.

To a solution of amino-oxyphosphorane (0.10 g, 0.30 mmol) in chloroform-d (0.5 mL), ethanol (0.02 mL, 0.30 mmol) was added at room temperature and stirred for 5 minutes.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.5 - 7.6 (m, 5 H, C**H$_{Ar}$**) 7.4 - 7.5 (m, 3 H, C**H$_{Ar}$**) 7.3 - 7.3 (m, 6 H, C**H$_{Ar}$**) 7.1 - 7.2 (m, 5 H, C**H$_{Ar}$**) 3.8 (s, 2 H, C**H$_2$**) 3.6 (q, *J*=7.0 Hz, 2 H, C**H$_2$**) 1.7 (s, 6 H, 2 x C**H$_3$**) 1.2 (t, *J*=7.0 Hz, 3 H, C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 156.4 (d, *J*=6.1 Hz, $C_q$) 153.8 - 154.0 (m, $CH_{Ar}$) 153.7 - 154.0 (m, $CH_{Ar}$) 137.4 (d, *J*=8.4 Hz, $CH_{Ar}$) 137.2 (d, *J*=2.3 Hz, $CH_{Ar}$) 135.3 (d, *J*=14.6 Hz, $CH_{Ar}$) 133.9 (s, $CH_{Ar}$) 133.1 - 133.3 (m, $CH_{Ar}$) 133.0 - 133.2 (m, $CH_{Ar}$) 133.0 (s, $CH_{Ar}$) 132.8 (s, $CH_{Ar}$) 131.5 - 132.0 (m, $C_q$) 130.3 - 131.3 (m, $CH_{Ar}$) 130.2 (s, $C_q$) 129.0 (s, $CH_{Ar}$) 128.4 - 128.4 (m, $CH_{Ar}$) 128.3 (t, *J*=3.5 Hz, $CH_{Ar}$) 127.8 (d, *J*=10.0 Hz, $CH_{Ar}$) 127.4 (d, *J*=15.3 Hz, $CH_{Ar}$) 127.2 (s, $CH_{Ar}$) 126.8 (s, $CH_{Ar}$) 126.2 - 126.7 (m, $C_q$) 125.2 - 125.5 (m, $CH_{Ar}$) 77.2 (s, $C_q$) 57.6 (s, $CH_2$) 45.7 (s, $CH_2$) 32.2 (d, *J*=3.8 Hz, 2 x $CH_3$) 18.1 (s, $CH_3$)

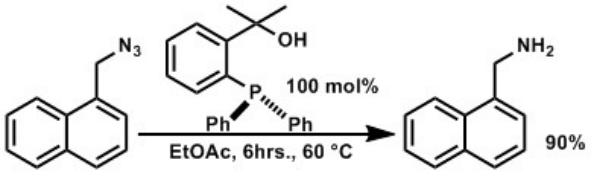
**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ ppm -47.4 (br. s., 1 P)

To a solution of amino-oxyphosphorane (0.10 g, 0.30 mmol) in chloroform-d (0.5 mL), sodium borohydride (0.04 g, 1.2 mmol) was added at room temperature and stirred for 30 minutes.

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -10.39.

**$^{11}$B NMR (128 MHz, $CDCl_3$):** δ -18.22 ($BnNHBH_4$) and -37.13 ($NaBH_4$).

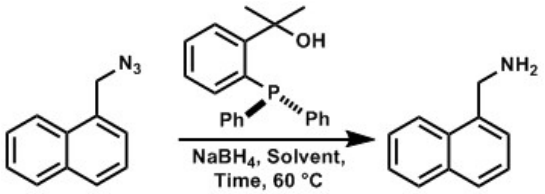
### 6.7.4 Catalytic Staudinger reduction using Sodium Borohydride – Screening of solvent, equivalents of sodium borohydride and time




To a solution of azomethylnaphthalene (0.18 g, 1 mmol) in ethyl acetate (3 mL), (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.32 g, 1 mmol [ ratio of Phosphine : Oxide, 1 : 0.1]) was added at 60°C. The reaction mixture was stirred for 6 hours. Water (6 mL) was added to quench the reaction. The product was extracted with ethyl acetate, dried with magnesium sulfate and solvent removed under vacuum. Crude $^{1}$H NMR showed 90% conversion of the azide to the amine.

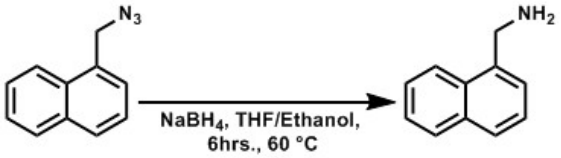
To a solution of naphthalene azide (0.18 g, 1 mmol) in tetrahydrofuran (3 mL), phosphine (0.03 g, 0.1 mmol) and sodium borohydride (0.06 g, 1.5 mmol) were added and the solution was heated to 60 °C for 24 hours. The reaction was quenched with water (3 x 20 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried with magnesium sulfate before the solvent was removed under vacuum. Crude $^{1}$H NMR showed 48 % conversion.

This procedure was used to screen various solvents, time frames, equivalents of reductant and catalyst amount, which is summarised in the table below.




| Entry | Catalyst amount (mol %) | Equivalents of reductant | Solvent | Time (h) | Conversion* (%) |
|---|---|---|---|---|---|
| **1** | 10 | 1.5 | THF | 24 | 48 |
| **2** | 20 | 1.5 | THF | 24 | 76 |
| **3** | 20 | 3 | THF | 24 | 89 |
| **4** | 20 | 1.5 | THF/Methanol (1:1) | 24 | 100 |
| **5** | 20 | 1.5 | THF/Propan-2-ol (1:1) | 24 | 50 |
| **6** | 20 | 1.5 | THF/Butanol (1:1) | 24 | 100 |
| **7** | 20 | 1.5 | THF/Ethanol (1:1) | 5 | 100 |
| **8** | 0 | 1.5 | THF/Ethanol (1:1) | 5 | 18 |

**Control for Catalytic Staudinger Reduction using sodium borohydride**

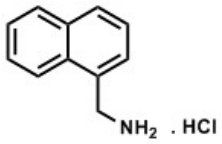



To a solution of azomethylnaphthalene (0.18 g, 1 mmol) in tetrahydrofuran (1.5 mL) and ethanol (1.25 mL), sodium borohydride (0.05 g, 1.5 mmol) was added at 60°C. The reaction mixture was stirred for 6 hours before water (6 mL) was added. The product was extracted with ethyl acetate, dried with magnesium sulfate and solvent removed under vacuum. Crude $^{1}$H NMR showed 18% conversion of the azide to the amine.

### 6.7.5 General procedure for the catalytic Staudinger reduction

To a solution of (azomethyl) naphthalene (0.5 g, 2.7 mmol) in tetrahydrofuran (4 mL), (2-(2-hydroxypropan-2-yl)phenyl)diphenylphosphine (0.17 g, 0.5 mmol) [ratio oxide : phosphine 1:1]), sodium borohydride (0.15 g, 4 mmol) and ethanol (4 mL) were added. The reaction mixture was heated to 60°C and stirred for 5 hours. The reaction was cooled to room temperature before being quenched with water (4 mL). The product was extracted with ethyl acetate (3x 5 mL) and dried with magnesium sulphate before solvent was removed. The crude amine was re-dissloved in ethyl acetate (3 mL) before 2M hydrochloric acid (3 mL) was added and stirred for 30 minutes. The solvent was then removed and the crude oil was dissolved in water, filtered and the water was removed to yield a white solid 0.37 g (72%).

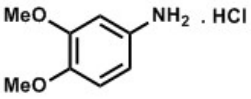
**naphthalen-1-ylmethanamine hydrochloride 187**[37]




**$^{1}$H NMR (400 MHz, DMSO-$d_6$):** δ 8.54 (br. s., 2 H, N**H$_3$**) 8.16 (d, *J*=8.4 Hz, 1 H, C**H$_{Ar}$**) 7.94 - 8.05 (m, 2 H, C**H$_{Ar}$**) 7.67 (s, 1 H, C**H$_{Ar}$**) 7.65 (d, *J*=1.1 Hz, 2 H, C**H$_{Ar}$**) 7.62 - 7.64 (m, 2 H, C**H$_{Ar}$**) 7.54 - 7.61 (m, 4 H, C**H$_{Ar}$**) 4.53 (q, *J*=5.7 Hz, 2 H, C**H$_2$**)

**$^{13}$C NMR (101 MHz, DMSO-$d_6$):** δ 133.2 (s, $CH_{Ar}$) 130.7 (s, $CH_{Ar}$) 130.0 (s, $CH_{Ar}$) 129.0 (s, $CH_{Ar}$) 128.7 (s, $CH_{Ar}$) 127.3 (s, $CH_{Ar}$) 126.8 (s, $CH_{Ar}$) 126.2 (s, $CH_{Ar}$) 125.4 (s, $CH_{Ar}$) 123.5 (s, $CH_{Ar}$) 39.1 (s, $CH_2$) [hidden under the DMSO-d peak]

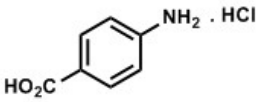
**3,4-dimethoxyaniline hydrochloride 188**[37]




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 10.29 (br. s., 3 H, N**H$_3$**) 7.00 - 7.07 (m, 2 H, C**H$_{Ar}$**) 6.92 - 6.97 (m, 1 H, C**H$_{Ar}$**) 3.77 (d, *J*=2.1 Hz, 6 H, 2 x OC**H$_3$**)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 148.9 (s, $C_q$) 148.0 (s, $C_q$) 124.3 (s, $C_q$) 114.8 (s, $CH_{Ar}$) 111.9 (s, $CH_{Ar}$) 106.9 (s, $CH_{Ar}$) 55.5 (s, $OCH_3$) 55.5 (s, $OCH_3$)

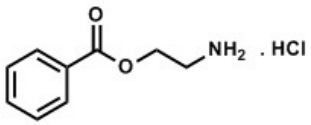
**4-aminobenzoic acid hydrochloride 189**[37]




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 7.92 (d, *J*=8.8 Hz, 2 H, C**H$_{Ar}$**) 7.27 (s, 3 H, N**H$_3$**) 6.61 - 6.71 (m, 2 H, C**H$_{Ar}$**) 3.79 - 4.50 (br. s, 1 H, O**H**)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 167.6 (s, $C_q$) 131.8 (s, $C_q$) 131.7 (s, $CH_{Ar}$) 131.6 (s, $CH_{Ar}$) 131.4 (s, $CH_{Ar}$) 119.5 (s, $CH_{Ar}$) 117.2 (s, $CH_{Ar}$)

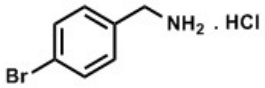
**2-aminoethyl benzoate hydrochloride 190**[75]




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.52 (br. s., 1 H, N**H$_3$**) 7.79 (d, *J*=7.3 Hz, 2 H, C**H$_{Ar}$**) 7.33 - 7.53 (m, 3 H, C**H$_{Ar}$**) 3.45 - 3.62 (m, 2 H, C**H$_2$**) 3.32 (q, *J*=5.6 Hz, 1 H, C**H$_2$**) 2.78 - 2.91 (m, 1 H, C**H$_2$**) 2.52 (br. s., 2 H, N**H$_3$**)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 168.0 (s, $C_q$) 134.2 (s, $C_q$) 132.0 (s, $CH_{Ar}$) 128.9 (s, $CH_{Ar}$) 127.6 (s, $CH_{Ar}$) 60.0 (s, $CH_2$) 57.7 (s, $CH_2$)

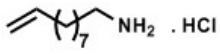
**(4-bromophenyl)methanamine hydrochloride 191**[76]




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.12 (br. s., 2 H, N**H$_3$**) 7.46 - 7.57 (m, 2 H, C**H$_{Ar}$**) 7.20 - 7.36 (m, 2 H, C**H$_{Ar}$**) 3.87 - 4.02 (m, 2 H, C**H$_2$**) 2.46 - 2.55 (m, 1 H), N**H$_3$**)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 133.5 (s, $C_q$) 133.2 (s, 2 x $CH_{Ar}$) 132.3 (s, 2 x $CH_{Ar}$) 123.6 (s, $C_q$) 43.4 (s, $CH_2$)

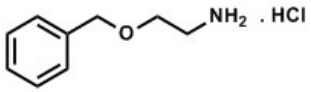
**dec-9-en-1-amine hydrochloride 192**[77]




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.55 (br. s., 3 H, N**H$_3$**) 5.77 - 5.79 (m, 1 H, C**H**) 5.74 - 5.81 (m, 2 H, C**H$_2$**) 5.72 - 5.84 (m, 2 H, C**H$_2$**) 5.63 - 5.92 (m, 2 H, C**H$_2$**) 4.78 - 5.08 (m, 4 H, C**H$_2$**) 1.99 (q, *J*=6.7 Hz, 2 H, C**H$_2$**) 1.14 - 1.58 (m, 10 H, 5 x C**H$_2$**)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 139.0 (s, $CH_2$) 114.9 (s, CH) 33.3 (s, $CH_2$) 28.8 (s, $CH_2$) 28.6 (s, $CH_2$) 28.5 (s, $CH_2$) 28.4 (s, $CH_2$) 27.0 (s, $CH_2$) 26.0 (s, $CH_2$)

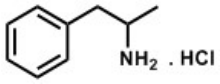
**2-(benzyloxy)ethan-1-amine hydrochloride 193**[78]




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.27 (br. s., 3 H, N**H$_3$**) 7.17 - 7.47 (m, 5 H, C**H$_{Ar}$**) 4.43 - 4.61 (m, 2 H, C**H$_2$**) 3.60 - 3.70 (m, 1 H, C**H$_2$**) 3.28 - 3.52 (m, 1 H, C**H$_2$**) 2.89 - 3.06 (m, 2 H, C**H$_2$**)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 137.9 (s, $C_q$) 128.2 (s, $CH_{Ar}$) 127.7 (s, $CH_{Ar}$) 127.6 (s, $C_q$) 72.1 (s, $CH_2$) 66.0 (s, $CH_2$) 38.5 (s, $CH_2$)

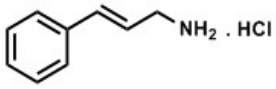
**1-phenylpropan-2-amine hydrochloride 194[79]**




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.16 (br. s., 3 H, N**H**$_3$) 6.99 - 7.43 (m, 5 H, C**H**$_{Ar}$) 3.32 (br. s., 1 H, C**H**) 2.96 - 3.10 (m, 1 H, C**H**$_2$) 2.53 - 2.68 (m, 1 H, C**H**$_2$) 1.04 (d, *J*=6.0 Hz, 3 H, C**H**$_3$)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 137.7 (s, $C_q$) 137.3 (s, $CH_{Ar}$) 129.9 (s, $CH_{Ar}$) 129.3 (s, $CH_{Ar}$) 128.1 (s, $CH_{Ar}$) 127.5 (s, $CH_{Ar}$) 56.8 (s, $CH(NH_3)$) 49.1 (s, $CH_2$) 17.9 (s, $CH_3$)

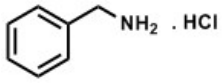
**(E)-3-phenylprop-2-en-1-amine hydrochloride 195[37]**




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.25 (br. s., 3 H, N**H**$_3$) 7.36 (d, *J*=7.5 Hz, 2 H, C**H**$_{Ar}$) 7.27 (d, *J*=14.6 Hz, 2 H, C**H**$_{Ar}$) 7.17 - 7.23 (m, 1 H, C**H**$_{Ar}$) 6.67 (d, *J*=15.9 Hz, 1 H, C**H**) 6.20 - 6.30 (m, 1 H, C**H**) 3.54 (d, *J*=5.1 Hz, 2 H., C**H**$_2$) 2.51 (br. s., 2 H, N**H**$_2$)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 136.4 (s,$C_q$) 135.6 (s, $CH_{Ar}$) 129.6 (s, $CH_{Ar}$) 129.2 (s, CH) 127.3 (s, $CH_{Ar}$) 122.2 (s, CH) 41.5 (s, $CH_2$)

**Benzyl amine 196[37]**




**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$):** δ 8.75 (br. s., 3 H, N**H**$_3$) 7.55 (d, *J*=6.6 Hz, 2 H, C**H**$_{Ar}$) 7.31 - 7.41 (m, 3 H, C**H**$_{Ar}$) 3.98 (q, *J*=5.7 Hz, 2 H, C**H**$_2$)

**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$):** δ 134.1 (s, $C_q$) 129.0 (s, $CH_{Ar}$) 128.5 (s, $CH_{Ar}$) 128.2 (s, $CH_{Ar}$) 128.3 (s, $CH_{Ar}$) 42.1 (s, $CH_2$)

## 6.8 Synthesis of Orangoazides

### Synthesis of the azide substrates

The azides were synthesised using two general methods; **A/B -** a displacement of either a halogen or a protected alcohol with sodium azide or **B -** a diazonamium coupling with the amine and TMS azide. These general procedures were monitored by HPLC to ensure full conversion to the product and minimising the amount of metal azide to be quenched at the end of the reaction and elimination the need for purification.

**WARNING!** Sodium azide will react with transition metals such as copper to form explosive metal azides. It is best to avoid using any metal spatulas and needles when handling azides. Sodium azide will also form hydrazoic acid under strongly acidic conditions. Hydrazoic acid is an extremely toxic and explosive vapour and has been the cause of numerous laboratory accidents. Avoid conditions in which there could be a build-up of hydrazoic acid. All waste should be bleached and pH should be >7. Trimethylsilyl azide is a highly volatile liquid which is extremely toxic and flammable. Should only be used in fumehood and double gloving maybe require avoiding contact with the skin. Again, avoid the use of metal instruments and strong acids with trimethylsilyl azide.

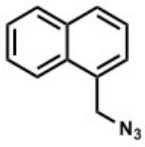
**General method A –**

Sodium azide (1.1 equivalents) was stirred in dimethyl sulfoxide (2mL per 1mmol) for 12 hours. At Room temperature, the halogen substrate (1 equivalent) was added. Stirred at room temperature and monitored via HPLC until all the starting material reacted. The reaction was then cooled to 0°C before being quenched with water (5mL per 1mmol) and stirred for 30 minutes.

The product was then extracted using *tert*-butyl methyl ether (3x 30 mL) was the organic layer was washed with water. The solution was dried with sodium sulphate before the solvent was removed under vacuum.

Sodium azide (2.00 g, 32 mmol) was stirred in dimethyl sulfoxide (63 mL) for 24 hours until the sodium azide dissolved. A solution of 1-(chloromethyl) naphthalene (5 g, 28 mmol) in dimethyl sulfoxide (20 mL) was added to the reaction mixture at room temperature. The reaction was stirred at room temperature for 3 hours. The reaction mixture was then cooled to 0°C before water (150 mL) was added. The mixture was left to stir at 0°C for 30 minutes. The product was then extracted with diethyl ether (3x 40 mL) and washed with water (50 mL). The organic layers were combined and dried with sodium sulphate. The solvent was removed under vacuum to yield orange oil (5 g, 98%).

**(Azomethyl)naphthalene 197**[37]

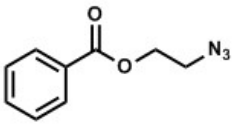



**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.92 (d, *J*=8.3 Hz, 1 H, C**H**$_{Ar}$) 7.80 (s, 2 H, C**H**$_{Ar}$) 7.39 - 7.52 (m, 2 H, C**H**$_{Ar}$) 7.29 - 7.35 (m, 2 H, C**H**$_{Ar}$) 4.60 (s, 2 H, C**H**$_2$)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 133.7 (s, $C_q$) 131.1 (s, $C_q$) 130.8 (s, $C_q$) 129.1 (s, $CH_{Ar}$) 128.6 (s, $CH_{Ar}$) 127.0 (s, $CH_{Ar}$) 126.5 (s, $CH_{Ar}$) 125.9 (s, $CH_{Ar}$) 125.0 (s, $CH_{Ar}$) 123.2 (s, $CH_{Ar}$) 52.6 (s, $CH_2$)

**IR υ/ cm$^{-1}$:** 2977(CH), 2102 (-$N_3$), 1253($CH_{Ar}$).

**2-azidoethyl benzoate 198**[80]

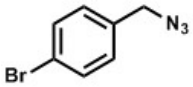


**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.9 (d, *J*=8.1 Hz, 1 H, C**H$_{Ar}$**) 7.4 - 7.4 (m, 1 H, C**H$_{Ar}$**) 7.2 - 7.3 (m, 2 H, C**H$_{Ar}$**) 4.3 - 4.3 (m, 2 H, C**H$_2$**) 3.4 (m, 2 H, C**H$_2$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 165.8 (s, $C_q$) 132.9 (s, $CH_{Ar}$) 129.4 (s, $C_q$) 129.3 (s, $CH_{Ar}$) 128.1 (s, $CH_{Ar}$) 63.3 (s, $CH_2$) 49.6 (s, $CH_2$)

**IR υ/ cm$^{-1}$:** 2977(CH), 2105 (-$N_3$), 1720 (C=O), 1269($CH_{Ar}$).

**1-(azidomethyl)-4-bromobenzene 199**[81]

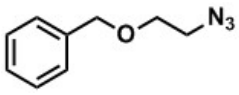


**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J*=8.4 Hz, 2 H, C**H$_{Ar}$**) 7.20 (d, *J*=8.4 Hz, 2 H, C**H$_{Ar}$**) 4.31 (s, 2 H, C**H$_2$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 134.3 (s, $C_q$) 131.0 (s, $CH_{Ar}$) 128.5 (s, $CH_{Ar}$) 122.2 (s, $C_q$) 54.0 (s, $CH_2$)

**IR υ/ cm$^{-1}$:** 2978 (CH), 2100 (-$N_3$), 1283 ($CH_{Ar}$), 1072(C-Br)

**((2-azidoethoxy)methyl)benzene 200**[82]

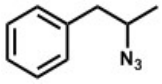


**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.36 (d, *J*=4.4 Hz, 2 H, C**H$_{Ar}$**) 7.25 - 7.33 (m, 3 H, C**H$_{Ar}$**) 4.58 (s, 2 H, C**H$_2$**) 3.57 - 3.72 (m, 2 H, C**H$_2$**) 3.40 (t, *J*=5.0 Hz, 2 H, C**H$_2$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 137.6 (s, $C_q$) 128.3 (s, $CH_{Ar}$) 127.6 (s, $CH_{Ar}$) 127.4 (s, $CH_{Ar}$) 73.1 (s, $CH_2$) 68.7 (s, $CH_2$) 50.6 (s, $CH_2$)

**IR υ/ cm$^{-1}$:** 2863 (CH), 2253 (-$N_3$), 1495(C-O), 1105 (C=C), 906 ($CH_{Ar}$).

**(2-azidopropyl)benzene 201**[83]

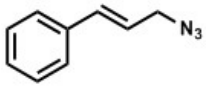


**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.30 - 7.53 (m, 5 H, C**H$_{Ar}$**) 3.79 (d, *J*=6.6 Hz, 1 H, C**H**) 2.78 - 3.03 (m, 2 H, C**H$_2$**) 1.01 - 1.13 (m, 3 H, C**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 137.5 (s, $C_q$) 128.7 (s, $CH_{Ar}$) 128.0 (s, $CH_{Ar}$) 126.4 (s, $CH_{Ar}$) 58.7 (s, $CHN_3$) 42.3 (s, $CH_2$) 18.7 (s, $CH_3$)

**IR υ/ cm$^{-1}$:** 2976 (CH), 2106 (-$N_3$), 1244 ($CH_{Ar}$).

**(E)-(3-azidoprop-1-en-1-yl)benzene 202**[37]



**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.46 - 7.51 (m, 1 H, C**H$_{Ar}$**) 7.40 - 7.46 (m, 1 H, C**H$_{Ar}$**) 7.34 - 7.39 (m, 2 H, C**H$_{Ar}$**) 6.71 (d, *J*=15.8 Hz, 1 H, C**H**) 6.30 (dt, *J*=15.8, 6.6 Hz, 1 H, C**H**) 3.97 (d, *J*=6.5 Hz, 2 H, C**H$_2$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 135.8 (s, $C_q$) 133.7 (s, $CH_{Ar}$) 128.2 (s, $CH_{Ar}$) 127.5 (s, $CH_{Ar}$) 125.7 (s, CH) 122.2 (s, CH) 52.1 (s, $CH_2$)

**IR υ/ cm$^{-1}$:** 3008 (CH), 2104 (-$N_3$), 1240 (C=C), 967 ($CH_{Ar}$).

**Preparation of dec-9-en-1-yl methanesulfonate 203**[84]



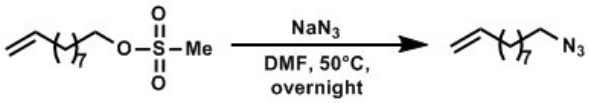

A solution of 9-decen-1-ol (1.95 mL, 10 mmol) and triethylamine (1.6 mL, 11 mmol) in dichloromethane (50 mL) was cooled to -10°C. Methanesulfonyl chloride (0.85 mL, 11 mmol) was added dropwise to the solution. Upon addition a small exotherm was seen and the reaction mixture was left to stir overnight at room temperature. The reaction was then quenched with ice water

(30 mL). The organic layer was then washed with 5% sodium bisulfite solution (30 mL), water (30 mL), 5% sodium carbonate solution (30 mL) and brine (30 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum to yield colourless oil 2.15 g (91.8%).

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ ppm 5.67 - 5.86 (m, 1 H, C**H**) 4.82 - 5.01 (m, 2 H, C**$H_2$**) 4.07 - 4.30 (m, 2 H, C**$H_2$**) 2.97 (s, 3 H, C**$H_3$**) 2.01 (q, *J*=7.3 Hz, 2 H, C**$H_2$**) 1.62 - 1.78 (m, 2 H, C**$H_2$**) 1.14 - 1.45 (m, 10 H, 2x C**$H_2$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 138.9 (s, CH) 114.0 (s, $CH_2$) 70.1 (s, $CH_3$) 37.1 (s, $CH_2$) 32.3 (s, $CH_2$) 29.0 (s, $CH_2$) 25.2 (s, $CH_2$)

**Preparation of 10-azidodec-1-ene 204[84]**




To a solution of 9-decen-1-yl methanesulfonate (2.15 g, 9.2 mmol) in dimethylformamide (15 mL), sodium azide (0.91 g, 14 mmol) was added. The reaction mixture was heated to 50°C and stirred overnight. The reaction mixture was then cooled to 0°C before water was added. The product was then extracted by *t*-butyl methyl ether (3 x 30 mL) and the organic layer was washed with water (30 mL). The organic layer was dried with magnesium sulfate and solvent removed under vacuum to yield a yellow oil 1.46g, (88%).

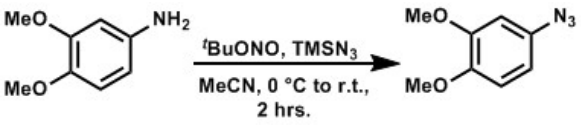
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 5.62 - 5.91 (m, 1 H, C**H**) 4.77 - 5.04 (m, 2 H, C**$H_2$**) 3.07 - 3.29 (m, 2 H, C**$H_2$**) 2.00 (q, *J*=6.8 Hz, 2 H, C**$H_2$**) 1.55 (quin, *J*=6.7 Hz, 2 H, C**$H_2$**) 1.19 - 1.41 (m, 10 H, 5 x C**$H_2$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$)**: δ 138.7 (s, CH) 113.9 (s, $CH_2$) 51.2 (s, $CH_2$) 33.5 (s, $CH_2$) 27.2 (s, $CH_2$) 25.4 (s, $CH_2$)

**IR υ/ $cm^{-1}$:** 2931 (CH), 2099 (-$N_3$), 1672 (C=C).

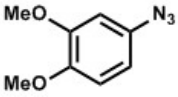
**General method B –**

Aniline derived substrates (1 equivalent) was dissolved in acetronitrile (2mL per 1 mmol) and then cooled to 0°C. To the solution, *tert*-butyl nitrite (1.5 equivalents) was added dropwise followed by the dropwise addition of trimethylsilyl azide (1.2 equivalents). The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was then concentrated and the solid formed was washed with hexanes.




To a solution of dimethoxyaniline (5 g, 32 mmol) in acetronitrile (60 mL) at 0°C, *tert* butyl nitrite (6.3 mL, 49 mmol) was added, followed by the drop wise addition of azidotrimethyl silane (5.6 mL, 39 mmol). The reaction mixture was then left to stir overnight at room temperature. The solvent was removed yielding dark brown crystals which were washed with heptane and water (3.4 g, 60%).

**4-azido-1,2-dimethoxybenzene 205[64]**

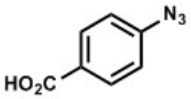



**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 6.82 (d, *J*=8.6 Hz, 1 H, C**H$_{Ar}$**) 6.58 (dd, *J*=8.6, 2.0 Hz, 1 H, C**H$_{Ar}$**) 6.51 (d, *J*=2.4 Hz, 1 H, C**H$_{Ar}$**) 3.85 (s, 6 H, 2 x OC**H$_3$**)

**$^{13}$C NMR (101 MHz, $CDCl_3$):** δ 148.3 (s, $C_q$) 144.9 (s, $C_q$) 131.0 (s, $C_q$) 110.4 (s, $CH_{Ar}$) 108.7 (s, $CH_{Ar}$) 101.5 (s, $CH_{Ar}$) 54.5 (s, $OCH_3$)

**IR υ/ cm$^{-1}$:** 2939 (CH), 2113 (-$N_3$), 1510 (C-O), 1229 (C=C), 1026 ($CH_{Ar}$).

**4-azidobenzoic acid 206[64]**




**$^{1}$H NMR (400 MHz, CDC$_3$):** δ 8.11 - 8.11 (m, 1 H, C**H$_{Ar}$**) 8.08 - 8.15 (m, 1 H, C**H$_{Ar}$**) 8.12 (d, *J*=8.6 Hz, 1 H, C**H$_{Ar}$**) 7.12 (d, *J*=8.6 Hz, 1 H, C**H$_{Ar}$**) 1.29 (s, 1 H, O**H**)

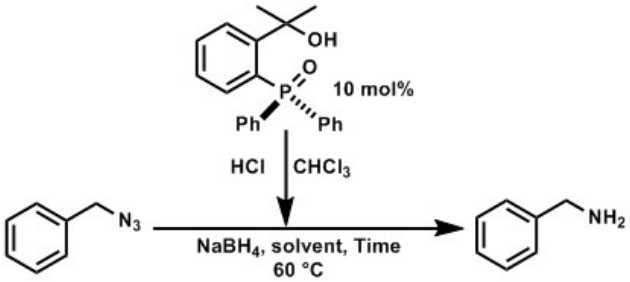
**$^{13}$C NMR (101 MHz, DMSO-d):** δ 166.6 (s, $C_q$) 144.0 (s, $C_q$) 131.3 (s, $CH_{Ar}$) 127.3 (s, $C_q$) 119.2 (s, $CH_{Ar}$)

**IR υ/ cm$^{-1}$:** 2109 (-$N_3$), 1693 (C=O), 1603 (C=C), 1285 ($CH_{Ar}$).

### 6.9 Catalytic Staudinger Reduction with a Pre-catalyst

To a solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine oxide (0.06 g, 0.2 mmol, 10 mol%) in chloroform (0.5 mL), hydrogen chloride solution (0.2 mL, 0.2 mmol, 1M in $Et_2O$) was added at room temperature and stirred for 30 minutes. The solvent was removed under vacuum before benzyl azide (0.25 mL, 2 mmol) in a solution of diglyme (6 mL) and sodium borohydride (0.1 g, 3 mmol). The reaction mixture was heated to 60 °C and stirred for 5 hours before being quenched at room temperature with water (10 mL). The mixture was extracted with ethyl acetate (2 x 20 mL) and washed with water (3 x 10 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum to yield crude yellow oil. The crude $^1$H NMR showed a 73% conversion to the amine.

The procedure was used to screen solvent for the catalytic Staudinger reduction using the phosphine oxide as a precatalyst, which is summarised in the table below.



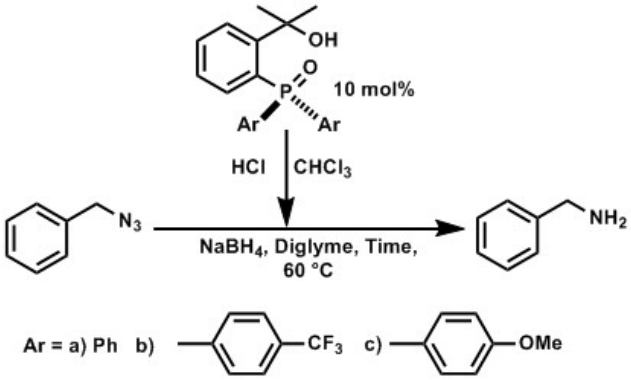

| | Solvent | Time (h) | Conversion (%)* |
|---|---|---|---|
| **1** | EtOH/THF | 5 | 46 |
| **2** | Diglyme | 5 | 73 |

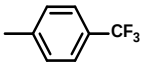
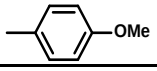
*Conversion based on $^1$H NMR

To a solution of the phosphine oxide (0.2 mmol, 10 mol%) in chloroform (0.5 mL), hydrogen chloride solution (0.2 mL, 0.2 mmol, 1M in $Et_2O$) was added at room temperature and stirred for 30 minutes. The solvent was then removed

under vacuum before benzyl azide (0.25 mL, 2 mmol) in a solution diglyme (6 mL) and sodium borohydride (0.1 g, 3 mmol) were added. The reaction mixture was heated to 60 °C and stirred for 5 hours before the reaction was quenched with water (10 mL). The product was extracted with ethyl acetate (2 x 20 ml) and washed with water (2 x 10 mL). The organic layer was dried with magnesium sulfate and the solvent was removed under vacuum yielding a yellow crude oil. The crude $^{1}$H NMR was used to determine the conversion.

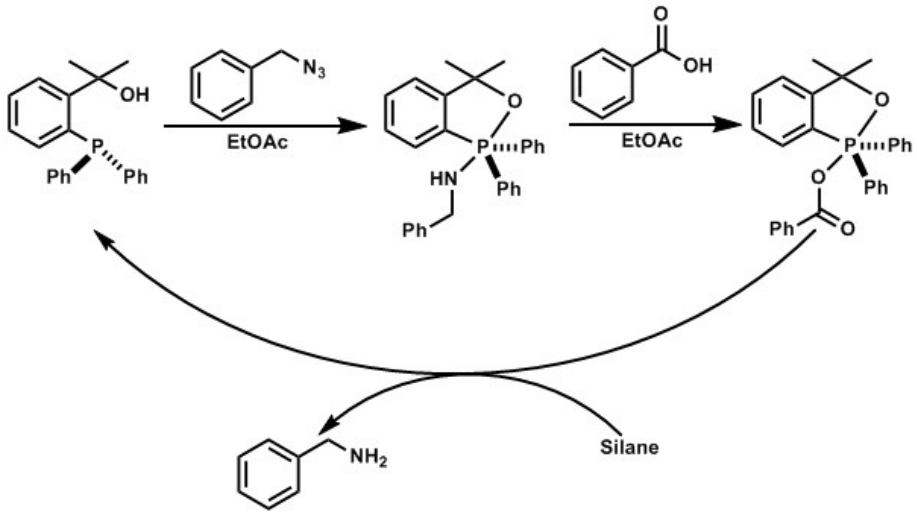
The procedure was used to screen different phosphine oxides for the use in a catalytic Staudinger reduction.




| | Ar | Time (h) | Conversion (%)* |
|---|---|---|---|
| **1** | Ph | 5 | 73 |
| **2** |  | 5 | 91 |
| **3** |  | 5 | 57 |

*Conversion based on $^{1}$H NMR.

**6.9 Catalytic Staudinger Ligation**




To a solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine (0.2 g, 0.6 mmol) in ethyl acetate (1 mL), benzyl azide (0.07 mL, 0.6 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 30 minutes before a sample (0.2 mL) was taken out for $^{31}$P NMR experiment.

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -58.59.

To the remaining reaction mixture, benzoic acid (0.07 g, 0.6 mmol) was added and stirred for 30 minutes before a sample (0.2 mL) was taken out for $^{31}$P NMR experiment.

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -35.82.

To the remaining reaction mixture, phenyl silane (0.14 mL, 1.2 mmol) was added and stirred for 30 minutes before a sample (0.2 mL) was taken out for $^{31}$P NMR experiment.

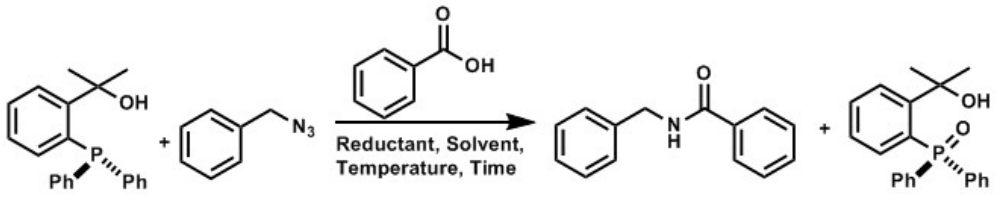
**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ -11.52.

The reaction mixture was quenched with water (10 mL) and the product was extracted with ethyl acetate (2 x 10 mL) and the organic layer was dried with magnesium sulfate. The solvent was removed under vacuum yielding crude

yellow oil. The crude $^{1}H$ NMR determined the conversion to the amine only at 57 %.

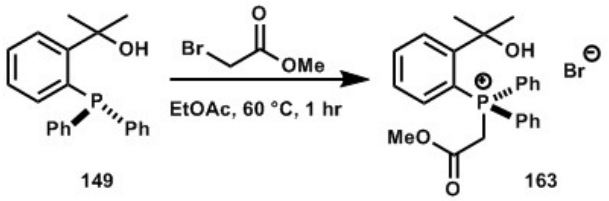
To a solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine (0.2 g, 0.6 mmol) in toluene (2 mL), benzyl azide (0.06 mL, 0.5 mmol) and benzoic acid (0.06 g, 0.5 mmol) was added. The reaction mixture was heated to 60 °C for three days. The reaction was quenched with water (10 mL) and the product was extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with water (3 x 10 mL) and dried with sodium sulfate, before the solvent was removed under vacuum yielding crude yellow oil. The crude $^{1}H$ NMR determined the products of the reaction.

The procedure was used to screen solvents and temperature as well as time for the coupling of the azide with acid using the Hydroxylmethyl-Aryl phosphine or phosphine oxide.




| Entry | Solvent | Temperature (° C) | Phosphine (Mol %) | Reductant | Time (Hrs) | Product |
|---|---|---|---|---|---|---|
| **1** | Toluene | 60 | 100 | - | 72 | Amine Only |
| **2** | Toluene | 100 | 100 | - | 1 | Amine Only |
| **3** | EtOAc | 60 | 100 | - | 24 | Amine and Amide |
| **4** | EtOAc | 60 | 10* | $NaBH_4$ | 24 | Amine |
| **5** | THF/EtOH | 60 | 10 | $NaBH_4$ | 24 | Amine |

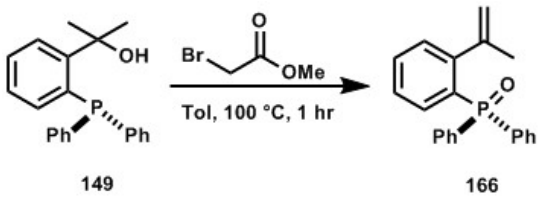
## 6.10 Catalytic Wittig Reaction




To a solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine (0.15 g, 0.5 mmol) in ethyl acetate (1 mL), methyl bromoacetate (0.04 mL, 0.5 mmol) was added at 60 °C and stirred at this temperature for 1 hour. A sample was taken for $^{1}$H and $^{31}$P NMR analysis.

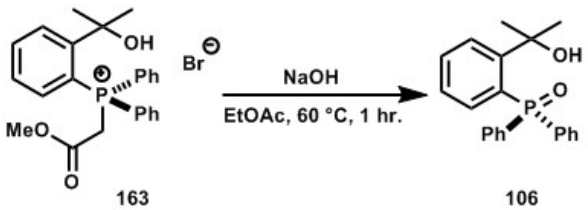
**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.14 - 7.31 (m, 4 H, C**H**$_{Ar}$) 6.89 - 7.10 (m, 7 H, C**H**$_{Ar}$) 6.64 - 6.86 (m, 3 H, C**H**$_{Ar}$) 4.33 (d, *J*=74.1 Hz, 2 H, C**H**$_2$) 3.39 - 3.48 (m, 3 H, C**H**$_3$) 3.21 - 3.33 (m, 3 H, C**H**$_3$) 3.09 - 3.18 (m, 3 H, C**H**$_3$)

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ 73.67, 27.18 (major).




To a solution of (2-(2-hydroxypropan-2-yl) phenyl) diphenylphosphine (0.15 g, 0.5 mmol) in Toluene (1 mL), methyl bromoacetate (0.04 mL, 0.5 mmol) was added at 100 °C and stirred at this temperature for 1 hour. A sample was taken for $^{1}$H and $^{31}$P NMR analysis.

**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ 74.43, 29.84 (Major).



To a solution of phosphonium salt (0.5 M in EtOAc), sodium hydroxide (0.04 g, 1 mmol) was added and was stirred at 60 °C for 1 hour.

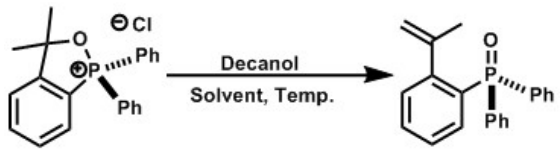
**$^{31}$P NMR (162 MHz, $CDCl_3$):** δ 73.70, 40.80, 28.79 (Major).

This procedure was used to screen bases for the ylide for the Wittig reaction, which is summarised in the table below.

| Entry | Base | Product |
|---|---|---|
| **1** | $Et_3N$ | Phosphonium salt |
| **2** | DBU | Phosphonium salt |
| **3** | $Cs_2CO_3$ | Phosphonium salt |

### 6.11 Catalytic Mitsunobu Reaction

#### 6.11.1 Formation of Dioxyphosphorane - The formation of the alkene phosphine oxide




147 166

To a solution of alkoxyphosphonium salt (0.10g, 0.3 mmol) was dissolved in dry solvent. X equivalents of decanol was added and the reaction was heated overnight. The solvent was removed to yield a yellow oil.

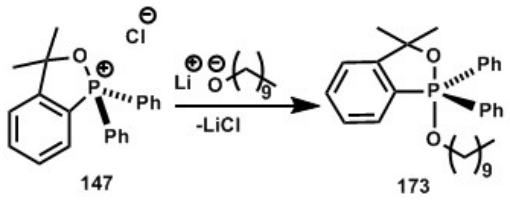
| | Equivalents of Decanol | Solvent | Temperature (°C) |
|---|---|---|---|
| **1** | 3 | Tol | 100 |
| **2** | 3 | Xylene | 150 |
| **3** | 3 | EtOAc | 70 |
| **4** | 30 | MeCN | 70 |
| **5** | 5 | DMF | 150 |

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.78 - 7.87 (m, 4 H, C**H$_{Ar}$**) 7.50 - 7.64 (m, 7 H, C**H$_{Ar}$**) 7.27 - 7.42 (m, 3 H, C**H$_{Ar}$**) 5.08 (t, *J*=1.6 Hz, 1 H, C=C**H$_2$**) 4.89 (d, *J*=0.6 Hz, 1 H C=C**H$_2$**) 2.02 (d, *J*=0.4 Hz, 3 H, C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 149.5 (d, *J*=8.4 Hz, $C_q$) 144.0 (d, *J*=3.8 Hz, $CH_{Ar}$) 137.4 (s, $H_2C$=C) 133.8 (d, *J*=12.3 Hz, $CH_{Ar}$) 131.9 (s, *J*=10.0 Hz, $CH_{Ar}$) 131.6 (d, *J*=3.1 Hz, $CH_{Ar}$) 131.3 (s, *J*=3.1 Hz, $CH_{Ar}$) 130.7 (s, *J*=103.5 Hz, $C_q$) 129.7 (d, *J*=10.0 Hz, $CH_{Ar}$) 128.6 (d, *J*=23.8 Hz, $CH_{Ar}$) 128.2 (s, *J*=12.3 Hz, $CH_{Ar}$) 128.0 (d, *J*=38.3 Hz, $CH_{Ar}$) 127.5 (d, *J*=23.8 Hz, $CH_{Ar}$) 126.0 (d, *J*=12.3 Hz, $CH_{Ar}$) 124.7 (d, *J*=24.5 Hz, $CH_{Ar}$) 118.2 (s, $H_2C$=C) 22.6 (s, $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 29.6 (s, 1 P)

**The formation of the Dioxyphosphorane**



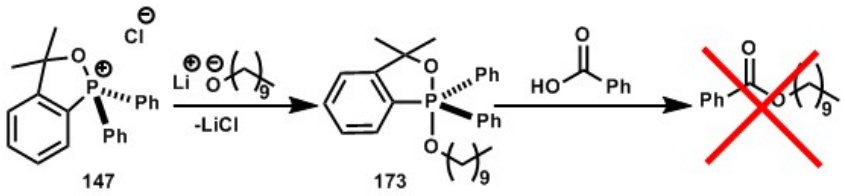

To a solution of decanol (0.1 mL, 0.6 mmol) in tetrahydrofuran-d (1 mL), *n*-Butyl lithium (0.38 mL, 0.6 mmol of a 1.6 M solution in hexanes) was added at -78°C and was stirred for 5 mins. The reaction mixture was then added to a solution of the alkoxyphosphonium salt (0.2 g, 0.6 mmol) in tetrahydrofuran-d (1 mL) at -78°C. The reaction was stirred for 30 minutes and allowed to warm to room temperature.

**$^{1}$H NMR (400 MHz, THF-d):** δ 7.46 - 7.58 (m, 8 H, C**H$_{Ar}$**) 7.42 (dd, *J*=7.3, 2.6 Hz, 5 H, C**H$_{Ar}$**) 7.04 - 7.15 (m, 2 H, C**H$_{Ar}$**) 3.67 - 3.75 (m, 2 H) 3.53 (t, *J*=6.8 Hz, 2 H) 1.82 (dt, *J*=6.7, 3.2 Hz, 2 H) 1.60 (s, 2 H) 1.23 (s, 2 H) 0.69 - 0.93 (m, 11 H, 4 x C**H$_2$** and C**H$_3$**)

**$^{13}$C NMR (100 MHz, THF-d):** δ 159.3 (d, *J*=27.6 Hz, $C_q$) 142.4 (d, *J*=170.2 Hz, $C_q$) 137.9 (d, *J*=8.4 Hz, $CH_{Ar}$) 136.9 (d, *J*=16.1 Hz, $CH_{Ar}$) 132.7 (d, *J*=60.6 Hz, $C_q$) 131.9 (d, *J*=10.0 Hz, $CH_{Ar}$) 129.3 (d, *J*=3.1 Hz, $CH_{Ar}$) 128.3 (d, *J*=15.3 Hz, $CH_{Ar}$) 128.1 (d, *J*=8.4 Hz, $CH_{Ar}$) 125.8 (d, *J*=14.6 Hz, $CH_{Ar}$) 122.9 (d, *J*=17.6 Hz, $CH_{Ar}$) 77.8 (s, *J*=3.1 Hz, $C_q$) 62.8 (d, *J*=7.7 Hz, $CH_2$) 32.7 (s, 2 x $CH_3$) 31.9 (d, *J*=5.4 Hz, $CH_2$) 30.7 (d, *J*=3.1 Hz, $CH_2$) 28.8 (s, $CH_2$) 27.9 (s, $CH_2$) 27.3 (s, $CH_2$) 21.2 (s, $CH_2$) 20.0 (s, $CH_2$) 15.9 (s, $CH_2$) 14.8 (s, $CH_3$)

**$^{31}$P NMR (162 MHz, THF-d):** δ -50.0 (br. s., 1 P)

**6.11.2 Nucleophilic Substitution of the Dioxyphosphorane** – The nucleophilic attack of Dioxyphosphorane

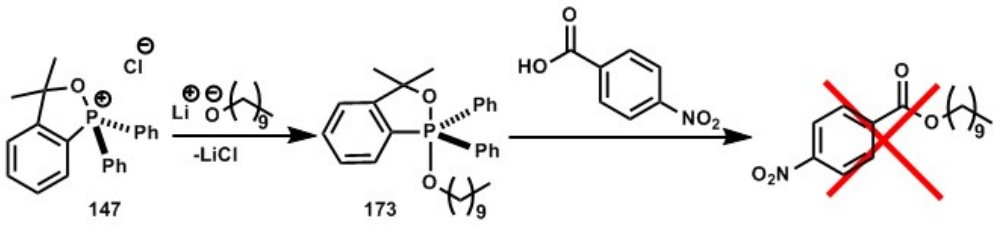



To a solution of decanol (0.1 mL, 0.6 mmol) in tetrahydrofuran (1 mL), *n*-Butyl lithium (0.38 mL, 0.6 mmol of a 1.6 M solution in hexanes) was added at -78°C and was stirred for 5 mins. The reaction mixture was then added to a solution of the alkoxyphosphonium salt (0.2 g, 0.6 mmol) at -78°C in tetrahydrofuran (1 mL). The reaction was stirred for 30 minutes and allowed to warm to room temperature. The reaction mixture was then cool to -78°C before a solution of benzoic acid (0.07 g, 0.6 mmol) in tetrahydrofuran (0.2 mL). The reaction was heated to 50°C and stirred overnight.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ ppm 7.93 (d, *J*=5.0 Hz, 1 H, C**H$_{Ar}$**) 7.68 (d, *J*=4.2 Hz, 3 H, C**H$_{Ar}$**) 7.05 - 7.53 (m, 11 H, C**H$_{Ar}$**) 4.80 (d, *J*=18.3 Hz, 2 H, C=C**H$_2$**) 1.72 (br. s., 3 H, C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 149.5 (d, *J*=8.4 Hz, $C_q$) 143.5 (d, *J*=3.1 Hz, $CH_{Ar}$) 134.2 (d, *J*=13.0 Hz, $CH_{Ar}$) 133.1 (s, $H_2C$=C) 132.1 (d, *J*=10.0 Hz, CH-$_{Ar}$) 130.1 (d, *J*=42.2 Hz, $C_q$) 128.8 (s, *J*=97.4 Hz, $C_q$) 128.4 (d, *J*=12.3 Hz, CH-$_{Ar}$) 126.4 (d, *J*=13.0 Hz, $CH_{Ar}$) 118.9 (s, $H_2C$=C) 29.1 (s, $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 31.6 (br. s., 1 P)

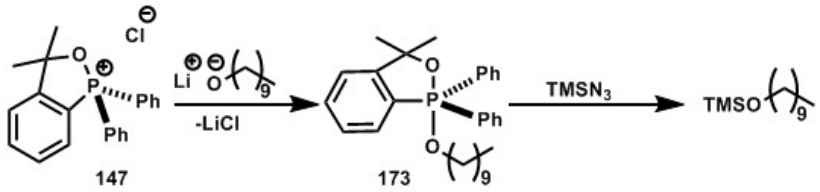



To a solution of decanol (0.1 mL, 0.6 mmol) in dry tetrahydrofuran (1 mL), *n*-Butyl lithium (0.38 mL, 0.6 mmol of a 1.6 M solution in hexanes) was added at -78°C and was stirred for 5 mins. The reaction mixture was then added to a solution of the alkoxyphosphonium salt (0.2 g, 0.6 mmol) at -78°C in dry tetrahydrofuran (1 mL). The reaction was stirred for 30 minutes and allowed to warm to room temperature. The reaction mixture was then cool to -78°C before a solution of nitrobenzoic acid (0.08 g, 0.6 mmol) in dry tetrahydrofuran (0.2 mL). The reaction was heated to 50°C and stirred overnight.

**$^{1}$H NMR (400 MHz, $CDCl_3$):** δ ppm 7.93 (d, *J*=5.0 Hz, 1 H, C**H$_{Ar}$**) 7.68 (d, *J*=4.2 Hz, 3 H, C**H$_{Ar}$**) 7.05 - 7.53 (m, 11 H, C**H$_{Ar}$**) 4.80 (d, *J*=18.3 Hz, 2 H, C=C**H$_2$**) 1.72 (br. s., 3 H, C**H$_3$**)

**$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 149.5 (d, *J*=8.4 Hz, $C_q$) 143.5 (d, *J*=3.1 Hz, $CH_{Ar}$) 134.2 (d, *J*=13.0 Hz, $CH_{Ar}$) 133.1 (s, $H_2C$=C) 132.1 (d, *J*=10.0 Hz, CH-$_{Ar}$) 130.1 (d, *J*=42.2 Hz, $C_q$) 128.8 (s, *J*=97.4 Hz, $C_q$) 128.4 (d, *J*=12.3 Hz, CH-$_{Ar}$) 126.4 (d, *J*=13.0 Hz, $CH_{Ar}$) 118.9 (s, $H_2C$=C) 29.1 (s, $CH_3$)

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 31.6 (br. s., 1 P)




To a solution of decanol (0.1 mL, 0.6 mmol) in dry THF (1 mL), $^{n}$Butyl lithium 1.6M in hexane (0.38 mL, 0.6 mmol) was added at -78°C and was stirred for 5 mins. The reaction mixture was then added to a solution of the alkoxyphosphonium salt (0.2 g, 0.6 mmol) at -78°C in dry THF (1 mL). The reaction was stirred for 30 minutes and allowed to warm to room temperature. The reaction mixture was then cool to -78°C before trimethylsilyl azide (0.08 mL, 0.6 mmol) was added. The reaction was warmed to room temperature and stirred for 1 hour.

**$^{31}$P NMR (160 MHz, $CDCl_3$):** δ 73.4 (br. s., 1 P) 41.1 (d, *J*=7.8 Hz, 1 P) 30.2 (br. s., 1 P)

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# Development of a redox-free Mitsunobu reaction exploiting phosphine oxides as precursors to dioxyphosphoranes†

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The development of the first redox-free protocol for the Mitsunobu reaction is described. This has been achieved by exploiting triphenylphosphine oxide – the unwanted by-product in the conventional Mitsunobu reaction – as the precursor to the active P(V) coupling reagent. Multinuclear NMR studies are consistent with hydroxyl activation via an alkoxyphosphonium salt.

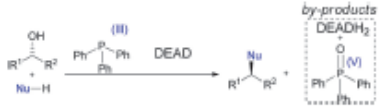
Bimolecular nucleophilic substitution reactions of alcohols are fundamentally important transformations in chemical synthesis. During the last sixty years phosphorus(V) compounds have emerged as widely used activating agents for nucleophilic coupling reactions through a process originally described by Mukaiyama as "redox dehydration",[1] the most familiar of these protocols being the 1967 Mitsunobu reaction[2] (Scheme 1).

Although this powerful protocol has been widely employed in chemical synthesis it suffers from low atom economy. Furthermore, the diazodicarboxylate oxidants are toxic, high energy compounds and the derived hydrazine and phosphine oxide by-products can complicate product isolation. To this end many creative strategies have been developed to aid purification. For example, tagged[3] or polymeric phosphine and diazodicarboxylate reagents have emerged. Notable work in this area includes bipyridyl-tagged phosphine reagents,[4] fluorous phosphines,[5] tetraaryl phosphonium salts incorporating phosphines,[6] rasta resins,[7] a "waste as catalyst strategy"[8] and "impurity annihilation" methods.[9]

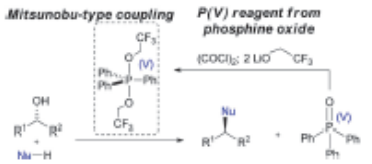
More recently the requirement for both a stoichiometric oxidant and phosphine in the Mitsunobu coupling and other phosphorus-mediated reactions has begun to be addressed.[10] In a pioneering study, Toy described a Mitsunobu system that employed substoichiometric DEAD and an iodine(III)-based terminal oxidant.[11] More recently still Taniguchi has demonstrated an impressive catalytic variant that exploits molecular oxygen as the terminal oxidant.[12] The necessity for an oxidant in the Mitsunobu procedure is a consequence of the fact that phosphorus(V) reagents have been accessed almost exclusively in an *oxidative* sense from phosphine precursors *e.g.* triphenylphosphine and DEAD (Scheme 1). A corollary of this conventional approach is that any phosphorus recycling or indeed catalysis[13,14] of such reactions must be achieved through the addition of a terminal reductant.[15]

In contemplating a method to improve the Mitsunobu reaction and eliminate hydrazine by-products we were attracted to a conceptually distinct alternative in which the active phosphorus(V) reagent would be accessed from a phosphorus(V) precursor,[16] specifically triphenylphosphine oxide – the unwanted by-product from the redox-based protocol (Scheme 2).[17]

Such a protocol was attractive since it would: (a) eliminate the need for an oxidant; (b) eliminate competing side reactions such as alkylation of the hydrazinedicarboxylate; and (c) result




Scheme 1 The 1967 Mitsunobu protocol based on the DEAD PPh$_3$ combination.




Scheme 2 This work: a redox free Mitsunobu process which relies upon generation of the active P(V) reagent from triphenylphosphine oxide.

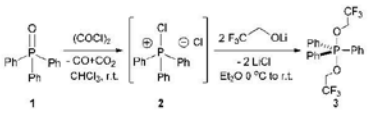
[a] School of Chemistry, University Park, University of Nottingham, Nottingham, UK. E-mail: ross.denton@nottingham.ac.uk; Tel: +44 (0)115 951 4184
[b] GlaxoSmithKline, Gunnels Wood Road, Stevenage, UK

† Electronic Supplementary Information (ESI) available: Details of Mitsunobu coupling procedure and full experimental supporting information. See DOI: 10.1039/c4cc02171a



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1 2 3

**Scheme 3** Synthesis of the Ishikawa phosphorane **3** from triphenylphosphine oxide.

in no net phosphorus waste. To the best of our knowledge this approach has only been investigated to date by Jenkins, whose detailed studies on the Hendrickson reagent ($Ph_3POPPh_3$-2OTf) indicated that the latter could function in analogy to the Mitsunobu system for esterification of primary alcohols. However, critically, in the case of secondary alcohols the ester products were obtained with retention of configuration[18]

In this communication we describe the successful implementation of redox-free Mitsunobu inversion reactions in which the active phosphorus(v) reagent is obtained from triphenylphosphine oxide.

The approach taken (Scheme 2) was contingent upon accessing the required dioxyphosphorane – of which many are known[19–22] – from triphenylphosphine oxide. While this was unprecedented at the time of our study we reasoned that the established conversion of phosphine oxides into chlorophosphonium salts[23,24] would provide a means to access the required dioxyphosphoranes following addition of the appropriate alkoxides. Gratifying this proved to be the case and several dioxyphosphoranes[25] were obtained through this protocol (Scheme 3) including dioxyphosphorane **3** ($^{31}P$ $\delta = -58.2$, $^2J_{C-F}J = 6.0$, $^{19}F$ $\delta = -74.3$, $^2J_{F-P}J = 9.0$ $CDCl_3$), which was originally described by Ishikawa and is known to promote a wide range of Mitsunobu-type coupling reactions.[22]

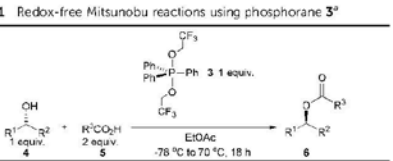
While these studies were instructive and guided our choice of phosphorane the stereochemical outcome of intermolecular coupling reactions using **3** remained unknown.[26] A further attractive feature of **3** was the presence of the $CF_3$ groups which allowed us to calculate the molarity of stock solutions of the reagent using $^{19}F$ NMR.[27]

Having developed a new method to access the Ishikawa dioxyphosphorane we next developed a Mitsunobu-type alcohol inversion protocol using reagent **3** and ethyl acetate as solvent (Table 1).

The redox-free coupling reactions took place with inversion of configuration with both non-activated (entries 1 and 2) as well as an activated secondary alcohol (entry 3 and 4). The process depicted in entry 1 was equally efficient on 15 mmol scale (with respect to the alcohol) and, in this case, 86% of triphenylphosphine oxide was recovered for reuse in subsequent coupling reactions. Furthermore, we determined that the stereochemical outcome of the reaction was independent of the order of addition of the alcohol and carboxylic acid.

Additional secondary alcohols underwent esterification in good yield (entries 5 and 6). Acetic acid could also be employed in place of the aromatic carboxylic acids (entry 9); however, the isolated yield in this case was moderate. Finally, menthol underwent esterification with inversion of configuration albeit in low yield (entries 10 and 11).

**Table 1** Redox-free Mitsunobu reactions using phosphorane **3**[a]




4 5 6

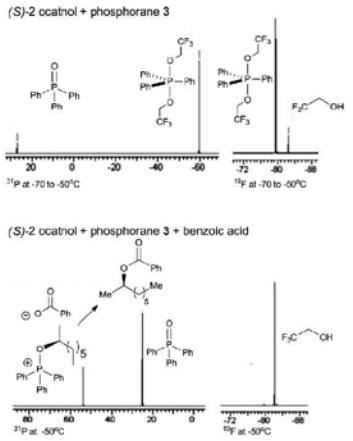
| Entry | Product | Yield e.e. | Entry | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | **6a** | 73%<br>>99:1<br>e.r. | 7 | **6g** | 70 |
| 2 | **6b** | 70%<br>>99:1<br>e.r. | 8 | **6h** | 72 |
| 3 | **6c** | 90%<br>96:4<br>e.r. | 9 | **6i** | 50 |
| 4 | **6d** | 79% | 10 | **6j** | 27 |
| 5 | **6e** | 76% | 11 | **6k** | 30 |
| 6 | **6f** 72% | | | | |

[a] For each entry the isolated yield after chromatography is reported.

With this protocol in hand we carried out a multinuclear NMR study in order to gain further insight into the course of the reaction. We were particularly interested in establishing whether or exchange of one of the trifluoroalkoxy ligands at phosphorus would occur in the presence of the alcohol alone to generate a mixed dioxyphosphorane of general structure $Ph_3P(OCH_2CF_3)(OR)$ as originally proposed by Ishikawa.

The results we obtained (Scheme 4) indicated that this was not the case with (*S*)-2-octanol. Thus a 0.25 M solution of **3** in ethyl acetate remained unchanged upon addition of one equivalent of the alcohol. However, upon addition of benzoic acid the $^{31}P$ resonance at −59.6 ppm was replaced by a new signal at 53.4 ppm which corresponds to the indicated alkoxyphosphonium salt with a carboxylate counteranion. The structure of this intermediate is corroborated by the presence of a *single* peak in the $^{19}F$ NMR, which corresponds to trifluoroethanol and rules out the formation of a "mixed" dioxyphosphorane of the type $Ph_3P(OCH_2CF_3)(OR)$. The former species then underwent slow Arbuzov collapse to

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Scheme 4 Multinuclear NMR study.

the afford ester product with inversion of configuration with concomitant generation of triphenylphosphine oxide.

In summary we have developed for the first time a redox-free approach to Mitsunobu inversion reactions that relies upon accessing the Ishikawa phosphorane **3** from triphenylphosphine oxide.

This new protocol eliminates the need for diazo-based oxidants and, given that reagent **3** is also known to promote C–N, C–S and other cyclodehydration reactions,[22] opens up a wide range of other useful Mitsunobu-type reactions that will not require the addition of an external oxidant. Furthermore, since triphenylphosphine oxide is used to prepare the coupling reagent no net phosphorus waste is generated.

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