STUDIES TOWARDS A PHOSPHORUS(V)-CATALYSED MITSUNOBU REACTION

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

JULY 2016

Abstract

A novel manifold has been developed, catalytic in phosphorus (V), that promotes the dehydration reaction of an alcohol to give the symmetrical ether product. This has been achieved through the development of a novel dioxyphosphorane catalyst that, in conjunction with a triflic acid cocatalyst, conducts the coupling reaction without the need for any additional stoichiometric reagents. This has allowed the omission of the explosive diazo-compounds that are required in the widely-accepted Mitsunobu conditions, and has reduced the amount of inconvenient and difficult-to-remove phosphorus waste that is usually associated with phosphorus-mediated reactions. This work constitutes the first example of a phosphorus (V)-catalysed Mitsunobu-type etherification reaction.

Acknowledgements

I would like to thank the University of Nottingham and Syngenta for funding this doctoral research and allowing me the opportunity to conduct this ambitious project, which has been challenging, yet ultimately extremely rewarding.

Those who I would like to thank in particular for their support and guidance throughout my academic career at the University of Nottingham are Dr. Ross Denton, whose expertise and ambition are sources of great inspiration, Dr. Steve Shanahan, whose intelligent and thoughtful contributions and support were highly valued, the Denton group members and other Nottingham chemists with whom I have shared camaraderie with, namely Dr. Xiaoping Tang, Dr. James Scragg, Dr. An Jie, Dr. Jan Saska, Adam Fearnley, Keith Andrews, Dr. Jamie Fraser, Christopher Wood, Harry Alexander, Toby Blundell, and of course Dr. Stéphanie Foltran, and those others in the laboratory who provided great company for the discussion of ideas, both regarding the project and otherwise, and brightened my time in synthetic chemistry.

I would also like to acknowledge the role of the various Organic Chemistry football teams, and the Spirit of Linda Brenda Football Club, that provided excellent diversion when most needed.

Most importantly, I would like to acknowledge my Mum and Dad for providing support and sound advice throughout my PhD, and indeed my entire life. Whenever uncertainty appeared, or drive deserted, they were always there to encourage and reassure.

Abbreviations

ATR – attenuated total reflection

BINAP – (2,2'-bis(diphenylphosphine)-1-1'-binaphthyl)

Boc – *tert*-butyloxycarbonyl

DCE – dichloroethane

DHP – dihydropyran

DMB – dimethoxybenzyl

DMF – dimethylformamide

DEAD – diethyl azodicarboxylate

DEPT – distortionless enhancement by polarisation transfer

DIAD – di*iso*-propyl azodicarboxylate

DTPP – diethoxytriphenylphosphorane

ESI – electrospray ionisation

FTIR – Fourier transform infrared spectroscopy

HMBC – heteronuclear multiple-bond correlation

HMQC – heteronuclear multiple-quantum correlation

HRMS – high-resolution mass spectrometry

LA – Lewis acid

MOM – methoxymethyl

MS – molecular sieves

Ms – mesyl (methanesulfonyl)

NOE – nuclear Overhauser effect

Nu – nucleophile

Pc – phthalocyanine

PMB – *para*-methoxybenzyl

PPTS – pyridinium *para*-toluenesulfonate

TBS – *tert*-butyldimethylsilyl

TES – triethylsilyl

Tf – triflyl (trifluoromethanesulfonyl)

THF – tetrahydrofuran

THP – tetrahydropyran

TIPS – tri*iso*-propylsilyl

TLC – thin layer chromatography

TMS – trimethylsilyl

Tr – trityl (triphenylmethyl)

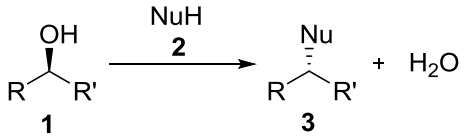
Ts – tosyl (*para*-toluenesulfonyl)

Contents

1 – Introduction

1.1 – Hydroxyl activation and substitution

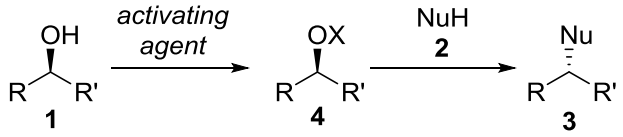
The activation of hydroxyl groups for substitution by a nucleophile is an extremely useful and important transformation in modern synthetic organic chemistry, and allows a simple route into complex molecules *via* the functionalisation of hydroxyl containing substrates.[1] The direct substitution of a hydroxyl group with a nucleophile can proceed *via* either an S_N1 or an S_N2 mechanism with the latter resulting in an inversion of stereochemistry through Walden inversion of the electrophile.[2] This transformation is particularly useful in the synthesis of target molecules with stereochemical centres as it provides a method of control of the product stereochemistry.



Equation 1.1 *– the ideal hydroxyl substitution reaction.*

The ideal S_N2 reaction would consist of direct attack of the nucleophile at the carbon centre of the hydroxyl group, displacing a hydroxide ion and giving the substituted product with inversion of stereochemistry, while eliminating water as the sole by-product (Equation 1.1).[3] There are a number of barriers to this reaction that prevent hydroxyl substitution occurring *via* the ideal mechanism, consisting of both thermodynamic and kinetic factors. The thermodynamic favourability of the reaction depends on the strength of the new C-Nu σ-bond compared to the broken C-O σ-bond, and whether any enthalpic deficit is compensated for by the formation of water. The kinetic barriers to the reaction result from the notoriously poor hydroxide leaving group;

the strength of the nucleophile will vary dependent on the reaction but the hydroxide ion will remain an extremely poor leaving group. These factors coupled with the low electrophilicity of the hydroxyl carbon means that the kinetic barrier to the ideal reaction is high.



Equation 1.2 *– activation and substitution through the use of an activating agent.*

A common and widely used method of overcoming the kinetic and thermodynamic barriers associated with the ideal hydroxyl substitution reaction is to use an additional reagent to convert the hydroxyl group into an activated leaving group (*e.g.* an acetate or a triflate), and then to further react this activated species with attack of a nucleophile to give the substitution reaction product (Equation 1.2).[4]

This approach of covalently activating the hydroxyl group overcomes some of the barriers of the ideal reaction by increasing the electrophilicity of the hydroxyl carbon centre and converting what would otherwise be the poor hydroxide leaving group into a much more favourable leaving group.

Although this method of hydroxyl activation provides an effective route into the nucleophilic substitution product seen in the ideal S_N2 reaction it comes with associated drawbacks; in contrast to the ideal reaction, where water is the sole by-product, this activation method produces stoichiometric amounts of waste from the activation process. For example, if triflic anhydride were used to convert the hydroxyl group into an alkyl triflate two equivalents of triflic acid would be produced as by-product: one during the activation step/triflate formation and another upon attack of the nucleophile

to achieve substitution. These associated waste products result in a more cumbersome reaction; in the example using triflic anhydride the triflic acid waste would alter the reaction conditions potentially causing disruptive complications to the reaction and meaning that work-up would be required between activation and substitution steps. The generation of the stoichiometric amounts of waste also has a severe, negative impact on the atom economy of the process.

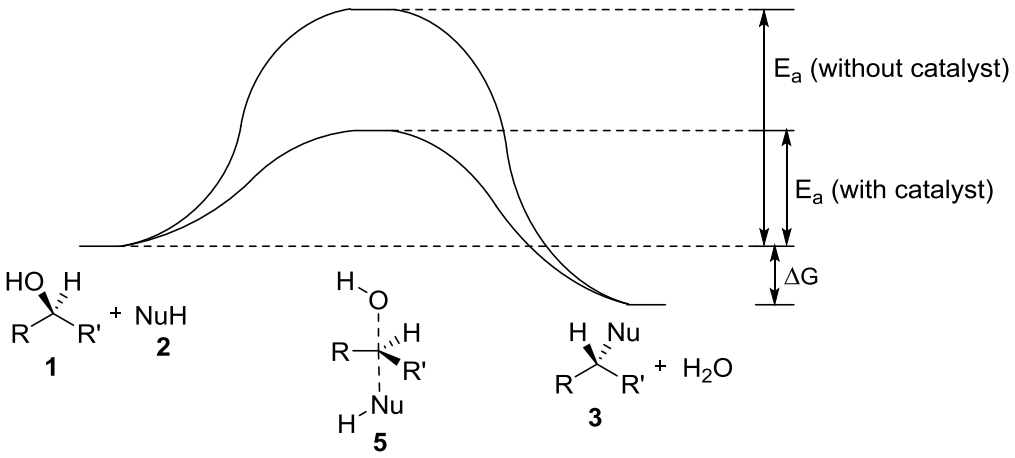
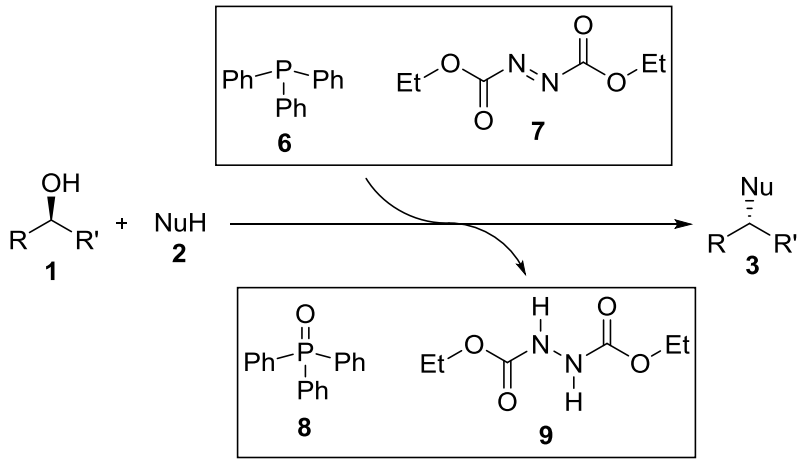


Figure 1.3 *– the potential effect of catalysis on the ideal S_N2 reaction.*

Another approach that could potentially be taken in order to achieve an S_N2 reaction would be to employ catalysis. Generally, catalysis is the process by which the introduction of an additional reagent increases the rate of the reaction by lowering the activation energy. The identification and application of a suitable catalyst into the ideal S_N2 reaction would allow this currently unviable reaction to be achievable under milder conditions through the lowering of the activation energy (Figure 1.3), without the introduction of the stoichiometric reagents mentioned previously in Equation 1.2.

1.1.1 – The Mitsunobu reaction

The state-of-the-art of mild hydroxyl activation and substitution is the Mitsunobu reaction, first developed by O. Mitsunobu but inspired by initial observations he had seen while working under T. Mukaiyama on methods of oxidising phosphites and phosphines.[5,6]



Scheme 1.4 *– the Mitsunobu reaction.*[7]

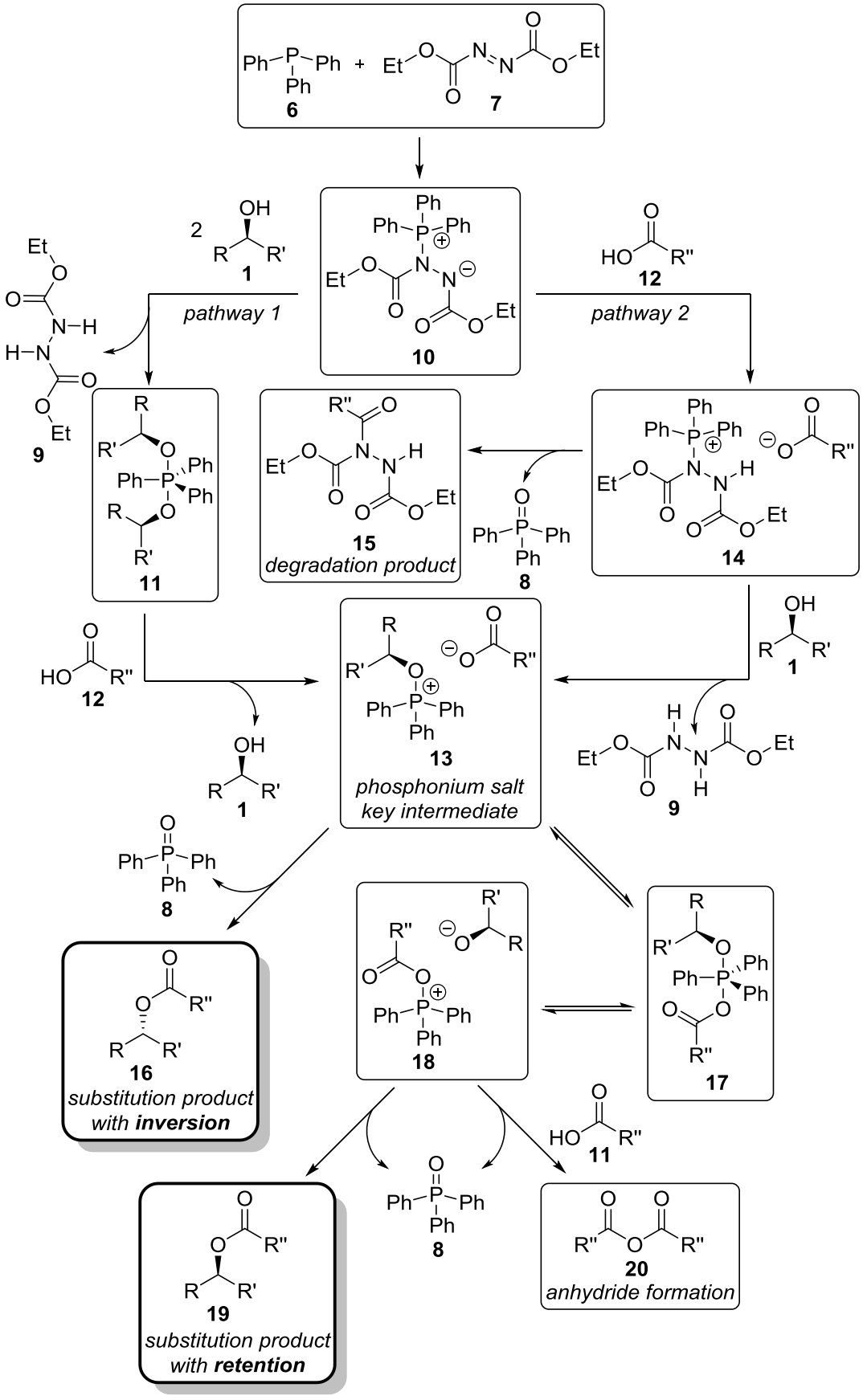
The reaction proceeds by using a phosphine and a diazo-compound to activate the hydroxyl group, before attack of the nucleophile occurs to give the substituted product, usually with inversion of stereochemistry, resulting in the production of phosphine oxide and hydrazine waste products (Scheme 1.4).[7-9] Several reviews have been published on the subject.[7,10-12]

The Mitsunobu conditions overcome the energetic barriers to the ideal reaction in a similar manner to the separate activation and substitution approach by, firstly, addressing the kinetic factors through conversion of the hydroxyl group into an activated leaving group *in situ*, and then addressing the thermodynamic factors through the elimination of phosphine oxide by-product. The formed P=O bond is very strong due to the backbonding of the oxygen p orbitals into the antibonding σ* orbitals of the P-C

bonds.[13] This strong P=O double bond can compensate for the formation of weaker C-Nu σ-bonds allowing a broad range of nucleophiles to be accommodated.[14]

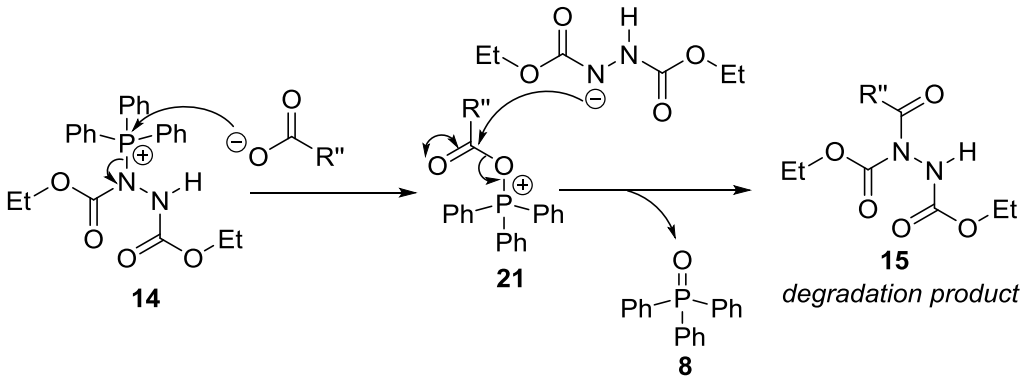
The Mitsunobu reaction represents the state-of-the-art in hydroxyl activation as it allows the nucleophilic substitution of hydroxyl groups in a one-pot process, rather than the need for separate activation and substitution steps, can tolerate a range of nucleophiles due to the strength of the P=O bond and can also accommodate acidic nucleophiles (indeed the nucleophile must have a pK_a of less than 15 for Mitsunobu conditions to successfully perform the transformation), where these nucleophiles would usually need to be deprotonated to displace covalently activated hydroxyl groups.

As outlined in Scheme 1.5 the Mitsunobu reaction proceeds by a complicated mechanism which firstly involves the attack of triphenylphosphine **6** onto diethyl azodicarboxylate (DEAD) **7** to give the Morrison-Brunn-Huisgen betaine **10** which serves to provide an activated phosphorus centre for further reaction with either the alcohol or the nucleophile (a carboxylic acid in Scheme 1.5).[15] Pathway 1 proceeds by the attack of two equivalents of the alcohol substrate at the phosphorus of betaine **10** to give dioxyphosphorane **11** with elimination of hydrazine DEAD-H_2 **9**. Dioxyphosphorane **11** then loses an alcohol ligand to give an alkoxyphosphonium salt **13** with a carboxylate counteranion in the presence of the carboxylic acid nucleophile.



Scheme 1.5 *– accepted mechanism of the classic Mitsunobu esterification reaction.*[10,11]

Pathway 2 involves deprotonation of the carboxylic acid nucleophile by the betaine nitrogen anion to produce ionic species **14**. Upon the reaction of ionic species **14** with an equivalent of alcohol substrate hydrazine DEAD-H_2 is eliminated to form the previously mentioned alkoxyphosphonium salt **13**.



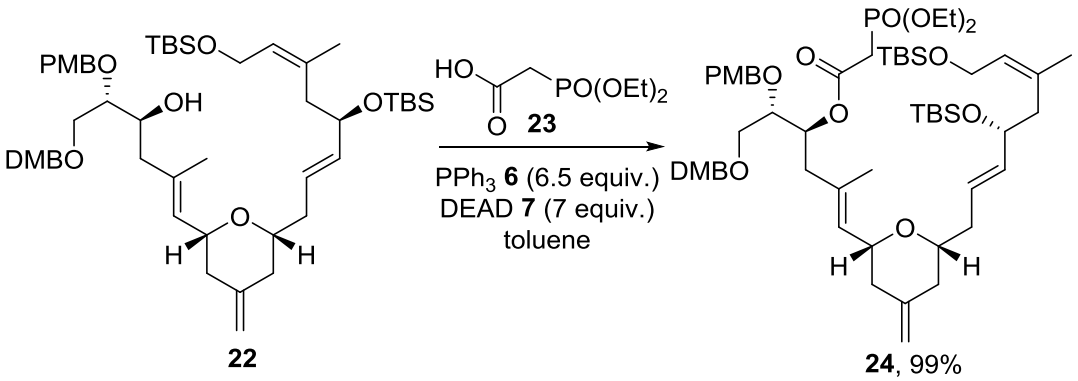
Scheme 1.6 *– degradation pathway of the Mitsunobu reaction.*

From ionic species **14** a degradation pathway is possible, involving attack of the carboxylate anion at the phosphonium centre and the subsequent attack of the hydrazine-anion at the activated electrophilic carbonyl centre of the resultant alkoxyphosphonium salt to give degradation product **15** and phosphine oxide (Scheme 1.6). This irreversible reaction consumes an equivalent each of both the diazo compound and the nucleophile.

The alkoxyphosphonium salt **13** represents an important intermediate in the Mitsunobu reaction as it is from this species that an Arbuzov collapse can occur to give substitution product **16** with inversion of stereochemistry. It is possible however for species **13** to undergo ligand exchange *via* phosphorane **17** to give acylphosphonium salt **18**. The latter, as an active ester, can then undergo nucleophilic attack by the alkoxide counteranion to give substitution product **19** with *retention* of stereochemistry. It is also possible for an additional equivalent of carboxylate to attack acylphosphonium salt **18** to

yield anhydride product **20**, which may presumably undergo reaction with alcohol substrate **1** to give substitution product **19**, again with retention of stereochemistry.

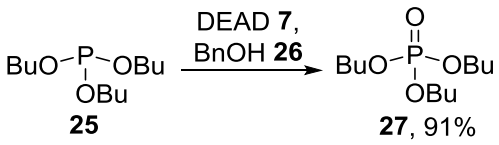
Although the Mitsunobu reaction can proceed to give the esterification substitution product with either inversion or retention of stereochemistry, it is more common for the inversion product to be observed as the key intermediate phosphonium salt **13** can react directly to give the inversion product, or undergo reversible ligand exchange to then eventually give product with retention. It follows that retention of stereochemistry is more commonly seen where nucleophilic substitution *via* an S_N2 pathway (giving product with inversion of stereochemistry) is slow due to hindrance at the alcohol substrate, allowing ligand exchange to occur so that reaction can proceed by nucleophilic acyl substitution (giving product with retention of stereochemistry). An example of this is observed by Smith III and co-workers in their synthetic route to (+)-Zampanolide and (+)-Dactylolide where a Mitsunobu esterification reaction proceeds to give the retention product (Equation 1.7).[16]



Equation 1.7 *–Mitsunobu esterification to produce an intermediate in the syntheses of (+)-Zampanolide and (+)-Dactylolide by Smith III that proceeds with* ***retention*** *of stereochemistry.*[16]

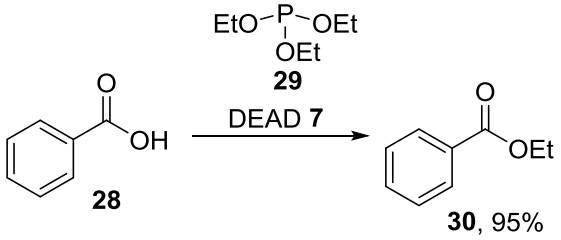
Initially, work by Mukaiyama and Mitsunobu focussed on oxidation of phosphorus (III) compounds in the presence of DEAD and an additional alcohol

reagent in the form of benzyl alcohol or allyl alcohol, progressing through a betaine intermediate equivalent to betaine **10** and giving the equivalent phosphorus (V) product (Equation 1.8).[6]

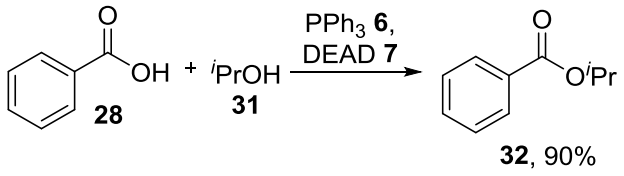


Equation 1.8 *– initial oxidation reactions by Mukaiyama and Mitsunobu.*[6]

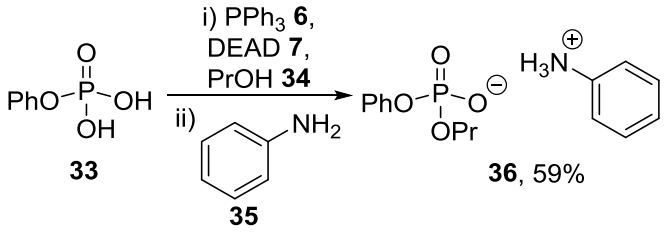
Independent work by Mitsunobu then progressed onto the formation of carboxylic esters through reaction of the equivalent carboxylic acid using, firstly, phosphites (Equation 1.9),[8] and later phosphines (Equation 1.10).[9] Phosphoric esters were also made from the appropriate phosphoric acid (Equation 1.11).[9] The triphenylphosphine-DEAD system developed and detailed in work by Mitsunobu and co-workers in 1971 remains in use as the standard conditions used in Mitsunobu-type coupling reactions.



Equation 1.9 *– initial esterification reaction by Mitsunobu and co-workers using triethylphosphite and DEAD.*[8]

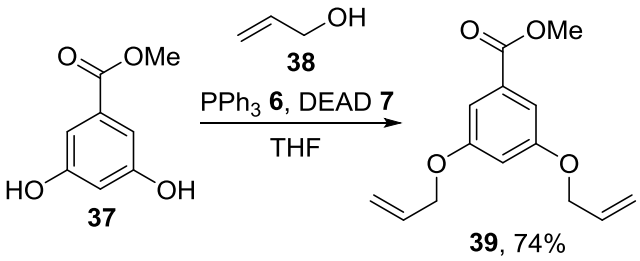


Equation 1.10 *– carboxylic esterification reaction conducted using widely used "standard" Mitsunobu conditions.*[9]

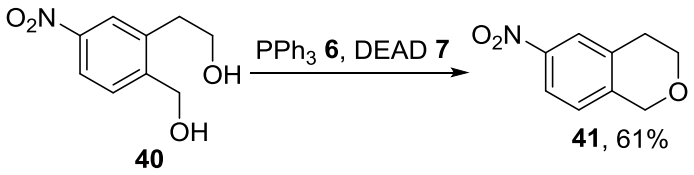


Equation 1.11 *– phosphoric esterification reaction using widely used Mitsunobu conditions, isolated as the anilinium salt.*[9]

Since the pioneering work by Mukaiyama and Mitsunobu the scope of the coupling reactions that can be performed using Mitsunobu conditions has been greatly broadened with reactions of alcohols including etherifications, both acyclic (Equation 1.12)[17] and cyclic (Equation 1.13).[18]

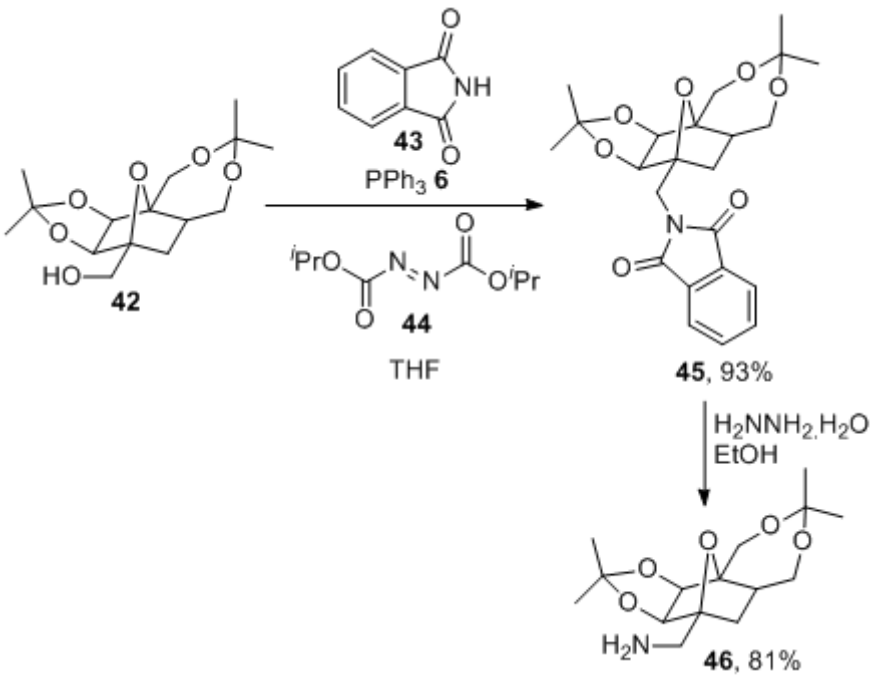


Equation 1.12 *– acyclic Mitsunobu etherification.*[17]

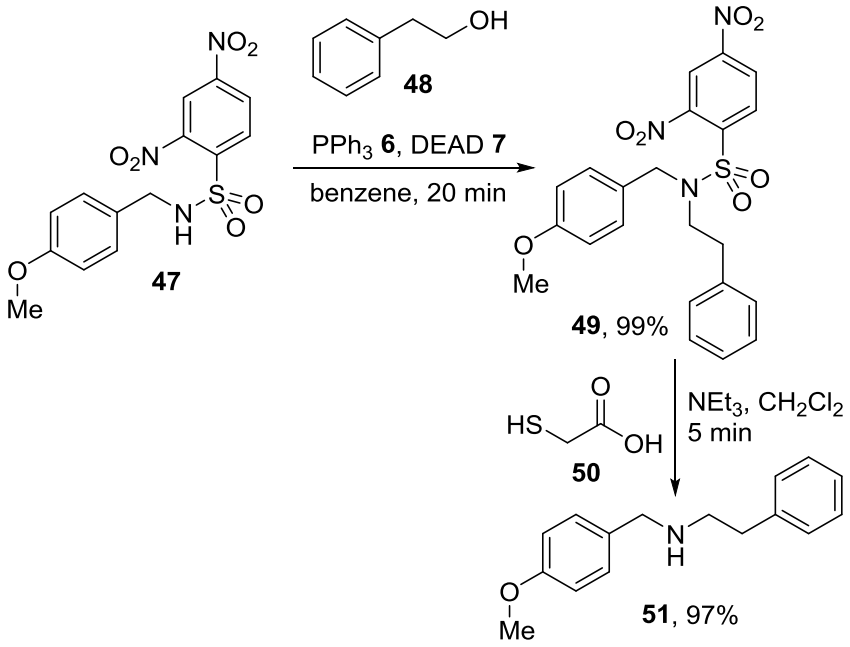


Equation 1.13 *– cyclic Mitsunobu etherification.*[18]

The scope of nitrogen-containing nucleophiles has also broadened with amination products accessible by using phthalimide followed by deprotection with hydrazine (Scheme 1.14)[19] and by using a sulfonamide nucleophile followed by removal of the sulfonyl group (Scheme 1.15).[20]

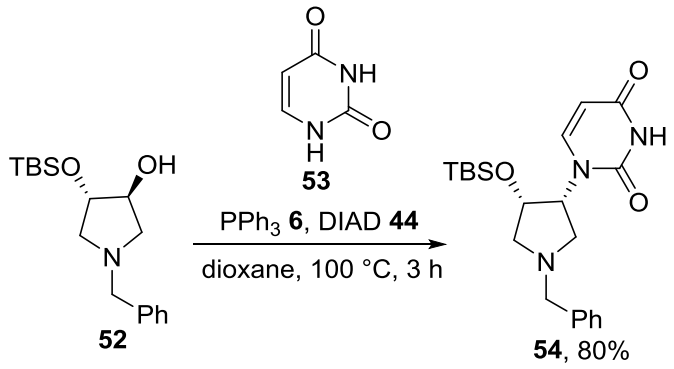


Scheme 1.14 *– Mitsunobu reaction using phthalimide as the nucleophile.*[19] *Further reaction with hydrazine gives a useful route to amines using Mitsunobu conditions.*

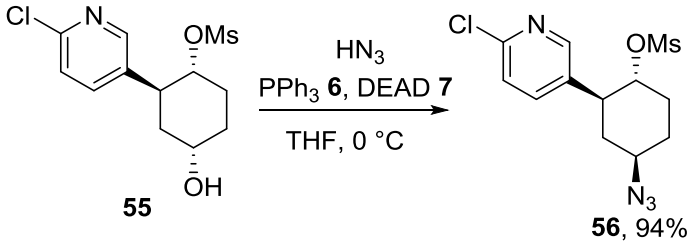


Scheme 1.15 *– Sulfonamides can also be used to provide nucleophilic nitrogen sources before being deprotected to give the Mitsunobu amine product.*[20]

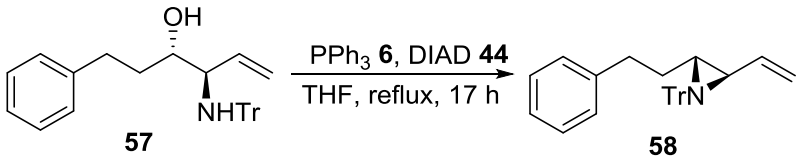
Heterocycles can also be used as nucleophiles (Equation 1.16),[21] azidations are possible (Equation 1.17)[22] potentially providing another route to amination products when coupled with the Staudinger reaction and intramolecular aziridination protocols have been conducted (Equation 1.18).[23]



Equation 1.16 *–heterocyclic nucleophiles are tolerated under Mitsunobu conditions.*[21]

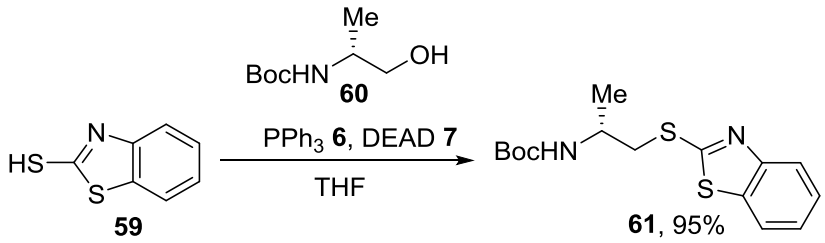


Equation 1.17 *– inversion is observed during a Mitsunobu azidation reaction using hydrazoic acid.*[22]

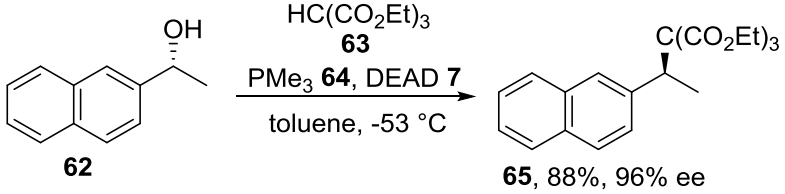


Equation 1.18 *–a Mitsunobu aziridination reaction.*[23]

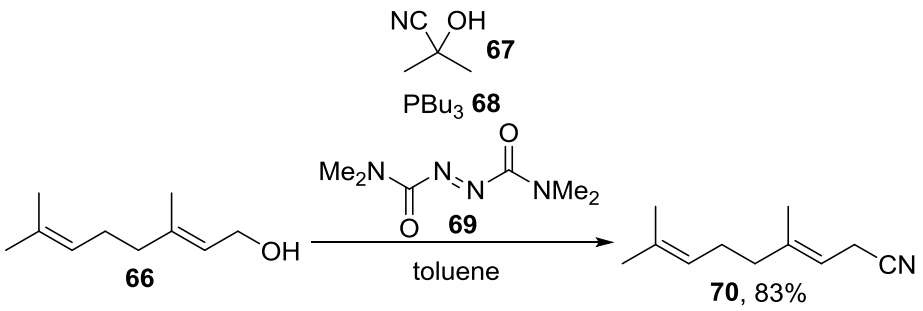
Work has also been conducted to show the ability of both sulfur nucleophiles (Equation 1.19)[24] and carbon nucleophiles (Equations 1.20 and 1.21) to react under Mitsunobu conditions.[25,26]



Equation 1.19 *– a sulfur nucleophile in the Mitsunobu reaction.*[24]



Equation 1.20 *– a carbon nucleophile in the Mitsunobu reaction.*[25]



Equation 1.21 *– Mitsunobu reaction with cyanide as the nucleophile with use of* ***65*** *as the pronucleophile.*[26]

It is important to note that, in several of the reactions detailed as examples of the Mitsunobu reaction, alternative reagents have been used to the traditional triphenylphosphine/diethyl azodicarboxylate system, with both different phosphines (*e.g.* tributylphosphine) and diazo compounds (*e.g.* di*iso*-propyl azodicarboxylate) being used.[12] These reagents work by the same Mitsunobu mechanism but provide subtle differences in reactivity and provide optimisation options for reactions involving particular substrates.

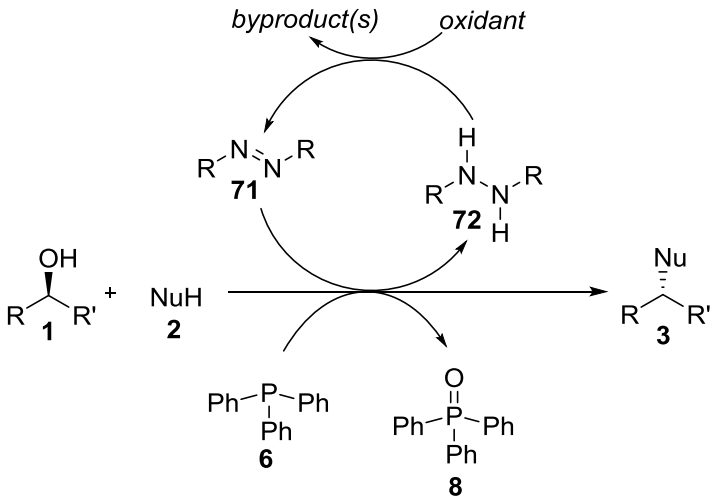
The Mitsunobu reaction is clearly a versatile and useful tool for manipulating hydroxyl containing compounds into a wide variety of useful substrates. The reaction does, however, possess significant intrinsic drawbacks essentially consisting of the stoichiometric amounts of phosphorus (phosphine oxide) waste generated, which makes purification difficult, and the use of explosive reagent DEAD in the reaction.[27] It should, however, be noted that more stable diazo alternatives are available, such as DIAD.[28] These factors mean that the reaction is not widely used in the chemical industries, indeed the ACS Green Chemistry Institute Pharmaceutical Roundtable has called for "safer more environmentally friendly Mitsunobu reactions" and, in a survey of their members, "Hydroxyl activation for nucleophilic substitution" received more votes for development prioritisation than anything other than improved reagents for amidation.[29] Attention has

also been drawn to the potentially unsustainable use of phosphorus in mining, farming, animal feeding, and household consumption,[30] so any development of an improved alternative to the Mitsunobu reaction for hydroxyl activation and substitution should seek to remove the need for phosphorus, or reduce it through use of sub-stoichiometric amounts by recycling phosphorus components through catalysis.

The drawbacks associated with the conventional Mitsunobu reaction highlight the demand for a method of hydroxyl activation that avoids or reduces the use of explosive diazo compounds and simplifies or removes the need for separation of the product from phosphine oxide waste. The best alternative would be to produce a *catalytic* alternative to the Mitsunobu reaction, using sub-stoichiometric amounts of the reagents that complicate the process.

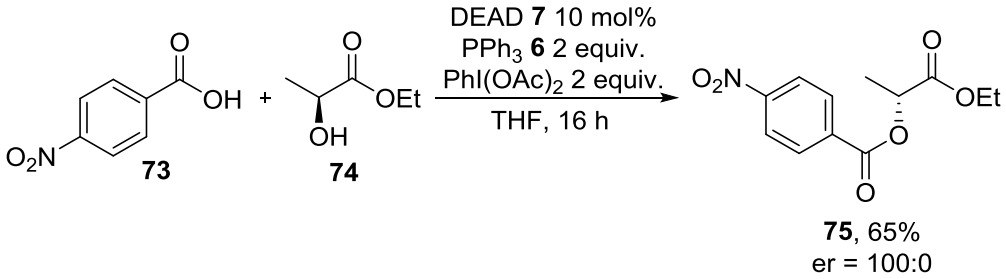
1.2 – Catalytic Mitsunobu reactions

Due to the widely recognised problems of the Mitsunobu reaction, and the accepted need for an alternative that addresses some of the associated issues, a catalytic variant of the Mitsunobu reaction has been (and remains) a highly sought after process.



Scheme 1.22 *– the catalytic cycle for diazo compound-catalysed Mitsunobu reactions.*

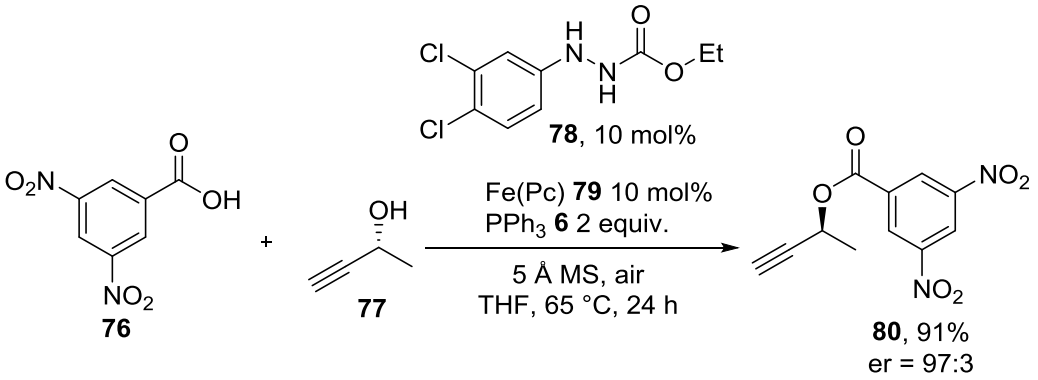
Catalytic variants of the Mitsunobu reaction developed to date have been catalytic in the diazo compound/hydrazine component of the reaction (Scheme 1.22). This catalytic system works by recycling the hydrazine by-product back to the reactive diazo compound by use of *in situ* oxidation, hence requiring only a substoichiometric amount of the explosive diazo compound to be used in the reaction, reducing both the amount of hydrazine waste and the amount of explosive diazo compound used.



Equation 1.23 *– the first example of a diazo compound-catalysed Mitsunobu reaction by Toy and co-workers.*[31]

A catalytic Mitsunobu reaction developed by Toy and co-workers is the first example of a catalytic Mitsunobu reaction, and is catalytic in DEAD (Equation 1.23).[31] The reaction proceeds by a standard Mitsunobu mechanism, with the reaction of triphenylphosphine and diethyl azodicarboxylate being the initial key step of the reaction. However, only a substoichiometric amount of DEAD is used, with the hydrazine byproduct being recycled using (diacetoxyiodo)benzene as the stoichiometric oxidant to achieve catalyst turnover (as outlined in Scheme 1.22). Because of the presence of an oxidant in the reaction large amounts of phosphine and oxidant are required due to an unavoidable *in situ* oxidation reaction of phosphine, which produces stoichiometric amounts of phosphine oxide by-product.

This reaction represents the first example of a catalytic Mitsunobu reaction and is pioneering work of high academic value. However the atom economy of Toy's Mitsunobu reaction is lower than using stoichiometric Mitsunobu conditions (12% *vs.* 24%)[32] so, despite the DEAD catalysis, the required large amounts of phosphine and oxidant mean that this reaction produces more waste than the stoichiometric Mitsunobu conditions. The end result of this catalytic reaction is that, although the required amount of explosive diazo compound has been reduced, this has been achieved at the expense of producing large amounts of both phosphorus- and iodine-containing waste.



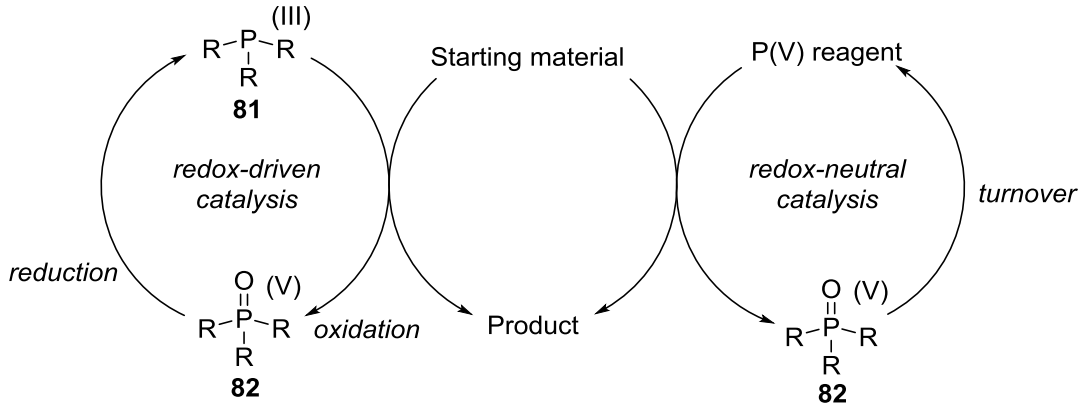
Equation 1.24 *– Taniguchi's Mitsunobu reaction.*[33]

Developed after Toy's reaction was a catalytic Mitsunobu reaction by Taniguchi and co-workers (Equation 1.24).[33] This variant was again catalytic in the diazo compound/hydrazine component with oxidative turnover of the catalyst but, rather than employing a stoichiometric oxidant as demonstrated in Toy's work, an iron catalyst with a phthalocyanine (Pc) ligand is used that allows the oxidation of hydrazine **78** using air as the oxidant. The use of air as a terminal oxidant in combination with an iron cocatalyst is an improvement on Toy's method and improves the atom economy of this catalytic reaction to slightly better than the traditional Mitsunobu reaction (26% *vs.* 24%).[32] The comparable atom economy and the reduced use of explosive diazo compounds make

Taniguchi's Mitsunobu variant an important improvement on the traditional Mitsunobu reaction. However the reaction still suffers from the large amounts of phosphine oxide by-product produced and the continued use (however reduced) of an explosive diazo compound. A further improvement would be to develop a Mitsunobu reaction catalytic in an active phosphorus compound that would reduce the amount of phosphorus waste and possibly also remove the need for any diazo compound to be present. In order to achieve a reaction that is fully independent of diazo compound an alternative method of initially activating the phosphorus reagent must be found.

1.3 – Phosphorus catalysis

Phosphorus catalysis[34] is a field that has emerged only recently despite many phosphorus-mediated reactions having been important staples of synthetic organic chemistry for decades (*i.e.* the Mitsunobu, Wittig,[35,36] Appel[37] and Staudinger[38] reactions). The field can be broadly split into two approaches: redox-driven phosphorus catalysis and redox-neutral phosphorus catalysis (Scheme 1.25).[3,39]



Scheme 1.25 *– the two broad approaches to phosphorus catalysis – redox-driven catalysis and redox-neutral catalysis.*[3]

1.3.1 – Phosphorus structure

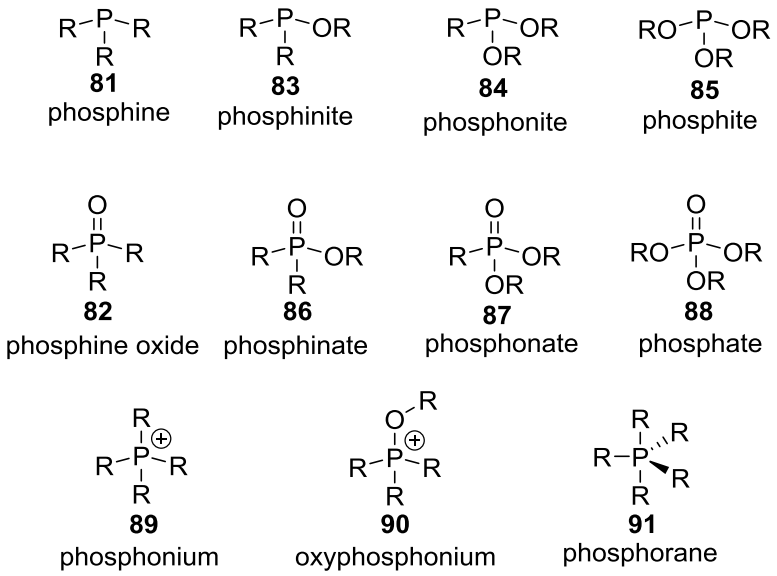


Figure 1.26 *– nomenclature of phosphorus species.*

The chemistry of phosphorus allows many compositions and bonding structures; organophosphorus is most commonly found in the P (III) (*e.g.* phosphine) and P (V) (*e.g.* phosphine oxide and phosphorane) oxidation states (Figure 1.26).

An interesting characteristic of phosphines is that they retain chirality, whereas amines, the nitrogen equivalent, cannot be considered chiral due to easy inversion of the trigonal pyramidal conformation. This is due to the barrier for nitrogen inversion being approximately 6 kcalmol^{-1} and the barrier to inversion for phosphines being approximately 32 kcalmol^{-1}.[40] The difference in barrier to inversion allows enantiomers of phosphines to retain their configuration, where amines will easily convert between the two enantiomers, resulting in a racemic mixture.

The phosphine oxide P=O bond is very strong (130 kcalmol^{-1}),[41] and forms the driving force for many phosphorus-mediated reactions. The P=O has previously been thought to have been a polarised charged betaine, similar to N-oxides, and alternatively to include the participation of d orbitals. Recent consensus is that the strong P=O bond

results from backbonding of the oxygen p orbitals into the σ* orbitals of the P-C bonds, explaining the strength of the bond.[13,14]

Generic phosphines and phosphine oxides are trigonal pyramidal and tetrahedral in shape respectively, both with C_{3v} symmetry when all R substituents are equal. Phosphoranes however, due being pentavalent, adopt a trigonal bipyramidal arrangement with D_{3h} symmetry. The symmetries of the different arrangements of phosphorus species are significant when considering the classification of such species using NMR, with equivalent R substituents on phosphine oxides and phosphines experiencing identical chemical environments.

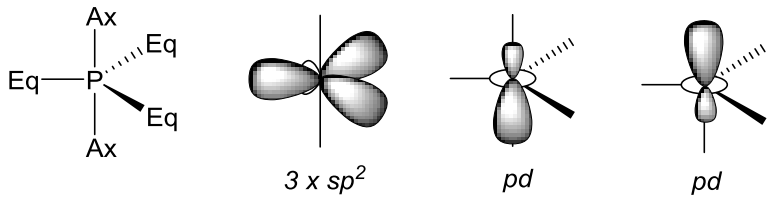


Figure 1.27 *– representations of the hybridised orbitals of phosphoranes.*[42-45]

The trigonal bipyramidal shape that is adopted by phosphoranes means that there are two differentiable environments for substituents – apical and equatorial – and this then allows the hybridised orbitals of phosphorus to be split into the equatorial sp^2 orbitals and the axial pd orbitals (Figure 1.27).[42] The bond angles would then, accordingly, be Eq-P-Eq = 120° and Ax-P-Eq = 90°. It has been found established that electronegative substituents are more apicophilic (more likely to populate the axial, or apical, position of the phosphorane) due to the more favourable overlap with a hybridised pd orbital.[43-45]

Electronegative substituents on phosphoranes are often the best leaving groups (*e.g.* halides), but when they occupy an apical position the angle of attack for a nucleophile is blocked by the presence of the opposing axial substituent. Nucleophilic

substitution reactions are still possible on phosphoranes where leaving groups would normally occupy the axial position, and this is due to the Berry pseudorotation.[46]

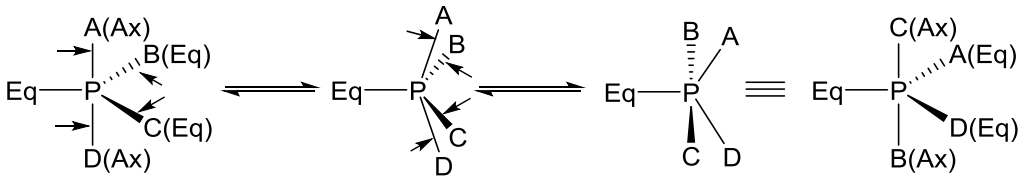


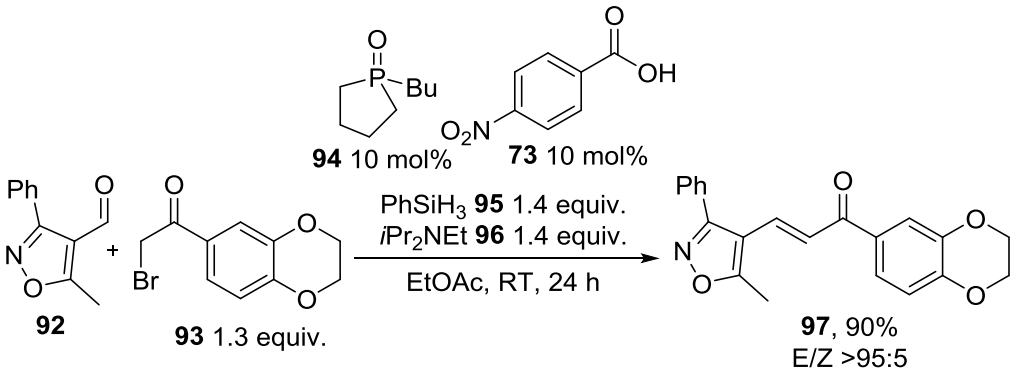
Figure 1.28 *– the Berry pseudorotation.*[46]

The Berry pseudorotation is the mechanism by which axial and equatorial substituents of a trigonal bipyramidal structure can interconvert (Figure 1.28). It has been used to explain why one environment is seen in the ^{19}F NMR of PF_5 at higher temperatures, when two environments are seen are low temperatures – the possible interconversion of substituents allows all fluorine atoms to be equivalent. The barrier to interconversion between arrangements is low – approximately 3 $kcalmol^{-1}$. This low barrier allows the apicophilic electronegative leaving groups to interconvert and sometimes occupy the equatorial position, where the angle of attack for nucleophilic substitution is unhindered.

1.3.2 – Redox-driven phosphorus catalysis

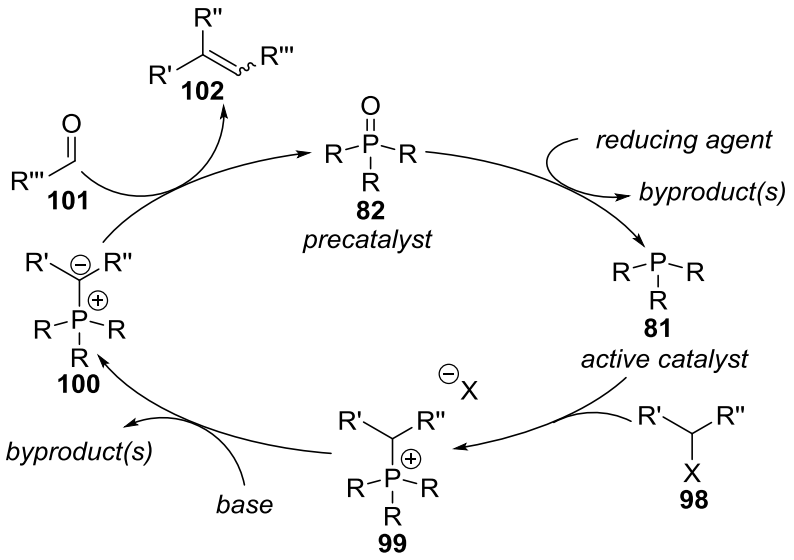
Redox-driven phosphorus catalysis involves a phosphorus (III) catalyst that promotes the reaction and is converted into a phosphorus (V) species during the course of the reaction. This stage of the catalytic cycle contains the conventional reactivity normally exhibited in phosphorus-mediated reactions such as the Wittig reaction,[35,36] but catalyst turnover is achieved *in situ* by the use of a stoichiometric reductant to regenerate the phosphorus (III) reagent. This approach is similar to the use of stoichiometric iodine (III) oxidant in the aforementioned catalytic Mitsunobu reaction developed by Toy and

co-workers. In the present case phosphine turnover is achieved *via* the reduction of phosphine oxide by-product through use of a stoichiometric reductant.



Equation 1.29 *– phosphorus-catalysed Wittig reaction by O'Brien.*[47]

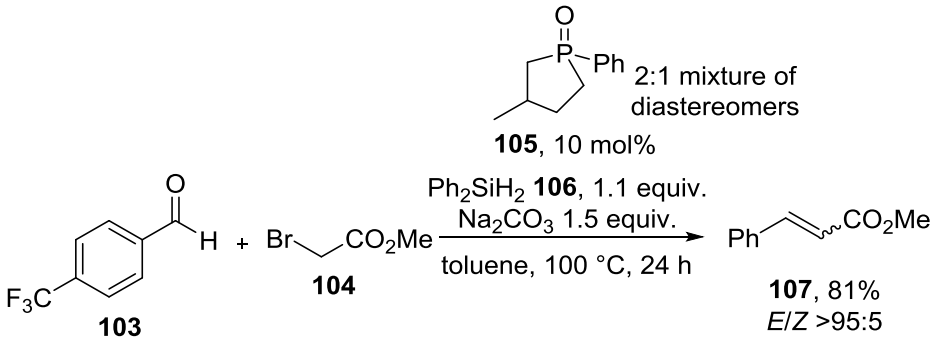
There are several examples that make use of this method of recycling phosphine oxide waste. A phosphorus-catalysed Wittig reaction developed by O'Brien and co-workers was the first example of an approach where the phosphine oxide by-product is turned over to phosphine catalyst by the use of a silane reductant (Equation 1.29).[47-49]



Scheme 1.30 *– catalytic cycle of O'Brien's Wittig reaction.*[48,49]

This reaction operates by forming the catalyst through chemoselective reduction of the phosphine oxide precatalyst **82** in the presence of potentially reducible aldehydes, ketones and alkyl halides to provide the active phosphorus (III) catalyst needed to conduct the Wittig reaction. The phosphine catalyst then enters into a normal Wittig reaction, reacting first with the alkyl halide to form phosphonium salt **99** and then with base to produce the phosphonium ylide **90**. Reaction of the phosphonium ylide with an aldehyde or ketone will then produce the alkene product with regeneration of the phosphine oxide **82** (Scheme 1.30).[48,49]

The key to successfully developing a catalytic Wittig reaction lay in the production of active phosphine catalyst from the phosphine oxide by-product under the reaction conditions while avoiding the unwanted reduction of substrates and product. In order to achieve reduction of a phosphine oxide under normal circumstances harsh reducing agents such as $LiAlH_4$ or $HSiCl_3$ have been known to have been used, but these would not have been able to chemoselectively reduce the phosphine oxide in the presence of the aldehyde substrate. A variety of mild methods of phosphine oxide reduction are known,[50] but a notable example is a highly chemoselective metal-free catalytic reduction using silane as the reducing agent, developed by Beller and co-workers.[51] Milder reducing agents in the form of silanes were, therefore, considered due to the known chemoselective reduction of phosphine oxides they exhibit.[52] O'Brien also exploited a phospholene oxide **105** since the ring-strain inherent in phospholene oxides (C-P-C bond angle = *c.* 90 °) means that the reduction to the phospholene proceeds more readily than in acyclic alternatives (triphenylphosphine oxide C-P-C bond angle = 106 °).[53,54]



Equation 1.31 *– the initial catalytic Wittig reaction by O'Brien, at 100 °C.*[48]

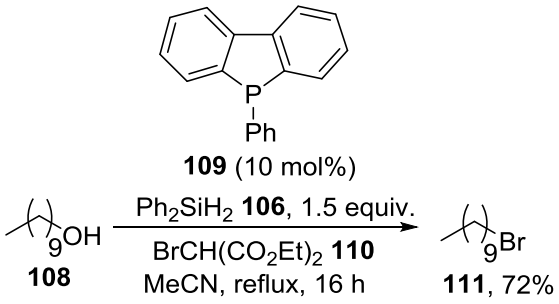
The milder silane reducing agents proved successful in achieving chemoselective reduction of phosphine oxide precatalyst, and when initially used in the presence of base with aldehyde and bromide substrates, a catalytic Wittig reaction was achieved in 24 h at 100 °C in toluene (Equation 1.31).[48]

The initial catalytic Wittig reaction was conducted at temperatures of 100 °C but O'Brien was able to achieve his aim of producing a room-temperature catalytic Wittig reaction by building upon his initial work with further studies that showed very fast reduction of phosphine oxides in the presence of phenylsilane and a protic acid in the form of 4-nitrobenzoic acid, proceeding in 2 min at RT. The presence of 4-nitrobenzoic acid also served to help solubilise the phosphonium salt intermediate in the greener (based on its environmental impact and toxicity)[55] EtOAc solvent at room temperature (shown in Equation 1.29).

O'Brien's work on the catalytic Wittig reaction was applied to examples of both stabilised and non-stabilised ylides and represented a large step forwards in phosphorus catalysis.[56]

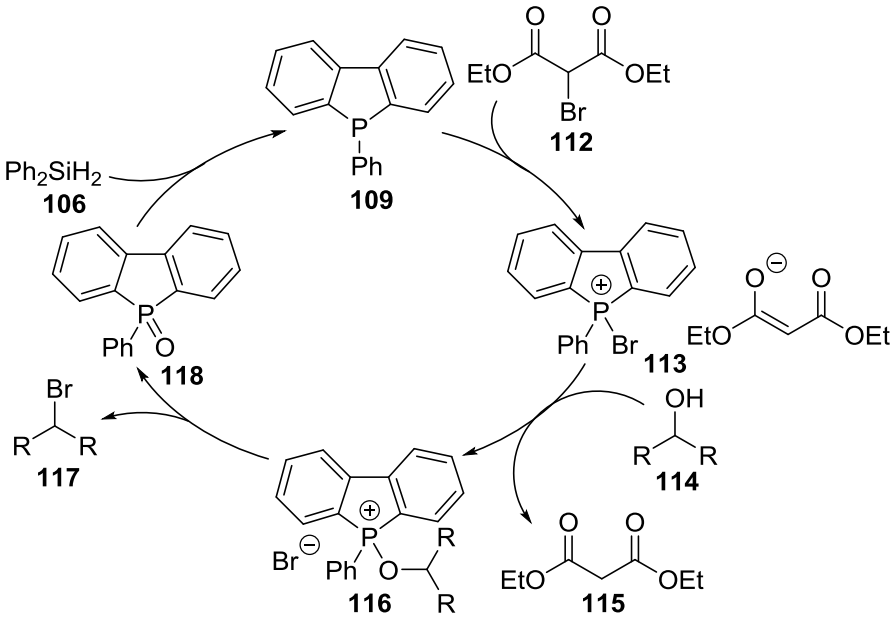
Another impressive body of redox-driven phosphorus-catalysed work is that by Rutjes and co-workers with the development of catalytic adaptations of both the Appel and Staudinger reactions,[57,58] and a procedure that uses an initial Staudinger reaction in

order to conduct an aza-Wittig reaction.[59] Also developed was a phosphorus-catalysed amidation reaction.[60]



Equation 1.32 *– phosphorus-catalysed Appel reaction by Rutjes and co-workers.*[57]

The catalytic Appel reaction developed by Rutjes and co-workers works by again making use of a strained phosphine in the form of catalyst **109**, which again allows a mild silane reductant to be used to achieve catalyst turnover (Equation 1.32).[57]

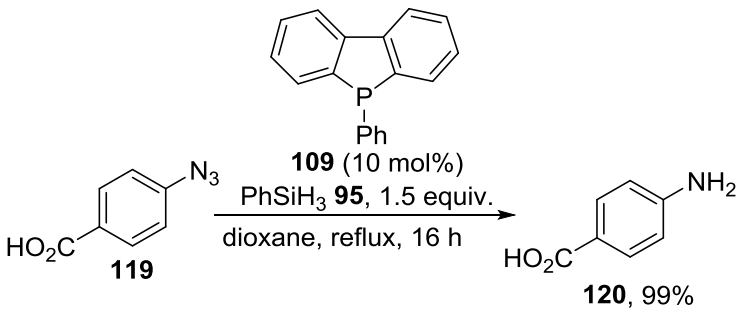


Scheme 1.33 *– catalytic cycle of Rutjes' catalytic Appel reaction.*

The reaction works by forming reactive bromophosphonium salt **113** through reaction of phosphine catalyst **109** with bromine source **112**. The bromophosphonium salt then reacts with alcohol substrate **114** to form the alkoxyphosphonium salt intermediate **116**, which then undergoes an Arbuzov reaction to give bromine product and phosphine oxide by-product. Catalyst turnover is then achieved by use of diphenylsilane reductant to reduce the susceptible phosphine oxide double bond (Scheme 1.33).

It is worth noting that the Appel reaction is a nucleophilic substitution reaction on an activated hydroxyl group and as such is a similar reaction to the Mitsunobu reaction, proceeding through a comparable alkoxyphosphonium salt intermediate (**116**).

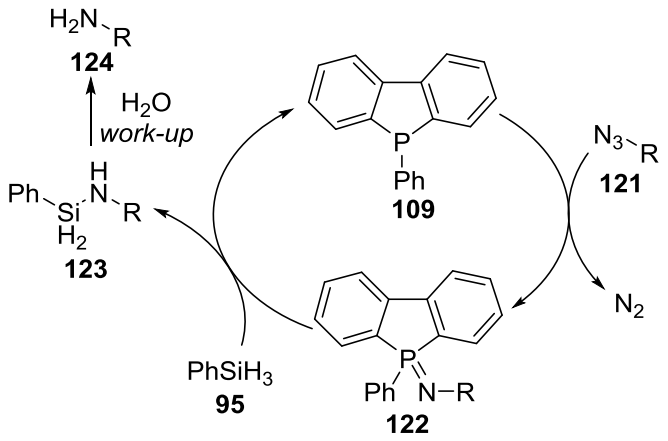
The limitations of the reaction are, first, the high temperature required to reduce the phosphine oxide and achieve catalyst turnover. Another drawback is that, although the reaction gives good yields for deoxybromination of primary alcohols, reactions with some of the secondary alcohols exhibit severely reduced yields or fail to provide product. There are also no examples of products showing inversion of stereochemistry, which is a key attribute of the conventional stoichiometric Appel reaction.



Equation 1.34 *– phosphorus-catalysed Staudinger reduction by Rutjes and co-workers.*[58]

Further work by Rutjes and co-workers provided a phosphorus-catalysed Staudinger reduction of azides (Equation 1.34).[58] This reaction builds on the earlier

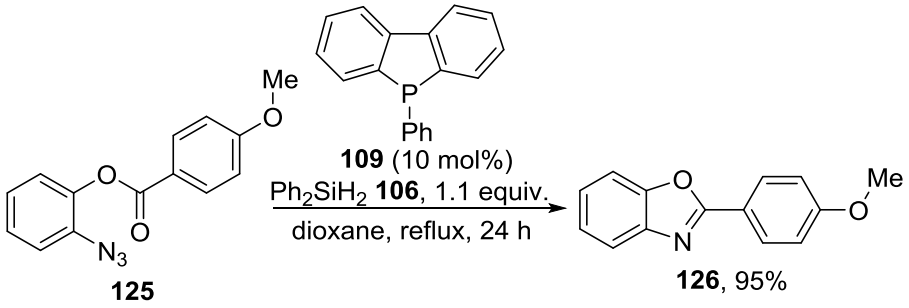
catalytic Appel reaction work conducted by Rutjes and expands to include the first example of a phosphorus-catalysed Staudinger reduction.



Scheme 1.35 *– catalytic cycle of Rutjes' Staudinger reduction.*

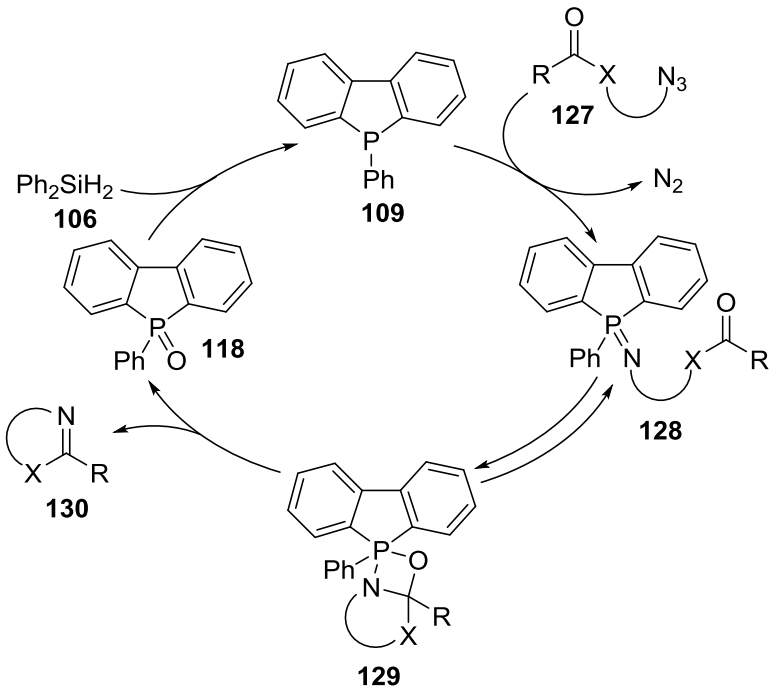
Usually, a Staudinger reduction proceeds by firstly forming the iminophosphorane **122**, followed by the reaction of **122** with water to yield amine product and phosphine oxide by-product. To approach the catalytic Staudinger reaction in a reductive manifold would require the presence of water in the reaction mixture in order to produce the phosphine oxide from the iminophosphorane intermediate. This approach would not be feasible as water would quench the silane reductant and would make catalyst turnover impossible. Instead, Rutjes and co-workers noted that it was possible to reduce the iminophosphorane **122** to give silylamine **123** and regenerate phosphine catalyst **109** (Scheme 1.35). Silylamine **123** can then be hydrolysed upon work-up to give amine product **124**, removing the need for water in the reaction mixture and bypassing the need for phosphine oxide reduction

The catalytic Staudinger reduction proceeds in good to excellent yields but still requires an elevated reaction temperature relative to classic Staudinger conditions.



Equation 1.36 *– phosphorus-catalysed Staudinger/aza-Wittig sequence by Rutjes and co-workers.*[59]

A further expansion by Rutjes and co-workers on the catalytic Staudinger reduction work was to incorporate the iminophosphorane intermediate into an aza-Wittig reaction, thus producing a catalytic Staudinger/aza-Wittig sequence (Equation 1.36).[59]

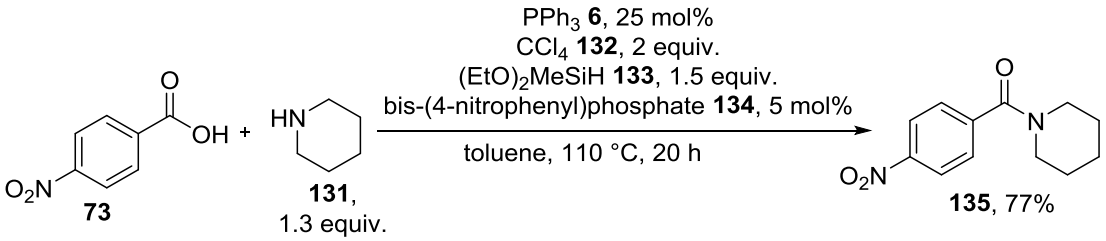


Scheme 1.37 *– catalytic cycle of the Staudinger/aza-Wittig sequence by Rutjes.*

The reaction progresses by first undergoing a Staudinger reaction to produce iminophosphorane intermediate **128** (Scheme 1.37). Silane is present in the reaction

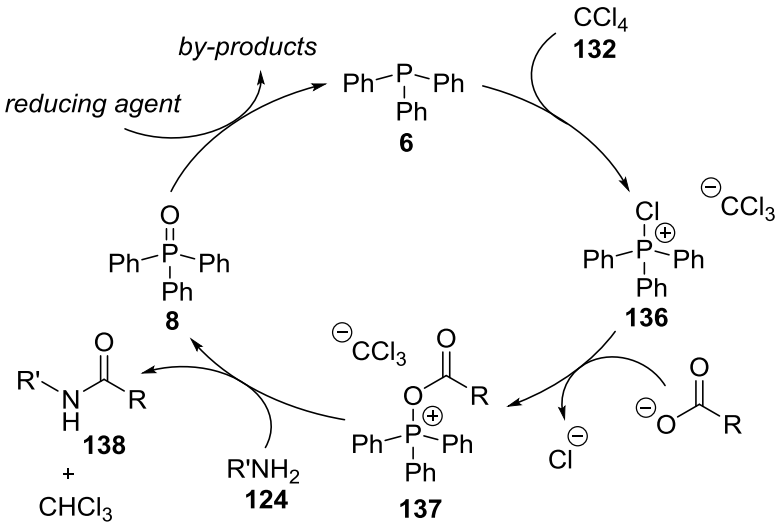
mixture in order to facilitate catalyst turnover and so the iminophosphorane is vulnerable to the same reduction reaction that the previously developed catalytic Staudinger process relied upon. However due to the presence of a carbonyl moiety (ester or ketone examples are given in the publication) tethered to the azide substrate an intramolecular aza-Wittig reaction can occur to give a cyclic imine product before reduction to the silylamine can occur; in this work benzoxazole and benzodiazepine products are produced. The aza-Wittig reaction results in the production of phosphine oxide by-product, which can then be turned over to regenerate the phosphine catalyst, completing the catalytic cycle.

The catalytic Staudinger/aza-Wittig sequence represents an impressive balance of reactivity in order to complete the reaction whilst demonstrating catalysis but has its drawbacks: the scope of the reaction is severely limited, with only benzoxazole and benzodiazepine products, largely due to the requirement of the use of intramolecular substrates to allow reactivity without the risk of the silane reductant reducing the iminophosphorane to the silylamine as demonstrated in the previous catalytic Staudinger work. This work is impressive but the limitations of substrate scope mean that it could only be useful in very particular cases.



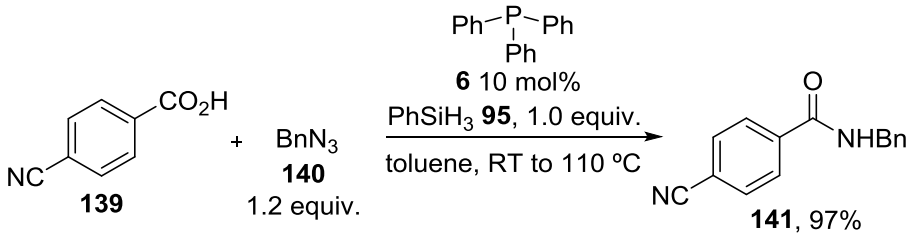
Equation 1.38 *– phosphorus-catalysed amidation reaction by Rutjes and co-workers.*[60]

A further example of phosphorus catalysis developed by Rutjes and co-workers is a triphenylphosphine catalysed amidation reaction (Equation 1.38).[60]



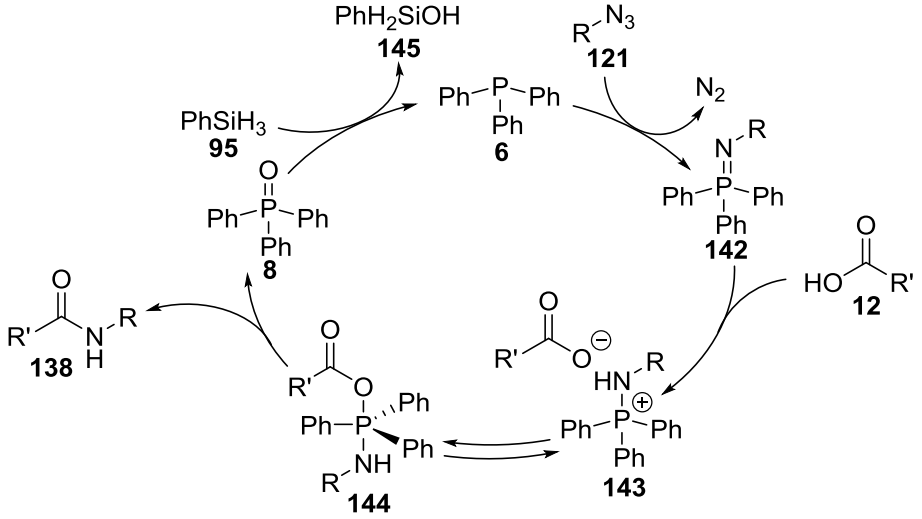
Scheme 1.39 *– catalytic cycle of Rutjes' amidation reaction.*

The amidation reaction works by, firstly, forming a chlorophosphonium salt intermediate from reaction of triphenylphosphine with carbon tetrachloride which is quickly converted to an acylphosphonium salt, in a similar manner to Rutjes' Appel reaction, through reaction with a carboxylate (Scheme 1.39). The acylphosphonium **137** provides an activated ester for nucleophilic attack by amine **124**, giving amide product and producing triphenylphosphine oxide by-product. The phosphorus (V) by-product is then turned over to phosphine catalyst *in situ* by a silane reducing agent in the same manner as previous work by Rutjes and co-workers. The use of a high equivalency of CCl_4 coupled with the high temperatures required for this reaction and the need for a stoichiometric amount of reducing agent mean that this reaction is not without drawbacks. However it provides another example of phosphorus-mediated deoxy-coupling catalytic chemistry.



Equation 1.40 *– phosphorus-catalysed Staudinger ligation by Ashfeld and co-workers.*[61]

In another recent study Ashfeld and co-workers reported a Staudinger amidation between an azide and a carboxylic acid (Equation 1.40).[61] This work adopts a similar approach to the catalytic Staudinger/aza-Wittig reaction developed by Rutjes and co-workers to trap the Staudinger intermediate through further reactivity, thus avoiding the use of water in the presence of sensitive silane reductants.



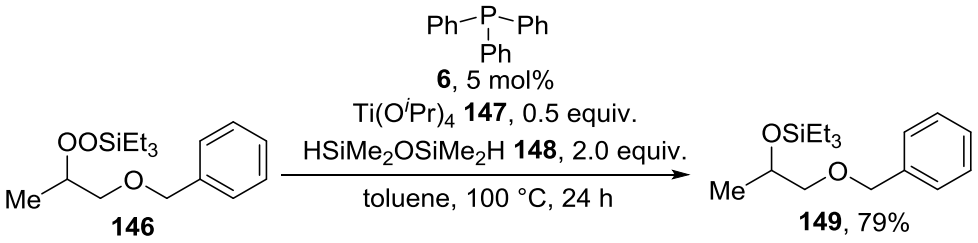
Scheme 1.41 *– catalytic cycle of Ashfeld's Staudinger ligation.*

The reaction begins with a typical Staudinger reaction between the phosphine catalyst and an azide substrate to produce an iminophosphorane intermediate (Scheme 1.41). The iminophosphorane will then deprotonate the carboxylic acid substrate leading to the formation of the phosphonium carboxylate salt intermediate **143**. It was proposed

that reversible ligand exchange at phosphorus can then occur to give reactive phosphorane **144**, which can then undergo an acyl substitution reaction to give amide product, along with the elimination of phosphine oxide by-product. Phosphine oxide reduction through the use of *in situ* silane reductant can then occur to achieve phosphine catalyst turnover.

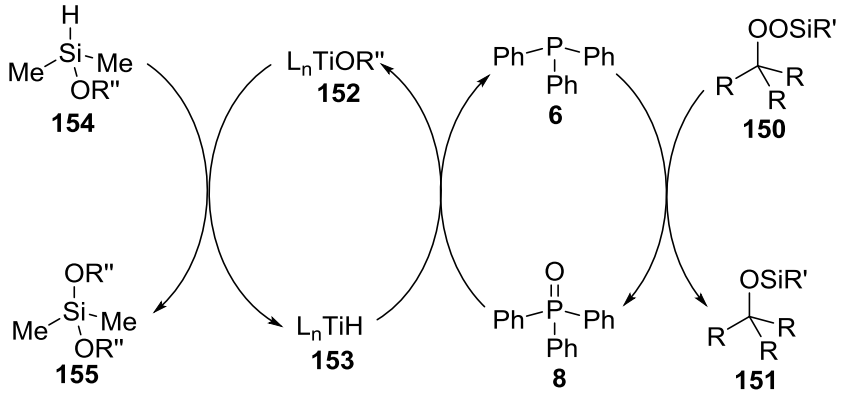
It is worth noting that triphenylphosphine is employed as the catalyst in Ashfeld's reaction, having been deemed not reactive enough with regards to the reduction reaction by both O'Brien and Rutjes in their work. The reason for this is that the iminophosphorane intermediate is very vulnerable to silane reduction. This reduction didn't present a problem in the Staudinger work by Rutjes, giving the desired amine product in the initial Staudinger reduction reaction and quickly reacting intramolecularly in the Staudinger/aza-Wittig reaction. The intermolecular Staudinger ligation presents an independent iminophosphorane that is required to avoid reduction in the presence of silane reducing agent; Ashfeld and co-workers employed triphenylphosphine (with the iminophosphorane formed from triphenylphosphine being less reactive to reduction than the cyclic phosphine equivalents used by Rutjes) in order to restrict the reduction of the required iminophosphorane intermediate and allow it to undergo the desired reaction with the carboxylic acid substrate to give amide product. The slow reduction of triphenylphosphine oxide to achieve catalyst turnover was accepted in order to protect the iminophosphorane intermediate from unwanted reduction.

The Staudinger ligation reaction proceeds in high yields with both intramolecular and intermolecular substrates and represents a useful example of phosphorus catalysis in the reductive manifold.



Equation 1.42 *– phosphorus-catalysed alkyl silyl peroxide reduction by Woerpel and co-workers.*[62]

A final example of redox-driven phosphorus catalysed chemistry is that by Woerpel and co-workers who use triphenylphosphine to reduce alkyl silyl peroxides to the corresponding silyl ethers with retention of stereochemistry (Equation 1.42).[62]



Scheme 1.43 *– catalytic cycle of Woerpel's alkyl silyl peroxide reduction.*

The reaction involves triphenylphosphine-mediated reduction of the alkyl silyl peroxide (Scheme 1.43). This results in the production of the desired silyl ether and triphenylphosphine oxide by-product. A titanium hydride/siloxane system is then employed to achieve reduction of the phosphine oxide alone and regenerate the phosphine catalyst. The titanium hydride/siloxane system was proven by Woerpel and co-workers to be unreactive with regards to the peroxide substrate so the peroxide reduction was determined to occur by a phosphorus-mediated route. This alkyl silyl peroxide reduction represents a catalytic mild method of peroxide reduction.

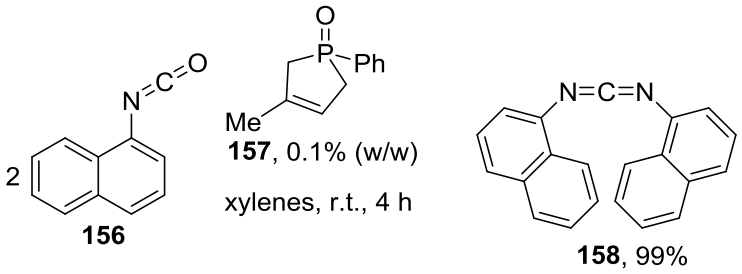
The aforementioned redox-driven phosphorus-catalysed reactions represent a step forwards in reducing the amount of phosphorus used in these processes, thus reducing the amount of phosphorus (V) waste and facilitating purification of the desired products. They also provide a knowledge base for the continual development of the field of phosphorus catalysis. However, the redox-driven processes are not without drawbacks; all of the redox-driven catalysis reactions require a stoichiometric silicon-based terminal reductant, which results in the generation of large amounts of silicon waste. The processes are academically progressive but practically essentially replace stoichiometric amounts of phosphorus waste with reduced phosphorus waste and stoichiometric amounts of silicon waste.

A better, alternative approach to redox-driven phosphorus catalysis would be to operate a redox-neutral method of phosphorus catalysis, with the active phosphorus catalyst directly turned over without a change in oxidation state. A redox-neutral approach would eliminate the presence of silicon-based reductants (which can cause reaction complications such as the need for a less-reactive phosphine in Ashfeld's catalytic Staudinger ligation) and the associated silicon-based waste while still reducing the amount of phosphorus used, and thereby the associated waste, to sub-stoichiometric amounts.

1.3.3 – Redox-neutral phosphorus catalysis

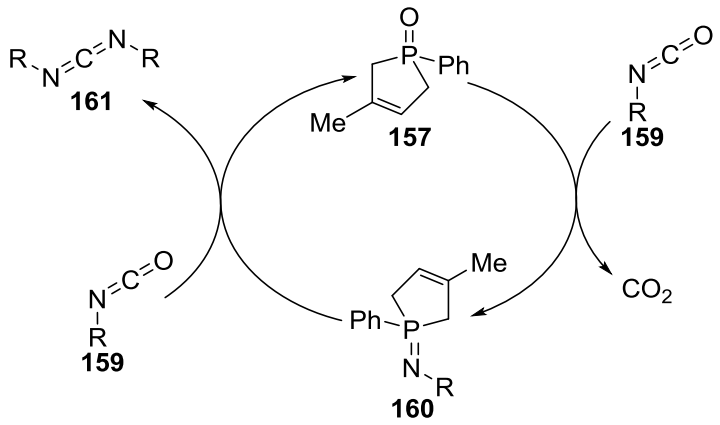
Redox-neutral catalysis involves an active phosphorus (V) catalyst that can be regenerated through direct turnover of the phosphine oxide by-product through use of an activating reagent. This approach, which maintains the phosphorus (V) oxidation state throughout the catalytic cycle, avoids the stoichiometric reductants present in redox-driven catalysis and so lacks the associated waste products. The activating reagent

that is used to achieve catalyst turnover depends on the nature of the active phosphorus (V) species and is specific to each reaction.



Equation 1.44 *– redox-neutral phosphorus-catalysed polymerisation of diisocyanates by Campbell and co-workers.*[63,64]

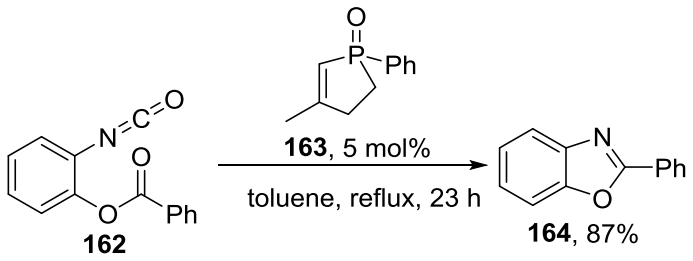
Catalytic phosphorus chemistry of this type was worked on as early as 1962 by Campbell and co-workers who used phosphine oxide catalyst **157** to polymerise diisocyanates to form a linear polymer (Scheme 1.44).[63,64]



Scheme 1.45 *– catalytic cycle of Campbell's formation of carbodiimides from isocyanates.*

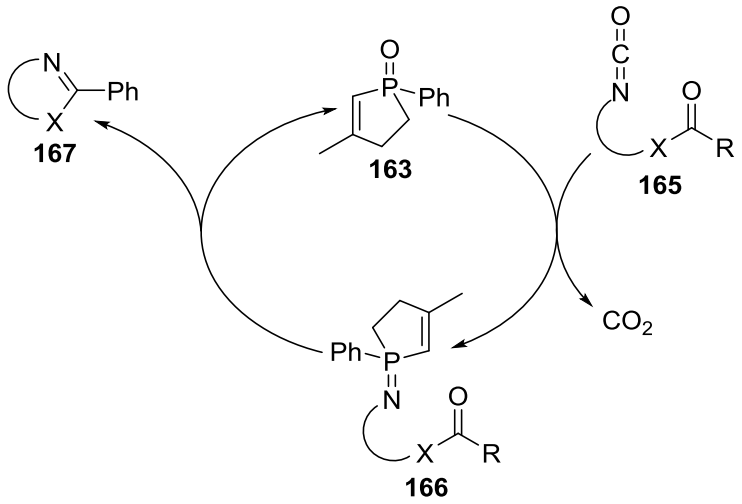
Campbell's catalytic cycle began with the formation of iminophosphorane **160** from reaction of isocyanate **159** with phospholene oxide catalyst **157** (Scheme 1.45). Catalyst could then react with another equivalent of isocyanate **159** to form the carbodiimide product **161**, whilst regenerating catalyst **157**. Due to this reaction

consisting of the coupling of two isocyanates, it can only be used for the coupling of two identical substrates to avoid multiple combination products. This work was later supplemented by Aksnes and Frøyen who achieved similar couplings using a triphenylphosphine oxide catalyst.[65]



Equation 1.46 *– redox-neutral phosphorus-catalysed aza-Wittig reaction by Marsden and co-workers.*[66]

The work conducted by Campbell and co-workers, and Aksnes and Frøyen, was built upon by Marsden and co-workers who used a phospholene oxide catalyst to convert an isocyanate with a pendant carbonyl group into a cyclic imine product (Equation 1.46).[66]



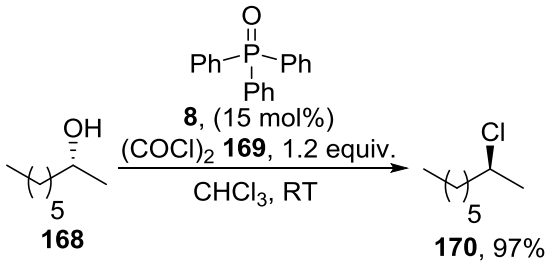
Scheme 1.47 *– catalytic cycle of Marsden's catalytic aza-Wittig reaction.*

Marsden's catalytic cycle starts with the reaction of phosphine oxide catalyst **163** with the isocyanate substrate to form iminophosphorane intermediate **166**, with loss of

carbon dioxide (Scheme 1.47). The iminophosphorane then undergoes an intramolecular aza-Wittig reaction with the carbonyl to form the imine and regenerate phosphine oxide catalyst, achieving catalyst turnover.

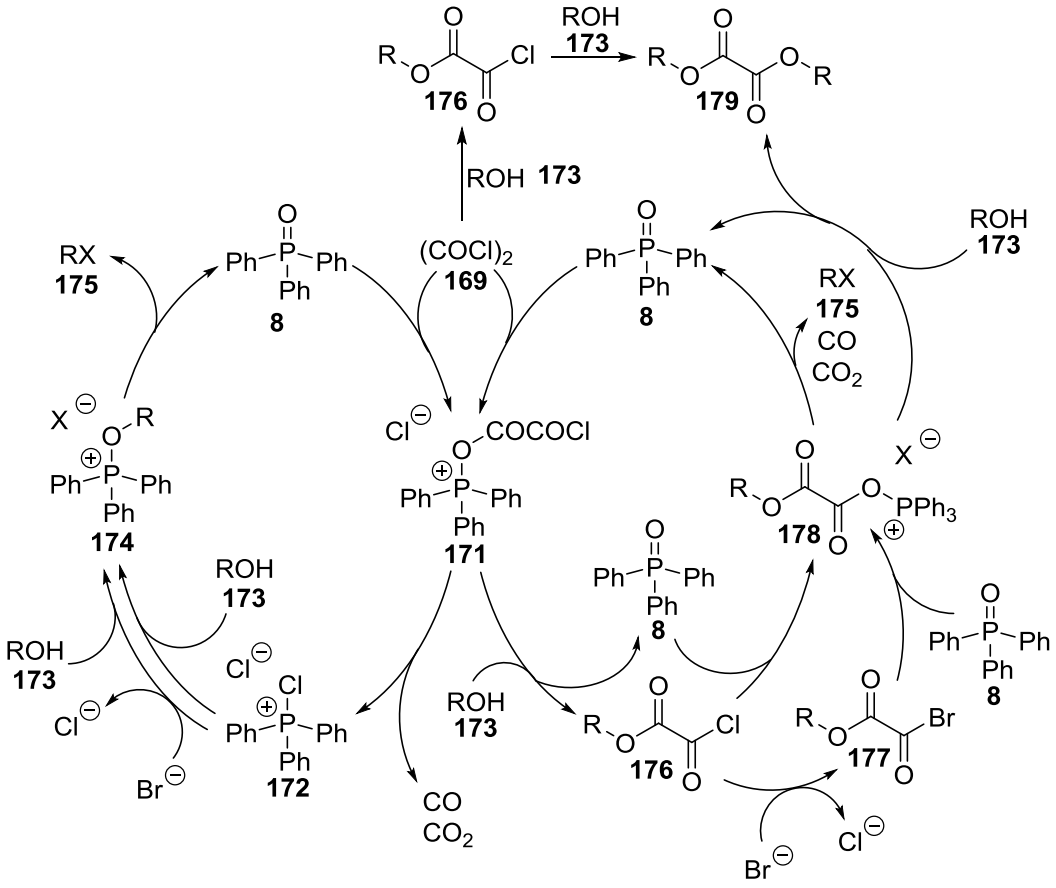
The reaction presents a useful method of synthesising benzoxazole and phenanthridine products in good to very good yields using a substoichiometric amount of phosphine oxide, thus greatly reducing the amount of phosphorus waste compared to that usually associated with an aza-Wittig protocol and producing carbon dioxide as the sole stoichiometric by-product.

The drawbacks of the catalytic aza-Wittig lie firstly in the scope of the reaction, with no intermolecular reactions having been reported and also, importantly, in the required use of isocyanate starting materials. Isocyanates are very electrophilic and so limit the use of nucleophile-containing substrates in the reaction. The synthesis of isocyanates requires either the treatment of amines with phosgene or, as in this work, the formation of acyl azides from carboxylic acids which are then refluxed in toluene to produce the isocyanate. The use of harsh conditions and reagents involved in the production of the required isocyanate starting materials detracts from the usefulness of the work and subsequent examples of phosphorus-catalysed aza-Wittig reactions have been developed from easily produced organic azide starting materials (work by Rutjes, mentioned previously and shown in Equation 1.36). That said, the work by Marsden and co-workers on this catalytic aza-Wittig reaction marks an important advancement in the field of phosphorus catalysis as it was the first demonstration of redox-neutral phosphorus catalysis and was the *first example of a catalytic variant of a classical P (V) process*. As such, the reaction possesses none of the associated waste from the stoichiometric reductants in redox-driven phosphorus catalysis, producing only carbon dioxide as stoichiometric waste.



Equation 1.48 *– redox-neutral phosphorus-catalysed Appel reaction by Denton and co-workers.*[67,68]

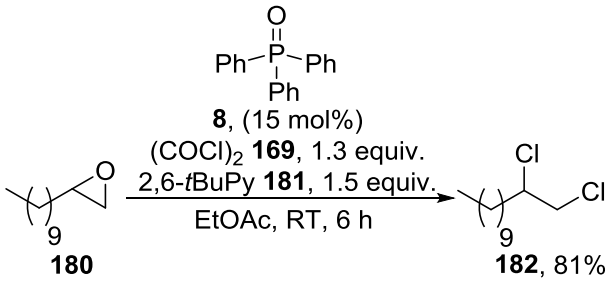
Work was conducted by Denton and co-workers towards developing redox-neutral phosphorus-catalysed Appel chlorination and bromination reactions using a triphenylphosphine oxide catalyst, with oxalyl chloride used to achieve direct turnover to an active phosphorus (V) species (Equation 1.48).[67,68]



Scheme 1.49 *– complex catalytic cycles of Denton's catalytic Appel chlorination and bromination reactions.*

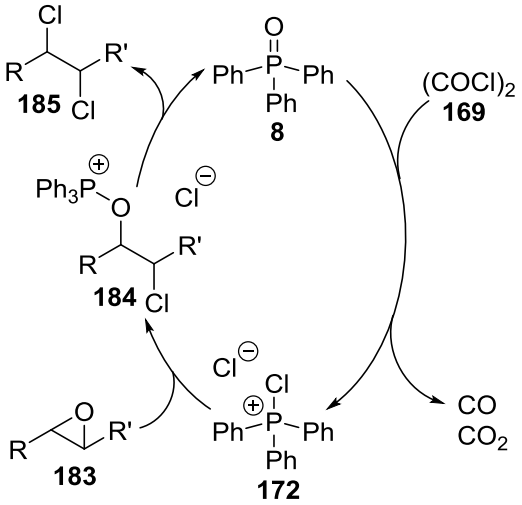
The combination of triphenylphosphine oxide, oxalyl chloride and alcohol substrate in the same reaction mixture results in a very complicated reaction mechanism (Scheme 1.49). Ideally, the reaction would consist of reaction between triphenylphosphine oxide and oxalyl chloride to give firstly salt **171**, which can then collapse with loss of carbon monoxide and carbon dioxide to give chlorophosphonium salt **172**. Reaction of phosphine oxides with oxalyl chloride has been known, but not widely used, since the 1970s.[69-71] Reaction of chlorophosphonium salt **172** with the alcohol substrate would then give HCl and alkoxyphosphonium salt **174** (a common intermediate for hydroxyl-activation for nucleophilic substitution as discussed throughout this work), which could then collapse *via* an Arbuzov mechanism to give halide with inversion of stereochemistry and regenerate triphenylphosphine oxide catalyst. Unfortunately, and as detailed in Scheme 1.49, the combination of the many different components required for this process results in a number of potential side-reactions, involving formation of alkyloxalyl chloride **176**, which may then react through different pathways to form dialkyl oxalate **179**, a terminal by-product. A careful balance of the different reaction components had to be achieved in order to ensure that the reaction proceeded by the desired pathway, and this was achieved by the use of two syringe pumps running in tandem in order to achieve the correct proportion of alcohol and oxalyl chloride reactants in the reaction mixture and allow the successful formation of alkyl chloride product.

The addition of LiBr as a bromide source allowed the same catalytic manifold, employing oxalyl chloride, to be used for the formation of alkyl bromides as well as alkyl chlorides. The chlorination and bromination reactions proceeded in good yields and, due to the direct turnover of triphenylphosphine catalyst upon formation of product, no additional reagents were required to complete the catalytic cycle, with oxalyl chloride being used as both the activating agent for phosphorus and the source of chloride.



Equation 1.50 *– redox-neutral phosphorus-catalysed Appel dichlorination of epoxides by Denton and co-workers.*[72]

Further work by Denton, using the same catalytic manifold, yielded a catalytic dichlorination reaction of epoxides (Equation 1.50).[72] This makes use of the same reactivity as the previously developed catalytic monochlorination reaction of alcohols, but incorporates both oxalyl chloride chlorine atoms into the product with formation of carbon monoxide and carbon dioxide gases, but no formation of HCl by-product as was seen in the catalytic monochlorination reaction.



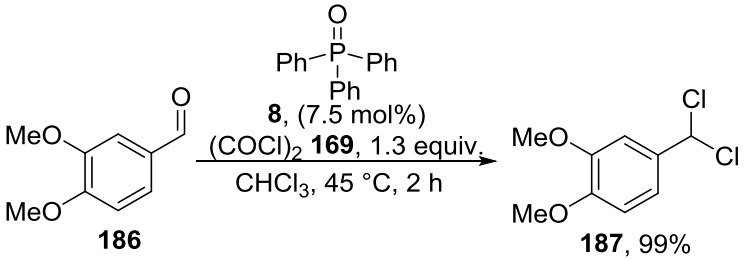
Scheme 1.51 *– catalytic cycle of Denton's catalytic Appel dichlorination of epoxides.*

The reaction proceeds to firstly form the familiar chlorophosphonium salt **172**, with which the epoxide reacts to give alkoxyphosphonium salt **184**, followed by Arbuzov

collapse of **184** to give 1,2-dichloride product **185** and regenerated triphenylphosphine oxide catalyst (Scheme 1.51).

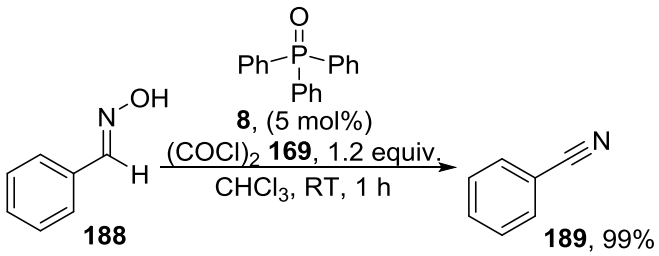
It was suspected that the epoxide substrate may react with oxalyl chloride and generate problems of the same sort observed in the catalytic monochlorination reaction, and the formation of oxalates *via* this process was indeed an observed background reaction, competitive with the desired dichlorination process. However, the yield of the dichloride product was improved by increasing the reaction time. The presence of base in the reaction mixture was used to neutralise any HCl that may be present in the oxalyl chloride and could lead to formation of a chlorohydrin by-product. It was found that, as expected, inversion of stereochemistry took place at both stereogenic centres of disubstituted epoxides, with *trans* isomers giving the *syn*-dichloride and *cis* isomers giving the *anti*-dichloride.

This dichlorination reaction represents an example of the usefulness and versatility of the triphenylphosphine oxide/oxalyl chloride catalytic chlorination conditions and provides a useful route of stereoselective chlorination from alkenes (*via* epoxides) which may be used as important building blocks for further synthesis or taken as important structural components in their own right (*e.g.* chlorosulfolipids).[73]



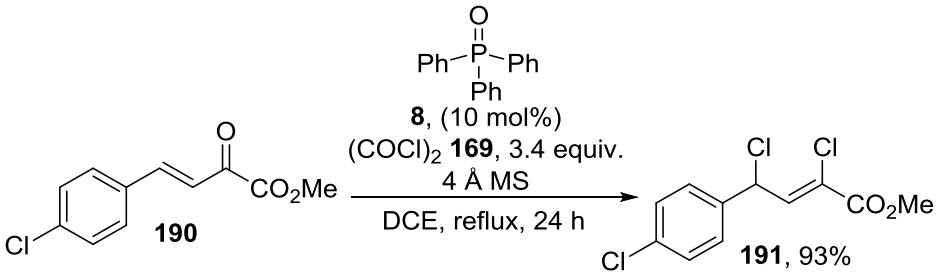
Equation 1.52 *– redox-neutral phosphorus-catalysed Appel geminal dichlorination of aldehydes by Denton and co-workers.*[74]

A further, similar, deoxydichlorination reaction using the triphenylphosphine oxide/oxalyl chloride catalytic Appel manifold is the catalytic geminal dichlorination of aldehydes (Equation 1.52).[74] The reaction proceeds through careful addition of oxalyl chloride to a solution of triphenylphosphine oxide catalyst and triphenylphosphine oxide, thereby producing the reactive chlorophosphonium salt while limiting the by-products formed through the unwanted reaction of aldehyde with oxalyl chloride. Excellent yields are obtained and this represents a useful method to access geminal dichlorides.



Equation 1.53 *– redox-neutral phosphorus-catalysed dehydration of oximes by Denton and co-workers.*[75]

Another reaction developed by Denton and co-workers using the triphenylphosphine oxide/oxalyl chloride catalyst manifold is the catalytic dehydration of oximes to give nitriles (Equation 1.53).[75] The reaction proceeds at room temperature in 1 h and delivers a variety of nitrile substrates in good to excellent yields. This reaction provides an example of how phosphorus (V) chemistry can effectively and catalytically promote dehydration reactions.



Equation 1.54 *– redox-neutral phosphorus-catalysed 1,3-dichlorination of unsaturated ketoesters by Xu and co-workers.*[76]

An additional example of the usefulness of the chlorophosphonium salt made from oxalyl chloride and a triphenylphosphine oxide catalyst is a 1,3-dichlorination reaction of unsaturated ketoesters by Xu and co-workers (Equation 1.54).[76] This reaction however, requires elevated temperatures with an increased equivalency of oxalyl chloride in order to be effective. Despite these operational drawbacks the reaction proceeds in generally very good yields.

The redox-neutral phosphorus-catalysed reactions developed by Marsden, Denton and Xu exhibit chemistry that has a distinct advantage over the redox-driven phosphorus-catalysed chemistry mentioned previously; the direct turnover of phosphine oxide catalyst means that there is a lack of any requirement for stoichiometric reducing agents to be used, thus resulting in the absence of the stoichiometric waste products associated with the reductive turnover process central to redox-driven phosphorus catalysis. The lack of waste products is evident in Marsden's aza-Wittig reaction where carbon monoxide and carbon dioxide are the sole by-products of the reaction, whereas the chlorophosphonium salt chemistry by Denton and Xu produces carbon monoxide and carbon dioxide along with waste associated with the chlorine source oxalyl chloride.

Reducing the waste and the materials used are two of the fundamental purposes of pursuing organocatalytic chemistry and, while the redox-driven catalysis highlighted

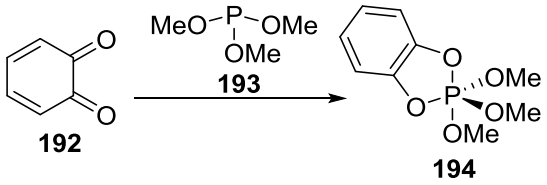
firstly is effective at reducing the phosphorus waste and thereby facilitating the purification involved with the highlighted processes, the reduction of phosphorus waste comes at the cost of increased amounts of silicon waste and (generally) elevated reaction temperatures. The redox-neutral catalysis provides a much cleaner operating template, with both reduced phosphorus waste and, due to the direct catalyst turnover, no further waste associated with catalyst regeneration.

Regarding work towards a phosphorus-catalysed Mitsunobu reaction, it would be much more preferable to operate in a redox-neutral manifold than a redox-driven alternative. If a way could be found of converting the phosphine oxide by-product of the Mitsunobu reaction into an active reagent through direct use of an activating agent, without reverting to phosphorus (III), this would conquer the main obstacle to a phosphorus-catalysed Mitsunobu reaction.

1.4 – Dioxyphosphoranes

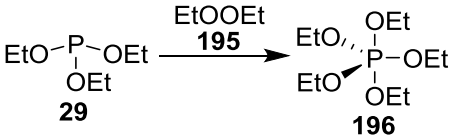
The principle requirement for a redox-neutral phosphorus-catalysed Mitsunobu reaction is a phosphorus (V) reagent that can conduct Mitsunobu chemistry, with the additional property of being producible from the equivalent phosphine oxide under reaction conditions.

There exists a phosphorus (V)-containing compound class that promotes Mitsunobu-type coupling reactions – namely oxyphosphoranes. Investigations into the synthesis and properties of oxyphosphoranes began in the 1960s with work into pentaalkoxyphosphoranes by Ramirez[77-87] and Denney.[88,89]

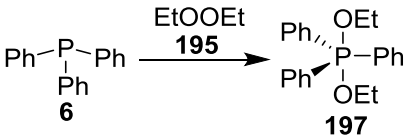


Equation 1.55 *– Ramirez's synthesis of a cyclic pentaoxyphosphorane by reaction of a phosphite ester and 1,2-benzoquinone.*[87]

Ramirez's interest in these pentaalkoxyphosphoranes derived firstly from their oxidative formation through reaction of quinones with phosphite esters (Equation 1.55), and later in ligand exchange at phosphorus to produce a greater range of pentaoxyphosphoranes and finally examination of their role in coupling reactions with ketones to produce dihydroxyketones.



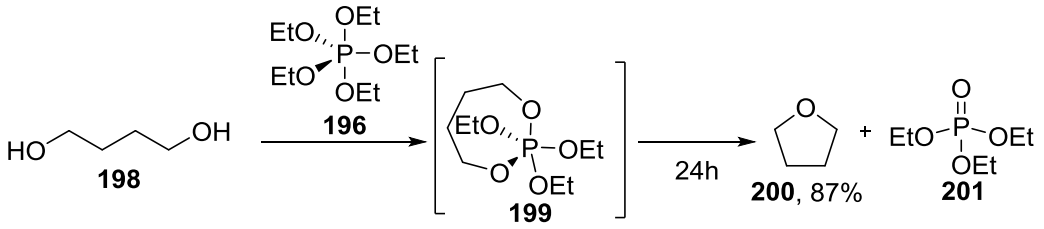
Equation 1.56 *– Denney's synthesis of pentaethoxyphosphorane by peroxide.*[88]



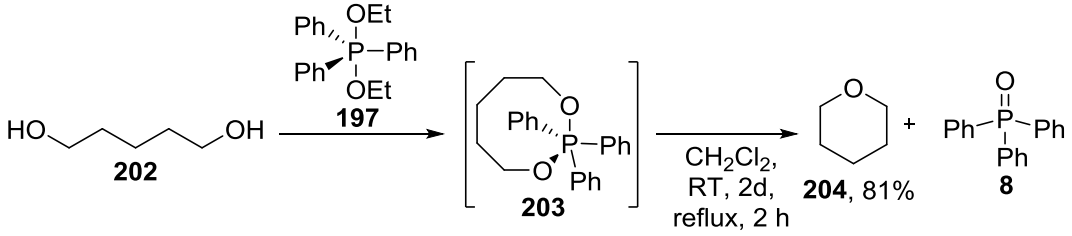
Equation 1.57 *– Denney's synthesis of diethoxytriphenylphosphorane by peroxide.*[90]

Denney's work initially focussed on the synthesis of pentaalkoxyphosphoranes through reaction of phosphite esters with peroxides and their basic chemistry (equilibria with phosphonium salts *etc.*) (Equation 1.56). Further work by Denney expanded into

dioxyphosphoranes produced by reaction of phosphines with peroxides (Equation 1.57).[90-92]

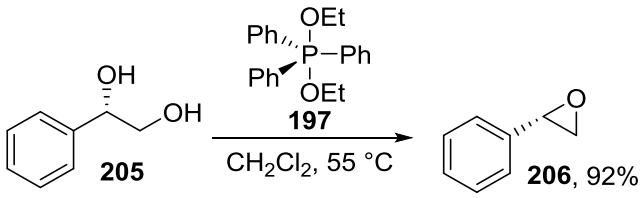


Scheme 1.58 *– Denney's pentaoxyphosphorane mediated cyclisation of 1,4-butanediol to THF.*[93]

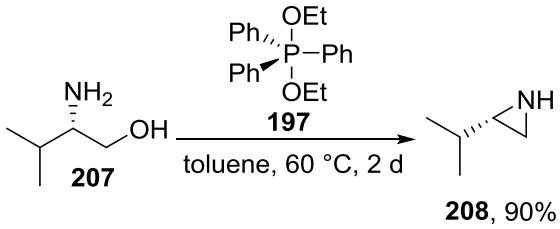


Scheme 1.59 *– Denney's dioxyphosphorane mediated cyclisation of 1,5-pentanediol to tetrahydropyran.*[93]

It was found that upon treatment of diols with both pentaoxyphosphoranes (Scheme 1.58)[94,95] and dioxyphosphoranes (Scheme 1.59)[93] that ligand exchange at phosphorus could occur to give cyclic oxyphosphoranes, which could then react further to give cyclic ether products with phosphate ester or phosphine oxide by-product respectively. This early work by Denney shows the potential of oxyphosphoranes towards promoting dehydration reactions.



Equation 1.60 *– a DTPP mediated epoxidation reaction by Evans and co-workers.*[96]

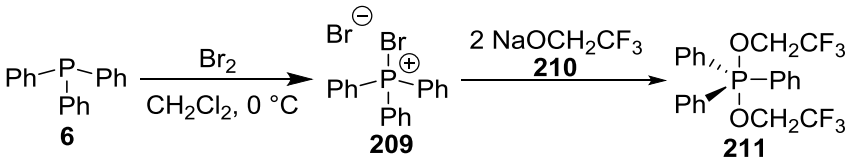


Equation 1.61 *– an example of the broadened reaction scope achieved by Evans and co-workers; an aziridination using DTPP.*[97]

Further work in the 1980s by Evans Jr. and co-workers expanded upon the preliminary reactivity of diethoxytriphenylphosphorane (DTPP) observed by Denney by further investigating its reactivity in coupling reactions (Equation 1.60).[98] It was found that DTPP could undergo the ligand exchange chemistry reported by Denney to form cyclic dioxyphosphoranes which would then undergo cyclodehydration reactions to form cyclic ether products.[96,99] DTPP could also promote the formation of nitrogen- and sulfur-containing heterocycles,[100-102] epoxides[103] and aziridines (Equation 1.61).[97] In the examples shown in Equations 1.54 and 1.55 stereochemistry can be seen to be retained at the secondary centre; this is due to the primary alcohol forming a more electrophilic species than would be formed by either the secondary alcohol (Equation 1.60) or the secondary amine (Equation 1.61). The activated primary alcohol will then react with the secondary alcohol or amine respectively to give product with retention of stereochemistry at the secondary centre in both cases.

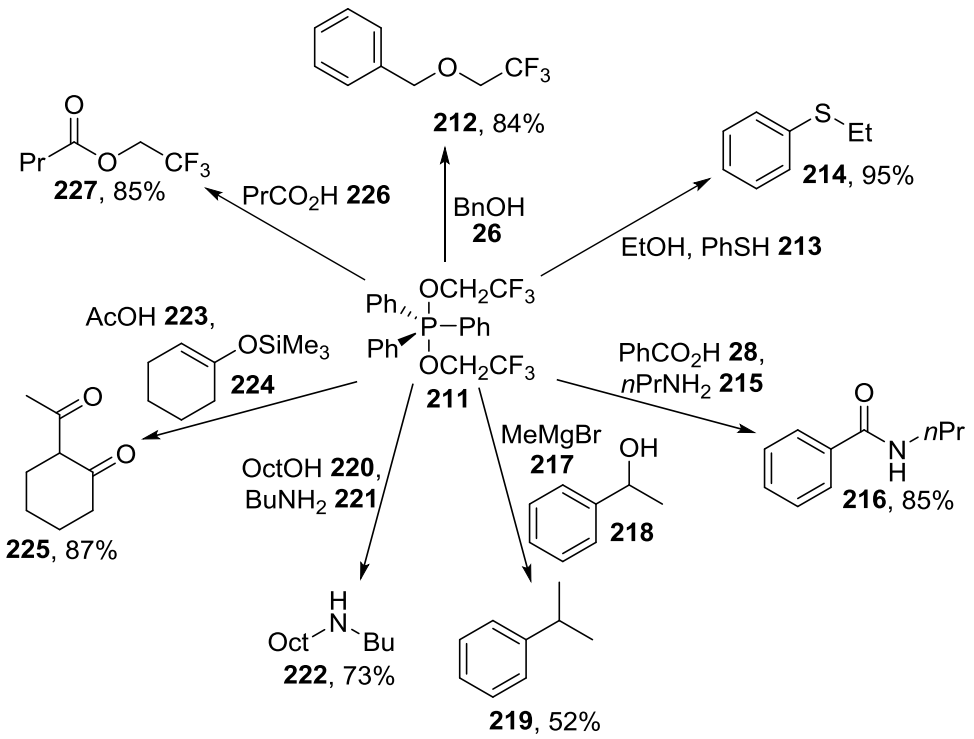
As shown previously in Scheme 1.4, dioxyphosphoranes are an intermediate species in the Mitsunobu reaction, and investigations were also conducted into the mechanistic role of dioxyphosphoranes in the Mitsunobu reaction, with a similar phosphorane in the form of diacyloxyphosphorane synthesised from triphenylphosphine and benzoyl peroxide.[104,105] Reaction of this diacyloxyphosphorane with alcohol gave the expected Mitsunobu esterification product.

Importantly, detailed studies were also conducted that investigated the effect that the addition of Lewis acids had on reaction rate. It was found that upon addition of a Lewis acid in the form of $ZnCl_2$ to an epoxidation reaction an increase in rate of 3 orders of magnitude was observed, despite a significant drop in the reaction temperature.[106]



Scheme 1.62 *– synthesis of the Ishikawa phosphorane via bromophosphonium salt.*[107]

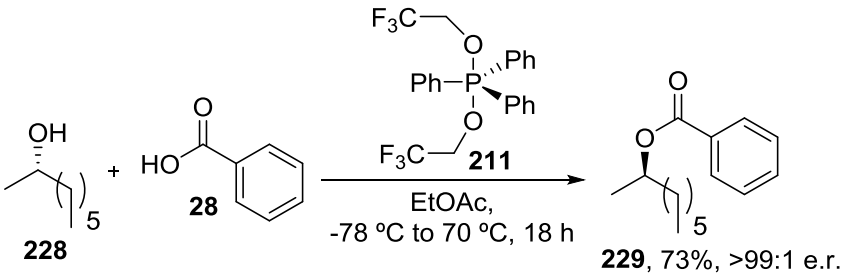
Work was conducted on a similar dialkoxyphosphorane by Ishikawa.[107-109] The Ishikawa phosphorane was synthesised from triphenylphosphine *via* the bromophosphonium salt through reaction with bromine and the appropriate fluorinated sodium alkoxide (Scheme 1.62).



Scheme 1.63 *– scope of the reactions mediated by the Ishikawa phosphorane.*[107]

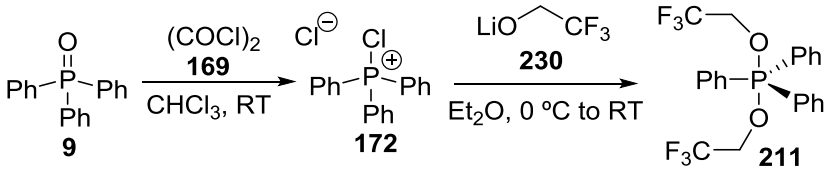
It was found that the Ishikawa phosphorane, bis(trifluoroethoxy)triphenylphosphorane, promoted a range of coupling reactions in generally good yields as shown in Scheme 1.63. The range of deoxy-coupling reactions exhibited by the Ishikawa phosphorane clearly shows the ability of dioxyphosphoranes to act as a phosphorus (V) alternative to the phosphine/diazo compound system of the traditional Mitsunobu reaction.

The reactivity towards deoxy-coupling reactions shown by oxyphosphoranes is encouraging as it represents an important prerequisite for a redox-neutral phosphorus-catalysed Mitsunobu reaction. A phosphorus (V) reagent that promoted Mitsunobu-type chemistry was required and oxyphosphoranes show promise for satisfying that demand. Due to the propensity of alkoxy-ligands to exchange in the presence of other alcohols (as seen in the ligand exchange shown in cyclisation reactions with oxyphosphoranes), and the greater amount of work that has been conducted on the study of dioxyphosphoranes compared to pentaoxyphosphoranes, it is sensible to focus on dioxyphosphoranes as potential phosphorus (V)-based active reagents for a catalytic Mitsunobu reaction. It should also be noted that the synthesis routes to dioxyphosphoranes employed by Denney, Evans Jr. and Ishikawa all start from phosphine, *i.e.* phosphorus (III), starting materials, either by using peroxides or through reaction with bromine to form a bromophosphonium salt intermediate. A new route to dioxyphosphoranes from a phosphorus (V) source, ideally a phosphine oxide, would be required for dioxyphosphoranes to be viable catalyst candidates.



Equation 1.64 *– esterification work by Denton and co-workers using the Ishikawa phosphorane.*[110]

Work was conducted by Denton and co-workers that further investigated the Ishikawa phosphorane with respect to esterification reactions, the most common use for Mitsunobu reactions (Equation 1.64).[110]



Scheme 1.65 *– formation of the Ishikawa phosphorane from a phosphorus (V) source by Denton.*

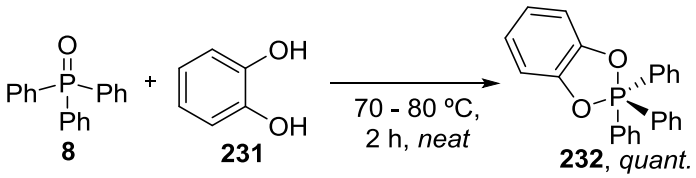
The first, important point highlighted by the esterification work by Denton and co-workers was that the esterification reactions conducted with enantioenriched, secondary alcohols gave ester products with inversion of stereochemistry (as proven by ^{31}P and ^{19}F data) suggesting an S_N2 reaction mechanism, rather than a nucleophilic acyl substitution, that proceeds through an alkoxyphosphonium salt intermediate (as seen in the traditional Mitsunobu reaction). Secondly, very importantly, the Ishikawa phosphorane is prepared by Denton and co-workers from triphenylphosphine oxide – a phosphorus (V) starting material (Scheme 1.65). The production of the Ishikawa phosphorane from a phosphorus (V) source is a very significant result as it displays a method of obtaining a dioxyphosphorane that can promote Mitsunobu chemistry in a

redox-neutral manner, thus making important progress towards a redox-neutral catalytic cycle. An active Mitsunobu reagent can be produced from the phosphine oxide waste by-product of the Mitsunobu reaction.

The redox-neutral method of producing the Ishikawa phosphorane described by Denton and co-workers does not, however, hold the answer to a catalytic Mitsunobu reaction; the requirement for oxalyl chloride and an alkoxide to be used to synthesise the Ishikawa phosphorane prevent this from being produced *in situ*. It does though show the promise of dioxyphosphorane compounds towards catalysing a Mitsunobu reaction. What is now required is a method of producing a dioxyphosphorane from a phosphine oxide *in situ*, without the use of incompatible reagents.

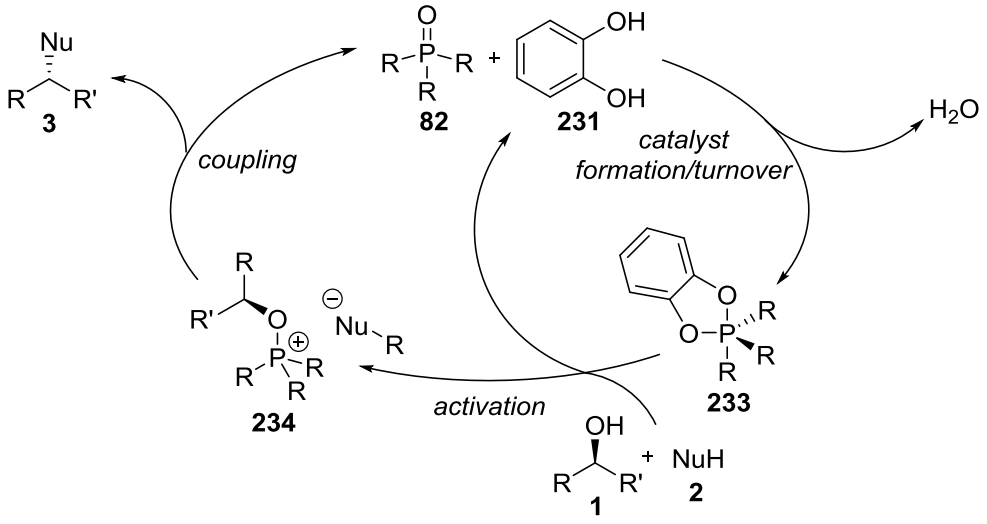
1.5 – Cyclic dioxyphosphoranes

Having established that dioxyphosphoranes (and in particular DTPP and the Ishikawa phosphorane) promote Mitsunobu coupling chemistry, and also that it is indeed possible to synthesise a reactive dioxyphosphorane from the phosphorus (V) phosphine oxide by-product of the coupling reaction, a suitable dioxyphosphorane must be identified that will promote Mitsunobu chemistry but that can also be produced *in situ* in order to allow a dioxyphosphorane catalyst to be recycled within the reaction.



Equation 1.66 *– Bidman's direct production of a cyclic dioxyphosphorane by neat reaction of catechol and triphenylphosphine oxide.*[111]

A method of producing cyclic dioxyphosphoranes has been reported by Bidman (Equation 1.66).[111] Heating triphenylphosphine oxide and catechol together without solvent yields a cyclic dioxyphosphorane. This reaction in principle represents a method to achieve turnover in a catalytic Mitsunobu reaction, should this particular dioxyphosphorane promote Mitsunobu reactivity in the same manner as the Ishikawa phosphorane.



Scheme 1.67 *– potential catalytic cycle based around triphenyl(catechol)phosphorane* ***233****.*

The potential catalytic cycle for a reaction based around the cyclic dioxyphosphorane produced by Bidman is shown in Scheme 1.67 and consists of three steps: firstly the catalyst formation step from phosphine oxide **82** and catechol **231** precatalysts to produce reactive dioxyphosphorane **233**; then the activation step in which alcohol substrate **1** and nucleophile **2** displace the catechol (regenerating one precatalyst) to give the familiar, reactive alkoxyphosphonium salt intermediate **234**; this is finally followed by the coupling step where an Arbuzov-type reaction occurs with alkoxyphosphonium salt **234** to give product **3** with inversion of stereochemistry and

regeneration of the phosphine oxide precatalyst. The phosphine oxide and catechol are then again available to turnover and reproduce the reactive dioxyphosphorane.

A catalytic cycle based on the work by Bidman as outlined above would be an extremely effective reaction, satisfying all of the desired attributes of a phosphorus-catalysed Mitsunobu reaction. The driving force of the reaction would be the formation and removal of water, rather than the formation of the strong P=O bond that drives the traditional Mitsunobu reaction. It would not require any explosive diazo compound to be used thus making the reaction safer and removing the hydrazine waste from the equation. The sub-stoichiometric amount of phosphorus catalyst used would reduce the phosphorus waste and facilitate the purification of reaction products as well as reducing the demand of mild nucleophilic substitution processes on available phosphorus stocks. There is no redox-active chemistry involved in catalyst turnover, as exhibited in much contemporary phosphorus catalysis, removing both the need for stoichiometric reducing agents and the resulting waste associated with them. The lack of reducing agents may also lead to the reaction tolerating a greater range of reaction substrates that may not have been compatible with reducing agents. And finally the direct reaction between catechol and phosphine oxide means that no promoting reagents need to be added to achieve catalyst turnover, further reducing the waste and making the reaction conditions milder, again potentially leading to the tolerance of a greater substrate scope.

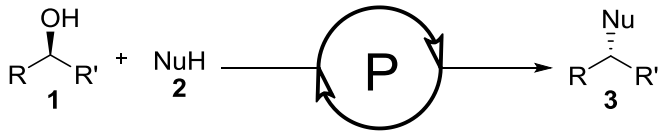
With the difficult catalyst turnover step of the catalytic cycle addressed by the solvent-free reaction of triphenylphosphine oxide and catechol reported by Bidman, it remained to determine whether catecholphosphoranes of this type are able to react to promote Mitsunobu-type chemistry. This would provide a working catalytic cycle and this is where investigations began.

2 – Project aim

This project aimed to develop a redox-free, phosphorus-mediated catalytic method for hydroxyl activation and substitution to be used as an alternative to the current state-of-the-art – the triphenylphosphine oxide/diethyl azodicarboxylate conditions of the Mitsunobu reaction. The design of the newly developed reaction was to focus around a phosphorus catalyst and seek to avoid the use of explosive diazo reagents and the generation of large amounts of hydrazine and phosphine oxide waste.

Work began with investigations into the suitability of a dioxyphosphorane reported by Bidman towards promoting a reaction of the sort described above. Attempts were to be made to synthesise several Bidman-type phosphoranes in order to develop a small portfolio of potential catalyst candidates and to gauge the difference in reactivity of phosphoranes of this structure depending on the substituents at phosphorus.

Once a viable catalytic manifold was developed, the scope of the reaction was to be explored by testing the effectiveness of the catalytic system on traditional Mitsunobu substrates.

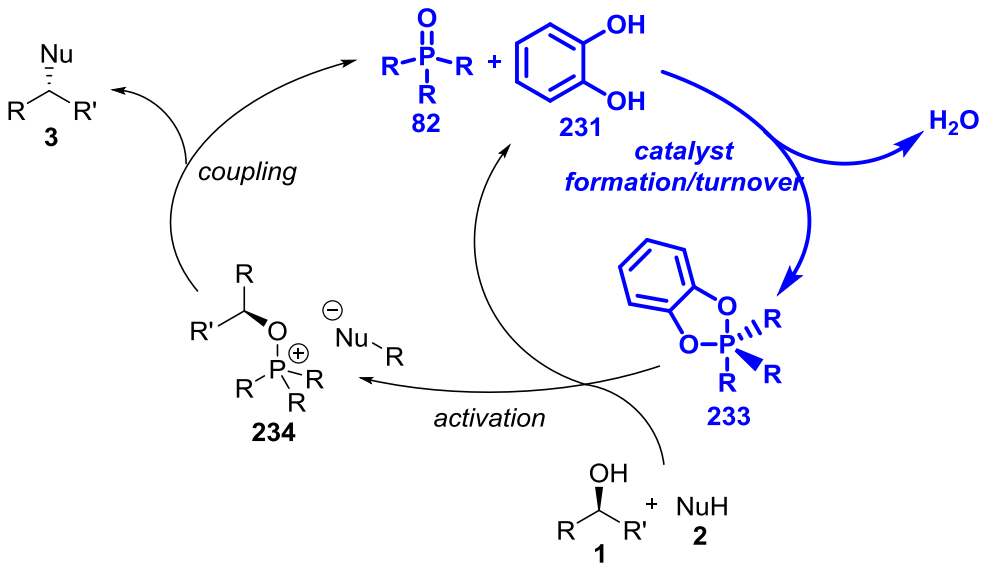


Scheme 2.1 *– phosphorus-catalysed Mitsunobu reaction – the project aim.*

3 – Results and discussion

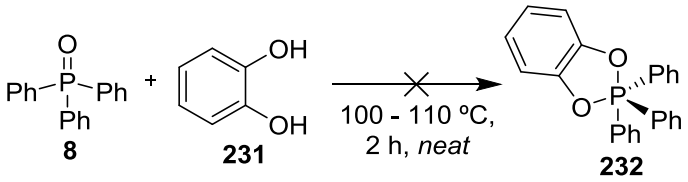
3.1 – Catecholphosphoranes

In order to fully examine the proposed catalytic system that is based around the triphenylphosphine oxide and catechol precatalysts it was first prudent to examine the range of catechol-phosphoranes that could be formed under the reaction conditions outlined by Bidman. Knowledge of a larger range of catechol-phosphoranes, and the ease at which they can be formed using Bidman's methodology, was desirable in order to allow reaction optimisation should catechol-phosphoranes prove useful compounds for catalysis. Once a small library of catechol-phosphoranes had been compiled investigations would proceed into the reactivity of these compounds regarding the formation of the important alkoxyphosphonium salt intermediate upon reaction with an alcohol substrate and a nucleophile in the activation step of the catalytic cycle.



Scheme 3.1 *– catalyst turnover step of the proposed catalytic cycle.*

As was outlined previously, the ability of dioxyphosphoranes to conduct a Mitsunobu coupling has been established with both DTPP and the Ishikawa phosphorane. The key to achieving successful phosphorus catalysis is the *in situ* formation of a reactive dioxyphosphorane from the phosphine oxide by-product. This catalyst formation/turnover step is crucial to the success of the catalytic reaction (Scheme 3.1).

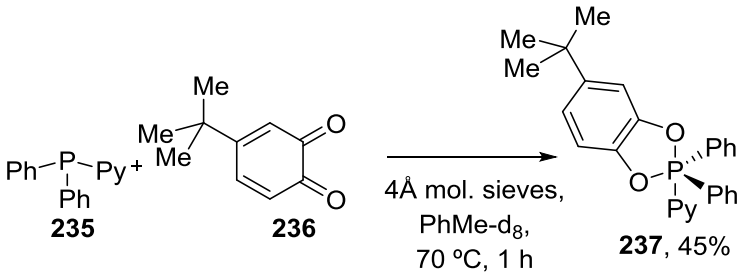


Equation 3.2 *– unsuccessful replication of Bidman's catechol-phosphorane synthesis method.*

However, it was found that no phosphorane product (expected in the ^{31}P NMR at $\delta = -18.9$ ppm) was observed upon replication of Bidman's methodology (Equation 3.2). The original work by Bidman did not provide NMR data to support the findings, rather stating the absence of absorption bands at 1190 cm^{-1} (P=O) and 3470 and 3350 cm^{-1} (OH) in the IR spectroscopy, with supporting elemental analysis data, as proof of production. The change in the IR spectroscopy could be explained by causes other than phosphorane formation and may be due to hydrogen bonding between the reagents rather than formation of the phosphorane.

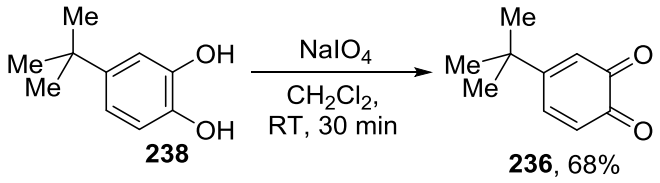
The apparent unreliability of Bidman's method for the formation of cyclic dioxyphosphoranes was disappointing, but work progressed onto examining other ways of accessing the catechol-phosphoranes as the compound class could still present the solution to developing catalysis if a method of *in situ* production could be developed.

3.1.1 – Quinone-based formation of catechol-phosphoranes



Equation 3.3 *– the quinone method of catechol-phosphorane synthesis.*

A known method of producing catechol-phosphoranes is by reacting phosphine with quinone. This method was used by Ramirez to produce pentaoxyphosphoranes.[87] This method of catechol-phosphorane formation was successfully performed to produce a compound with a ^{31}P NMR shift of −26.7 ppm, typical of dioxyphosphorane compounds (Equation 3.3).



Equation 3.4 *– synthesis of tert-butyl quinone* ***236****.*

The quinone could be easily produced from the equivalent catechol using sodium periodate (Equation 3.4).[112] It was observed that the catechol-phosphorane **237** decomposed to phosphine oxide (^{31}P NMR = 19.9 ppm) over 24 h due to hydrolysis by trace amounts of H_2O present in the reaction mixture. The hydrolysis of this compound shows susceptibility towards nucleophilic attack (by water in this case), exhibiting the reactivity that could be exploited to perform a Mitsunobu coupling.

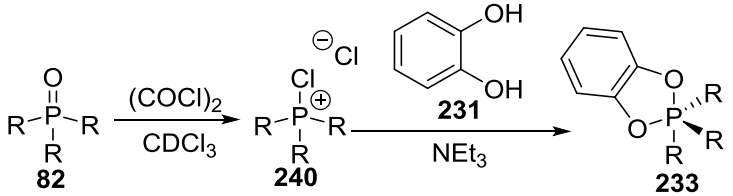
However, although the catechol-phosphoranes could be easily reached through use of a quinone, the use of these catechol-phosphoranes would give catechol and phosphine oxide as by-products (as shown in Scheme 3.1, coupling step). Practically it is not possible to use the quinone-based method of phosphorane production in a catalytic cycle; in order to produce the necessary materials for phosphorane catalyst regeneration (*i.e.* the phosphine and quinone) from the reaction by-products it would be required to have both reduction and oxidation occurring together *in situ*. Apart from being a very difficult, if not impossible, feat the presence of stoichiometric oxidants or reductants is undesirable and contradicts the core project aim of developing a *redox-free* catalytic Mitsunobu reaction.

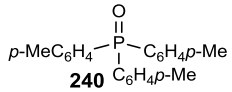
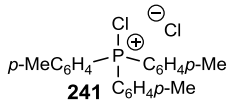
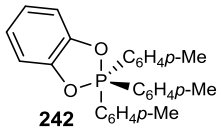
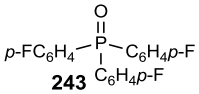
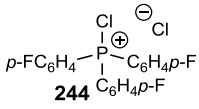
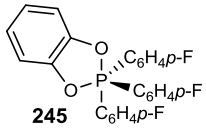
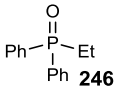
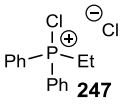
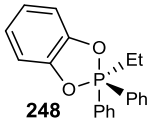
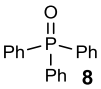
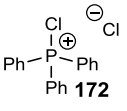
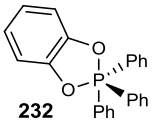
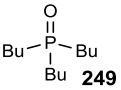
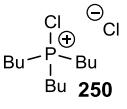
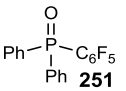
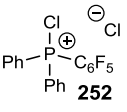
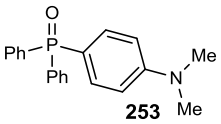
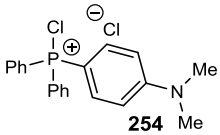
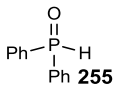
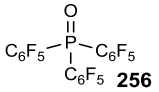
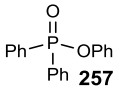
3.1.2 – Catechol-phosphoranes *via* a reactive intermediate

Other methods of forming catechol-phosphoranes were explored in the redox-free manifold, synthesising the phosphoranes from the catechol and phosphine oxide by-products of the proposed catalytic cycle.

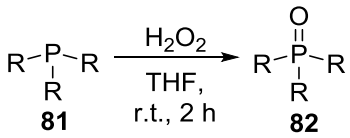
One such method is to use oxalyl chloride to convert phosphine oxide into a chlorophosphonium salt intermediate which can then react with catechol to give the desired catechol-phosphorane. This is the method used by Denton and co-workers to produce the Ishikawa phosphorane, reported to promote Mitsunobu couplings, from a phosphorus V source.[110] The oxalyl chloride approach was successful at producing a small selection of catechol-phosphoranes (table 3.5).

Table 3.5 *– the oxalyl chloride method of catechol-phosphorane synthesis.*



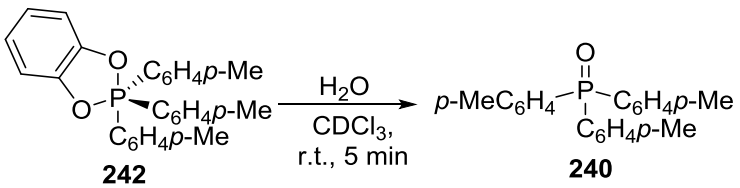
Entry	Phosphine	Result (all shifts in ^{31}P NMR)	Phosphorane
1	 **240**	 **241** 65.3 ppm.	 **242** - 83% after 5 min (−10.4 ppm).
2	 **243**	 **244** 58.8 ppm.	 **245** - 77% after 5 min (−23.8 ppm).
3	 **246**	 **247** 80.2 ppm.	 **248** - 76% after 5 min (−9.2 ppm).
4	 **8**	 **172** 50.6 ppm.	 **232** - 76% after 5 min (−18.9 ppm).
5	 **249**	 **250** 106.7 ppm.	No phosphorane formed.
6	 **251**	 **252** 51.8 ppm.	No phosphorane formed.
7	 **253**	 **254** 63.5 ppm.	No phosphorane formed.
8	 **255**	Multiple species visible by ^{31}P NMR.	-
9	 **256**	No reaction.	-
10	 **257**	No reaction	-

From the range of substrates investigated using the oxalyl chloride method of catechol-phosphorane synthesis (table 3.5) it became apparent that substrates with aryl or weakly electron-withdrawing aryl substituents are most successful (table 3.5, entries 1-4) forming the catechol-phosphoranes in reasonable conversions. Trialkylphosphine oxides are shown not to proceed past the chlorophosphonium salt stage with tributylphosphine oxide (table 3.5, entry 5) given as an example. Strongly electron-withdrawing aryl substituents are shown either to not proceed past the phosphonium salt stage (table 3.5, entry 6) or to fail to form the chlorophosphonium salt (table 3.5, entry 9). Electron-donating groups such as *para*-amino- and phenoxy- containing substrates again fail to form the catechol-phosphoranes (table 3.5, entries 7 and 10). And finally an example of an H-phosphine oxide produces multiple peaks in the ^{31}P NMR (table 3.5, entry 8), likely due to the presence of trivalent tautomers of H-phosphine oxide **255** and the lability of the P-H bond.



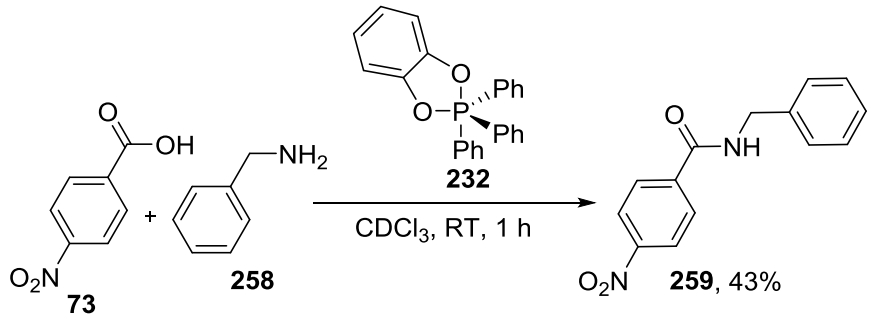
Equation 3.6 *– the production of phosphine oxides through the oxidation of phosphines.*

The phosphine oxide starting materials used were either commercially available or were easily produced through reaction of the phosphine with hydrogen peroxide with no further purification needed after work-up (Equation 3.6).



Equation 3.7 *– facile hydrolysis of catechol-phosphoranes.*

It was observed that all catechol-phosphoranes produced showed gradual hydrolysis by ^{31}P NMR to return the equivalent phosphine oxide, and if one equivalent of water was added to the reaction complete hydrolysis was seen in under 5 min in all cases (Equation 3.7). The observed reaction with water proves the electrophilic nature of the catechol-phosphorane and demonstrates the reactivity towards nucleophiles that is required in order to promote a Mitsunobu-type coupling reaction.



Equation 3.8 *– a catechol-phosphorane promoted amidation reaction.*[113]

In unpublished work conducted within the group the catechol-triphenylphosphorane was shown to perform a deoxy-coupling dehydration reaction in the form of an amidation reaction between *para*-nitrobenzoic acid and benzylamine (Equation 3.8).[113] Although this reaction must proceed by a nucleophilic acyl-substitution pathway and therefore cannot be said to proceed by a Mitsunobu mechanism, the successful promotion of a dehydrating coupling reaction by a catechol-phosphorane shows that the species may have a similar promise regarding Mitsunobu reactivity to that of the Ishikawa phosphorane.

Despite the successful production of catechol-phosphoranes and the example of amide coupling that has been demonstrated, the inability to replicate the methodology of Bidman and form these phosphoranes directly from catechol and phosphine oxide means that, because of the requirement for the use of oxalyl chloride, the catechol-

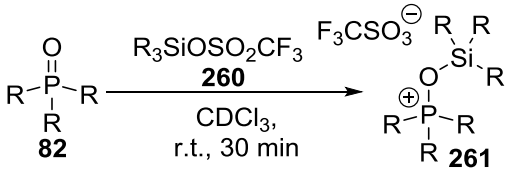
phosphoranes are potentially only as effective as the previously detailed Ishikawa phosphorane. The reliance on using oxalyl chloride to generate an intermediate chlorophosphonium salt means that, at present, catechol-phosphoranes would not be suitable for use in a catalytic reaction unless a better method of *in situ* catechol-phosphorane formation can be found that would be compatible with the Mitsunobu substrates that would be present under reaction conditions.

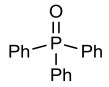
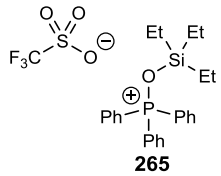
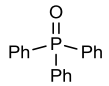
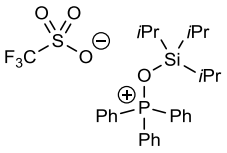
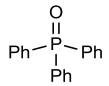
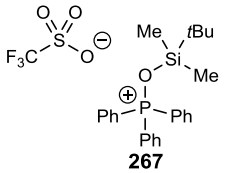
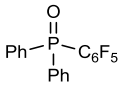
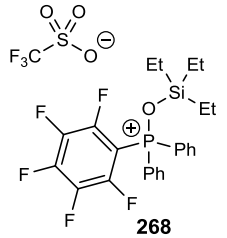
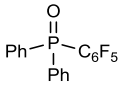
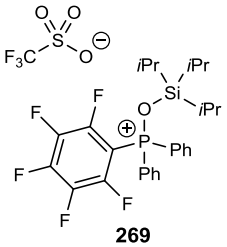
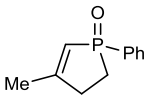
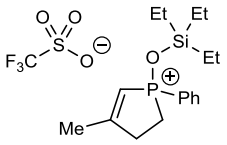
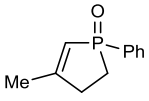
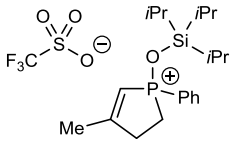
3.1.2.1 – Silyloxyphosphonium salts

While exploring methods of catechol-phosphorane synthesis and in particular the use of additional reagents to facilitate phosphorane formation, the reaction of phosphine oxides with silyl triflates to form silyloxyphosphonium salts was explored. The formation of trimethylsilyltriphenylphosphonium salt by this method has been previously conducted.[114,115] It was found that silyloxyphosphonium salts could be easily formed directly by combining the reagents, and that the reaction tolerated a variety of substrates (table 3.9).

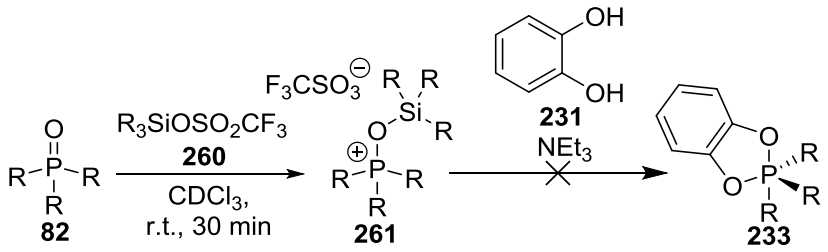
The silyloxyphosphonium salts that were formed exhibited a range of shifts in the ^{31}P NMR suggesting that the perfluorophenyl-containing phosphonium salts (table 3.9, entries 4 and 5) became slightly more deshielded (compared to the parent phosphine oxide shift of 20.6 ppm) as would be expected in a phosphonium salt.

Table 3.9 *– the formation of silyloxyphosphonium salts from phosphine oxides.*



Entry	Phosphine oxide	Silyl triflate	Silyloxyphosphonium salt	Result (all shifts in ^{31}P NMR)
1	 **8**	Et_3SiOSO_2CF (**262**)	 **265**	Quantitative formation (51.5 ppm)
2	 **8**	*i*-$Pr_3SiOSO_2CF_3$ (**263**)	 **266**	Quantitative formation (53.4 ppm)
3	 **8**	*t*-$BuMe_2SiOSO_2CF_3$ (**264**)	 **267**	Quantitative formation (53.4 ppm)
4	 **251**	$Et_3SiOSO_2CF_3$ (**262**)	 **268**	Quantitative formation (35.5 ppm)
5	 **251**	*i*-$Pr_3SiOSO_2CF_3$ (**263**)	 **269**	Quantitative formation (24.8 ppm)
6	 **163**	$Et_3SiOSO_2CF_3$ (**262**)	 **270**	Quantitative formation (89.4 ppm)
7	 **163**	*i*-$Pr_3SiOSO_2CF_3$ (**263**)	 **271**	Quantitative formation (89.0 ppm)

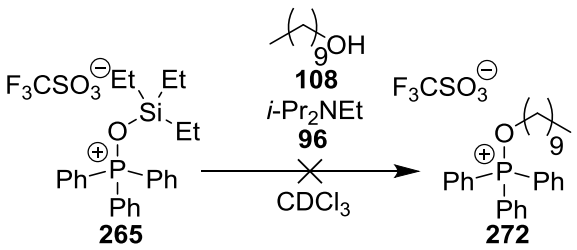
The triphenylphosphonium salts show shifts in the mid 50s (table 3.9, entries 1-3), typical of triphenylphosphonium salts and the phospholene oxide derived salts exhibit a shift much more deshielded than the parent compound (phospholene oxide **163** shift of 20.6 ppm) in the range indicative of cyclic phosphonium salts (table 3.9, entries 6 and 7).



Scheme 3.10 *– unsuccessful synthesis of catechol-phosphoranes via silyloxyphosphonium salts.*

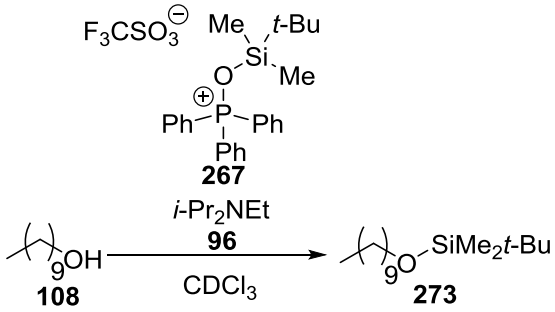
It was found that on attempting to react silyloxyphosphonium salts with catechol in the presence of base (to neutralise the triflic acid by-product) that no phosphorane formation was observed (Scheme 3.10). Instead phosphine oxide was seen to be returned.

With only phosphine oxide observed upon the reaction of a silyloxyphosphonium salt with catechol two reaction pathways were possible upon attack of a nucleophile on a silyloxyphosphonium salt: attack at the phosphorus centre, displacing silyloxide and giving a different phosphonium salt (*e.g.* attack of an alkoxide would give an alkoxyphosphonium salt); or attack at the silicon centre, eliminating phosphine oxide and giving silylated nucleophile (*e.g.* attack of an alkoxide would give a silyl ether). Should an alkoxide or alcohol nucleophile attack at phosphorus this would give an alkoxyphosphonium salt which, as previously mentioned is an important intermediate in phosphorus-mediated nucleophilic substitution reactions (*e.g.* the Appel and Mitsunobu reactions) and thus could prove very useful.



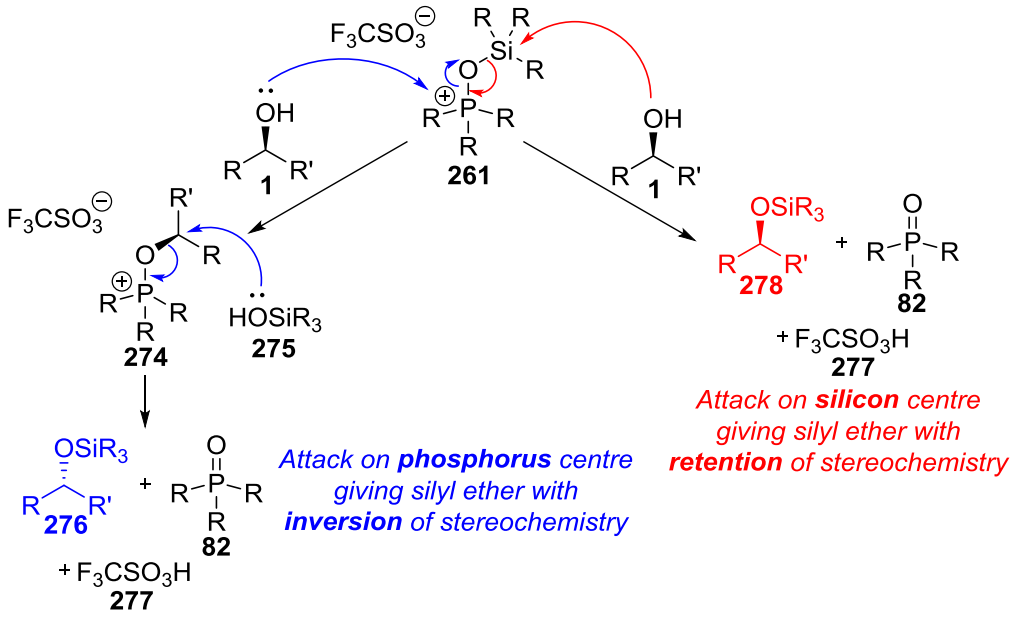
Equation 3.11 *– unsuccessful alkoxyphosphonium salt formation via a silyloxyphosphonium salt.*

It was found that upon reacting a selection of the phosphonium salts outlined in table 3.9 with alcohol and base that the reaction did not proceed to give alkoxyphosphonium salt by ^{31}P NMR, instead returning the phosphine oxide starting material (an example is given in Equation 3.11).



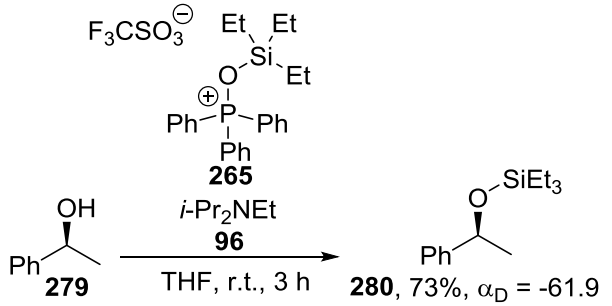
Equation 3.12 *– silyloxyphosphonium salt-mediated silyl ether formation.*

It was observed instead that the decanol was converted by the silyloxyphosphonium salt to *t*-butyldimethylsilyloxydecane (Equation 3.12). It was also found that triethylsilyloxydecane and tri*iso*propylsilyloxydecane were seen on reaction of decanol with the corresponding silyloxyphosphonium salts and agreed with the literature values for these compounds.[116]



Scheme 3.13 – *mechanistic possibilities for the silylation of alcohols using silyloxyphosphonium salts.*

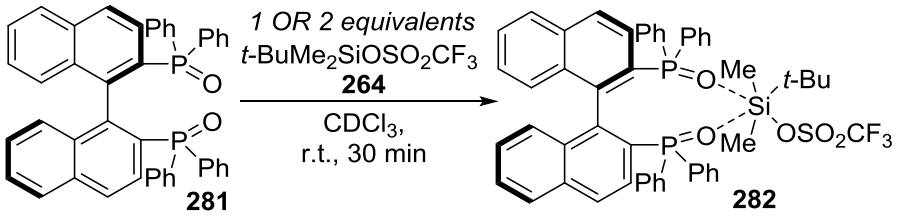
The observed silylation of alcohols has proven that stable alkoxyphosphonium salts cannot be made but it does not elucidate the mechanism by which the alcohol nucleophile attacks the silyloxyphosphonium salt; the alcohol may react directly at silicon giving silyl ether product with retention of stereochemistry and no cleavage of the C-O σ-bond, or the alcohol may attack at phosphorus to give a short-lived phosphonium salt intermediate which can then undergo Arbuzov-type collapse, cleaving the C-O σ-bond to give phosphine oxide and the silyl ether product with inversion of stereochemistry (Scheme 3.13). The mechanism could be determined by conducting an oxygen isotopic labelling study by enriching the alcohol oxygen or oxidising the phosphine with enriched hydrogen peroxide and then monitoring the phosphine oxide by-product to determine the fate of the ^{18}O. An alternative method is to use a secondary alcohol in the reaction and to determine the stereochemistry of the product.



Equation 3.14 *– silyloxyphosphonium salt-mediated silylation of secondary alcohols.*

Upon reacting a secondary alcohol with silyloxyphosphonium salt successful silylation was observed with retention of stereochemistry (Equation 3.14). The optical rotation values were in agreement with silyl ethers experimentally prepared directly from reaction of the secondary alcohol with silyl triflate and also with literature values.[117]

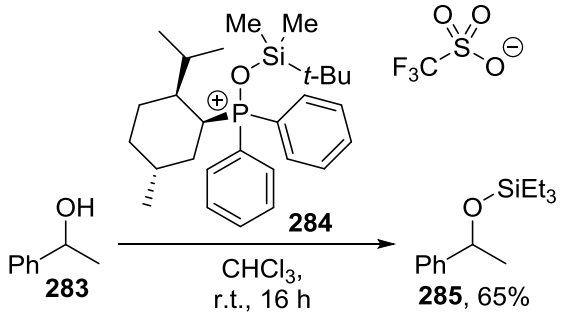
With retention of stereochemistry established in the silylation reaction it could be concluded that nucleophiles react at the silicon centre of the silyloxyphosphonium salt, silylating the nucleophile and directly eliminating phosphine oxide by-product. Although a method of synthesising silyl ethers with inversion of chemistry would have been a very useful reaction, the reaction with retention of stereochemistry could still be useful in a kinetic resolution reaction with the use of a chiral phosphine oxide.



Equation 3.15 *– reaction of BINAP-O_2 to give the proposed complex.*

(*R*)-BINAP-O_2 was identified as a chiral phosphine oxide compound for potential use in the development of a kinetic resolution reaction. It could be easily

formed from the phosphine through treatment with hydrogen peroxide as has been outlined previously. It was found that (*R*)-BINAP-O_2 produced the same, single ^{31}P NMR shift when reacted with both one and two equivalents of silyl triflate at 43.4 ppm (parent diphosphine oxide at 28.2 ppm). This suggests a coordinated complex rather than the formation of a formal bond, where the (*R*)-BINAP-O_2 has coordinated to the silyl triflate reagent (as shown in Equation 3.15). Use of a chiral phosphine oxide in which only one P=O bond is present may have prevented complexation of the type seen with BINAP-O_2 and allowed the formation of a formal bond.



Equation 3.16 *– silylation of a secondary alcohol using chiral phosphonium salt* ***284****.*

A chiral phosphine oxide with a single phosphorus atom was found in (*S*)-(+)-neomenthyldiphenylphosphine oxide, which could again be formed by oxidising the parent phosphine with hydrogen peroxide. This phosphine oxide formed the silyloxyphosphonium salt upon reaction with *tert*-butyldimethylsilyl triflate in the same manner as the achiral phosphine oxides investigated previously and it was found in preliminary studies with a racemic secondary alcohol that the silyloxyphosphonium salt reacted with alcohol to provide silyl ether again in the same manner as had been previously observed (Equation 3.16).

The work conducted to date with silyloxyphosphonium salts showed promise with regards to the development of a kinetic resolution reaction. The potential success

of such a reaction will be determined when further studies into the rate at which different enantiomers of chiral alcohols react with chiral silyloxyphosphonium salts have been completed. If silyloxyphosphonium salt **284** is not successful at adequately separating the isomers then other chiral phosphines and phosphine oxides are known and are available for investigation.

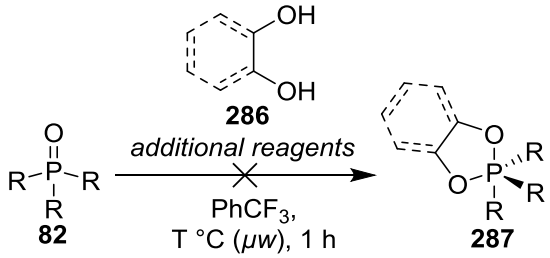
Overall silyloxyphosphonium salts, despite the interesting reactivity shown regarding the silylation of alcohols, are not a viable route to dioxyphosphoranes of any kind due to the electrophilic silicon centre being more reactive to nucleophilic attack than the phosphorus centre as would be necessary for a dioxyphosphorane formation reaction. Even if they had presented a viable route to dioxyphosphoranes the necessity for an equivalent of silyl triflate to be present in order to activate the phosphine oxide would not be acceptable for the same reasons as the chlorophosphonium salt intermediates were discarded: the stoichiometric waste products associated with phosphine oxide activation (in this case triflic acid and silanol); and the presence of a reactive reagent in the reaction (in this case silyl triflate) which could interfere with desirable substrates. A more desirable route to dioxyphosphoranes would make use of redox-neutral, activating agent-free conditions.

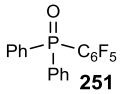
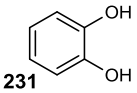
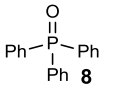
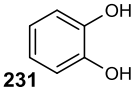
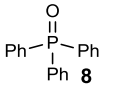
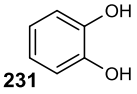
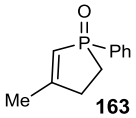
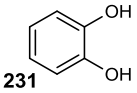
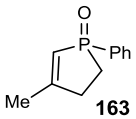
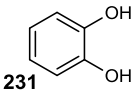
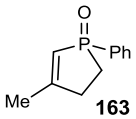
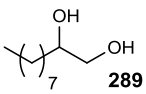
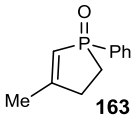
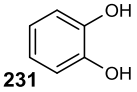
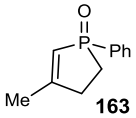
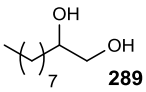
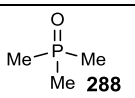
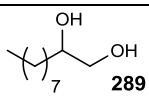
3.1.3 – Redox-free catechol-phosphorane formation without promoters

Although the successful amidation reaction promoted by a catechol-phosphorane and the coupling reactions observed by Denton and co-workers with the Ishikawa phosphorane provide preliminary evidence of the reactivity exhibited by the species towards the promotion of dehydration reactions, the necessity for the use of oxalyl chloride to synthesise the phosphoranes presents a barrier for the use of these

phosphoranes in a catalytic Mitsunobu reaction, for reasons described previously. Ideally, a method of forming cyclic dioxyphosphoranes from a phosphine oxide and a catechol or diol, without the need for any additional reagents that may complicate the reaction through interaction with reactants, and particularly a method that can be employed *in situ* would be key to accomplishing a catalytic Mitsunobu reaction.

Table 3.17 *– attempted formation of phosphoranes under microwave conditions.*



Entry	Phosphine oxide	Diol	Additional reagents	Temperature (°C)
1	 **251**	 **231**	-	150
2	 **8**	 **231**	$(MeO)_3CH$ **290**	200
3	 **8**	 **231**	$(MeO)_3CH$ **290**, TsOH **270** (10 mol%)	150
4	 **163**	 **231**	-	150
5	 **163**	 **231**	$(MeO)_3CH$ **290**, TsOH **291** (10 mol%)	200
6	 **163**	 **289**	$(MeO)_3CH$ **290**, TsOH **291** (10 mol%)	200
7	 **163**	 **231**	$Ti(O\textit{i}\text{-}Pr)_4$ **147**, TsOH **291** (10 mol%)	200
8	 **163**	 **289**	$Ti(O\textit{i}\text{-}Pr)_4$ **147**, TsOH **291** (10 mol%)	200
9	 **288**	 **289**	$Ti(O\textit{i}\text{-}Pr)_4$ **147**, TsOH **291** (10 mol%)	200

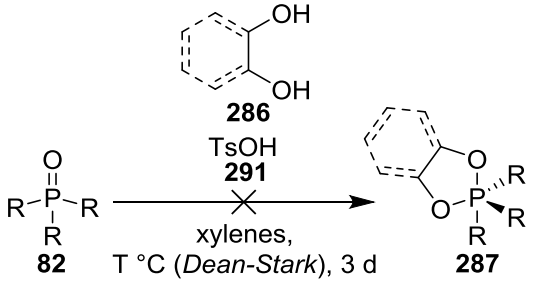
A potential method of forming cyclic dioxyphosphoranes directly from phosphine oxide and catechol/diol would be to employ a microwave to establish whether the high temperatures and increased pressures of the reaction would encourage reactivity (Table 3.17).

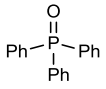
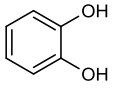
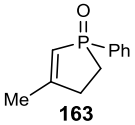
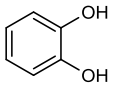
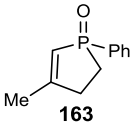
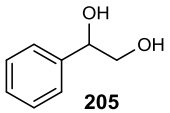
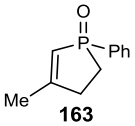
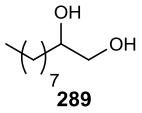
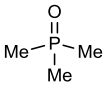
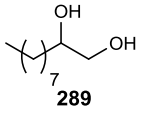
All reactions were conducted over 1 h using α,α,α-trifluorotoluene as solvent. The initial reactions with only phosphine oxide and catechol present (table 3.17, entries 1 and 4) showed no phosphorane by ^{31}P NMR. It had been noted previously however, that the catechol-phosphoranes previously synthesised had reacted readily hydrolysed in the presence of one equivalent of water to give phosphine oxide and catechol – the starting materials in this microwave reaction. It is therefore possible that the phosphorane could be formed under reaction conditions (with elimination of water) and then hydrolysed by the water present to return phosphine oxide and catechol starting materials. Scavengers triethylorthoformate and titanium (IV) *iso*-propoxide were employed to attempt to remove the eliminated water from the reaction conditions and also attempted was the addition of an acid catalyst, to promote the elimination of water. Unfortunately attempts to observe phosphoranes after by ^{31}P NMR after subjection to these reaction conditions proved unsuccessful when using both catechol (table 3.17, entries 2, 3, 5, and 7) and decane-1,2-diol (table 3.17, entries 6, 8 and 9). The absence of observed cyclic dioxyphosphorane species may be explained by either the decomposition of the phosphoranes through reaction of water not adequately removed by the molecular scavengers or by a reaction barrier to formation of the phosphorane that cannot be overcome without the use of an additional compound to create a reactive intermediate (*e.g.* a chlorophosphonium salt).

To test whether it is a large reaction barrier preventing direct catechol-phosphorane formation, or whether the observed starting materials are present due to hydrolysis of the phosphorane, alternative dehydrating reaction conditions were

investigated. The use of a Dean-Stark apparatus with a high-boiling solvent allows investigation of the catechol-phosphorane formation reaction under high temperature, constantly dehydrating azeotropic reaction conditions (table 3.18).

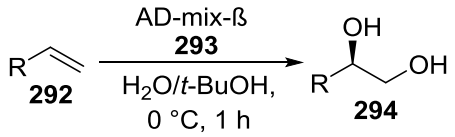
Table 3.18 *– attempted formation of phosphoranes under Dean-Stark conditions.*



Entry	Phosphine Oxide	Diol	Temperature (°C)
1	 **8**	 **231**	150
2	 **163**	 **231**	160
3	 **163**	 **205**	195
4	 **163**	 **289**	195
5	 **288**	 **289**	200

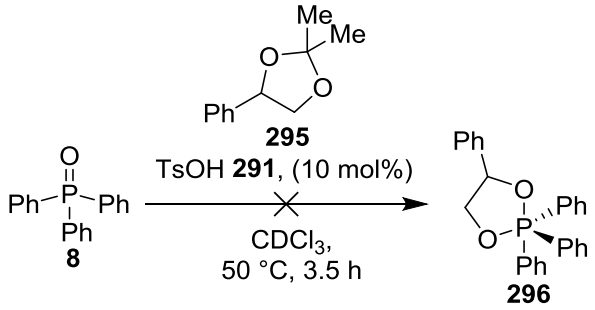
All reactions were conducted over 3 d using xylenes as solvent and using acid catalyst to promote the elimination of water. It was found that conducting these formation experiments with a small but electronically diverse range of phosphine oxides gave no observable dioxyphosphorane species, despite the constant azeotropic dehydrating conditions. This suggests that, rather than the potential hydrolysis reaction preventing the observation of phosphorane product, it is instead simply not possible to

synthesise cyclic dioxyphosphoranes directly from phosphine oxide and catechol/diol in this manner.



Equation 3.19 *– Sharpless dihydroxylation of alkenes to give diols* ***294****.*

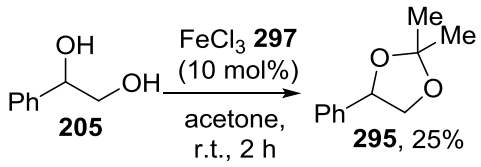
The diols using in the investigation were synthesised through use of AD-mix-β in a Sharpless dihydroxylation reaction (Equation 3.19). This reaction was chosen for the availability of reagents rather than for any desired stereochemical outcome and proceeded in good yields.



Equation 3.20 *– unsuccessful synthesis of catechol-phosphorane with acetone by-product.*

In order to finally determine whether the hydrolysis of the dioxyphosphorane was the factor behind the failure to observe any dioxyphosphorane product a reaction was conducted with dry phosphine oxide and a ketal (Equation 3.20). This reaction was designed to operate under dry conditions with elimination of acetone, so no water would be present should a successful phosphorane formation occur. Should this reaction have been successful an isotopic labelled study would have been required in order to elucidate

the mechanism. The reaction was also conducted in $CDCl_3$ so that NMR studies could be performed quickly to minimise the effect that any decomposition would have on the observation of dioxyphosphorane product. However, no phosphorane product was observed, indicating that direct synthesis of cyclic dioxyphosphoranes from phosphine oxides was not possible.



Equation 3.21 *– Lewis-acid catalysed ketal formation.*

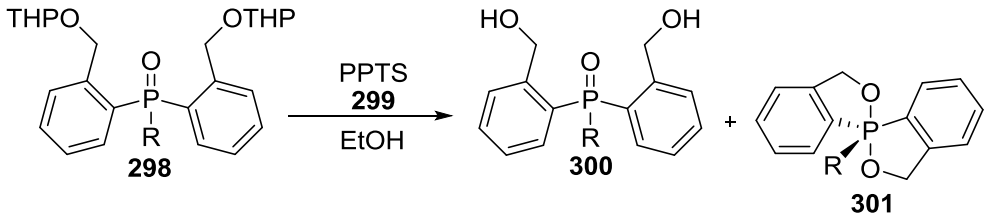
The ketal used in the dry dioxyphosphorane reaction was synthesised from reaction of the diol in acetone using an iron (III) catalyst (Equation 3.21).

The unsuccessful attempts to synthesise catechol-phosphoranes directly from a phosphine oxide source meant that the catalyst formation/turnover step of the currently proposed catalytic cycle was unfeasible. Although the target catalyst candidate could be synthesised *via* a chlorophosphonium salt intermediate and was seen to successfully promote an amide coupling reaction, the absence of a route to the cyclic dioxyphosphorane catalyst candidate from a phosphine oxide without the need for an additional reagent meant that the system represented an equivalent (if less investigated) alternative to the work conducted by Denton and co-workers on the Ishikawa phosphorane.

Due to these promising but ultimately unworkable results it was clear that the focus of the project must remain on methods of easily accessing dioxyphosphoranes from phosphine oxide sources, but that catechol-phosphoranes were not to be part of a catalytic cycle.

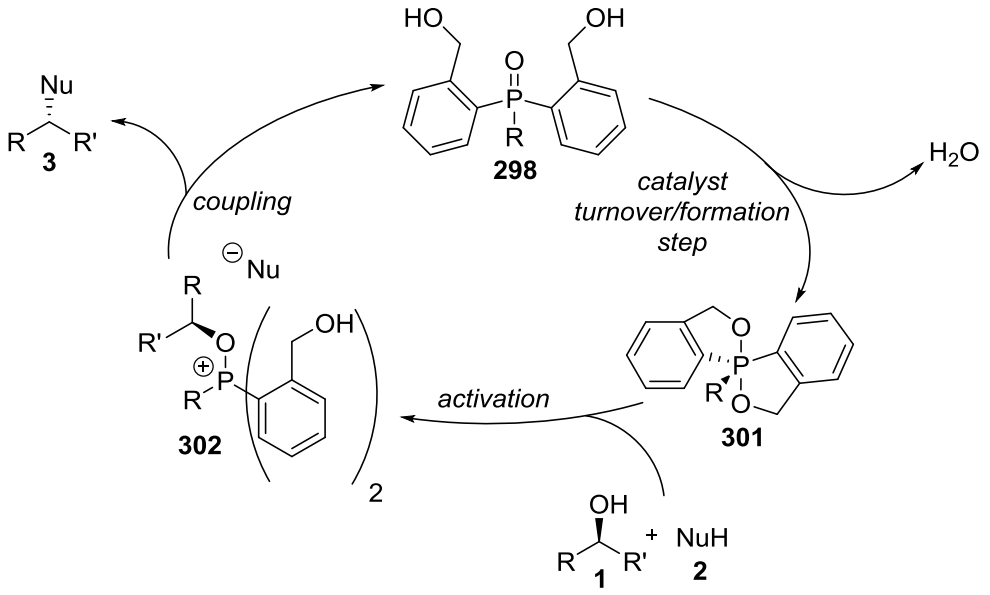
3.2 – Spirocyclic dioxyphosphoranes

In the work completed thus far towards a catalytic Mitsunobu reaction the need had been established for a method of synthesising dioxyphosphoranes from a phosphine oxide source without the need for an additional activating agent, representing the catalyst formation/turnover step of the catalytic cycle model. Catechol-phosphoranes had been rejected because of the necessity for an activating agent in the phosphorane formation reaction but a similar system in which a phosphine oxide can react with a diol or two alcohols to form the dioxyphosphorane would be ideal if phosphorane formation could be observed without the need for an additional activating agent.



Equation 3.22 *– spontaneous spirocyclic dioxyphosphorane formation observed by Kiełbasiński and co-workers.*[118]

It was observed by Kiełbasiński and co-workers that a phosphine oxide with two pendant hydroxyl groups would spontaneously form the spirocyclic dioxyphosphorane at room temperature (Equation 3.22). This occurred with no reagents other than the PPTS and ethanol present for the deprotection of the hydroxyl groups (which may not have been necessary for the ring-closure). Kiełbasiński and co-workers reported some observed spontaneous closure when R = phenyl, and complete spontaneous closure when R = methyl, suggesting that there would be room for optimisation of the catalyst candidate should initial investigations into the species prove successful.

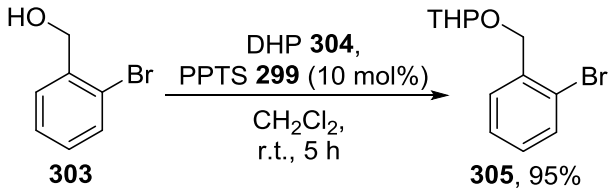


Scheme 3.23 *– amended proposed catalytic cycle with unimolecular phosphorane formation.*

This reported spontaneous spirocyclisation is certainly a promising result and would solve the key problem of the project by providing an easy reaction for the catalyst formation/turnover step of the catalytic cycle. An updated proposed catalytic cycle (shown in Scheme 3.23) would include the unimolecular catalyst formation but would otherwise operate in a similar manner to the previously proposed catechol-phosphorane based cycle; the initial catalyst formation step would involve internal dehydration of the phosphine oxide precatalyst to eliminate water and to provide a reactive dioxyphosphorane catalyst, the activation step would include reaction of the alcohol with the dioxyphosphorane catalyst to form the reactive alkoxyphosphonium salt intermediate, Arbuzov collapse of the alkoxyphosphonium salt intermediate would then provide the nucleophilic substitution product with inversion of stereochemistry and return the starting phosphine oxide and finally catalyst turnover could occur by the same mechanism as the catalyst formation step, regenerating the dioxyphosphorane catalyst. The problem that prevented the catechol-phosphorane system from being successfully

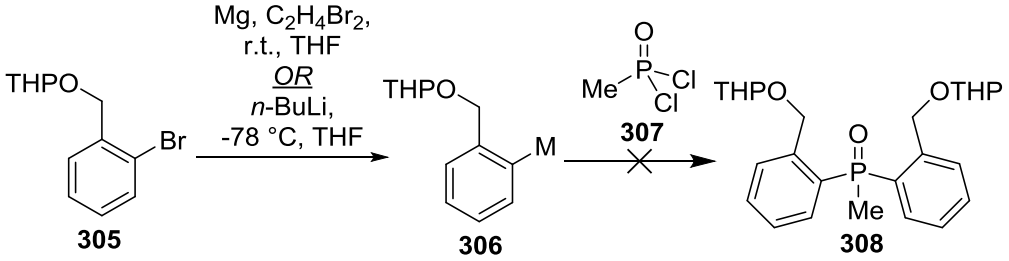
applied to a catalytic reaction was the failure to form the phosphorane under operating reaction conditions. The results reported by Kiełbasiński and co-workers provide a viable method of overcoming this problem and, depending on the reactivity of the Kiełbasiński phosphorane, potentially a route to a successful catalytic system.

3.2.1 – Synthesis of the Kiełbasiński phosphorane



Equation 3.24 *– protection of 2-bromobenzyl alcohol as a THP ether.*

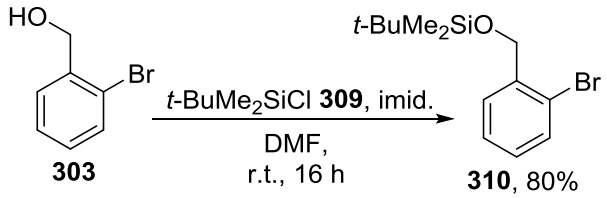
To reach the phosphine oxide **318** Kiełbasiński and co-workers employed a THP ether protecting group. The initial approach of the project was to mimic the Kiełbasiński synthetic route to the deprotected phosphine oxide/phosphorane. The initial protection of the benzyl alcohol proceeded in good yield (Equation 3.24).



Scheme 3.25 *– unsuccessful formation of protected phosphine oxide* ***308****.*

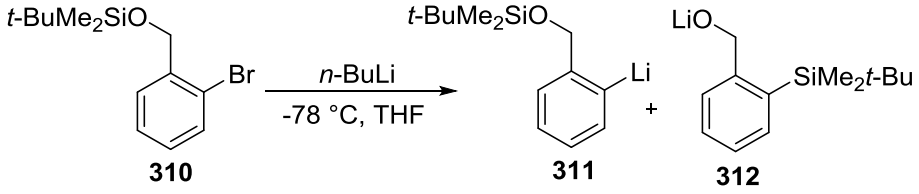
It was found on replication of Kiełbasiński's organometallic addition of the protected bromide that multiple products were observed by ^{31}P NMR, suggesting that

both Grignard and organolithium additions to a phosphinic dichloride are not suitably clean methods of synthesis (Scheme 3.25). A concern was that the THP ether protecting group was too labile under the reaction conditions and was cleaving, allowing an alkoxide to form.



Equation 3.26 *– protection of 2-bromobenzyl alcohol as a silyl ether.*

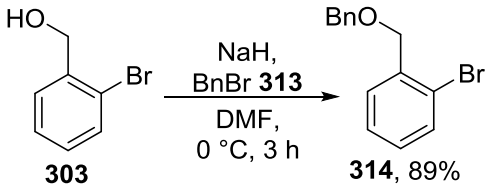
Because of the difficulties observed upon attempts to use a THP ether protected organometallic reagent a change of protecting group was necessary. A silyl ether protecting group was employed and the protected benzyl alcohol easily synthesised using a chlorosilane (Equation 3.26).



Equation 3.27 *– retro-Brook rearrangement reaction of the lithiated silyl ether.*

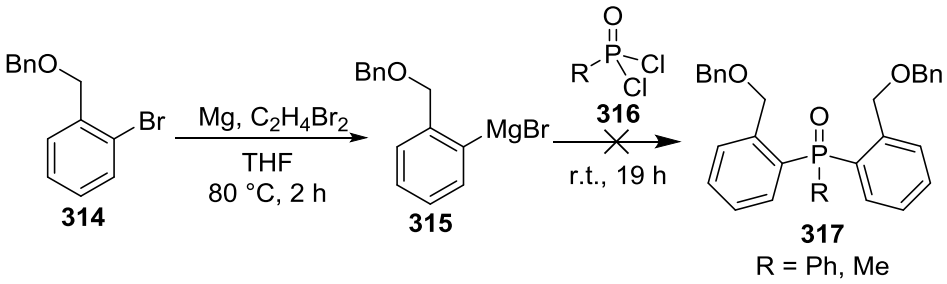
It was found however that upon treatment of silyl ether protected bromide with *n*-butyllithium a retro-Brook rearrangement occurred resulting in a mixture of the desired phenyllithium and the alkoxide retro-Brook product, as observed in both the ^{1}H and the ^{13}C NMR spectra of the crude reaction mixture by the presence of peaks associated with both the starting material and the rearranged analogue (Equation 3.27). This again means

that the protecting group is unsuitable for the desired organometallic addition to a phosphinic dichloride. Direct lithiation of the unprotected benzyl alcohol was also found to have similar associated problems.



Equation 3.28 *– protection of 2-bromobenzyl alcohol as a benzyl ether.*

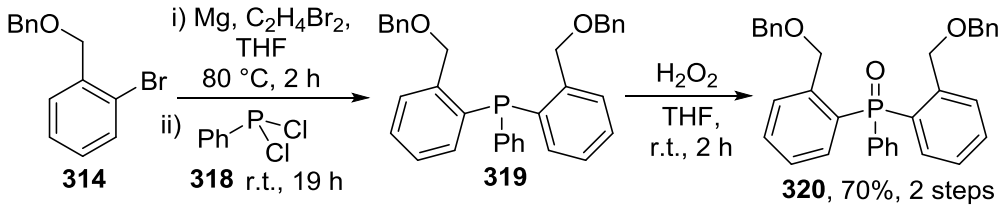
A benzyl ether was identified as a more stable protecting group that could withstand organometallic reaction conditions. Protection of 2-bromobenzyl alcohol was achieved in good yield using sodium hydride and benzyl bromide (Equation 3.28).



Equation 3.29 *– unsuccessful formation of protected phosphine oxide* ***317****.*

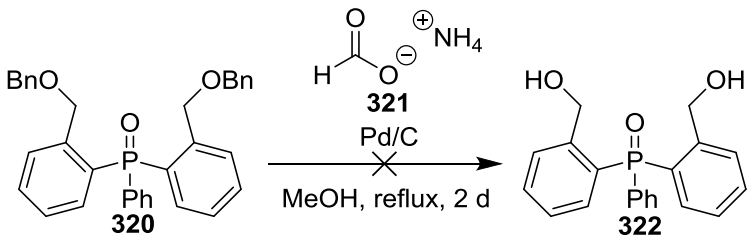
A Grignard reaction was conducted using the benzyl ether protected bromide (Equation 3.29). A single peak was observed by ^{31}P NMR in the phosphine oxide region, but the crude yield was very low, suggesting a large amount of the phosphinic dichloride had been hydrolysed and removed with the aqueous washings. It was proposed that the Grignard addition be made to phosphorus (III) rather than phosphorus (V) as dichlorophosphines have been observed to be better electrophiles than phosphonic

dichlorides.[119] Facile oxidation could then be conducted to provide the desired phosphine oxide.

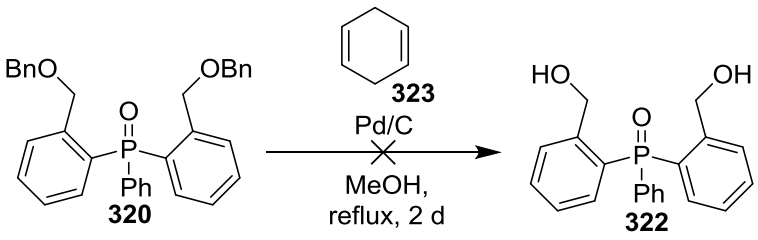


Scheme 3.30 *– successful synthesis of the bis benzyl ether protected phosphine oxide* ***320****.*

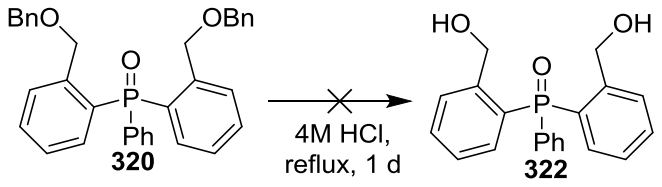
The Grignard addition to the phosphorus (III) dichloride with subsequent oxidation provided the protected phosphine oxide in good yield (Scheme 3.30). The only remaining step required to produce the Kiełbasiński phosphine oxide was deprotection of the benzyl ethers.



Equation 3.31 *– unsuccessful deprotection by transfer hydrogenolysis using ammonium formate.*

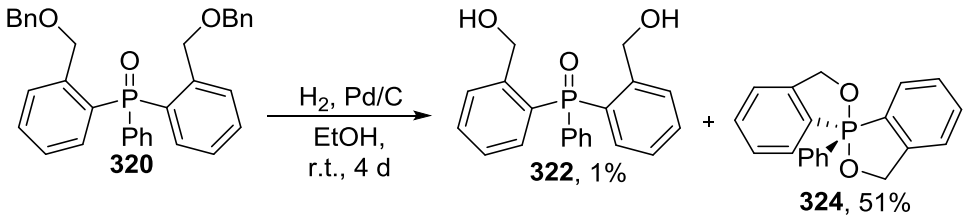


Equation 3.32 *– unsuccessful deprotection by transfer hydrogenolysis using 1,4-cyclohexadiene.*



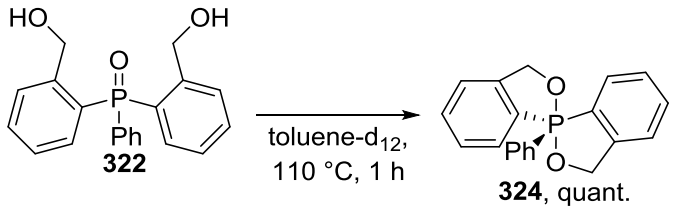
Equation 3.33 *– unsuccessful benzyl ether deprotection under acidic conditions.*

Attempts were made to deprotect the bis benzyl ethers firstly by transfer hydrogenolysis using ammonium formate and 1,4-cyclohexadiene (Equations 3.31 and 3.32 respectively) and also by refluxing in HCl (Equation 3.33). The acid reflux showed no signs of deprotection by ^{31}P NMR while the transfer hydrogenolysis experiments showed only very slight deprotection under forcing reaction conditions.



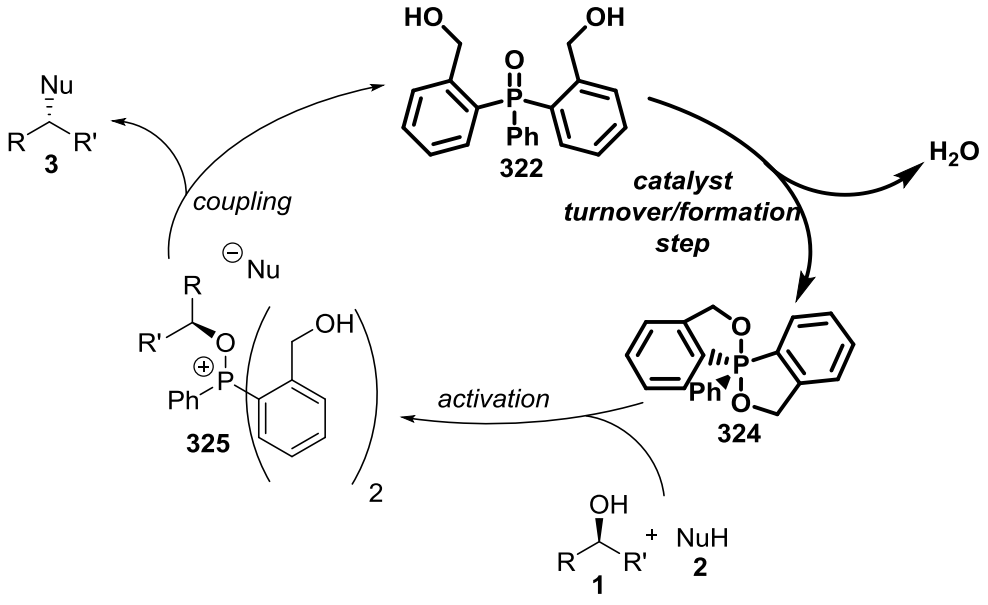
Equation 3.34 *– successful benzyl ether deprotection by palladium catalysed hydrogenolysis.*

Successful cleavage of the benzyl ethers was eventually achieved using a palladium on charcoal catalyst under a hydrogen atmosphere (Equation 3.34). The products provided by the deprotection reaction corroborated the reports by Kiełbasiński and co-workers that spontaneous ring-closure occurred, providing both the spirophosphorane **324** at −36.6 ppm (51%) and the deprotected phosphine oxide **322** at 40.5 ppm (1%) in the ^{31}P NMR.



Equation 3.35 *– facile closure of phosphine oxide* ***322*** *to spirocyclic dioxyphosphorane* ***324****.*

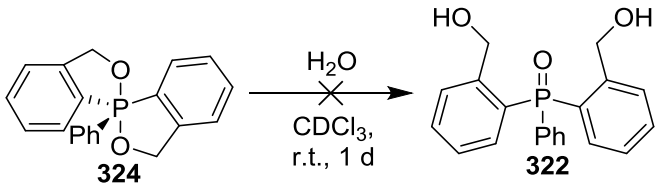
It was found that deprotected phosphine oxide **322** could be easily cyclised to the spirocyclic dioxyphosphorane with the application of elevated temperatures without the need for any additional reagents (Equation 3.35), and indeed samples of the Kiełbasiński phosphine oxide were seen to spontaneously cyclise when stored, showing the ease at which phosphorane formation can occur in comparison to the forcing conditions required for the formation of the Bidman-type dioxyphosphoranes mentioned previously.



Scheme 3.36 *– the successfully achieved catalyst turnover/formation step of the proposed catalytic cycle.*

The spontaneous spirocyclisation of the deprotected phosphine oxide provides evidence that dioxyphosphoranes can be formed *in situ* in a catalytic reaction and thus that the catalyst formation/turnover step of the proposed phosphorus (V) mediated catalytic cycle is feasible (Scheme 3.36). With the observed reactivity of the Ishikawa phosphorane and the observed spontaneous formation of the Kiełbasiński phosphorane all required steps of a redox-neutral phosphorus catalysed Mitsunobu reaction have been separately achieved by dioxyphosphoranes, providing further justification of this approach, but also observed was the varying reactivity of different dioxyphosphoranes highlighted by the drastic difference in ease of formation between the Kiełbasiński phosphorane and the Bidman-type phosphoranes, outlining the large potential for the optimisation of dioxyphosphoranes should the need arise. Should this spirocyclic dioxyphosphorane have proven reactive in the presence of alcohols and form the key alkoxyphosphonium salt intermediate then a catalytic reaction based on this catalyst would have been possible.

3.2.2 – Investigating the reactivity of the Kiełbasiński phosphorane

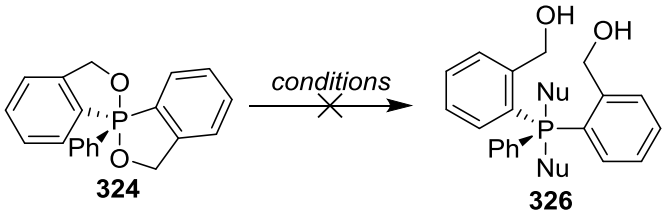


Equation 3.37 *– unsuccessful hydrolysis of the Kiełbasiński phosphorane.*

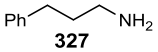
Attempts to react the Kiełbasiński phosphorane with water in a hydrolysis reaction proved unsuccessful (Equation 3.37), in marked contrast to the equivalent experiments with the Bidman-type phosphoranes in which hydrolysis occurred in 5 minutes (shown in

Equation 3.7). The lack of reactivity of the Kiełbasiński phosphorane with water may have been an encouraging result, showing that the hydrolysis reaction would not occur under reaction conditions to return the parent phosphine oxide and compete with the reaction of the phosphorane with reaction substrates. The absence of reactivity with water would be a positive result providing that the Kiełbasiński phosphorane proves as reactive towards Mitsunobu substrates as other dioxyphosphoranes such as the Ishikawa phosphorane.

Table 3.38 *– the unsuccessful reaction of the Kiełbasiński phosphorane with a selection of nucleophiles.*



324 **326**

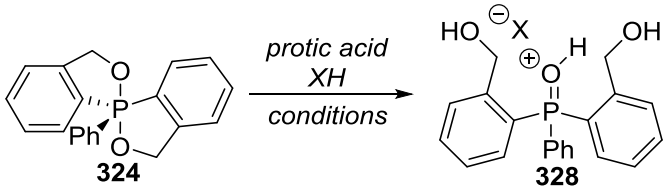
Entry	Nucleophile	Solvent	Temperature (°C)	Reaction time
1	MeOH	MeOH	65	20 h
2	MeOH (w/ 10% NaH)	MeOH	65	24 h
3	*t*-BuOH	*t*-BuOH	83	32 h
4	 **327**	$CHCl_3$	61	24 h

The reactivity of the Kiełbasiński phosphorane was tested with alcohol and amine nucleophiles (table 3.38). No change was observed by ^{31}P NMR when using refluxing alcohol as a solvent (table 3.38, entries 1 and 3), when using a primary amine nucleophile in refluxing chloroform (table 3.38, entry 4) and in refluxing methanol with the addition of a base catalyst (table 3.38, entry 2) suggesting no reaction under any of the tested conditions.

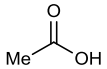
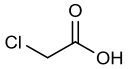
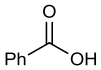
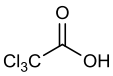
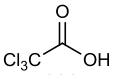
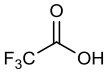
Reaction of the Kiełbasiński phosphorane with a range of protic acids was tested (table 3.39). It was found that when reacted with protic acids of a pK_a of −0.25 and above the Kiełbasiński phosphorane remained unreacted, even under forcing conditions (table 3.39, entries 1 – 7). A change of ^{31}P NMR shift was seen, however, upon reaction with acids of a pK_a of −0.4 and below in HBF_4 (table 3.39, entry 11) and sulfonic acids

(table 3.39, entries 8 – 10); the shifts were all seen to be in the region expected of a protonated phosphine oxide (40 – 60 ppm) and it is proposed that the acid catalysed hydrolysis by trace amounts of water present in the reaction conditions, as shown in the Equation of table 3.39.

Table 3.39 *– the reaction of the Kiełbasiński phosphorane with a selection of protic acids.*

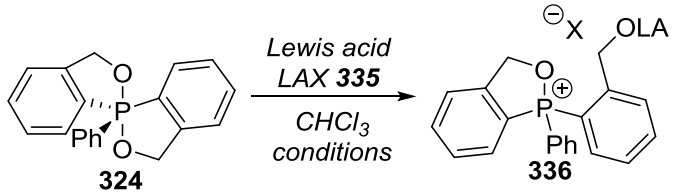


324 **328**

Entry	Acid (pK_a)	Solvent	Temperature (°C)	Reaction time	Result (all shifts in ^{31}P NMR)
1	 **223** (4.76)	$CDCl_3$	r.t.	2 d	No reaction
2	 **329** (2.86)	$CDCl_3$	60	2 d	No reaction
3	 **28** (4.2)	Toluene	90	22 h	No reaction
4	 **330** (0.65)	Toluene	120	2 d	No reaction
5	 **330** (0.65)	Xylenes	159	4 d	No reaction
6	 **331** (10.37)	$CDCl_3$	r.t.	3 d	No reaction
7	 **332** (−0.25)	Xylenes	159	3 d	No reaction
8	TfOH (**277**) (−14)	$CHCl_3$	r.t.	30 m	Phosphonium salt formation (57.2 ppm)
9	MsOH (**333**) (−2.6)	$CDCl_3$	r.t.	1 h	Phosphonium salt formation (47.4 ppm)
10	TsOH (**291**) (−2.8)	$CDCl_3$	r.t.	1 h	Phosphonium salt formation (41.4, 2.0 ppm)
11	HBF_4 (**334**) (−0.4)	$CDCl_3$	r.t.	1 h	Phosphonium salt formation (40.7, 39.0, 2.1 ppm)

The exhibited reactivity of the Kiełbasiński phosphorane is an encouraging result; the observed opening of the spirocycle under strong acidic conditions may provide a route to reaction of the phosphorane with nucleophilic substrates.

Table 3.40 *– the reaction of the Kiełbasiński phosphorane with a selection of Lewis acids.*



324 **336**

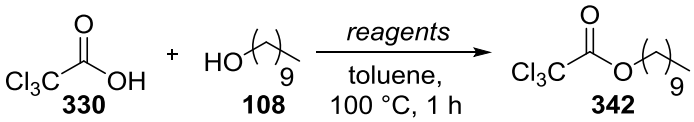
Entry	Reagent/Acid	Temperature (° C)	Reaction time	Result (all shifts in ^{31}P NMR)
1	TMSOTf (**337**)	r.t.	5 m	Phosphonium salt formation (56.5 ppm)
2	TESOTf (**262**)	r.t.	5 m	Phosphonium salt formation (56.9 ppm)
3	TIPSOTf (**263**)	r.t.	5 m	Phosphonium salt formation (53.5 ppm)
4	TBSOTf (**264**)	r.t.	1 h	Phosphonium salt formation (53.3 ppm)
5	$Sc(OTf)_3$ (**338**)	r.t.	5 m	Phosphonium salt formation (49.2 ppm)
6	$Bi(OTf)_3$ (**339**)	r.t.	5 m	Phosphonium salt formation (53.9 ppm)
7	$Yb(OTf)_3$ (**340**)	60	15 h	No reaction
8	$Sm(OTf)_3$ (**341**)	r.t.	2 d	No reaction
9	$Ti(O\textit{i}\text{-}Pr)_4$ (**147**)	60	2 d	No reaction

Reaction between the Kiełbasiński phosphorane and a selection of silyl triflates and Lewis acids was attempted to determine whether phosphonium species similar to those formed from reaction with protic acids could be observed (table 3.40). It was found that on reaction with some silyl triflates a species with a ^{31}P NMR shift indicating a phosphonium species (50 – 60 ppm) was observed (table 3.40, entries 1-4). Species indicating a cyclic phosphonium species were again seen upon reaction of the Kiełbasiński phosphorane with scandium and bismuth triflates (table 3.40, entries 5 and 6), however reaction with other metal triflates and also with titanium *iso*-propoxide showed only unreacted phosphorane by ^{31}P NMR (table 3.40, entries 7 – 9).

The species observed on reaction of the Kiełbasiński phosphorane with Lewis acids in the 50 – 60 ppm region of the ^{31}P NMR spectrum represent promising results; the opening of the phosphorane, which had proven previously unreactive in the presence of alcohol nucleophiles, is an important step towards achieving useful reactivity using the

phosphorane. As mentioned previously, work by Evans Jr. and co-workers had established that Lewis acids allowed phosphorane-mediated cyclodehydration reactions to proceed at lower reaction temperatures by accelerating the breakdown of the dioxyphosphorane intermediate. This work coupled with the opening of the phosphorane that has been observed experimentally shows potential for a coupling reaction mediated by Kiełbasiński phosphorane and a Lewis acid.

Table 3.41 *– the effect of the Kiełbasiński phosphorane and Lewis acid on an esterification reaction.*



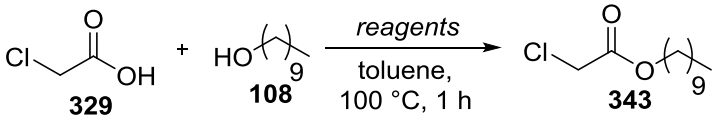
Entry	Kiełbasiński Phosphorane	$Sc(OTf)_3$	% 312*
1	-	-	20%
2	1 equiv.	-	13%
3	-	1 equiv.	87%
4	1 equiv.	1 equiv.	92%
5	-	10 mol%	25%
6	1 equiv.	10 mol%	24%

*determined by ^{1}H NMR analysis of the crude reaction mixture.

Due to the promising result seen in opening the previously unreactive Kiełbasiński phosphorane with Lewis acids a study was undertaken in which the esterification reaction between trichloroacetic acid and decanol was conducted and the influence of both the Kiełbasiński phosphorane and a Lewis acid in the form of scandium triflate was examined (table 3.41). It was found that the addition of one equivalent of the Kiełbasiński phosphorane in the absence of any Lewis acid (table 3.41, entry 2) had no advantage over the control reaction (table 3.41, entry 1), confirming as had been previously observed that the Kiełbasiński phosphorane is unreactive regarding the promotion of coupling reactions when applied without the presence of a Lewis acid to aid the opening of the spirocyclic structure. It was found that where both one equivalent of phosphorane and one equivalent of $Sc(OTf)_3$ were added the conversion to

ester product was greatly increased (table 3.41, entry 4). However it was seen that on addition of one equivalent of $Sc(OTf)_3$ in the absence of phosphorane the conversion to ester was comparable (table 3.41, entry 3) indicating Lewis acid activation of the carboxylic acid rather than a Mitsunobu reaction pathway. Indeed, on reduction of the loading of the Lewis acid to 10 mol% reactions both containing and excluding phosphorane again gave comparable conversions to product (table 3.41, entries 5 and 6) confirming that the increase of reaction conversion is due to Lewis acid promotion.

Table 3.42 *– the effect of the Kiełbasiński phosphorane and Lewis acid on a less favourable esterification reaction.*



Entry	Kiełbasiński phosphorane	$Sc(OTf)_3$	% 313*
1	-	-	2%
2	1 equiv.	-	3%
3	-	10 mol%	98%
4	1 equiv.	10 mol%	>99%

*determined by ^{1}H NMR analysis of the crude reaction mixture.

The esterification experiment was repeated with chloroacetic acid as a less electrophilic carboxylic acid substrate (table 3.42). It was found that the control reaction exhibited a lower conversion (table 3.42, entry 1), as expected considering the change of substrate, and again the phosphorane had no influence on the success of the reaction in the absence of a Lewis acid (table 3.42, entry 2). The addition of 10 mol% $Sc(OTf)_3$ to reactions with and without one equivalent of Kiełbasiński phosphorane again gave comparable conversions (table 3.42, entries 3 and 4) confirming that the Kiełbasiński phosphorane/Lewis acid system does not promote Mitsunobu reactivity in esterification reactions when compared to the sole addition of a Lewis acid.

That there was no increased reactivity shows that the combination of the Kiełbasiński phosphorane with a Lewis acid promoter has no advantage over inclusion

of the Lewis acid without the phosphorane. The change in conversion to ester observed on reduction of the equivalency of $Sc(OTf)_3$ in the trichloroacetic acid experiments where phosphorane is present (table 3.41, entries 4 and 6) suggest that the esterification reaction is proceeding by Lewis acid catalysis rather than *via* a phosphorus-mediated pathway.

The observed lack of reactivity of the Kiełbasiński phosphorane, by itself and with acid promoters, indicates that the Kiełbasiński phosphorane is not a suitable catalyst candidate for a catalytic Mitsunobu reaction. Though the phosphine oxide system with two pendant alcohols and the accompanying spirocyclic dioxyphosphorane exhibit characteristics that would be ideal for a catalytic Mitsunobu reaction, the stability of the Kiełbasiński phosphorane prevents it from being useful. An alternative compound that possessed similar structural characteristics to the Kiełbasiński phosphorane but in which the spirocyclic dioxyphosphorane form was less stable and more reactive could be a viable system for catalysis.

3.3 – Inverting the aryl linker

The Kiełbasiński phosphine oxide/spirocyclic dioxyphosphorane system had proven unsuitable as a catalyst candidate so a compound of a similar structure but with more favourable reactivity was needed, ideally another phosphine oxide/spirocyclic dioxyphosphorane system in which the spirocyclic dioxyphosphorane form could be more easily reacted with nucleophilic substrates, with or without the inclusion of a Lewis acid promoter.

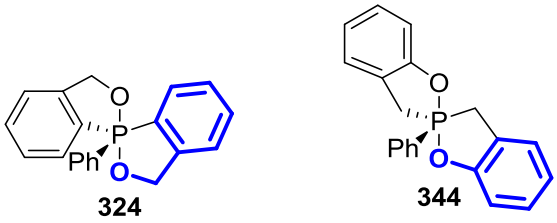
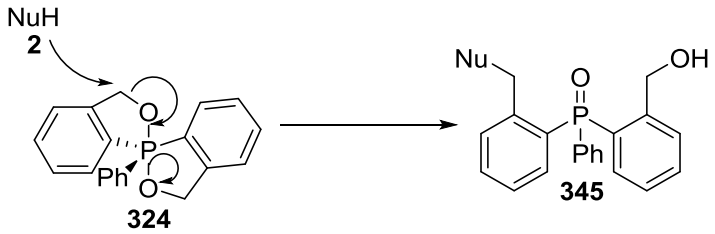


Figure 3.43 *– proposed inversion of the aryl linker to give an altered phosphorane structure.*

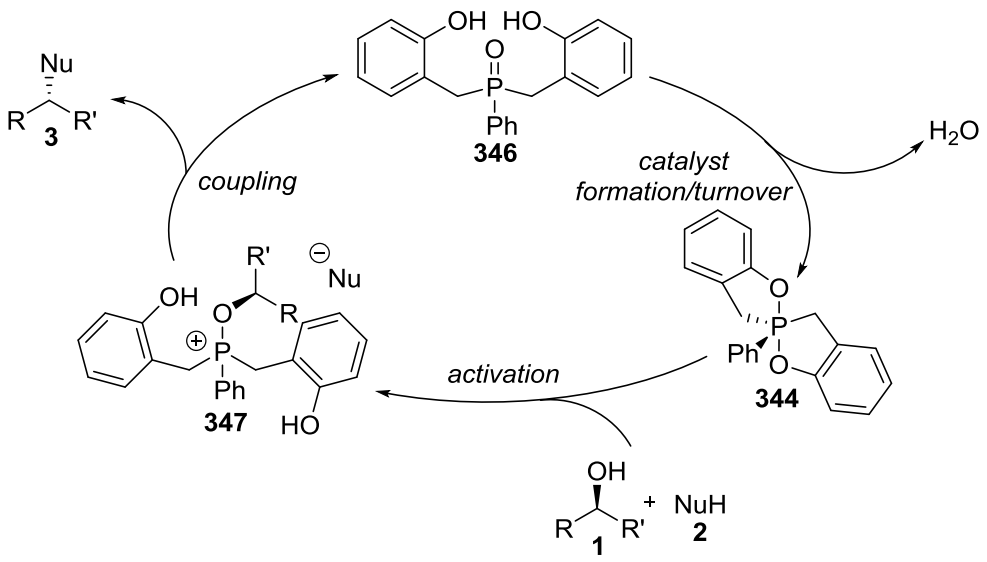
An inversion of the aryl linker resulting in the reversed connectivity of both of the benzyl fragments was proposed as an effective way of changing the nature of the P-O σ-bonds whilst preserving the structure of the spirocyclic core of the phosphorane (Figure 3.43). This alteration of the structure would possess phenolic rather than benzylic oxygens as part of the spirocyclic core of the phosphorane and, because of the better phenolic leaving group, this was expected to result in a more reactive species.



Scheme 3.44 *– potential catalyst deactivation of Kiełbasiński based phosphoranes due to sp^3 hybridisation adjacent to the dioxyphosphorane oxygen.*

The adoption of a phenolic linker also has the advantage of having an sp^2 hybridised carbon adjacent to the oxygen, rather than an sp^3 hybridised carbon as present in the Kiełbasiński phosphorane; this change of hybridicity prevents the undesirable attack of a nucleophilic substrate at this carbon centre which, although not observed with the Kiełbasiński system, could develop into a catalyst design problem should the

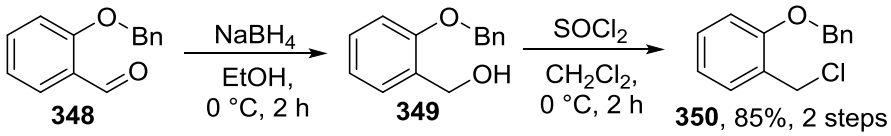
structure of the catalyst candidate be changed to build on the Kiełbasiński phosphorane rather than consist of a change to the inverted aryl linker system (Scheme 3.44).



Scheme 3.45 *– the new proposed catalytic cycle with the inverting aryl linker phosphine oxide/spirocyclic dioxyphosphorane system.*

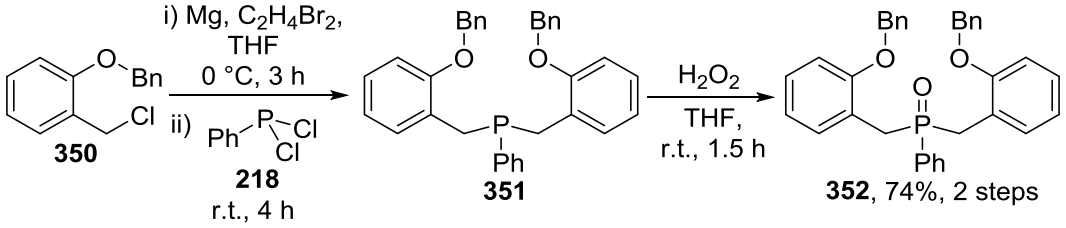
The catalytic cycle for the inverted linker phosphorane catalyst would remain much the same as that proposed for the Kiełbasiński system, given that the two molecules are of similar design (Scheme 3.45). Should **344** be successfully formed by the spirocyclisation of a bis-phenoxyphosphine oxide, in the same manner as was seen in the formation of the Kiełbasiński phosphorane, then the mechanism of formation would also be elucidated: the phosphoryl oxygen would have to leave in the formation of **344** from **346**, whereas in the Kiełbasiński system it is not clear whether it was the phosphoryl oxygen or the benzylic linker oxygen that was displaced in the deoxy-cyclisation.

3.3.1 – Synthesis of a novel phosphine oxide



Scheme 3.46 *– preparation of the inverted aryl linker Grignard precursor.*

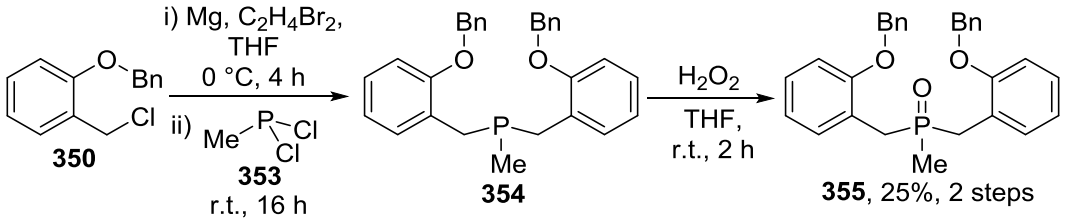
The synthesis of the inverted aryl linker was based upon the synthesis method that had been used to produce the Kiełbasiński phosphorane, and started with the preparation of an aryl chloride precursor from commercially available benzyl-protected salicylaldehyde by, firstly, reducing the aldehyde with sodium borohydride and then chlorinating the resultant alcohol using thionyl chloride to give the desired chloride **350** in good yield (Scheme 3.46).



Scheme 3.47 *– Grignard reaction to provide the protected phosphine oxide* ***352****.*

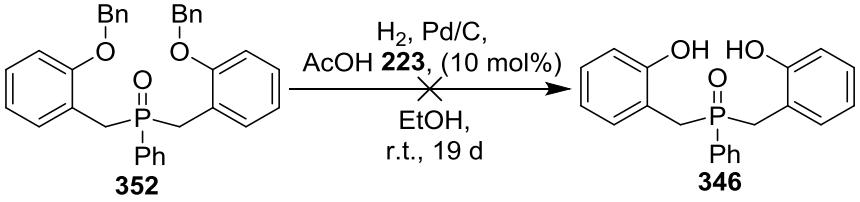
The protected phosphine oxide was then produced *via* a Grignard reaction with subsequent oxidation in good yield (Scheme 3.47). The benzyl chloride was converted into the magnesium chloride Grignard reagent using magnesium turnings and dibromoethane at 0 °C, rather than the high formation temperatures usually associated with Grignard reagent formation. The dibromoethane was included in order to activate the magnesium turnings by removing the passivating layer of magnesium oxide from the

surface, thus allowing reaction with the alkyl chloride. The low reaction temperature applied was due to the benzylic nature of the chloride which made magnesium insertion in the C-Cl σ-bond easier but also presented the problem of a potential dimerisation reaction between the Grignard reagent and any unreacted chloride through a Wurtz reaction.[120,121] The low reaction temperatures applied decrease the rate at which dimerisation occurs while still allowing Grignard reagent formation. The alkyl magnesium chloride so obtained was then reacted with dichlorophosphine to give protected phosphine and subsequent oxidation with hydrogen peroxide gave the protected phosphine oxide **352**.



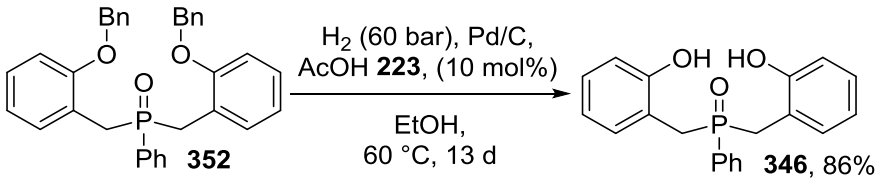
Scheme 3.48 *– synthesis of the protected methyl-substituted phosphine oxide* ***355****.*

The methyl-substituted analogue of phosphine oxide **352** was also synthesised in order to provide both aryl and alkyl examples of the new structure of phosphine oxides. It was prepared by adapting the synthesis route to **352** (Scheme 3.48). It was found that the synthesis of the methyl-substituted variant proceeded with a much poorer yield than the phenyl-substituted equivalent, which was likely to be due to the highly reactive nature of chlorophosphine **333**, reducing the purity of the stored reagent.



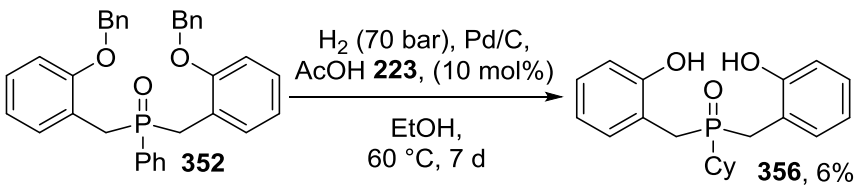
Equation 3.49 *– unsuccessful deprotection of* ***352****.*

The deprotection of the benzyl ethers was found to be much more difficult with the reversed aryl linker compounds than with the Kiełbasiński precursors; attempts to remove the benzyl ethers and yield the desired phosphine oxide were unsuccessful under the hydrogenolysis conditions that had worked on the protected Kiełbasiński phosphine oxide in 4 d, and with the addition of 10 mol% of acetic acid and application of reaction conditions for 19 days the reaction was still not seen to progress (Equation 3.49). All hydrogenolysis reactions to this point had utilised H_2 gas at room temperature from balloons. The use of a high-pressure apparatus was investigated in order to increase the rate of reaction.



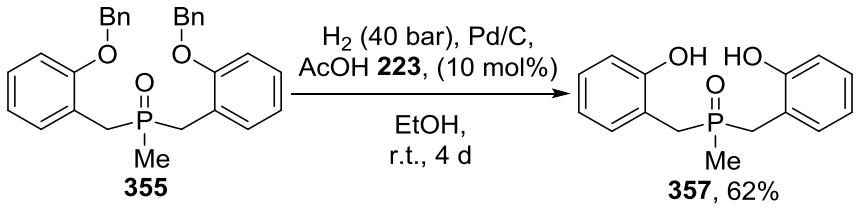
Equation 3.50 *– successful deprotection of the benzyl ethers to give* ***346*** *under forcing conditions.*

It was found than H_2 gas applied under high pressure (60 bar) and at raised temperature (60 °C) with an AcOH catalyst could give the desired phosphine oxide in good yield over 13 days (Equation 3.50). The reaction was conducted on a 2.02 mmol scale with respect to compound **352,** and further attempts to conduct the reaction saw the yields suffer drastically as the scale was increased.



Equation 3.51 *– unintended hydrogenation of the phenyl ring under harsh conditions to give cyclohexyl-substituted* ***356****.*

The benzyl groups proved to be difficult to cleave and under the forcing conditions required hydrogenation of the phenyl group was observed (Equation 3.51).



Equation 3.52 *– Successful deprotection to give phosphine oxide* ***357****.*

Deprotection also proceeded well on a 1.00 mmol scale with the methyl-substituted **355** (Equation 3.52). The conditions required to deprotect in this instance were much lower than with the reported deprotection of the phenyl-substituted equivalent with the reaction proceeding at room temperature but based on the patterns observed this is most likely due to the smaller scale on which the reaction was conducted.

Most pleasingly, on acquisition of the novel reversed linker phosphine oxides there was an absence of any corresponding spirocyclic dioxyphosphoranes as product, indicating that the reversed linker phosphine oxide did indeed differ in reactivity to the Kielbasiński system.

The structure of the novel reversed linker phosphine oxides was confirmed by acquisition of an X-ray crystal structure of the phenyl-substituted variant (Figure 3.53). It is worth noting that a hydrogen bond between one of the hydroxyl groups and the phosphine oxide would be expected but, due to the solid state of the crystal, one unit of an arrangement where intermolecular hydrogen bonds are thought to be present was observed instead.

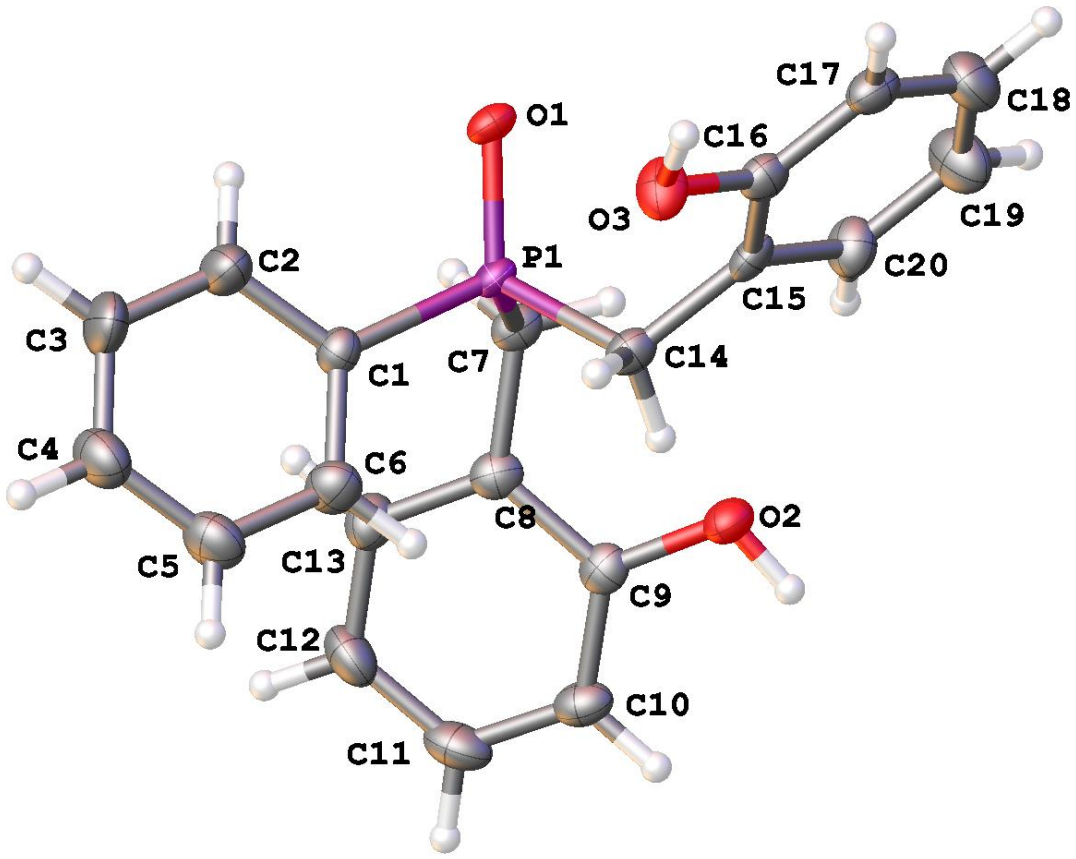
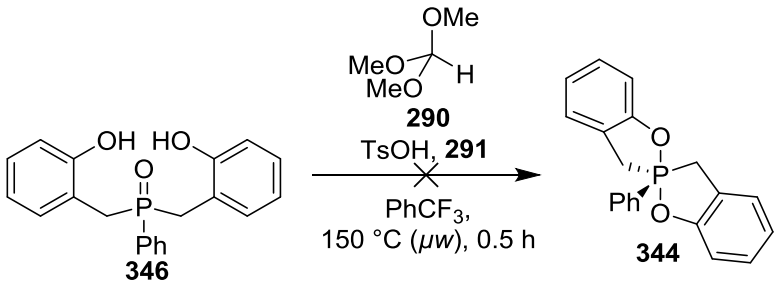
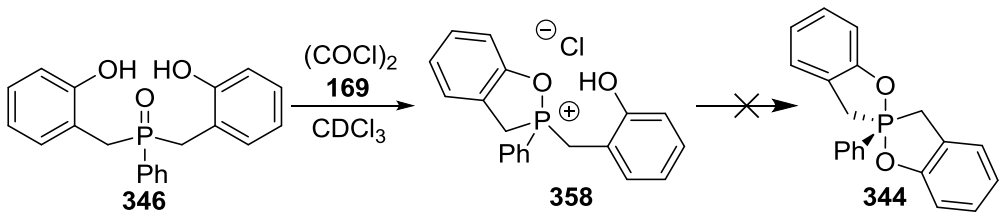


Figure 3.53 *– crystal structure of the phenyl-substituted reversed linker phosphine oxide* ***346****.*



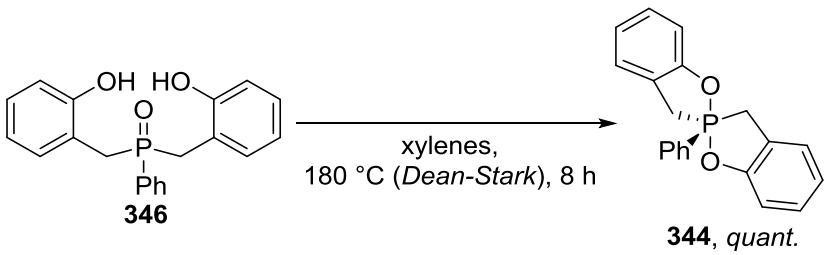
Equation 3.54 *– unsuccessful spirocyclisation of phosphine oxide* ***346*** *using a microwave.*

Attempts were then made to close the inverted linker phosphine oxide into the corresponding spirocyclic dioxyphosphorane. Initial attempts involved the use of a microwave reactor to allow superheating of the solvent and were unsuccessful (Equation 3.54).

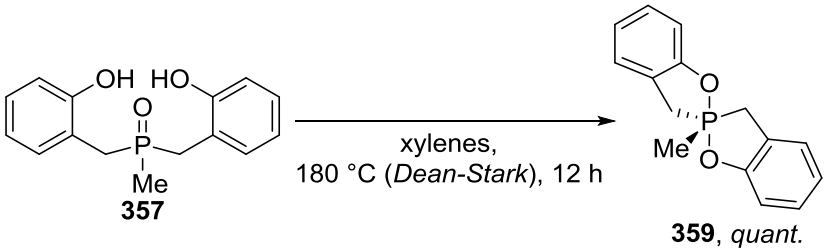


Scheme 3.55 *– unsuccessful spirocyclisation of phosphine oxide* ***346*** *when reacted with oxalyl chloride.*

Attempts were also made to form the spirocyclic dioxyphosphorane *via* the chlorophosphonium salt in the same manner that formation of the Bidman-type phosphoranes had been achieved. It was found that upon reaction with oxalyl chloride a species was formed that exhibited a ^{31}P NMR shift of 85.5 ppm, indicating a phosphonium salt, but with two benzylic environments observed in both the ^{1}H and ^{13}C NMR spectra; this showed the formation of a cyclic phosphonium chloride salt where the phosphoryl oxygen had been lost as CO_2 upon collapse of the short-lived oxalate intermediate and the resultant chlorophosphonium intermediate has quickly reacted with a pendant phenolic group (Scheme 3.55). The lack of any observed spirocyclic dioxyphosphorane formation under these conditions shows a large difference in behaviour when contrasted against the spontaneous spirocyclisation of the Kiełbasiński phosphine oxide.



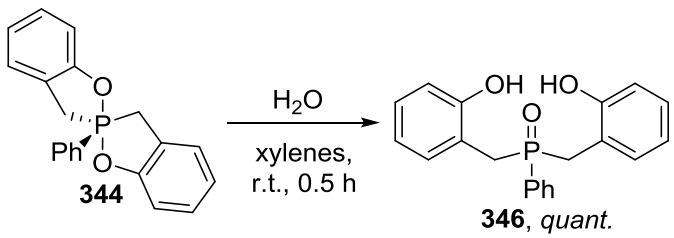
Equation 3.56 *– successful formation of* ***344*** *under Dean-Stark conditions.*



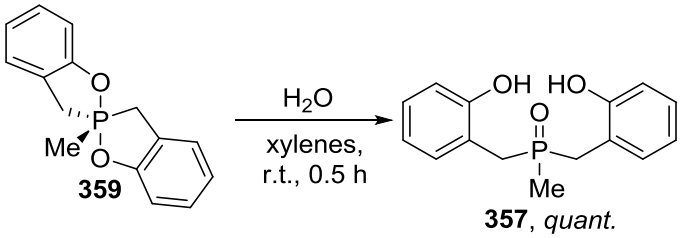
Equation 3.57 *– successful formation of* ***359*** *under Dean-Stark conditions.*

The successful ring-closure of the phenyl- and methyl-substituted inverted linker phosphine oxides was finally achieved at 180 °C in xylenes in a Dean Stark apparatus (Equations 3.56 and 3.57 respectively). Attempts at closure under lower temperatures in benzene were seen to provide the spirophosphorane but progressed at a much slower rate. The phenoxy groups would occupy the axial positions due to the apicophilicity of the oxygen atom, as discussed in chapter 1.3.1.

Interestingly, it was seen in the ^{1}H NMR that two aliphatic environments were present for the bridging CH_2 groups. The CH_2 groups themselves are equivalent which indicated that the two hydrogen atoms on a given CH_2 group would be in different environments; this is due to the rotational symmetry of the molecules. Both catalyst candidate phosphoranes possess C_2 symmetry with the rotational symmetry axis being the P-R bond (with R being phenyl or methyl); this then means that each hydrogen on a the bridging CH_2 group is different from its geminal neighbour, but equivalent to the symmetrical hydrogen on the opposing bridging linker.

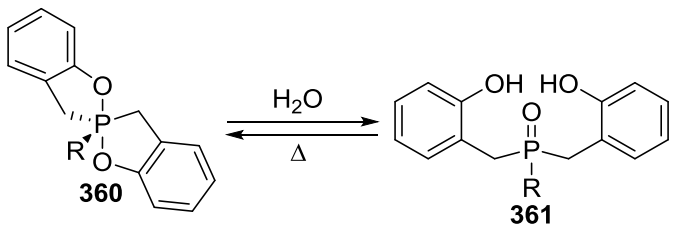


Equation 3.58 *– hydrolysis of phosphorane* ***344****.*



Equation 3.59 *– hydrolysis of phosphorane* ***359****.*

With the spirocyclic dioxyphosphorane now successfully formed the reactivity could be tested; it was found that both the phenyl- and methyl-substituted variants could be hydrolysed in less than 30 min upon addition of one equivalent of water (Equations 3.58 and 3.59 respectively). The observed reactivity with water represents an important result; the Kiełbasiński phosphorane had been proven completely unreactive with water at room temperature whereas the inverted linker phosphoranes readily hydrolyse to regenerate the parent phosphine oxides.



Scheme 3.60 *– the combination of the spirocyclisation reaction and the hydrolysis reaction represents the first example of a system capable of shuttling between phosphorane and phosphine oxide.*

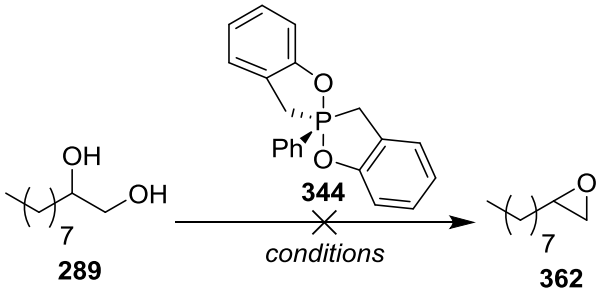
Combining the spirocyclisation reaction and the hydrolysis reaction resulted in a system where the two forms of the catalyst candidate could be easily shuttled between, producing a system in which interchangeability of this type has been observed for the first time (Scheme 3.60). This result is extremely positive regarding the potential suitability of the inverted linker catalyst candidate for a catalytic system; the observed

interchangeability between the phosphine oxide and the spirophosphorane showcases the behaviour required from a catalyst candidate, possessing the turnover step through cyclisation and showing reactivity with a nucleophile (in this case water) from the phosphorane form. Should the spirocyclic dioxyphosphorane prove reactive with nucleophiles other than water to produce a coupled product while regenerating phosphine oxide then all steps of the catalytic cycle would have been achieved.

3.3.2 – Exploring the reactivity of the inverted system

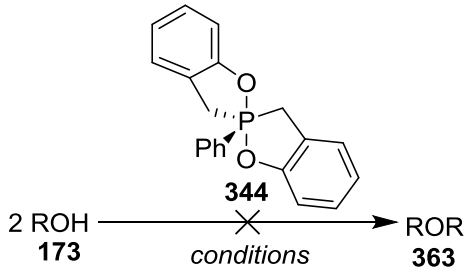
Since relatively high reaction temperatures are required to form the spirophosphorane **314** investigative reactions were conducted with substrates where the thermal background reaction would be relatively slow. The epoxidation of 1,2-diols and the etherification of primary alcohols were identified as good examples to explore.

Table 3.61A *– reaction of phosphorane* ***344*** *with alcohols in etherification reactions.*



Entry	Additional reagents	Solvent	T (°C)	Reaction time
1	-	Xylenes	r.t.	1 d
2	-	Xylenes	110	1 d
3	-	Xylenes	160	1 d
4	Na_2SO_4	Xylenes	160	5 d
5	Na_2SO_4, TsOH (**261**)	Xylenes	160	5 d

Table 3.61B *– reaction of phosphorane* ***344*** *with primary alcohols in etherification reactions.*



Entry	Substrate/Solvent	T (°C)	Reaction time
1	MeOH	65	1 d
2	 **108**	160	19 d

The epoxidation and etherification reactions were attempted on a 0.100 mmol scale with respect to catalyst candidate **344**, which was pre-formed from the phosphine oxide prior to the reaction (Tables 3.61A and 3.61B). It was found that the reactions failed under a wide range of conditions.

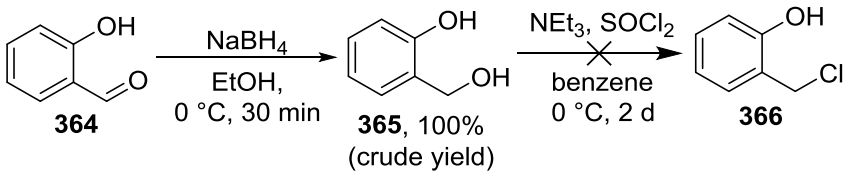
It was observed by ^{31}P NMR in the reactions that employed lower temperatures (Table 3.61A, entries 1 and 2, and Table 3.61B, entry 1) that **344** was quickly converted back to the phosphine oxide. The same was seen upon reducing the temperature of the higher temperature reaction, indicating that the reaction conditions were not anhydrous. The presence of residual amounts of water in the reaction mixture would present a competing hydrolysis reaction with phosphorane **344**.

In order to prevent this competing hydrolysis reaction more effective removal of residual water was required. This could be achieved by conducting these reactions on a larger scale, with a correspondingly larger amount of solvent continuously refluxing. This would lower the proportional loss of solvent through the joins of the apparatus and allow higher reaction temperatures to be used without risking the disruptive loss of solvent possible on smaller scales. These higher reaction temperatures would allow more effective azeotropic removal of the residual water by the Dean-Stark apparatus. The

increased scale would also permit higher reaction concentrations to be applied and, as such, could also increase the rate at which product may form.

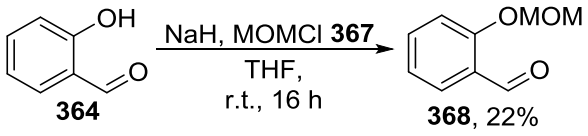
The initial synthetic route *via* hydrogenolysis of the benzyl protecting groups could not deliver the large quantities of phosphorane **344** that would be needed for these larger scale Dean-Stark reactions and, therefore, a new synthesis was needed that avoided this difficult hydrogenolysis.

3.3.3 – Changing the synthetic approach



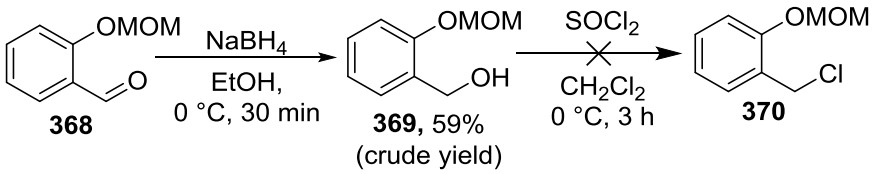
Scheme 3.62 *– unsuccessful formation of a protecting group-free Grignard precursor.*

Work towards finding an alternative synthesis that avoided the difficult hydrogenolysis deprotection step began with the investigation of a protecting group-free approach (Scheme 3.62). It was found that, although the reduction of the salicylaldehyde starting material proceeded well, upon chlorination of the resulting alcohol polymerisation occurred, consistently producing a gummy residue. A similar polymerisation outcome had been observed when exploring protecting group-free synthesis routes to the Kielbasiński phosphorane and so the protecting group-free approach was ruled out.



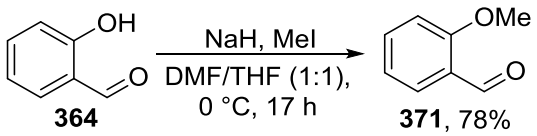
Equation 3.63 *– successful protection of salicylaldehyde to give* ***368****.*

An alternative protecting group to the benzyl ether was identified in a methoxymethyl ether. This protecting group is generally more labile than the benzyl ether and could be removed with acid. Initial reactions to provide the methoxymethyl ether of salicylaldehyde were conducted successfully but in poor yield due to the quality of the methoxymethyl chloride used (Equation 3.63).



Scheme 3.64 *– unsuccessful formation of methoxymethyl ether protected* ***370****.*

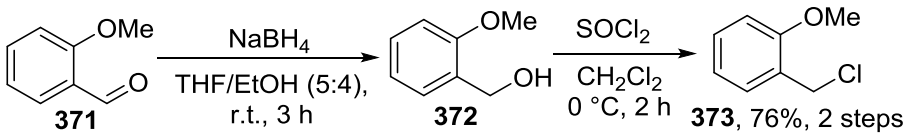
Results observed when conducting the necessary preparation reactions for a methoxymethyl ether protected Grignard precursor gave similar results to the protecting group-free approach (Scheme 3.64). The reduction step proceeded well but on application of chlorination conditions polymerised by-product was observed. This could be due to the HCl by-product of the chlorination reaction by thionyl chloride removing the methoxymethyl ether followed by polymerisation by the same pathway observed with the protecting group-free approach.



Equation 3.65 *– successful protection of salicylaldehyde to give methyl ether* ***371****.*

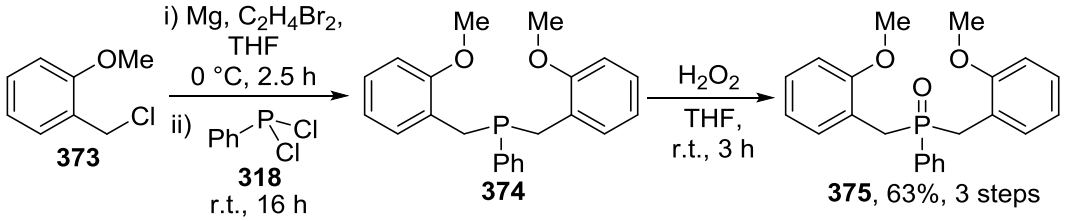
Because of the difficulties encountered when using a methoxymethyl ether instead proposed was a methyl ether protecting group. A methyl ether would not be

sensitive to the acidic conditions of the chlorination reaction and could be removed in the final step of the synthesis by using BCl_3. The protection of salicylaldehyde using methyl iodide proceeded in good yield (Equation 3.65).

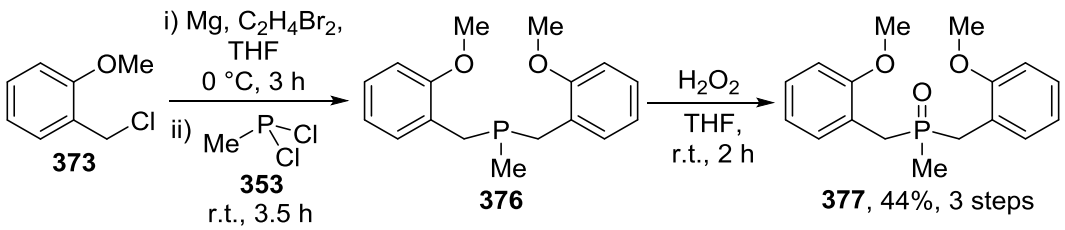


Scheme 3.66 *– successful reduction and chlorination of* ***371*** *to give chloride* ***373****.*

The reduction and subsequent chlorination of the methyl ether protected salicylaldehyde proceeded well and with none of the polymerisation problems encountered when using a methoxymethyl ether protecting group (Scheme 3.66). It was found after establishing the viability of the chlorination of a methyl-ether protected substrate that the methyl-ether protected benzyl alcohol **373** was commercially available; all synthetic processes from this point were conducted using **373** as the starting material with the thionyl chloride chlorination as the first step of the synthesis.

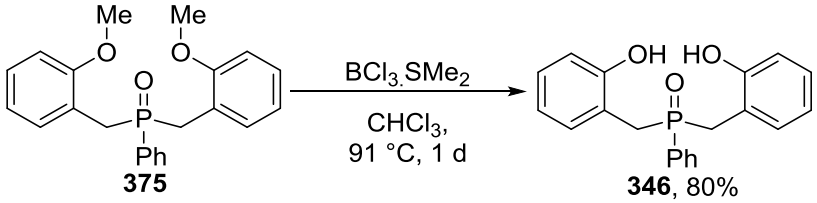


Scheme 3.67 *– Grignard reaction followed by oxidation using hydrogen peroxide to give* ***375****.*



Scheme 3.68 *– Grignard reaction followed by oxidation using hydrogen peroxide to give* ***377****.*

The Grignard reaction using the methyl-ether protected benzyl chloride proceeded successfully and subsequent oxidation gave the methyl-ether protected inverted linker phosphine oxides, both phenyl- and methyl-substituted (Schemes 3.67 and 3.68 respectively). The synthesis routes proceeded in 3 steps from the commercially available (2-methoxyphenyl)methanol starting material with no purification conducted until the phosphine oxide had been obtained.



Equation 3.69 *– deprotection of the bis methyl-ethers proceeded relatively quickly and in good yield.*

Deprotection of the methyl-ether protecting groups proceeded successfully when reacted with boron trichloride (Equation 3.69). The deprotection was successfully conducted on multi-gram scales and, crucially, occurred over 24 h in refluxing chloroform. The advantages of the methyl-ether protecting group over the previously employed benzyl-ether protecting group are numerous: the BCl_3 deprotection reflux can be conducted using standard laboratory apparatus rather than the high-pressure equipment required for the difficult hydrogenolysis; the yields for the methyl-ether deprotection, although comparable to the benzyl-ether deprotection on small scales, do not suffer when expanded to multi-gram reactions, where the hydrogenolysis yields suffered drastically; and, most usefully, the deprotection of the methyl-ether occurs over a period of 1 day, rather than requiring periods of greater than a week, allowing a higher throughput of catalyst candidate and therefore expediting investigations into the catalyst candidate's usefulness.

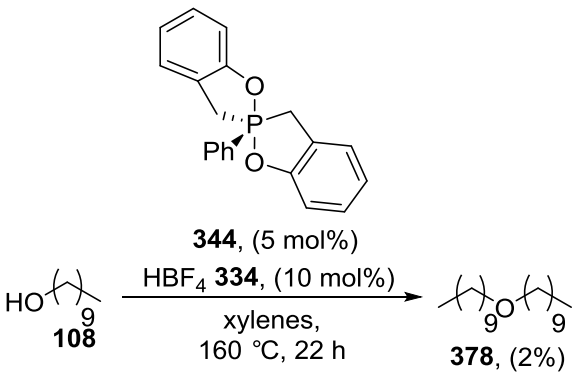
With a reliable method of producing the quantities of inverted-linker phosphine oxide now secured, work could begin on the large-scale, constantly-dehydrating reactions that had been identified as crucial if the effectiveness of the catalyst candidate were to be fully investigated.

3.3.4 – Attempting catalysis

With a reliable route to increased quantities of catalyst candidate established, investigations of the large-scale reactions under continuously-dehydrating conditions were conducted with the etherification of decanol, again due to the relatively slow thermally-driven background reaction.

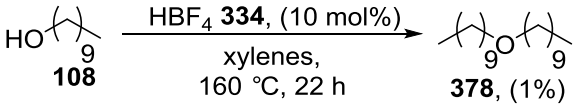
Investigations began with a substoichiometric, rather than stoichiometric, amount of phosphorus-based catalyst candidate in order to make most effective use of the limited amount of catalyst candidate **344** available.

An anhydrous Brønsted acid catalyst, in the form of HBF_4, was included as the spirocyclic dioxyphosphorane form of the catalyst candidate is kinetically stable. The inclusion of a protic acid may open the stable phosphorane to the alkoxyphosphonium salt, which should be more reactive as witnessed by Evans Jr. and co-workers.



Equation 3.70 *– low-yielding yet successful etherification reaction mediated by phosphorane* ***344****.*

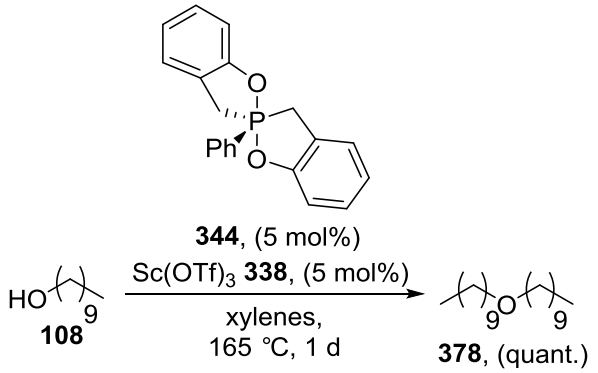
The etherification of decanol experiment was conducted on a 70 mmol scale with 5 mol% of **344** and 10 mol% of the HBF_4 acid catalyst (Equation 3.70). The spirocyclic dioxyphosphorane was pre-formed in the reaction apparatus and solvent overnight under Dean-Stark conditions, ensuring no water was present from the catalyst formation step. The reaction successfully gave didecyl ether product in low yield.



Equation 3.71 *– the etherification background reaction containing HBF_4.*

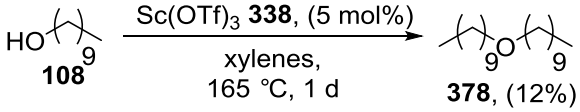
The background reaction was conducted with 10 mol% of HBF_4, again giving didecyl ether product in low yield (Equation 3.71). Due to the low yields observed in both the trial reaction and its control reaction the effectiveness of the catalyst could not be deduced.

On examination of the reaction apparatus it became apparent that the $HBF_4.Et_2O$ complex (b.p. 130 °C) had boiled under the high reaction temperatures and become trapped in the Dean-Stark apparatus. Effectively the reactions were only exposed to the presence of the HBF_4 for a short period of time before it was removed from the reactions conditions. The phosphorus-catalysed reaction pathway would be limited by this removal of the acid catalyst and so other possible higher-boiling acid catalysts were considered; $Sc(OTf)_3$ was selected because of the high boiling point, removing the problem of trapping of the acid catalyst in the Dean-Stark apparatus, and also because of the successful opening of the Kiełbasiński phosphorane observed in the presence of this Lewis acid.



Equation 3.72 *– successful phosphorus-mediated etherification of decanol.*

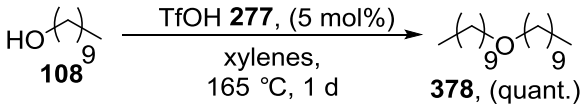
The etherification of decanol was conducted over 24 h with 5 mol% of phosphorane **344** (again pre-formed from phosphine oxide **346** before the reaction) and 5 mol% of $Sc(OTf)_3$ giving didecyl ether product in quantitative yield (Equation 3.72).



Equation 3.73 *– the etherification background reaction containing $Sc(OTf)_3$.*

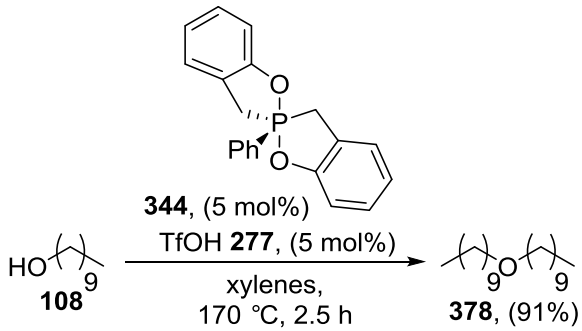
The control reaction gave didecyl ether in a comparatively much reduced yield (Equation 3.73). It was therefore clear that, with the background reaction excepted, the phosphorus-mediated pathway gave 88% yield.

Despite the highly encouraging result of the phosphorus-mediated reaction there was some concern that the reaction may not be proceeding by the phosphorus-catalysed pathway that was anticipated. It could have been possible that the phosphorus catalyst was interacting with the $Sc(OTf)_3$ to release triflic acid into the reaction mixture, which could have then acted as a simple acid catalyst to promote the etherification, rather than the reaction proceeding by phosphorus catalysis.



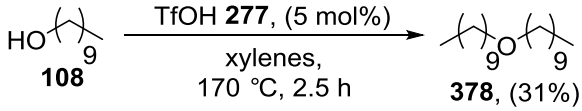
Equation 3.74 *– the etherification background reaction containing TfOH.*

A further control reaction was conducted to determine whether triflic acid released through reaction of **344** with scandium triflate could be promoting the etherification (Equation 3.74). Quantitative yield was also observed with the triflic acid catalyst.



Equation 3.75 *– phosphorane **344** and triflic acid mediated etherification of decanol.*

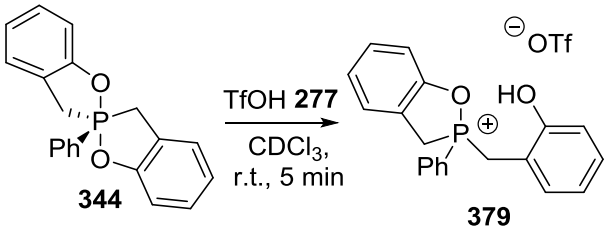
In order to fully understand whether triflic acid present in the reaction mixture could be driving the etherification reaction, rather than phosphorane **344**, it was necessary to observe both etherification reactions over a shorter period of time. The etherification reaction was repeated with **344** and triflic acid catalysts over 2.5 h giving 91% yield (Equation 3.75).



Equation 3.76 *– the etherification background reaction containing triflic acid.*

The control reaction was then conducted giving a comparatively low 31% yield (Equation 3.76). This showed, firstly, that triflic acid is a more effective catalyst for this reaction than scandium triflate, but most importantly that the phosphorus-mediated pathway proceeded in much improved yield compared to the control reaction, with a difference of 60%. This gave proof of a phosphorus-catalysed etherification reaction in the presence of a triflic acid cocatalyst and provided proof-of-concept for the use of spirocyclic dioxyphosphoranes as catalysts in Mitsunobu-type deoxy-coupling reactions; control reactions have been considered and investigated and the action of the two cocatalysts is clearly responsible for the promotion of the etherification reaction. The investigation of triflic acid *vs.* scandium triflate as cocatalyst has proven that the reaction is mainly promoted *via* a phosphorus-mediated pathway and that it is not *in situ* released triflic acid that is promoting the reaction. The use of triflic acid as cocatalyst is also beneficial as triflic acid is cheaper than scandium triflate, making the reaction more readily useable.

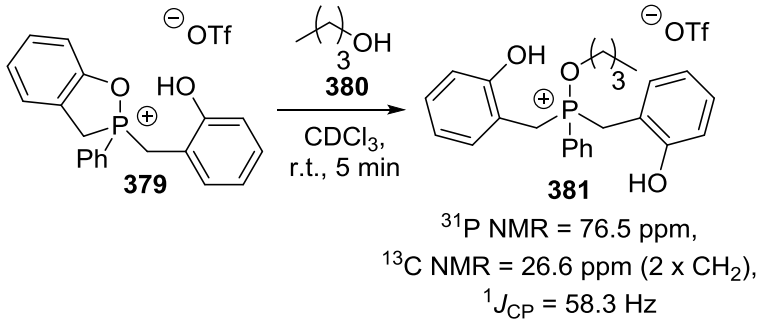
With the results obtained in investigations with the phosphorane **344**/triflic acid cocatalyst system it can be stated that the conducted reactions represent the first example of a redox-neutral phosphorus (V)-catalysed coupling reaction. Further investigations must be conducted to examine the scope of the reaction, whilst attempting to optimise the reaction conditions and potentially the catalyst design and, importantly, determining the stereochemical outcome of the reaction for chiral enantiopure substrates, which will give confirmation of a Mitsunobu-type reaction mechanism.



^{31}P NMR = 104 ppm,
^{13}C NMR = 29.1 (CH_2), 28.7 ppm (CH_2),
$^{1}J_{CP}$ = 60.6 Hz, 59.0 Hz

Equation 3.77 *– reaction of phosphorane* ***344*** *with triflic acid to give a monocyclic phosphonium salt.*

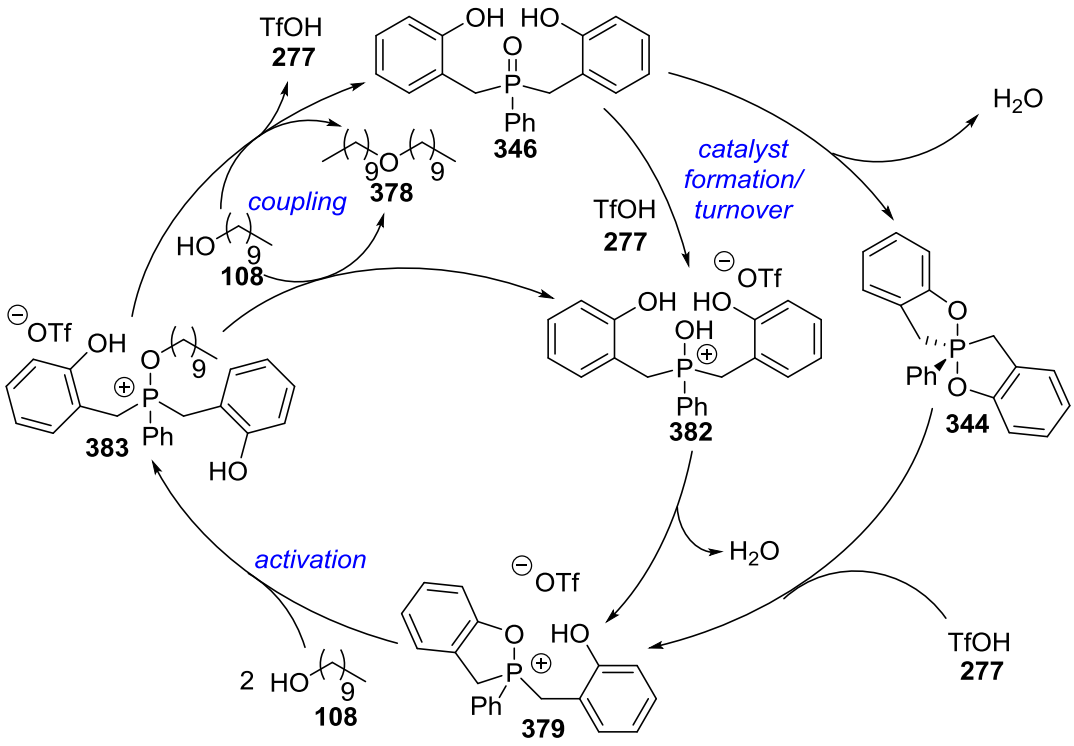
Investigations were undertaken to identify the intermediates formed within the successful catalytic reaction, starting with the reaction of the inverted-linker spirocyclic dioxyphosphorane and the triflic acid cocatalysts (Equation 3.77). It was found in the ^{31}P NMR shift that a species was formed at 104 ppm, suggesting a phosphonium salt that is shifted downfield due to ring strain. In the ^{13}C NMR it was found that there were two CH_2 environments present, with $^{1}J_{PC}$ coupling constants of 60.6 Hz and 59.0 Hz, which indicated that two separate CH_2 environments were directly bonded to phosphorus. The observed phosphonium salt shift coupled with the two separate CH_2 shifts corresponded to the proposed structure of a monocyclic phosphonium salt, as shown in Equation 3.77. The formation of this monocycle would occur when one of the P-O bond oxygen atoms was protonated on contact with the triflic acid, which would then lead to cleavage of the P-O σ-bond to provide the phosphonium salt described.



Scheme 3.78 *– reaction of the monocyclic phosphonium salt intermediate* ***379*** *with butanol to provide the important alkoxyphosphonium salt intermediate* ***381****.*

Further reaction of the monocyclic phosphonium salt with butanol was conducted in preparation for an attempted etherification of butanol to form dibutyl ether (Scheme 3.78). A change in shift in the ^{31}P NMR was observed to 69 ppm, indicating an acyclic phosphonium salt, and one CH_2 peak was seen in the ^{13}C NMR which outlines symmetrisation of the pendant linkers, *i.e.* opening of the remaining phosphocycle by butanol, as shown in Scheme 3.78.

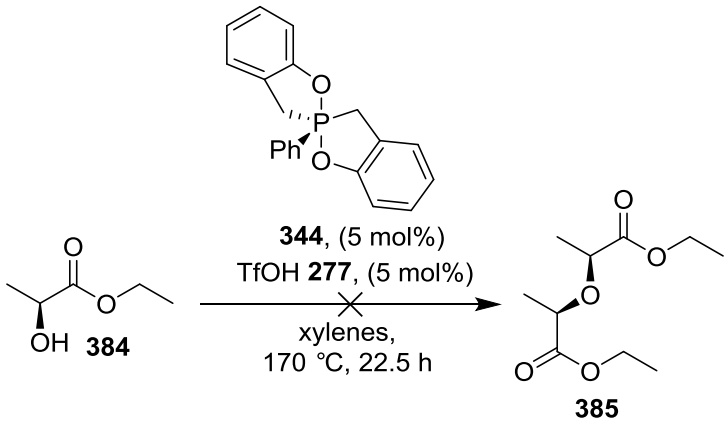
These species, observed by multinuclear NMR, confirmed the expected reaction of the phosphorane and triflic acid catalysts to give a cyclic phosphonium salt intermediate which could then react with substrate to give the key alkoxyphosphonium salt intermediate that is required for nucleophilic substitution chemistry of this type.



Scheme 3.79 *– catalytic cycle for the phosphorus-mediated etherification of decanol.*

With the phosphonium intermediates experimentally determined, a complete representation of the catalytic cycle can be arranged (Scheme 3.79). The catalyst formation/turnover step had been an established attribute of spirocyclic dioxyphosphoranes, firstly with the observed spontaneous closure of the Kiełbasiński phosphine oxide and then also observed under more forcing conditions with the inverted-linker phosphine oxide **346**. It is at this stage that the actual release of water from the dehydration reaction occurs, with the eliminated water removed from the reaction by a xylene azeotrope with trapping in the Dean-Stark apparatus. Dioxyphosphorane **344** can then react with the triflic acid cocatalyst to form reactive monocyclic phosphonium intermediate **379** in the activation step of the catalytic cycle. **379** can then react with one equivalent of alcohol to produce alkoxyphosphonium salt **383**, which has been highlighted throughout this work as a key reactive intermediate in phosphorus-mediated nucleophilic substitution reactions. Finally, in the coupling step of

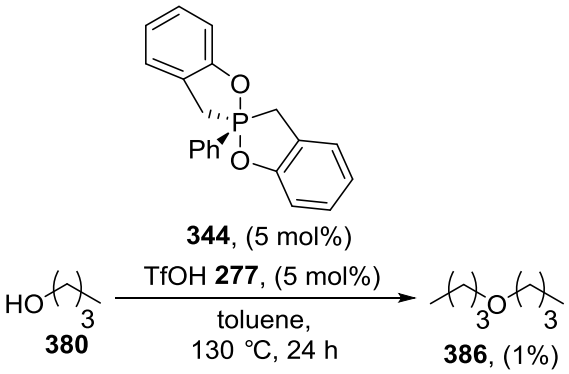
the catalytic cycle, another equivalent of alcohol reacts with the activated hydroxyl group of the initial alcohol molecule, now incorporated in alkoxyphosphonium salt **383** in an Arbuzov-type reaction to provide ether product **378** and give protonated phosphine oxide **382** rather than regenerating phosphine oxide **346**, due to the presence of triflic acid. **382** can then dehydrate directly to give reactive monocyclic intermediate **379**.



Equation 3.80 *– unsuccessful etherification of ethyl lactate.*

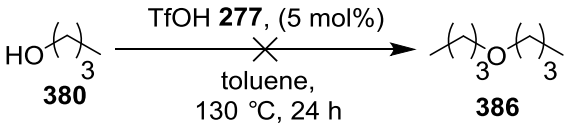
Work was begun into investigating the mechanism of the phosphorus-catalysed etherification reaction. An etherification reaction was attempted with a secondary hydroxyl group in the form of (−)-ethyl L-lactate (Equation 3.80). Should the reaction have proceeded by a Mitsunobu-type pathway as was expected then the resulting ether product would possess one C-O centre where stereochemistry had been retained (the nucleophile) and one where the stereochemistry had inverted where the alcohol had been converted into the electrophilic alkoxyphosphonium salt by the catalysts. Unfortunately, most likely due to the elevated reaction temperatures, a great number of signals were observed in the ^{1}H NMR indicating many background reactions. Polymerisation/transesterification is a likely cause of the reaction failure. The mechanistic investigations with secondary hydroxyl groups will still need to be conducted

but will require substrates that are less susceptible to other reactive pathways *i.e.* unadorned secondary alcohols.



Equation 3.81 *– low-yielding reduced-temperature etherification of butanol.*

Work was also conducted on the optimisation of reaction conditions with the aim of investigating whether such harsh reaction conditions were required. In previous reactions temperatures of between 160 and 180 °C were needed in order to ensure the effective operation of the Dean-Stark apparatus whilst employing xylenes as the reaction solvent. A reaction was conducted in toluene which possesses a lower boiling point than xylenes. It was found that phosphorane catalyst formation from the phosphine oxide precatalyst still occurred at 130 °C but over a much longer timeframe (full conversion was not seen over 24 h). Nevertheless the observed formation of catalyst in toluene at lower temperatures confirmed that the high temperature conditions previously used were not strictly necessary. An etherification reaction was conducted in toluene with butanol (Equation 3.81). The reaction gave dibutyl ether in 1% yield but the mass balance of the reaction was severely reduced, indicating that the boiling point of butanol (117 °C) was not sufficiently above the boiling point of toluene (111 °C) to prevent the substrate being removed by trapping in the Dean-Stark apparatus. The observation of product despite the removal of starting material is an encouraging result.



Equation 3.82 *– etherification background reaction of butanol.*

The control reaction of the etherification of butanol yielded no dibutyl ether product whatsoever, but the full balance was severely reduced in the same manner as with the phosphorus-mediated reaction (Equation 3.82). In order to prevent the loss of starting material in this manner it would be necessary to conduct future reactions in a lower boiling solvent such as benzene in order to ensure the effective operation of the Dean-Stark apparatus whilst maintaining the presence of starting material.

The successful development of the first example of a redox-neutral Mitsunobu reaction that is catalytic in phosphorus (V) is a significant achievement in the field of phosphorus catalysis. The room for optimisation of the reaction as it stands is great with potential improvement in the areas of reaction conditions, the identity of the acid cocatalyst and the structure of the phosphorane cocatalyst, and when this is considered the reaction has the potential to provide a workable catalytic alternative to the current Mitsunobu reaction as the state-of-the-art for nucleophilic substitution of hydroxyl groups.

4 – Conclusions

This project was initiated with the aim of developing a redox-free, phosphorus-mediated catalytic method for hydroxyl activation and substitution to be used as an alternative to the current state-of-the-art – the triphenylphosphine oxide/diethyl azodicarboxylate conditions of the Mitsunobu reaction. The design of the newly developed reaction was to focus around a phosphorus catalyst and to avoid the use of explosive diazo reagents and also the generation of large amounts of hydrazine and phosphine oxide waste.

The focus of the project had been centred around using a dioxyphosphorane catalyst and over the duration of the project several systems were investigated in order to achieve the stated aims. This led to the production of several novel dioxyphosphoranes and further investigation into silyloxyphosphonium salts.

Regarding the project aims: a novel phosphine oxide/spirocyclic dioxyphosphorane system has been invented that exhibits unusual reactivity and is the first example of an arrangement in which shuttling between two forms is easily achievable. This characteristic of the novel phosphine oxide/spirocyclic dioxyphosphorane system allowed the development of a uniquely reactive phosphorus compound and thus gave the first example of a phosphorus-catalysed Mitsunobu reaction, with initial experiments demonstrating the etherification of decanol to didecyl ether.

Currently the first example of the catalytic reaction requires high reaction temperatures in order to effectively achieve catalyst turnover and ensure complete removal of the water by-product; ideally the harsh reaction conditions will be reduced upon work towards the optimisation of the reaction. The reaction scope is currently limited to the etherification of primary alcohols, but this serves as proof-of-concept for

the reaction and it is hoped that the exploration of further traditional Mitsunobu substrates will see the reaction scope expanded.

The novel catalyst operates in a manifold where dehydrating coupling reactions can be achieved with only the requirement for 5 mol% of both novel phosphorane and triflic acids catalysts. Thus a system has been developed where a redox-free, phosphorus catalysed Mitsunobu reaction proceeds without the need for the use of explosive diazo compounds and without the large amounts of hydrazine and phosphine oxide waste that posed a significant drawback to standard Mitsunobu conditions; the only stoichiometric waste product of the novel reaction is water.

5 – Future work

With the development of a catalytic Mitsunobu reaction successfully achieved the direction that future work should take is clear: the optimisation of the reaction conditions and the examination of the scope of the reaction.

The current reaction is required to operate at elevated reaction conditions to ensure the continuous dehydration of the reaction by the boiling of an azeotropic mixture and currently employs xylenes as solvent. The formation of the phosphorane catalyst has also been conducted in toluene and should be investigated in benzene, in order to test the minimum temperature at which the reaction can operate whilst still remaining dry and maintaining a reasonable rate of catalyst turnover. If the reaction can be conducted at lower temperatures then this would make the reaction conditions much more acceptable and would allow the investigation of substrates with lower boiling points.

Mechanistically, it has yet to be determined whether the novel catalytic reaction proceeds with inversion or retention of stereochemistry, as in preliminary studies to date only primary alcohols have been investigated. Conducting the reaction with simple chiral secondary alcohols will allow elucidation of the reaction mechanism by monitoring the stereochemistry of the product. It is expected that the reaction will be found to proceed with inversion of stereochemistry, as in the traditional Mitsunobu reaction, because of the phosphonium intermediates that have been composed and characterised independently in this work, but confirmation of the mechanism must be conducted in order to confirm this theory.

As mentioned above, presently preliminary studies have been conducted solely with decanol. Further work on this project should explore the range of substrates that can be reacted using the new catalytic manifold, particularly focussing on traditional

Mitsunobu areas of use such as esterification reactions and others detailed in the introduction of this work. It is of particular importance to conduct an experiment where an alcohol is reacted with a different nucleophile – *i.e.* not reacted with another equivalent of itself; the measurement of the reaction of the alcohol with the nucleophile rather than with more alcohol would provide insight into the potential of this reaction for widespread use with a wider variety of substrates.

Other work that should be conducted in order to further experiments performed in this work is the completion of the investigations into the potential kinetic resolution reaction using silyloxyphosphonium salts. The silyloxyphosphonium salt compounds are easily made and a kinetic resolution using them could provide a useful way to enantioenriched silylated alcohols. This route to enantioenriched silyl ethers could prove a very useful reaction in the construction of complex organic molecules by potentially protecting the alcohol and isolating the desired isomer of a racemic mixture of alcohols in one step. Immediate further work on this project would first start with the investigation of how the silyloxydiphenylmenthylphosphonium triflate salt reacts with a racemic chiral secondary alcohol and whether a difference in reaction is observed between the isomers. If the menthylphosphonium salt is unsuccessful at separating the isomers then other chiral phosphine oxides are available for investigation.

One final, important area for improvement and optimisation in future work is with the catalyst structure itself; the inverted linker phosphine oxide/spirocyclic dioxyphosphorane system has many areas for optimisation that could prove key to the development of a more widely applicable reaction. The current rate-limited step of the catalytic reaction is the catalyst turnover (phosphorane formation) step; at the lower temperatures that are desired with this reaction the turnover of the catalyst becomes a slow process. It is evident from the studies conducted across a range of dioxyphosphoranes that small differences in structure can have large effects concerning

reactivity and therefore small changes in the structure of the catalyst could prove key to allowing catalyst turnover to occur at lower temperatures. The catalyst structure can be changed with the "fifth substituent" – the substituent that is not part of the spirocyclic ring system – which can alter the electronics at phosphorus to produce a more electrophilic catalyst reactive centre; this may allow catalyst turnover to occur more quickly and may also make the catalyst more reactive towards reaction substrates. The aryl linkers also have many areas in which catalyst optimisation can be conducted: the phenyl rings can be electronically altered by the addition of electron-withdrawing or -donating groups in order to change the reactivity of the phenolic oxygens, which may help to facilitate catalyst turnover at lower reaction temperatures; and the CH_2 bridge between the central phosphorus atom and the phenolic group could be adorned with sterically bulky groups to decrease the bond-angle of the ring-forming substituents, making use of the Thorpe-Ingold effect and allowing more favourable formation of the phosphorane, again facilitating catalyst turnover at lower temperatures.[122] The danger with altering the catalyst to allow turnover at lower temperatures is that, should the phosphorane structure be more favourable and stable, the catalyst may become unreactive towards reaction substrates as was seen with the Kiełbasiński phosphorane in this work. It is important to be wary of the balance that must be struck between ease of formation of the phosphorane catalyst and reactivity of the catalyst once formed.

6 – Experimental

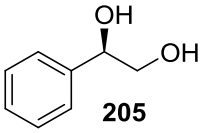
6.1 – General experimental

All glassware was flame-dried or oven-dried and allowed to cool under a stream of argon before use. Cooling to −78 °C was effected using dry ice/acetone mixtures. Degassing was achieved by purging nitrogen through the appropriate solution for 10 min. The petrol used refers to the fraction with b.p. 40–60 °C. Commercial solvents and reagents were used as supplied with the following exceptions: THF was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl or obtained from a solvent tower, where degassed THF was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure; Et_2O was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl or obtained from a solvent tower, where degassed Et_2O was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure; toluene was pre-dried over sodium wire and distilled under an atmosphere of nitrogen from sodium benzophenone ketyl or obtained from a solvent tower, where degassed toluene was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure; CH_2Cl_2 was dried over calcium hydride powder, filtered, distilled and stored over 4 Å molecular sieves or purchased as analytical grade and stored over 4 Å molecular sieves; DMF was dried over calcium hydride powder, filtered, distilled and stored over 4 Å molecular sieves or purchased as analytical grade and stored over 4 Å molecular sieves. Activation of 4 Å molecular sieves was achieved by heating to 200 °C under high vacuum for 15 h. Microwave reactions were carried out on a Biotage Initiator microwave. Reactions were monitored using TLC on Polygram® SIL G/UV254 0.25 mm silica gel pre-coated glass sheets with fluorescent indicator. Sheets were visualised using ultra-violet light (254 nm) and/or anisaldehyde or $KMnO_4$ solutions as appropriate. Flash

chromatography was performed using Fluorochem silica gel 60, 35–70 micron. Melting points were acquired on a Stuart® SMP3 melting point instrument. Infrared spectra were recorded on a Pelkin-Elmer 1600 FTIR instrument as a dilute solution in the indicated solvent or as neat solids using an ATR accessory. ^{1}H and ^{13}C NMR spectra were recorded on either Bruker DPX 400 or Bruker AV(III) 500 instruments as dilute solutions in the indicated deuterated solvent. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. All chemical shifts are reported relative to $CHCl_3$ (δH = 7.27 ppm, δC = 77.0 ppm). Coupling constants (*J*) are reported in Hertz (Hz) and are recorded after averaging. The multiplicity of a ^{1}H NMR signal is designated by one of the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal. ^{13}C multiplicities were assigned using a DEPT sequence; where appropriate HMQC, HMBC and NOE experiments were performed to aid assignment. Mass spectra were acquired on either VG Micromass 70E, VG Autospec or Micromass LCTOF instruments. Some compounds could not be isolated due to their instability and therefore solely multinuclear NMR data is reported. References for experimental procedures from the literature are provided after the written method and references for literature values for experimental data are provided after each compound.

6.2 – Compound experimental

1-Phenylethane-1,2-diol (**205**)



205

To a stirred solution of AD-mix-β (14.0 g) in H_2O/*t*-BuOH (1:1, 100 mL) at 0 °C was added styrene (1.15 mL, 10.0 mmol). After 2 h the reaction was quenched by stirring with Na_2SO_3 (14.0 g). After 1 h the organic layer was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 9:1, petroleum ether/Et_2O) gave 1-phenylethane-1,2-diol as a white amorphous solid (1.17 g, 84%, m.p. 41 °C).[123]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 - 7.28 (ArH, m, 5 H), 4.83 (CH, dd, *J* = 8.2, 3.6 Hz, 1 H), 3.78 (CH_2, dd, *J* = 11.4, 3.6 Hz, 1 H), 3.67 (CH_2, dd, *J* = 11.4, 8.2 Hz, 1 H), 2.16 (OH, br. s, 2 H) ppm.

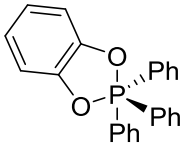
^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.6 (Cq), 128.7 (CH, 2 C), 128.2 (CH), 126.2 (CH, 2 C), 74.8 (CH), 68.2 (CH_2) ppm.

HRMS (ESI+): *m*/*z* 161.0575 (*m*/*z* calculated for $C_8H_{10}O_2Na$ – 161.0573).

IR υ_{max} ($CHCl_3$): 3612 (O-H), 3009 (O-H), 1454 (C-Ph), 1061, 888 cm^{-1}.

Consistent with literature values.[124]

2,2,2-Triphenyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphole (**232**)



232

To a stirred solution of triphenylphosphine oxide (334 mg, 1.20 mmol) in $CDCl_3$ (4.5 mL) under an Ar atmosphere at r.t. was added oxalyl chloride (85.9 μL, 1.00 mmol) and

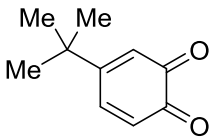
the evolution of gas was observed. After 5 min catechol (165 mg, 1.50 mmol) and triethylamine (418 μL, 3.00 mmol) were added simultaneously. The reaction continued to be stirred whilst being monitored by ^{31}P NMR with samples analysed immediately and then at 30 min intervals. The maximum conversion observed to 2,2,2-triphenyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphole by ^{31}P NMR was 76% after 5 min. Complete hydrolysis was seen within 5 min upon addition of water (18.0 μL, 1.00 mmol) to return triphenylphosphine oxide (^{31}P NMR = 29.9 ppm).[125]

^{31}P NMR (162 MHz, $CDCl_3$): δ = −18.9 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 - 7.11 (ArH, m, 15 H), 6.95 - 6.88 (ArH, m, 2 H), 6.67 - 6.57 (ArH, m, 2 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.3 (Cq), 139.0 (Cq), 135.9 (Cq, d, *J* = 11.0 Hz, 3 C), 131.0 (CH, d, *J* = 10.2 Hz, 6 C), 129.3 (CH, d, *J* = 2.9 Hz, 3 C), 127.4 (CH, d, *J* = 14.6 Hz, 6 C), 122.1 (CH, d, *J* = 2.9 Hz, 2 C), 107.6 (CH, d, *J* = 10.2 Hz, 2 C) ppm. Consistent with literature values.[126]

4-(*tert*-Butyl)cyclohexa-3,5-diene-1,2-dione (**236**)



236

To a stirred solution of 4-*tert*-butyl catechol (1.01 g, 6.09 mmol) in CH_2Cl_2 (30 mL) was added a solution of sodium periodate (1.30 g, 6.09 mmol) in H_2O (6 mL). After stirring vigorously for 30 min the mixture was separated. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL) before all organic extracts were combined, dried over $MgSO_4$, decolourised with charcoal and concentrated to give 4-(*tert*-butyl)cyclohexa-3,5-diene-1,2-dione as a brown amorphous solid (0.681 g, 68%).[127]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (CH, dd, *J* = 10.4, 2.4 Hz, 1 H), 6.39 (CH, dd, *J* = 10.4, 0.5 Hz, 1 H), 6.28 (CH, dd, *J* = 2.4, 0.5 Hz, 1 H), 1.23 (CH_3, s, 9 H) ppm.

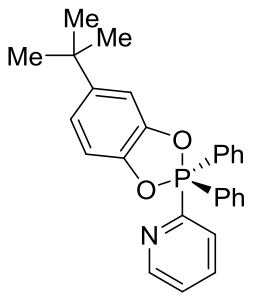
^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.5 (Cq), 180.4 (Cq), 162.2 (Cq), 140.2 (CH), 129.6 (CH), 124.0 (CH), 35.8 (Cq), 27.9 (CH_3, 3 C) ppm.

HRMS (ESI+): *m/z* 165.0915 (*m/z* calculated for $C_{10}H_{13}O_2$ – 165.0910).

IR υ_{max} ($CHCl_3$): 2972, 1690 (C=O), 1667 (C=O), 1286 cm^{-1}.

Consistent with literature values.[112]

2-(5-(*tert*-Butyl)-2,2-diphenyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphol-2-yl)pyridine (**237**)



237

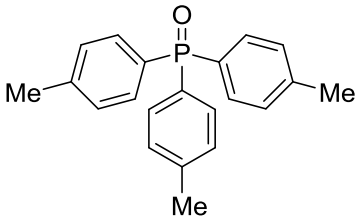
To a stirred solution of diphenyl-2-pyridylphosphine (263 mg, 1.00 mmol) and 4Å mol. sieves in toluene-d_8 (6 mL) under an atmosphere of N_2 was added 4-(*tert*-butyl)cyclohexa-3,5-diene-1,2-dione (246 mg, 1.50 mmol). The solution continued to be stirred and was monitored hourly by ^{31}P NMR spectroscopy. The maximum conversion to 2-(5-(*tert*-butyl)-2,2-diphenyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphol-2-yl)pyridine observed by ^{31}P NMR was 45% after 1 h. After this point a slow hydrolysis was seen to give diphenyl-2-pyridylphosphine oxide (^{31}P NMR = 19.9 ppm) over 24 h.[128]

^{31}P NMR (162 MHz, $CDCl_3$): δ = −26.7 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 - 7.38 (ArH, m, 5 H), 7.26 - 7.13 (ArH, m, 9 H), 7.05 - 7.00 (ArH, m, 1 H), 6.95 - 6.89 (ArH, m, 1 H), 6.84 - 6.78 (ArH, m, 1 H), 1.10 (CH_3, s, 9 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.0 (Cq, d, *J* = 13.2 Hz), 144.1 (Cq, d, *J* = 134.7 Hz), 142.5 (Cq), 139.6 (Cq, d, *J* = 129.5 Hz), 135.9 (Cq, d, *J* = 11.0 Hz), 133.8 (CH, d, *J* = 19.8 Hz), 131.0 (CH, d, *J* = 10.2 Hz, 4 C), 129.3 (CH, d, *J* = 2.9 Hz), 128.8 (CH, 2 C), 128.4 (CH, d, *J* = 7.3 Hz, 4 C), 127.4 (CH, d, *J* = 14.6 Hz), 122.1 (CH, d, *J* = 2.9 Hz), 116.2 (CH), 108.9 (CH, d, *J* = 11.0 Hz), 107.6 (CH, d, *J* = 10.2 Hz), 34.3 (Cq), 31.4 (CH_3, 3 C) ppm.

Tri-*p*-tolylphosphine oxide (**240**)



240

To a stirred solution of tris(*p*-tolyl)phosphine (609 mg, 2.00 mmol) in THF (10 mL) was added hydrogen peroxide solution in H_2O (12% w/w) (2.83 mL, 10 mmol). After stirring for 2 h the organic solvent was removed and the residue diluted with H_2O (20 mL) before being washed with $CHCl_3$ (3 x 30 mL). The organic washings were dried over $MgSO_4$ and concentrated to give tri-*p*-tolylphosphine oxide as a white amorphous solid (578 mg, 90%, m.p. 119 °C).[68]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.2 (OPR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (ArH, dd, *J* = 11.8, 8.2 Hz, 6 H), 7.26 - 7.21 (ArH, m, 6 H), 2.39 (CH_3, s, 9 H) ppm.

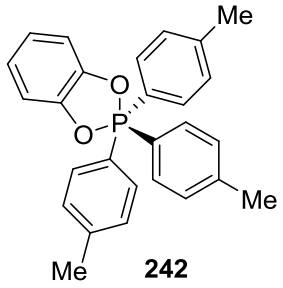
^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.3 (Cq, d, *J* = 2.7 Hz, 3 C), 132.2 (CH, d, *J* = 10.4 Hz, 6 C), 129.8 (Cq, d, *J* = 106.7 Hz, 3 C), 129.3 (CH, d, *J* = 12.3 Hz, 6 C), 21.7 (CH_3, d, *J* = 0.9 Hz, 3 C) ppm.

HRMS (ESI+): *m/z* 321.1394 (*m/z* calculated for $C_{21}H_{22}OP$ – 321.1403).

IR υ_{max} ($CHCl_3$): 2981, 1602, 1171 (P=O), 1117, 660 cm^{-1}.

Consistent with literature values.[129]

2,2,2-Tri-*p*-tolyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphole (**242**)



242

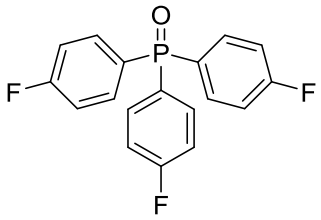
To a stirred solution of tris(*p*-tolyl)phosphine oxide (288 mg, 0.900 mmol) in $CDCl_3$ (3.5 mL) under an Ar atmosphere at r.t. was added oxalyl chloride (64.4 μL, 0.750 mmol) and the evolution of gas was observed. After 5 min catechol (124 mg, 1.13 mmol) and triethylamine (314 μL, 2.25 mmol) were added simultaneously. The reaction continued to be stirred whilst being monitored by ^{31}P NMR with samples analysed immediately and then at 30 min intervals. The maximum conversion observed to 2,2,2-tri-*p*-tolyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphole by ^{31}P NMR was 83% after 5 min. Complete hydrolysis was seen within 5 min upon addition of water (13.5 μL, 0.75 mmol) to return tris(*p*-tolyl)phosphine oxide (^{31}P NMR = 31.3 ppm).[125]

^{31}P NMR (162 MHz, $CDCl_3$): δ = −10.4 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (ArH, dd, *J* = 12.5, 8.1 Hz, 6 H), 7.03 (ArH, dd, *J* = 8.1, 3.6 Hz, 6 H), 6.76 - 6.72 (ArH, m, *J* = 2.2, 5.7 Hz, 2 H), 6.63 - 6.59 (ArH, m, *J* = 3.5 Hz, 2 H), 2.23 (CH_3, s, 9 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.3 (Cq, d, *J* = 3.8 Hz), 139.9 (Cq, d, *J* = 3.1 Hz, 3 C), 136.9 (Cq, d, *J* = 119.6 Hz, 3 C), 131.5 (CH, d, *J* = 10.7 Hz, 6 C), 128.4 (CH, d, *J* = 13.8 Hz, 6 C), 119.9 (CH, 2 C), 110.8 (CH, d, *J* = 10.0 Hz, 2 C), 21.2 (CH_3, d, *J* = 1.5 Hz, 3 C) ppm.

Tris(4-fluorophenyl)phosphine oxide (**243**)



243

To a stirred solution of tris(4-fluorophenyl)phosphine (158 mg, 0.500 mmol) in THF (2.5 mL) was added hydrogen peroxide solution in H_2O (12% w/w) (709 μL, 2.50 mmol). After stirring for 2 h the organic solvent was removed and the residue diluted with H_2O (20 mL) before being washed with EtOAc (3 x 30 mL). The organic washings were dried over $MgSO_4$ and concentrated to give tris(4-fluorophenyl)phosphine oxide as a white amorphous solid (167 mg, quant.).[68]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.1 (OPR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (ArH, ddd, *J* = 11.7, 8.8, 5.5 Hz, 6 H), 7.18 (ArH, dt, *J* = 8.8, 2.1 Hz, 6 H) ppm.

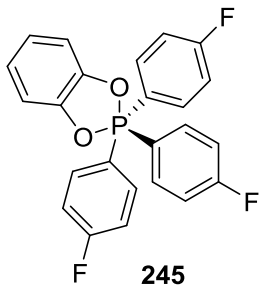
^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4 (Cq, dd, *J* = 254.6, 3.1 Hz, 3 C), 134.7 (CH, dd, *J* = 11.5, 9.2 Hz, 6 C), 127.8 (Cq, dd, *J* = 108.9, 3.8 Hz, 3 C), 116.4 (CH, dd, *J* = 21.5, 13.8 Hz, 6 C) ppm.

HRMS (ESI+): *m/z* 355.0464 (*m/z* calculated for $C_{18}H_{12}F_3OPNa$ – 355.0470).

IR υ_{max} ($CHCl_3$): 2990, 1594, 1500, 1398 (P-Ph), 1182 (P=O), 1161, 1118, 831 cm^{-1}.

Consistent with literature values.[68]

2,2,2-Tris(4-fluorophenyl)-2λ^5-benzo[*d*][1,3,2]dioxaphosphole (**245**)



245

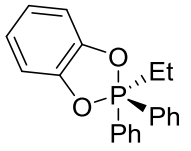
To a stirred solution of tris(4-fluorophenyl)phosphine oxide (399 mg, 1.20 mmol) in $CDCl_3$ (4.5 mL) under an N_2 atmosphere at r.t. was added oxalyl chloride (85.9 μL, 1.00 mmol) and the evolution of gas was observed. After 5 min catechol (165 mg, 1.50 mmol) and triethylamine (418 μL, 3.00 mmol) were added simultaneously. The reaction continued to be stirred whilst being monitored by ^{31}P NMR with samples analysed immediately and then at 30 min intervals. The maximum conversion observed to 2,2,2-tris(4-fluorophenyl)-2λ^5-benzo[*d*][1,3,2]dioxaphosphole by ^{31}P NMR was 77% after 5 min. Complete hydrolysis was seen within 5 min upon addition of water (18.0 μL, 1.00 mmol) to return tris(4-fluorophenyl)phosphine oxide (^{31}P NMR = 27.1 ppm).[125]

^{31}P NMR (162 MHz, $CDCl_3$): δ = −23.8 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (ArH, ddd, *J* = 12.0, 8.8, 5.6 Hz, 6 H), 6.88 (ArH, dt, *J* = 8.8, 2.9 Hz, 6 H), 6.74 (ArH, dd, *J* = 6.0, 3.5 Hz, 2 H), 6.64 (ArH, dd, *J* = 5.7, 3.5 Hz, 2 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.0 (Cq, dd, *J* = 251.5, 3.1 Hz, 3 C), 145.2 (Cq), 144.6 (Cq), 137.8 (Cq, dd, *J* = 123.4, 3.1 Hz, 3 C), 133.8 (CH, dd, *J* = 11.9, 8.1 Hz, 6 C), 120.4 (CH, 2 C), 114.8 (CH, dd, *J* = 21.5, 15.3 Hz, 6 C), 110.1 (CH, d, *J* = 11.5 Hz, 2 C) ppm.

2-Ethyl-2,2-diphenyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphole (**248**)



248

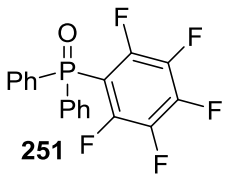
To a stirred solution of ethyldiphenylphosphine oxide (276 mg, 1.20 mmol) in $CDCl_3$ (4.5 mL) under an Ar atmosphere at r.t. was added oxalyl chloride (85.9 μL, 1.00 mmol) and the evolution of gas was observed. After 5 min catechol (165 mg, 1.50 mmol) and triethylamine (418 μL, 3.00 mmol) were added simultaneously. The reaction continued to be stirred whilst being monitored by ^{31}P NMR with samples analysed immediately and then at 30 min intervals. The maximum conversion observed to 2-ethyl-2,2-diphenyl-2λ^5-benzo[*d*][1,3,2]dioxaphosphole by ^{31}P NMR was 76% after 5 min. Complete hydrolysis was seen within 5 min upon addition of water (18.0 μL, 1.00 mmol) to return ethyldiphenylphosphine oxide (^{31}P NMR = 35.5 ppm).[125]

^{31}P NMR (162 MHz, $CDCl_3$): δ = −9.2 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 - 7.48 (ArH, m, 2 H), 7.37 (ArH, s, 4 H), 7.16 - 7.14 (ArH, m, 4 H), 6.71 (ArH, dd, *J* = 5.8, 3.6 Hz, 2 H), 6.63 (ArH, dd, *J* = 5.5, 3.5 Hz, 2 H), 2.37 (CH_2, dd, *J* = 7.7, 4.8 Hz, 2 H), 0.98 (CH_3, t, *J* = 7.0 Hz, 3 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.2 (Cq, d, *J* = 15.3 Hz, 2 C), 141.2 (Cq, d, *J* = 105.0 Hz, 2 C), 129.9 (CH, d, *J* = 9.2 Hz, 4 C), 129.0 (CH, d, *J* = 3.1 Hz, 2 C), 127.5 (CH, d, *J* = 12.3 Hz, 4 C), 119.4 (CH, d, *J* = 6.1 Hz, 2 C), 109.8 (CH, d, *J* = 10.0 Hz, 2 C), 32.6 (CH_2, d, *J* = 94.3 Hz), 6.0 (CH_3, d, *J* = 7.7 Hz) ppm.

(Perfluorophenyl)diphenylphosphine oxide (**251**)



251

To a stirred solution of (pentafluorophenyl)diphenylphosphine (880 mg, 2.50 mmol) in THF (12.5 mL) was added hydrogen peroxide solution in H_2O (12% w/w) (3.54 mL, 12.5 mmol). After stirring for 2 h the organic solvent was removed and the residue diluted with H_2O (30 mL) before being washed with $CHCl_3$ (3 x 30 mL). The organic washings were dried over $MgSO_4$ and concentrated to give (perfluorophenyl)diphenylphosphine oxide as a white amorphous solid (868 mg, 94%).[68]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.6 (OPR_3) ppm.

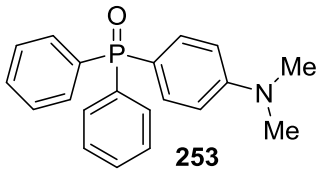
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 - 7.70 (ArH, m, 4 H), 7.66 - 7.58 (ArH, m, 2 H), 7.55 - 7.48 (ArH, m, 4 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.0 (CH, d, *J* = 3.1 Hz, 2 C), 131.3 (CH, d, *J* = 10.7 Hz, 4 C), 131.7 (Cq, d, *J* = 112.7 Hz, 2 C), 129.0 (CH, d, *J* = 13.0 Hz, 4 C) ppm. Note: signals for the perfluorophenyl group were exceptionally weak and could not be distinguished from the baseline.

HRMS (ESI+): *m/z* 391.0277 (*m/z* calculated for $C_{18}H_{10}F_5OPNa$ – 391.0282).

IR υ_{max} ($CHCl_3$): 2999, 1643, 1520, 1480, 1439 (P-Ph), 1388, 1299, 1192 (P=O), 1106, 984, 909 cm^{-1}.

(4-(Dimethylamino)phenyl)diphenylphosphine oxide (**253**)



253

To a stirred solution of 4-(dimethylamino)phenyldiphenylphosphine (1.53 g, 5.00 mmol) in THF (25 mL) was added hydrogen peroxide solution in H_2O (12% w/w) (7.09 mL, 25 mmol). After stirring for 2 h the organic solvent was removed and the residue diluted with H_2O (20 mL) before being washed with $CHCl_3$ (3 x 30 mL). The organic washings were dried over $MgSO_4$ and concentrated to give (4-dimethylamino)phenyl)diphenylphosphine oxide as a white amorphous solid (1.27 g, 79%, m.p. 160 °C).[68]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.6 (OPR_3) ppm.

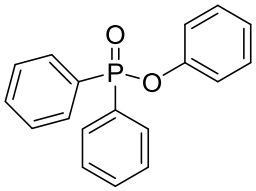
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 - 7.63 (ArH, m, 4 H), 7.54 - 7.39 (ArH, m, 8 H), 6.70 (ArH, dd, *J* = 9.1, 2.3 Hz, 2 H), 3.01 (CH_3, s, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.6 (Cq, d, *J* = 2.3 Hz), 133.8 (Cq, d, *J* = 104.0 Hz, 2 C), 133.6 (CH, d, *J* = 11.4 Hz, 2 C), 132.2 (CH, d, *J* = 10.0 Hz, 4 C), 131.6 (CH, d, *J* = 2.7 Hz, 2 C), 128.4 (CH, d, *J* = 12.3 Hz, 4 C), 116.9 (Cq, d, *J* = 116.3 Hz), 111.4 (CH, d, *J* = 13.2 Hz, 2 C), 40.1 (CH_3, 2 C) ppm.

HRMS (ESI+): *m/z* 344.1168 (*m/z* calculated for $C_{20}H_{20}NOPNa$ – 344.1175).

IR υ_{max} ($CHCl_3$): 2979, 1560, 1518, 1437 (P-Ph), 1367, 1167 (P=O), 1119 cm^{-1}.

Phenyl diphenylphosphinate (**257**)



257

To a stirred solution of diphenylphosphinic chloride (983 μL, 5.00 mmol) in dry benzene (10 mL) was added freshly distilled triethylamine (697 μL, 5.00 mmol). A solution of phenol (471 μL, 5.00 mmol) in dry benzene (5 mL) was added dropwise over 5 min with stirring before the reaction was heated to reflux at 80 °C. After 30 min the reaction was cooled and the solids removed by filtration. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure to give phenyl diphenylphosphinate as a white amorphous solid (815 mg, 55%, m.p. 100 °C).[130]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.3 (OPR_2OR) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 - 7.85 (ArH, m, 4 H), 7.57 - 7.50 (ArH, m, 2 H), 7.49 - 7.44 (ArH, m, 4 H), 7.25 - 7.16 (ArH, m, 4 H), 7.10 - 7.04 (ArH, m, 1 H) ppm.

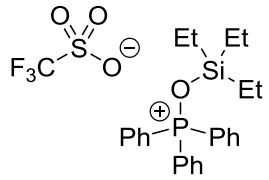
^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.0 (Cq, d, *J* = 8.4 Hz), 132.6 (CH, d, *J* = 3.1 Hz, 2 C), 132.0 (CH, d, *J* = 10.7 Hz, 4 C), 131.2 (Cq, d, *J* = 138.0 Hz, 2 C), 129.8 (CH, 2 C), 128.7 (CH, d, *J* = 13.8 Hz, 4 C), 124.7 (CH), 120.9 (CH, d, *J* = 4.6 Hz, 2 C) ppm.

HRMS (ESI+): *m/z* 295.0881 (*m/z* calculated for $C_{18}H_{16}O_2P$ – 295.0882).

IR υ_{max} ($CHCl_3$): 3002, 1593, 1491, 1439 (P-Ph), 1193 (P=O), 1132 (P-O-C), 922 cm^{-1}.

Consistent with literature values.[130]

Triphenyl((triethylsilyl)oxy)phosphonium trifluoromethanesulfonate (**265**)



265

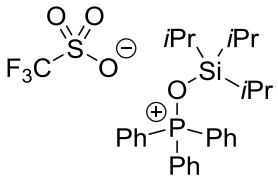
To a stirred solution of triphenylphosphine oxide (278 mg, 1.00 mmol) in $CDCl_3$ (1 mL) under an Ar atmosphere was added triethylsilyl trifluoromethanesulfonate (226 μL, 1.00 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 51.5 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (ArH, t, *J* = 7.2 Hz, 3 H), 7.69 - 7.62 (ArH, m, 6 H), 7.59 (ArH, dd, *J* = 7.2, 3.4 Hz, 6 H), 0.91 (CH_3, t, *J* = 8.0 Hz, 9 H), 0.51 (CH_2, q, *J* = 8.0 Hz, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.1 (CH, 3 C), 132.7 (CH, d, *J* = 11.7 Hz, 6 C), 129.7 (CH, d, *J* = 13.9 Hz, 6 C), 123.2 (Cq, d, *J* = 109.0 Hz, 3 C), 119.8 (Cq, d, *J* = 319.1 Hz), 6.7 (CH_3, 3 C), 6.4 (CH_2, 3 C) ppm.

Triphenyl((tri*iso*-propylsilyl)oxy)phosphonium trifluoromethanesulfonate (**266**)



266

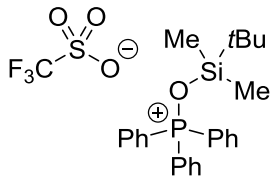
To a stirred solution of triphenylphosphine oxide (139 mg, 0.500 mmol) in $CDCl_3$ (1 mL) under an Ar atmosphere was added tri*iso*-propylsilyl trifluoromethanesulfonate (134 μL, 0.500 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 53.4 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (ArH, d, *J* = 7.3 Hz, 3 H), 7.70 (ArH, dd, *J* = 4.0, 13.7 Hz, 6 H), 7.59 (ArH, dd, *J* = 7.3, 13.7 Hz, 6 H), 1.22 - 1.13 (CH, m, 3 H), 0.92 (CH_3, d, *J* = 7.4 Hz, 18 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.3 (CH, d, *J* = 3.1 Hz, 3 C), 132.6 (CH, d, *J* = 12.3 Hz, 6 C), 130.4 (CH, d, *J* = 13.8 Hz, 6 C), 121.6 (Cq, d, *J* = 111.2 Hz, 3 C), 16.7 (CH_3, 6 C), 12.1 (CH, 3 C) ppm.

((*tert*-Butyldimethylsilyl)oxy)triphenylphosphonium trifluoromethanesulfonate (**267**)



267

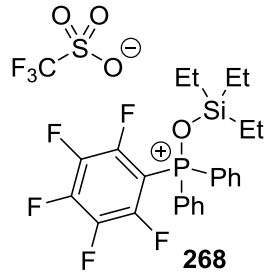
To a stirred solution of triphenylphosphine oxide (139 mg, 0.500 mmol) in $CDCl_3$ (1 mL) under an Ar atmosphere was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (115 μL, 0.500 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 53.4 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 - 7.78 (ArH, m, 3 H), 7.78 - 7.67 (ArH, m, 6 H), 7.66 - 7.60 (ArH, m, 6 H), 0.92 (CH_3, s, 9 H), 0.39 (CH_3, s, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.3 (CH, 3 C), 132.7 (CH, d, *J* = 12.3 Hz, 6 C), 130.5 (CH, d, *J* = 13.8 Hz, 6 C), 121.2 (Cq, d, *J* = 110.4 Hz, 3 C), 25.6 (CH_3, 3 C), 18.5 (Cq), −3.1 (CH_3, 2 C) ppm.

(Perfluorophenyl)diphenyl((triethylsilyl)oxy)phosphonium trifluoromethanesulfonate (**268**)



268

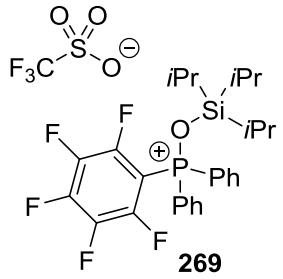
To a stirred solution of (pentafluorophenyl)diphenylphosphine oxide (184 mg, 0.500 mmol) in $CDCl_3$ (4.5 mL) under an Ar atmosphere was added triethylsilyl trifluoromethanesulfonate (113 μL, 0.500 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 35.5 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 - 7.72 (ArH, m, 6 H), 7.70 - 7.62 (ArH, m, 4 H), 0.89 (CH_3, d, *J* = 7.6 Hz, 9 H), 0.57 - 0.46 (CH_2, m, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.5 (CH, 2 C), 131.9 (CH, d, *J* = 12.4 Hz, 4 C), 131.2 (Cq, d, *J* = 35.9 Hz, 2 C), 130.0 (CH, d, *J* = 14.6 Hz, 4 C), 5.9 (CH_3, 3 C), 4.9 (CH_2, 3 C) ppm. Note: signals for the perfluorophenyl group were exceptionally weak and could not be distinguished from the baseline.

(Perfluorophenyl)diphenyl((tri*iso*-propylsilyl)oxy)phosphonium trifluoromethanesulfonate (**269**)



269

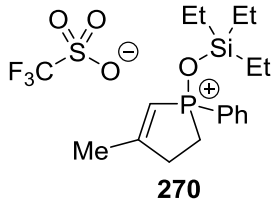
To a stirred solution of (pentafluorophenyl)diphenylphosphine oxide (184 mg, 0.500 mmol) in $CDCl_3$ (4.5 mL) under an Ar atmosphere was added tri*iso*-propylsilyl trifluoromethanesulfonate (135 μL, 0.500 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.8 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (ArH, dd, *J* = 7.7, 13.4 Hz, 4 H), 7.69 - 7.61 (ArH, m, 2 H), 7.60 - 7.49 (ArH, m, 4 H), 1.41 - 1.35 (CH, m, 3 H), 1.15 (CH_3, d, *J* = 7.4 Hz, 18 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.4 (CH, 2 C), 131.7 (CH, d, *J* = 11.7 Hz, 4 C), 129.6 (CH, d, *J* = 13.9 Hz, 4 C), 127.4 (Cq, d, *J* = 116.4 Hz, 2 C), 17.0 (CH_3, 6 C), 12.4 (CH, 3 C) ppm. Note: signals for the perfluorophenyl group were exceptionally weak and could not be distinguished from the baseline.

4-Methyl-1-phenyl-1-((triethylsilyl)oxy)-2,3-dihydro-1*H*-phosphol-1-ium trifluoromethanesulfonate (**270**)



270

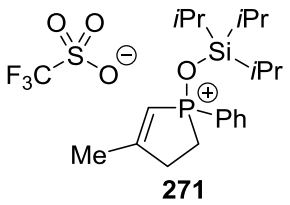
To a stirred solution of 3-methyl-1-phenyl-2-phospholene 1-oxide (96.1 mg, 0.500 mmol) in $CDCl_3$ (4.5 mL) under an Ar atmosphere was added triethylsilyl trifluoromethanesulfonate (113 μL, 0.500 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 89.4 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 - 7.59 (ArH, m, 5 H), 6.05 (CH, dd, *J* = 27.9, 1.1 Hz, 1 H), 3.25 - 2.76 (CH_2, m, 4 H), 2.26 (CH_3, s, 3 H), 0.92 (CH_3, t, *J* = 8.0 Hz, 9 H), 0.51 (CH_2, q, *J* = 8.0 Hz, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.1 (Cq, d, *J* = 28.5 Hz), 134.7 (CH, d, *J* = 2.9 Hz), 131.1 (CH, d, *J* = 12.4 Hz, 2 C), 129.6 (CH, d, *J* = 13.9 Hz, 2 C), 123.1 (Cq, d, *J* = 112.7 Hz), 119.7 (Cq, d, *J* = 318.3 Hz), 111.5 (CH, d, *J* = 110.3 Hz), 34.7 (CH_2, d, *J* = 8.8 Hz), 24.4 (CH_2, d, *J* = 66.6 Hz), 21.5 (CH_3, d, *J* = 18.3 Hz), 6.7 (CH_3, 3 C), 6.3 (CH_2, 3 C) ppm.

4-Methyl-1-phenyl-1-((tri*iso*-propylsilyl)oxy)-2,3-dihydro-1*H*-phosphol-1-ium trifluoromethanesulfonate (**271**)



271

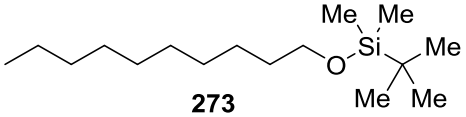
To a stirred solution of 3-methyl-1-phenyl-2-phospholene 1-oxide (96.1 mg, 0.500 mmol) in $CDCl_3$ (4.5 mL) under an Ar atmosphere was added tri*iso*-propylsilyl trifluoromethanesulfonate (135 μL, 0.500 mmol). After 30 min the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 89.0 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 - 7.66 (ArH, m, 5 H), 6.23 (CH, dd, *J* = 29.1, 1.3 Hz, 1 H), 3.36 - 2.87 (CH_2, m, 4 H), 2.33 (CH_3, s, 3 H), 1.27 - 1.18 (CH, m, 3 H), 1.09 - 1.05 (CH_3, m, 18 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.3 (Cq, d, *J* = 29.3 Hz), 135.4 (CH, d, *J* = 2.9 Hz), 131.1 (CH, d, *J* = 12.4 Hz, 2 C), 130.2 (CH, d, *J* = 13.9 Hz, 2 C), 123.6 (Cq, d, *J* = 112.7 Hz), 120.1 (Cq, d, *J* = 296.4 Hz), 111.4 (CH, d, *J* = 101.7 Hz), 35.3 (CH_2, d, *J* = 8.8 Hz), 25.5 (CH_2, d, *J* = 70.3 Hz), 22.1 (CH_3, d, *J* = 18.3 Hz), 17.3 (CH_3, 6 C), 12.5 (CH, 3 C) ppm.

tert-Butyl(decyloxy)dimethylsilane (**273**)



273

To a stirred solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.13 g, 7.50 mmol) and dimethylaminopyridine (2.14 g, 17.5 mmol) in DMF (8 mL) was added 1-decanol (332 μL, 5 mmol). After 3 h the solution was quenched with water (30 mL)

before the organic layer was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 1:1, petroleum ether/Et_2O) gave *tert*-butyl(decyloxy)dimethylsilane as a colourless oil (464 mg, 55%).

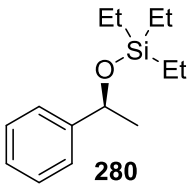
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (CH_2, t, *J* = 6.8 Hz, 2 H), 1.51 (CH_2, quin, *J* = 6.8 Hz, 2 H), 1.36 - 1.22 (CH_2, m, 14 H), 0.89 (CH_3, s, 9 H), 0.88 (CH_3, m, 3 H), 0.05 (CH_3, s, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 63.5 (CH_2), 33.1 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 26.1 (CH_3, 3 C), 26.0 (CH_2), 22.8 (CH_2), 18.5 (Cq), 14.3 (CH_3), −5.1 (CH_3, 2 C) ppm.

HRMS (ESI+): *m*/*z* 295.2415 (*m*/*z* calculated for $C_{16}H_{36}OSiNa$ – 295.2428).

Consistent with literature values.[116]

(*S*)-Triethyl(1-phenylethoxy)silane (**280**)



280

To a stirred solution of triphenylphosphine oxide (334 mg, 1.20 mmol) in dry THF (2 mL) under an Ar atmosphere was added triethylsilyl trifluoromethanesulfonate (271 μL, 1.20 mmol). After 1 h a solution of (*S*)-1-phenylethanol (121 μL, 1.00 mmol) and di*iso*-propylethylamine (244 μL, 1.40 mmol) in dry THF (2 mL) was added dropwise over 5 min. After 3 h the reaction was quenched with NH_4Cl (sat. aq.) (10 mL). The organic layer was then extracted with Et_2O (3 x 20 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 1:1, petroleum ether/Et_2O) gave (*S*)-triethyl(1-phenylethoxy)silane as a colourless oil (172 mg, 73%, $[\alpha]_D^{25}$ = −61.9 (*c* = 1.34, $CHCl_3$)).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 - 7.27 (ArH, m, 4 H), 7.25 - 7.19 (ArH, m, *J* = 7.0 Hz, 1 H), 4.87 (CH, q, *J* = 6.4 Hz, 1 H), 1.43 (CH_3, d, *J* = 6.4 Hz, 3 H), 0.91 (CH_3, t, *J* = 8.0 Hz, 9 H), 0.57 (CH_2, dq, *J* = 4.0, 7.9 Hz, 6 H) ppm.

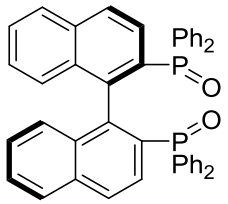
^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.0 (Cq), 128.2 (CH, 2 C), 126.9 (CH), 125.4 (CH, 2 C), 70.7 (CH), 27.4 (CH_3), 6.9 (CH_3, 3 C), 5.0 (CH_2, 3 C) ppm.

HRMS (ESI+): *m/z* 259.1486(*m/z* calculated for $C_{13}H_{21}BrOSiNa$ – 259.1489).

IR υ_{max} ($CHCl_3$): 2958, 2877, 1465 (C-Ph), 1370, 1240 (Si-C), 1095 (C-O), 1018 (Si-O), 953 cm^{-1}.

Consistent with literature values.[117,131]

(*R*)-[1,1'-Binaphthalene]-2,2'-diylbis(diphenylphosphine oxide) (**281**)



281

To a stirred solution of (*R*)-BINAP (300 mg, 0.482 mmol) in THF (2.4 mL) was added hydrogen peroxide solution in H_2O (12% w/w) (1.31 mL, 4.82 mmol). After stirring for 2 h the reaction was quenched with $NaHCO_3$. The organic solvent was removed and the residue diluted with H_2O (20 mL) before being washed with CH_2Cl_2 (3 x 30 mL). The organic washings were dried over $MgSO_4$ and concentrated to give crude product. Purification by recrystallization from EtOH provided (*R*)-[1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphine oxide) as a white amorphous solid (170 mg, 54%).[68]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.2 (OPR_3, 2 P) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 - 7.79 (ArH, m, 4 H), 7.72 - 7.65 (ArH, m, 4 H), 7.46 - 7.32 (ArH, m, 12 H), 7.26 - 7.20 (ArH, m, 8 H), 6.79 (ArH, d, *J* = 3.5 Hz, 4 H) ppm.

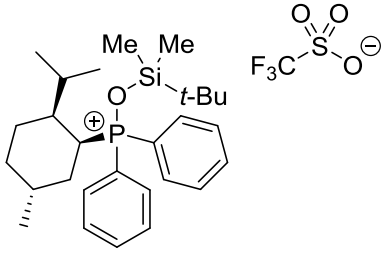
^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.6 (Cq, d, *J* = 100.4 Hz, 2 C), 133.9 (Cq, d, *J* = 49.1 Hz, 2 C), 132.7 (CH, d, *J* = 10.0 Hz, 8 C), 132.2 (CH, d, *J* = 9.2 Hz, 8 C), 131.3 (CH, d, *J* = 3.1 Hz, 2 C), 131.1 (CH, d, *J* = 3.1 Hz, 2 C), 129.2 (Cq, d, *J* = 103.5 Hz, 4 C), 128.3 (Cq, d, *J* = 13.0 Hz, 2 C), 128.2 (CH, d, *J* = 12.3 Hz, 2 C), 128.0 (CH, d, *J* = 12.3 Hz, 2 C), 127.9 (CH, d, *J* = 6.1 Hz, 2 C), 127.5 (Cq, d, *J* = 12.3 Hz, 2 C), 127.3 (CH, d, *J* = 6.9 Hz, 4 C), 126.0 (CH, 2 C) ppm.

HRMS (ESI+): *m/z* 677.1734 (*m/z* calculated for $C_{44}H_{32}O_2P_2Na$ – 677.1770).

IR υ_{max} ($CHCl_3$): 2970, 1437 (P-Ar), 1192 (P=O), 1117, 909 cm^{-1}.

Consistent with literature values.[132]

((*tert*-Butyldimethylsilyl)oxy)((1*S*,2*S*,5*R*)-2-*iso*-propyl-5-methylcyclohexyl)diphenylphosphonium trifluoromethanesulfonate (**284**)



284

To a stirred solution of ((1*S*,2*S*,5*R*)-2-*iso*-propyl-5-methlcyclohexyl)diphenylphosphine oxide (17.0 mg, 50.0 μmol) in $CDCl_3$ (1.5 mL) under an Ar atmosphere was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (11.5 μL, 50.0 μmol). After 1 h the reaction was submitted for NMR analysis. Quantitative conversion was observed by ^{31}P NMR.[114]

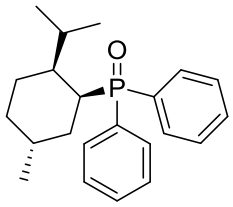
^{31}P NMR (162 MHz, $CDCl_3$): δ = 66.0 ($R_3SiO^+PR_3$) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (ArH, dd, *J* = 7.2, 12.3 Hz, 2 H), 7.81 (ArH, dd, *J* = 7.1, 12.1 Hz, 2 H), 7.73 - 7.66 (ArH, m, 2 H), 7.66 - 7.57 (ArH, m, 4 H), 3.26 (CH, quin., *J* = 4.3 Hz, 1 H), 1.94 - 1.29 (CH/CH_2, m, 7 H), 1.25 (CH, s, 1 H), 1.15 (CH, s, 1

H), 0.86 (CH_3, s, 9 H), 0.79 (CH_3, d, J = 6.4 Hz, 3 H), 0.72 (CH_3, d, J = 6.4 Hz, 3 H), 0.60 (CH_3, d, J = 6.3 Hz, 3 H), 0.01 (CH_3, s, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.5 (CH, d, J = 15.4 Hz, 2 C), 131.2 (CH, d, J = 11.0 Hz, 4 C), 129.9 (CH, d, J = 16.8 Hz, 4 C), 118.6 (Cq, d, J = 317.6 Hz, 2 C), 36.5 (CH), 36.1 (CH_2), 35.9 (CH), 34.3 (CH_2), 29.8 (CH, d, J = 2.9 Hz), 28.5 (CH, d, J = 2.2 Hz), 25.8 (CH_3, 3 C), 25.7 (CH_2, d, J = 2.2 Hz), 22.3 (CH_3), 21.8 (CH_3), 21.0 (CH_3), 18.3 (Cq), −2.8 (CH_3, 2 C) ppm.

((1*S*,2*S*,5*R*)-2-*iso*-Propyl-5-methlcyclohexyl)diphenylphosphine oxide (**2864A**)



284A

To a stirred solution of (*S*)-(+)-neomenthyldiphenylphosphine oxide (130 mg, 0.400 mmol) in THF (2 mL) was added hydrogen peroxide solution in H_2O (12% w/w) (545 μL, 2.00 mmol). After stirring for 2 h the reaction was quenched with $NaHCO_3$. The organic solvent was removed and the residue diluted with H_2O (20 mL) before being washed with CH_2Cl_2 (3 x 30 mL). The organic washings were dried over $MgSO_4$ and concentrated to give ((1*S*,2*S*,5*R*)-2-*iso*-propyl-5-methlcyclohexyl)diphenylphosphine oxide as a white amorphous solid (74.2 mg, 53%).[68]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 32.6 (OPR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 - 7.91 (ArH, m, 2 H), 7.87 - 7.80 (ArH, m, 2 H), 7.46 - 7.39 (ArH, m, 6 H), 2.90 - 2.82 (CH, m, 1 H), 2.23 (CH, dq, J = 3.7, 12.7 Hz, 1 H), 1.82 - 1.73 (CH, m, 1 H), 1.72 - 1.64 (CH, m, 1 H), 1.58 - 1.56 (CH_2, m, 2 H), 1.27 - 1.24 (CH_2, m, 2 H), 0.94 - 0.82 (CH_2, m, 2 H), 0.76 (CH_3, d, J = 6.4 Hz, 3 H), 0.61 (CH_3, d, J = 6.4 Hz, 3 H), 0.54 (CH_3, d, J = 6.3 Hz, 3 H) ppm.

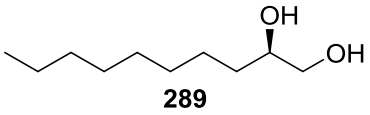
^{13}C NMR (101 MHz, $CDCl_3$): δ = 131.1 (CH, d, *J* = 3.1 Hz), 131.0 (CH, d, *J* = 8.4 Hz, 2 C), 130.9 (CH, d, *J* = 2.3 Hz), 130.9 (CH, d, *J* = 7.7 Hz, 2 C), 129.2 (Cq, d, *J* = 50.6 Hz, 2 C), 128.5 (CH, d, *J* = 6.1 Hz, 2 C), 128.4 (CH, d, *J* = 6.9 Hz, 2 C), 38.0 (CH_2), 37.1 (CH), 36.5 (CH), 35.7 (CH_2), 29.7 (CH, d, *J* = 2.3 Hz), 28.4 (CH, d, *J* = 2.3 Hz), 25.8 (CH_2,d , *J* = 1.5 Hz), 22.6 (CH_3), 22.5 (CH_3), 21.3 (CH_3) ppm.

HRMS (ESI+): *m/z* 363.1837 (*m/z* calculated for $C_{22}H_{29}OPNa$ – 363.1848).

IR υ_{max} ($CHCl_3$): 2959, 1438 (P-Ph), 1180 (P=O), 1111 cm^{-1}.

Consistent with literature values.[133]

Decane-1,2-diol (**289**)



289

To a stirred solution of AD-mix-β (17.5 g) in H_2O/*t*-BuOH (1:1, 125 mL) at 0 °C was added 1-decene (2.37 mL, 12.5 mmol). After 2 h the reaction was quenched by stirring with Na_2SO_3 (17.5 g). After 1 h the organic layer was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, gradient from 100% petroleum ether to 100% Et_2O) gave decane-1,2-diol as a white amorphous solid (1.89 g, 87%, m.p. 38 °C).[134]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 - 3.60 (CH_2, m, 2 H), 3.43 (CH, dd, *J* = 7.5, 10.9 Hz, 1 H), 1.94 - 1.88 (CH_2, m, 2 H), 1.49 - 1.20 (CH_2, m, 14 H), 0.88 (CH_3, t, *J* = 6.7 Hz, 3 H) ppm.

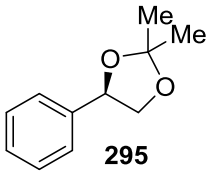
^{13}C NMR (101 MHz, $CDCl_3$): δ = 72.5 (CH), 67.0 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 25.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3) ppm.

HRMS (ESI+): *m/z* 197.1519 (*m/z* calculated for $C_{10}H_{22}O_2Na$ – 197.1512).

IR υ_{max} ($CHCl_3$): 2930 (O-H), 2857 (O-H), 1466, 1050 cm^{-1}.

Consistent with literature values.[134]

2,2-Dimethyl-4-phenyl-1,3-dioxolane (**295**)



295

To a stirred solution of 1-phenylethane-1,2-diol (276 mg, 2.00 mmol) in acetone (2 mL) at r.t. was added $FeCl_3.6H_2O$ (54.1 mg, 10 mol%). After 2 h the remaining acetone was removed to give crude product. Purification by flash chromatography (SiO_2, 9:1, petroleum ether/Et_2O) gave 2,2-dimethyl-4-phenyl-1,3-dioxolane as a colourless oil (90.2 mg, 25%).[135]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 - 7.27 (ArH, m, 5 H), 5.08 (CH_2, dd, *J* = 8.1, 6.1 Hz, 1 H), 4.31 (CH_2, dd, *J* = 8.1, 6.1 Hz, 1 H), 3.71 (CH, t, *J* = 8.1 Hz, 1 H), 1.56 (CH_3, s, 3 H), 1.49 (CH_3, s, 3 H) ppm.

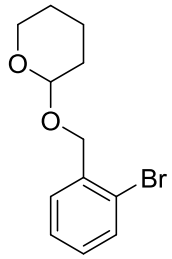
^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.2 (Cq), 128.7 (CH, 2 C), 128.2 (CH), 126.4 (CH, 2 C), 109.9 (Cq), 78.1 (CH), 71.8 (CH_2), 26.7 (CH_3), 26.1 (CH_3) ppm.

HRMS (ESI+): decomposes, no hit.

IR υ_{max} ($CHCl_3$): 2928, 2856, 1732, 1467 (C-Ph), 1376, 1249, 1105 (C-O-C) cm^{-1}.

Consistent with literature values.[136]

2-((2-Bromobenzyl)oxy)tetrahydro-*2H*-pyran (**305**)



305

To a stirred solution of 2-bromobenzyl alcohol (1.87 g, 10.0 mmol) in CH_2Cl_2 (32 mL) was added dihydropyran (1.37 mL, 15.0 mmol) and pyridinium *p*-toluenesulfonate (251 mg, 1.00 mmol). After 5 h the reaction was quenched with brine (20 mL). The organic layer was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 19:1, petroleum ether/Et_2O) gave 2-((2-bromobenzyl)oxy)tetrahydro-*2H*-pyran as a colourless oil (2.58 g, 95%).[118]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (ArH, td, *J* = 7.8, 1.0 Hz, 2 H), 7.32 (ArH, td, *J* = 7.6, 1.0 Hz, 1 H), 7.14 (ArH, td, *J* = 7.6, 1.7 Hz, 1 H), 4.83 (CH_2, d, *J* = 13.3 Hz, 1 H), 4.78 (CH, t, *J* = 3.4 Hz, 1 H), 4.58 (CH_2, d, *J* = 13.3 Hz, 1 H), 3.97 - 3.89 (CH_2, m, 1 H), 3.62 - 3.53 (CH_2, m, 1 H), 1.96 - 1.52 (CH_2, m, 6 H) ppm.

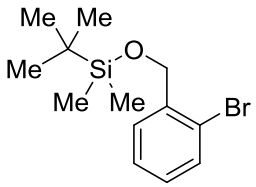
^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.0 (Cq), 132.6 (CH), 129.2 (CH), 128.9 (CH), 127.5 (CH), 122.9 (Cq), 98.5 (CH), 68.7 (CH_2), 62.3 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 19.5 (CH_2) ppm.

HRMS (ESI+): *m/z* 293.0142 (*m/z* calculated for $C_{12}H_{15}BrO_2Na$ – 293.0148).

IR υ_{max} ($CHCl_3$): 2947, 1442 (C-Ph), 1132, 1069 (C-O-C), 1025 (C-O-C) cm^{-1}.

Consistent with literature values.[118]

((2-Bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (**310**)



310

To a stirred solution of 2-bromobenzyl alcohol (1.87 g, 10.0 mmol) and imidazole (1.68 g, 24.7 mmol) in dry DMF (16 mL) under an Ar atmosphere was added a solution of *tert*-butyldimethylchlorosilane (1.80 g, 11.9 mmol) in dry DMF (3.5 mL). After 16 h the reaction was quenched with H_2O (10 mL). The organic layer was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 19:1, petroleum ether/Et_2O) gave ((2-bromobenzyl)oxy)(*tert*-butyl)dimethylsilane as a colourless oil (2.43 g, 80%).[137]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 - 7.54 (ArH, m, 1 H), 7.49 (ArH, dd, *J* = 8.0, 1.2 Hz, 1 H), 7.33 (ArH, td, *J* = 7.6, 1.2 Hz, 1 H), 7.15 - 7.08 (ArH, m, 1 H), 4.74 (CH_2, s, 2 H), 0.97 (CH_3, s, 9 H), 0.14 (CH_3, s, 6 H) ppm.

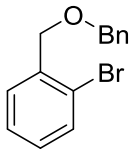
^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.5 (Cq), 132.1 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 121.2 (Cq), 64.7 (CH_2), 26.1 (CH_3, 3 C), 18.5 (Cq), -5.2 (CH_3, 2 C) ppm.

HRMS (ESI+): *m/z* 323.0433 (*m/z* calculated for $C_{13}H_{21}BrOSiNa$ – 323.0437).

IR υ_{max} ($CHCl_3$): 2931, 2858, 1471 (C-Ph), 1257 (Si-C), 1121, 1098 (C-O), 1026 (Si-O), 841 cm^{-1}.

Consistent with literature values.[137]

1-((Benzyloxy)methyl)-2-bromobenzene (**314**)



314

To a stirred solution of 2-bromobenzyl alcohol (5.00 g, 26.7 mmol) in dry DMF (27 mL) at 0 °C under an Ar atmosphere was added NaH (60% w/w) (1.18 g, 29.4 mmol). After 3 h benzyl bromide (3.15 mL, 26.5 mmol) was added dropwise over 5 min. After 3 h the reaction was quenched with H_2O (15 mL). The organic layer was extracted with Et_2O (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 1:1, petroleum ether/Et_2O) gave 1-((benzyloxy)methyl)-2-bromobenzene as a colourless oil (6.50 g, 89%).[138]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 - 7.51 (ArH, m, 2 H), 7.44 - 7.28 (ArH, m, 6 H), 7.16 (ArH, td, *J* = 7.7, 1.6 Hz, 1 H), 4.65 (CH_2, s, 2 H), 4.64 (CH_2, s, 2 H) ppm.

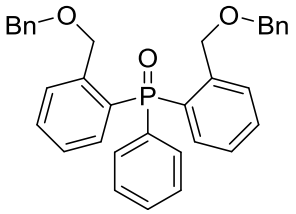
^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2 (Cq), 137.8 (Cq), 132.7 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH, 2 C), 127.9 (CH, 2 C), 127.9 (CH), 127.5 (CH), 122.9 (Cq), 72.9 (CH_2), 71.7 (CH_2) ppm.

HRMS (ESI+): *m/z* 299.0030 (*m/z* calculated for $C_{14}H_{13}BrONa$ – 299.0042).

IR υ_{max} ($CHCl_3$): 3067, 3010, 2863, 1697, 1454 (C-Ph), 1094 (C-O-C), 1028 cm^{-1}.

Consistent with literature values.[138]

Bis(2-((benzyloxy)methyl)phenyl)(phenyl)phosphine oxide (**320**)



320

A flask was charged with Mg turnings (611 mg, 25.4 mmol) under an Ar atmosphere before dry THF (1 mL) was added. To the stirring mixture was added 1,2-dibromoethane (6 drops) before the reaction was heated to initiation (observed by the browning in colour of the solution). To this mixture was added a solution of 1-((benzyloxy)methyl)-2-bromobenzene (5.00 g, 22.0 mmol) in dry THF (21 mL) dropwise, with heating, over 10 min before the reaction was heated to reflux at 80 °C. After 2 h the reaction was allowed to cool to r.t. before phenyldichlorophosphine (1.49 mL, 11.0 mmol) was added dropwise over 5 min. After 24 h the reaction was quenched with H_2O (20 mL) and the organic solvent was removed. The remains were diluted with NH_4Cl (sat. aq.) (20 mL) and the organic layer extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give crude phosphine. The crude phosphine was dissolved in THF (55 mL). To the stirred solution was added H_2O_2 (12 % w/w) (15.0 mL, 55.1 mmol). After 2 h the reaction was quenched with $NaHCO_3$. The organic solvent was removed and the residue diluted with H_2O (20 mL) before the organic layers were extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 9:1, CH_2Cl_2/MeOH) gave bis(2-((benzyloxy)methyl)phenyl)(phenyl)phosphine oxide as an orange oil (4.00 g, 70%).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 34.8 (OPR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (ArH, dd, *J* = 7.5, 3.7 Hz, 2 H), 7.68 - 7.60 (ArH, m, 2 H), 7.58 - 7.50 (ArH, m, 3 H), 7.43 (ArH, m, *J* = 7.4, 2.8 Hz, 2 H), 7.30 - 7.17

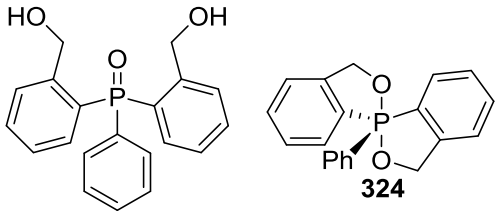
(ArH, m, 12 H), 7.07 (ArH, ddd, *J* = 14.2, 7.7, 1.0 Hz, 2 H), 5.00 (CH_2, s, 4 H), 4.41 (CH_2, s, 4 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.8 (Cq, d, *J* = 7.3 Hz, 2 C), 138.0 (Cq, 2 C), 132.6 (CH, d, *J* = 12.4 Hz, 2 C), 132.4 (Cq, d, *J* = 104.3 Hz), 132.1 (CH, d, *J* = 2.2 Hz, 2 C), 131.9 (CH, d, *J* = 10.2 Hz, 2 C), 131.8 (CH, d, *J* = 2.9 Hz), 129.6 (Cq, d, *J* = 102.1 Hz, 2 C), 128.6 (CH, d, *J* = 10.2 Hz, 2 C), 128.4 (CH, d, *J* = 11.7 Hz, 2 C), 128.1 (CH, 4 C), 127.4 (CH, 4 C), 127.2 (CH, 2 C), 126.6 (CH, d, *J* = 12.4 Hz, 2 C), 72.5 (CH_2, 2 C), 69.9 (CH_2, d, *J* = 4.4 Hz, 2 C) ppm.

HRMS (ESI+): *m/z* 541.1908 (*m/z* calculated for $C_{34}H_{31}O_3PNa$ – 541.1903).

IR υ_{max} ($CHCl_3$): 3066, 2985, 2865, 1730, 1693, 1439 (P-Ph), 1275, 1169 (P=O), 1109 (C-O-C), 1069, 909 cm^{-1}.

bis(2-(Hydroxymethyl)phenyl)(phenyl)phosphine oxide (**322**) and 1-phenyl-1,3,3'-trihydro-1λ^5-1,1'-spirobi[benzo[*d*][1,2]oxaphosphole (**324**)



322 **324**

To a stirred solution of bis(2-((benzyloxy)methyl)phenyl)(phenyl)phosphine oxide (2.83 g, 5.45 mmol) in EtOH (12.5 mL) was added Pd/C (5% w/w) (750 mg). The atmosphere was replaced with H_2. After 4 d the mixture was filtered through celite and the solvent was removed to give crude product. Purification by flash chromatography (SiO_2, 9:1, CH_2Cl_2/MeOH) gave 1-phenyl-1,3,3'-trihydro-1λ^5-1,1'-spirobi[benzo[*d*][1,2]oxaphosphole as an amorphous white solid (899 mg, 51%, m.p. 118 °C) and bis(2-(hydroxymethyl)phenyl)(phenyl)phosphine oxide as an amorphous white solid (16.9 mg, 1%, m.p. 120 °C).[139]

bis(2-(hydroxymethyl)phenyl)(phenyl)phosphine oxide (322)

^{31}P NMR (162 MHz, $CDCl_3$): δ = 40.5 (OPR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 - 7.50 (ArH, m, 9 H), 7.31 - 7.26 (ArH, m, 2 H), 6.92 (ArH, dd, *J* = 7.3, 14.5 Hz, 2 H), 4.66 (CH_2, dd, *J* = 7.5, 12.8 Hz, 2 H), 4.57 (CH_2, dd, *J* = 7.5, 12.8 Hz, 2 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.5 (Cq, d, *J* = 6.9 Hz, 2 C), 133.6 (CH, d, *J* = 13.0 Hz, 2 C), 133.4 (CH, d, *J* = 2.3 Hz, 2 C), 132.8 (CH, d, *J* = 2.3 Hz), 132.2 (CH, d, *J* = 10.7 Hz, 2 C), 131.8 (CH, d, *J* = 10.0 Hz, 2 C), 131.0 (Cq, d, *J* = 105.8 Hz), 130.3 (Cq, d, *J* = 102.0 Hz, 2 C), 129.0 (CH, d, *J* = 12.3 Hz, 2 C), 127.5 (CH, d, *J* = 13.8 Hz, 2 C), 64.4 (CH_2, 2 C) ppm.

HRMS (ESI+): *m/z* 339.1141 (*m/z* calculated for $C_{20}H_{20}O_3PNa$ – 339.1145).

IR υ_{max} ($CHCl_3$): 3346, 2873 (O-H), 1595 (C-Ph), 1156, 1127, 1021 (P=O), 825 (s) cm^{-1}.

Consistent with literature values.[118]

1-phenyl-1,3,3'-trihydro-1λ^5-1,1'-spirobi[benzo[*c*][1,2]oxaphosphole (324)

^{31}P NMR (162 MHz, $CDCl_3$): δ = −36.6 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 - 8.43 (ArH, m, 2 H), 7.76 - 7.65 (ArH, m, 2 H), 7.58 - 7.44 (ArH, m, 4 H), 7.39 - 7.30 (ArH, m, 5 H), 5.17 (CH_2, dd, *J* = 14.2, 6.0 Hz, 2 H), 4.97 (CH_2, dd, *J* = 14.2, 1.6 Hz, 2 H) ppm.

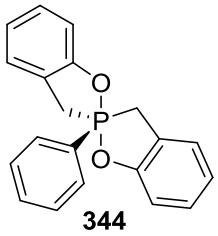
^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.4 (Cq, d, *J* = 27.0 Hz, 2 C), 140.0 (Cq, d, *J* = 164.7 Hz), 135.8 (CH, d, *J* = 10.0 Hz, 2 C), 131.9 (CH, d, *J* = 3.1 Hz, 2 C), 130.6 (CH, d, *J* = 11.5 Hz, 2 C), 130.6 (Cq, d, *J* = 169.4 Hz, 2 C), 129.2 (CH, d, *J* = 3.1 Hz), 127.9 (CH, d, *J* = 14.6 Hz, 2 C), 127.7 (CH, d, *J* = 13.0 Hz, 2 C), 122.5 (CH, d, *J* = 16.1 Hz, 2 C), 65.7 (CH_2, 2 C) ppm.

HRMS (ESI+): *m/z* 343.0858 (*m/z* calculated for $C_{20}H_{17}O_2PNa$ – 343.0858).

IR υ_{max} ($CHCl_3$): 1453 (C-Ph), 1258 (P-O), 1063 (C-O) cm^{-1}.

Consistent with literature values.[118]

2-Phenyl-2,3,3'-trihydro-2λ^5-2,2'-spirobi[benzo[*d*][1,2]oxaphosphole] (**344**)



344

A stirred solution of bis(2-hydroxybenzyl)(phenyl)phosphine oxide (33.8 mg, 0.100 mmol) in xylenes (12.5 mL) under an Ar atmosphere was placed in a Dean-Stark apparatus. The reaction was heated to 180 °C. After 8 h the reaction was cooled and the solvent removed to give 2-phenyl-2,3,3'-trihydro-2λ^5-2,2'-spirobi[benzo[*d*][1,2]oxaphosphole] in quantitative conversion as observed by multinuclear NMR.

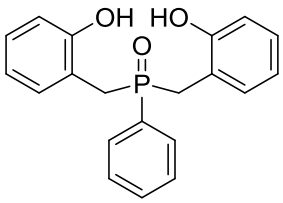
^{31}P NMR (162 MHz, $CDCl_3$): δ = −9.8 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 - 7.89 (ArH, m, 2 H), 7.44 - 7.33 (ArH, m, 3 H), 7.24 (ArH, d, *J* = 7.5 Hz, 2 H), 7.18 - 7.13 (ArH, m, 2 H), 6.87 - 6.79 (ArH, m, 4 H), 3.83 - 3.63 (CH_2, m, 4 H) ppm.[140]

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.8 (Cq, d, *J* = 5.4 Hz, 2 C), 134.6 (Cq, d, *J* = 143.4 Hz), 133.0 (CH, d, *J* = 11.5 Hz, 2 C), 131.4 (CH, d, *J* = 3.8 Hz, 2 C), 128.6 (CH, 2 C), 128.4 (CH), 125.6 (CH, d, *J* = 21.5 Hz, 2 C), 121.7 (Cq, d, *J* = 6.9 Hz, 2 C), 119.4 (CH, d, *J* = 1.5 Hz, 2 C), 111.8 (CH, d, *J* = 3.8 Hz, 2 C), 29.8 (CH_2, d, *J* = 115.0 Hz, 2 C) ppm.

IR υ_{max} (ATR): 1479 (C-Ph), 1246 (P-O), 749 cm^{-1}.

Bis(2-hydroxybenzyl)(phenyl)phosphine oxide (**346**)



346

To a stirred solution of bis(2-(benzyloxy)benzyl)(phenyl)phosphine oxide (1.05 g, 2.02 mmol) in EtOH (20 mL) was added glacial AcOH (12.0 μL, 10 mol%) and Pd/C (10% w/w) (200 mg). The mixture was placed into a high pressure vessel and the atmosphere was removed and replaced with H_2 at 60 bar. The reaction was then heated to 60 °C. After 13 days the reaction was allowed to completely cool before the pressure was released. The remaining Pd/C was removed by filtration through celite with washings of MeOH. The solvent was removed to give crude product. Purification by flash chromatography (SiO_2, 9:1, acetone/MeOH) gave bis(2-hydroxybenzyl)(phenyl)phosphine oxide as a white amorphous solid (585 mg, 86%, m.p. 179 °C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 50.7 (OPR_3) ppm.

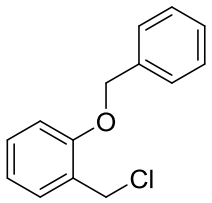
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (OH, br. s., 2 H), 7.68 - 7.61 (ArH, m, 2 H), 7.53 (ArH, dt, *J* = 1.7, 7.4 Hz, 1 H), 7.48 - 7.42 (ArH, m, 2 H), 7.15 - 7.08 (ArH, m, 2 H), 6.95 (ArH, dd, *J* = 0.9, 8.1 Hz, 2 H), 6.84 (ArH, td, *J* = 1.6, 7.5 Hz, 2 H), 6.74 (ArH, t, *J* = 7.2 Hz, 2 H), 3.58 (CH_2, dd, *J* = 14.0, 14.0 Hz, 2 H), 3.35 (CH_2, dd, *J* = 11.3, 15.0 Hz, 2 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9 (Cq, d, *J* = 4.4 Hz, 2 C), 132.9 (CH, d, *J* = 2.9 Hz), 131.6 (CH, d, *J* = 5.9 Hz, 2 C), 130.6 (CH, d, *J* = 9.5 Hz, 2 C), 129.4 (CH, d, *J* = 2.9 Hz, 2 C), 129.0 (CH, d, *J* = 12.4 Hz, 2 C), 128.1 (Cq, d, *J* = 96.3 Hz), 121.2 (CH, d, *J* = 2.2 Hz, 2 C), 119.6 (CH, d, *J* = 2.2 Hz, 2 C), 118.6 (Cq, d, *J* = 8.8 Hz, 2 C), 34.0 (CH_2, d, *J* = 63.9 Hz, 2 C) ppm.

HRMS (ESI+): *m/z* 361.0968 (*m/z* calculated for $C_{20}H_{19}O_3PNa$ – 361.0964).

IR υ_{max} (ATR): 3145 (O-H), 1455 (C-Ph), 1128, 1092 (P=O) cm^{-1}.

1-(Benzyloxy)-2-(chloromethyl)benzene (**350**)



350

To a stirred solution of 2-benzyloxybenzaldehyde (10.0 g, 47.1 mmol) in EtOH (236 mL) at 0 °C was added $NaBH_4$ (3.56 g, 94.2 mmol) in portions over 10 min. After 2 h the reaction was quenched with ice water (200 mL). The mixture was acidified with $HCl_{(aq).}$ (4 M) before the organic was extracted with Et_2O (3 x 30 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated to give crude alcohol. The crude alcohol was dissolved in CH_2Cl_2 (254 mL) at 0 °C and attached to a Dreschel bottle containing $NaOH_{(aq)}$ (1 M). To the stirred solution was added thionyl chloride (5.16 mL, 70.7 mmol) dropwise over 5 min. After 2 h the reaction was quenched with $NaHCO_3$ (sat. aq.) before the organic layer was washed with $NaHCO_{3(aq.)}$ (1 M) (30 mL), H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 1:1, petroleum ether/Et_2O) gave 1-(benzyloxy)-2-(chloromethyl)benzene as a colourless oil (9.32 g, 85%).[141]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 - 7.46 (ArH, m, 2 H), 7.43 - 7.27 (ArH, m, 5 H), 7.00 - 6.93 (ArH, m, 2 H), 5.16 (CH_2, s, 2 H), 4.72 (CH_2, s, 2 H) ppm.

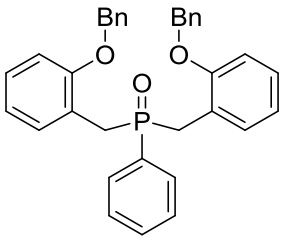
^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.6 (Cq), 137.0 (Cq), 130.8 (CH), 130.2 (CH), 128.7 (CH, 2 C), 128.1 (CH), 127.3 (CH, 2 C), 126.4 (Cq), 121.1 (CH), 112.3 (CH), 70.3 (CH_2), 41.9 (CH_2) ppm.

HRMS (ESI+): *m/z* 255.0537 (*m/z* calculated for $C_{14}H_{13}ClONa$ – 255.0547).

IR υ_{max} ($CHCl_3$): 3068, 1603, 1495 (C-Ph), 1454 (C-Ph), 1249, 1024 (C-O-C) cm^{-1}.

Consistent with literature values.[141]

Bis(2-(benzyloxy)benzyl)(phenyl)phosphine oxide (**352**)



352

A flask was charged with Mg turnings (522 mg, 21.8 mmol) at 0 °C under an Ar atmosphere before dry THF (44 mL) was added. To the stirring mixture was added 1,2-dibromoethane (225 μL, 2.61 mmol). To this mixture was added a solution of 1-(benzyloxy)-2-(chloromethyl)benzene (4.15 g, 17.9 mmol) in dry THF (11 mL) dropwise over 5 min. The reaction was allowed to warm slowly to r.t. and after 2 h the reaction was cooled to 0 °C before phenyldichlorophosphine (1.18 mL, 8.71 mmol) in dry THF (11 mL) was added dropwise over 5 min. After 4 h the reaction was quenched with NH_4Cl (sat. aq.) (20 mL) and the organic solvent was removed. The organic layer was extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give crude phosphine. The crude phosphine was dissolved in THF (44 mL). To the stirred solution was added H_2O_2 (12 % w/w) (11.9 mL, 43.5 mmol). After 1.5 h the reaction was quenched with $NaHCO_3$ (sat. aq.) (30 mL). The organic solvent was removed and the residue diluted with H_2O (20 mL) before the organic layers were extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 9:1, CH_2Cl_2/acetone) gave bis(2-(benzyloxy)benzyl)(phenyl)phosphine oxide as a yellow oil (3.35 g, 74%).[142]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 36.8 (OPR_3) ppm.

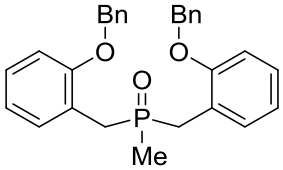
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 - 7.40 (ArH, m, 2 H), 7.39 - 7.27 (ArH, m, 13 H), 7.19 - 7.10 (ArH, m, 4 H), 6.88 - 6.75 (ArH, m, 4 H), 4.84 (CH_2, dd, *J* = 20.0, 12.0 Hz, 4 H), 3.52 (CH_2, 2 x dd – appears as quintet, *J* = 14.3 Hz, 4 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.1 (Cq, d, *J* = 5.1 Hz, 2 C), 137.0 (Cq, 2 C), 132.0 (Cq, d, *J* = 94.0 Hz), 131.6 (CH, d, *J* = 4.4 Hz, 2 C), 131.1 (CH, d, *J* = 8.8 Hz, 2 C), 128.5 (CH, 4 C), 128.0 (CH, d, *J* = 2.9 Hz, 2 C), 127.8 (CH, 3 C), 127.6 (CH, d, *J* = 11.7 Hz, 2 C), 127.2 (CH, 4 C), 120.9 (CH, d, *J* = 2.9 Hz, 2 C), 120.7 (Cq, d, *J* = 8.1 Hz, 2 C), 111.6 (CH, d, *J* = 2.2 Hz, 2 C), 69.9 (CH_2, 2 C), 30.9 (CH_2, d, *J* = 64.6 Hz, 2 C) ppm.

HRMS (ESI+): *m/z* 541.1886 (*m/z* calculated for $C_{34}H_{31}O_3PNa$ – 541.1903).

IR υ_{max} ($CHCl_3$): 2979, 1601, 1494 (C-Ph), 1453 (P-Ph), 1246 (P=O), 1025 (C-O-C) (s) cm^{-1}.

Bis(2-(benzyloxy)benzyl)(methyl)phosphine oxide (**355**)



355

A flask was charged with Mg turnings (252 mg, 10.5 mmol) at 0 °C under an Ar atmosphere before dry THF (32 mL) was added. To the stirring mixture was added 1,2-dibromoethane (108 μL, 1.26 mmol). To this mixture was added a solution of 1-(benzyloxy)-2-(chloromethyl)benzene (2.00 g, 8.60 mmol) in dry THF (5.5 mL) dropwise over 5 min. The reaction was allowed to warm slowly to r.t. and after 4 h the reaction was cooled to 0 °C before methyldichlorophosphine (583 μL, 4.30 mmol) in dry THF (5.5 mL) was added dropwise over 5 min. After 16 h the reaction was quenched with NH_4Cl (sat. aq.) (20 mL) and the organic solvent was removed. The organic layer was

extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give crude phosphine. The crude phosphine was dissolved in THF (22 mL). To the stirred solution was added H_2O_2 (12 % w/w) (5.86 mL, 21.5 mmol). After 2 h the reaction was quenched with $NaHCO_3$ (sat. aq.) (30 mL). The organic solvent was removed and the residue diluted with H_2O (20 mL) before the organic layers were extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 9:1, CH_2Cl_2/acetone) gave bis(2-(benzyloxy)benzyl)(methyl)phosphine oxide as a colourless oil (491 mg, 25%).[142]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 45.5 (OPR_3) ppm.

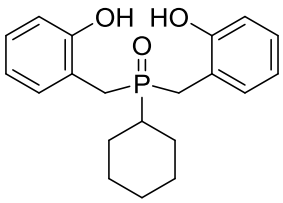
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 - 7.27 (ArH, m, 14 H), 6.95 - 6.89 (ArH, m, 4 H), 4.99 (ArH, s, 4 H), 3.36 (CH_2, s, 2 H), 3.21 (CH_2, s, 2 H), 1.18 (CH_3, d, *J* = 12.7 Hz, 3 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0 (Cq, d, *J* = 5.1 Hz, 2 C), 136.7 (Cq, 2 C), 131.7 (CH, d, *J* = 4.4 Hz, 2 C), 128.6 (CH, 4 C), 128.2 (CH, d, *J* = 2.2 Hz, 2 C), 127.9 (CH, 2 C), 127.2 (CH, 4 C), 121.2 (CH, d, *J* = 2.2 Hz, 2 C), 120.9 (Cq, d, *J* = 7.3 Hz, 2 C), 111.8 (CH, d, *J* = 1.5 Hz, 2 C), 70.1 (CH_2, 2 C), 31.5 (CH_2, d, *J* = 62.2 Hz, 2 C), 13.0 (CH_3, d, *J* = 67.3 Hz) ppm.

HRMS (ESI+): *m/z* 479.1731 (*m/z* calculated for $C_{29}H_{29}O_3PNa$ – 479.1747).

IR υ_{max} ($CHCl_3$): 3011, 1494 (C-Ph), 1453 (C-Ph), 1246, 1136, 1024 (C-O-C), 907 cm^{-1}.

Cyclohexylbis(2-hydroxybenzyl)phosphine oxide (**356**)



356

To a stirred solution of bis(2-(benzyloxy)benzyl)(phenyl)phosphine oxide (1.05 g, 2.02 mmol) in EtOH (20 mL) was added glacial AcOH (12.0 μL, 10 mol%) and Pd/C (10% w/w) (141 mg). The mixture was placed into a high pressure vessel and the atmosphere was removed and replaced with H_2 at 70 bar. The reaction was then heated to 60 °C. After 7 days the reaction was allowed to completely cool before the pressure was released. The remaining Pd/C was removed by filtration through celite with washings of MeOH. The solvent was removed to give crude product. Purification by flash chromatography (SiO_2, 9:1, acetone/MeOH) gave cyclohexylbis(2-hydroxybenzyl)phosphine oxide as a white amorphous solid (40.2 mg, 6%, m.p. 156 °C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 61.8 (OPR_3) ppm.

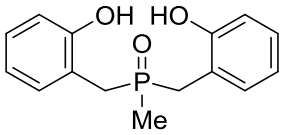
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.02 (OH, s, 2 H), 7.16 (ArH, tt, *J* = 1.5, 7.6 Hz, 2 H), 7.04 (ArH, d, *J* = 7.6 Hz, 2 H), 6.95 (ArH, dd, *J* = 0.9, 8.0 Hz, 2 H), 6.86 (ArH, t, *J* = 7.5 Hz, 2 H), 3.22 (CH_2, dd, *J* = 4.2, 12.0 Hz, 4 H), 1.93 - 1.66 (CH/CH_2, m, 5 H), 1.32 - 1.14 (CH_2, m, 6 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6 (Cq, d, *J* = 3.7 Hz, 2 C), 131.4 (CH, d, *J* = 5.1 Hz, 2 C), 129.1 (CH, d, *J* = 2.2 Hz, 2 C), 120.9 (CH, d, *J* = 1.5 Hz, 2 C), 118.8 (CH, d, *J* = 2.9 Hz, 2 C), 118.7 (Cq, d, *J* = 7.3 Hz, 2 C), 36.4 (CH, d, *J* = 63.7 Hz), 29.5 (CH_2, d, *J* = 58.5 Hz, 2 C), 26.2 (CH_2, d, *J* = 12.4 Hz, 2 C), 25.8 (CH_2), 25.3 (CH_2, d, *J* = 2.2 Hz, 2 C) ppm.

HRMS (ESI+): *m/z* 367.1425 (*m/z* calculated for $C_{20}H_{25}O_3PNa$ – 367.1434).

IR υ_{max} ($CHCl_3$): 2936 (O-H), 1488 (C-Ph), 1250 (P=O) cm^{-1}.

Bis(2-hydroxybenzyl)(methyl)phosphine oxide (**357**)



357

To a stirred solution of bis(2-(benzyloxy)benzyl)(methyl)phosphine oxide (457 mg, 1.00 mmol) in EtOH (20 mL) was added glacial AcOH (5.7 μL, 10 mol%) and Pd/C (5% w/w) (138 mg). The mixture was placed into a high pressure vessel and the atmosphere was removed and replaced with H_2 at 40 bar. After 4 days the reaction was allowed to completely cool before the pressure was released. The remaining Pd/C was removed by filtration through celite with washings of MeOH. The solvent was removed to give crude product. Purification by flash chromatography (SiO_2, 4:1, CH_2Cl_2/acetone) gave bis(2-hydroxybenzyl)(methyl)phosphine oxide as a white amorphous solid (172 mg, 62%, m.p. 300 °C).

^{31}P NMR (162 MHz, DMSO-d_6): δ = 47.7 (OPR_3) ppm, **(162 MHz, $CDCl_3$):** δ = 57.4 (OPR_3) ppm.

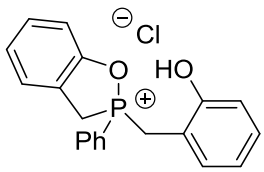
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.75 (OH, s, 2 H), 7.18 (ArH, d, *J* = 7.6 Hz, 2 H), 7.11 (ArH, t, *J* = 7.6 Hz, 2 H), 6.87 (ArH, d, *J* = 7.6 Hz, 2 H), 6.81 (ArH, t, *J* = 7.6 Hz, 2 H), 3.30 - 3.08 (CH_2, m, 4 H), 1.26 (CH_3, d, *J* = 12.7 Hz, 3 H)

^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.2 (Cq, d, *J* = 5.1 Hz, 2 C), 132.4 (CH, d, *J* = 5.1 Hz, 2 C), 128.8 (CH, d, *J* = 2.9 Hz, 2 C), 120.4 (Cq, d, *J* = 8.0 Hz, 2 C), 120.2 (CH, d, *J* = 2.9 Hz, 2 C), 116.8 (CH, d, *J* = 2.2 Hz, 2 C), 32.5 (CH_2, d, *J* = 62.2 Hz, 2 C), 13.7 (CH_3, d, *J* = 66.6 Hz).

HRMS (ESI+): *m/z* 299.0806 (*m/z* calculated for $C_{15}H_{17}O_3PNa$ – 299.0808).

IR υ_{max} (ATR): 3072 (O-H), 1457 (C-Ph), 1096 (P=O), 1073 cm^{-1}.

2-(2-hydroxybenzyl)-2-phenyl-2,3-dihydrobenzo[*d*][1,2]oxaphosphol-2-ium chloride (**358**)



358

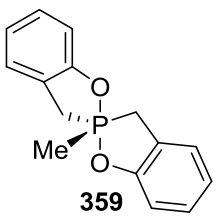
To a stirred solution of bis(2-hydroxybenzyl)(phenyl)phosphine oxide (67.7 mg, 0.200 mmol) in $CDCl_3$ (2.5 mL) under an Ar atmosphere at r.t. was added oxalyl chloride (15.5 µL, 0.180 mmol) and the evolution of gas was observed. The reaction was monitored by ^{31}P NMR and complete conversion was observed after 5 min.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 85.5 (Cl^+PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (ArH, dd, *J* = 7.7, 14.2 Hz, 1 H), 7.50 - 7.27 (ArH, m, 7 H), 7.25 - 7.17 (ArH, m, 3 H), 6.88 - 6.81 (ArH, m, 2 H), 5.15 (CH_2, d, *J* = 9.5 Hz, 2 H), 4.88 (CH_2, s, 2 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.7 (Cq, d, *J* = 5.9 Hz, 2 C), 136.2 (Cq), 135.5 (CH), 135.4 (Cq), 133.0 (CH, d, *J* = 5.9 Hz, 2 C), 132.7 (CH, d, *J* = 12.4 Hz), 130.6 (CH, d, *J* = 5.1 Hz), 129.7 (CH, d, *J* = 13.9 Hz), 128.8 (CH, 2 C), 128.2 (CH), 127.4 (CH, 2 C), 121.6 (CH, d, *J* = 3.7 Hz), 115.0 (Cq, d, *J* = 11.0 Hz), 112.2 (CH, d, *J* = 3.7 Hz), 70.3 (CH_2), 31.5 (CH_2, d, *J* = 37.3 Hz) ppm.

2-Methyl-2,3,3'-trihydro-2λ^5-2,2'-spirobi[benzo[*d*][1,2]oxaphosphole] (**359**)



359

A stirred solution of bis(2-hydroxybenzyl)(phenyl)phosphine oxide (27.6 mg, 0.100 mmol) in xylenes (25 mL) under an Ar atmosphere was placed in a Dean-Stark apparatus. The reaction was heated to 180 °C. After 12 h the reaction was cooled and the solvent

removed to give 2-methyl-2,3,3'-trihydro-2λ^5-2,2'-spirobi[benzo[*d*][1,2]oxaphosphole] in quantitative conversion as observed by multinuclear NMR.

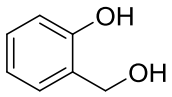
^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.1 (O_2PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (ArH, d, *J* = 7.6 Hz, 2 H), 7.13 (ArH, t, *J* = 7.6 Hz, 2 H), 6.79 (ArH, t, *J* = 7.6 Hz, 2 H), 6.71 (ArH, d, *J* = 7.6 Hz, 2 H), 3.49 (2 x C<u>H</u>H, d, *J* = 2.6 Hz, 2 H), 3.44 (2 x CH<u>H</u>, d, *J* = 4.4 Hz, 2 H), 1.93 (CH_3, d, *J* = 15.5 Hz, 3 H) ppm.[140]

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.7 (Cq, d, *J* = 4.4 Hz, 2 C), 128.7 (2 C), 125.8 (CH, d, *J* = 21.2 Hz, 2 C), 121.1 (CH, d, *J* = 6.6 Hz, 2 C), 119.2 (CH, d, *J* = 1.5 Hz, 2 C), 111.8 (CH, d, *J* = 3.7 Hz, 2 C), 29.0 (CH_2, d, *J* = 107.6 Hz, 2 C), 19.0 (CH_3, d, *J* = 111.2 Hz) ppm.

IR υ_{max} (ATR): 1479 (C-Ph), 1252 (P-O), 750 cm^{-1}.

2-(Hydroxymethyl)phenol (**365**)



365

To a stirred solution of salicylaldehyde (2.13 mL, 20.0 mmol) in EtOH (34 mL) at 0 °C was added $NaBH_4$ (379 mg, 10.0 mmol). After 30 min the solvent removed and the residue diluted with 1 M $HCl_{(aq.)}$ (30 mL). The organic layer was then extracted with Et_2O (3 x 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude 2-(hydroxymethyl)phenol as an amorphous white solid (100% crude yield, m.p. 67 °C).[143]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (ArH, dt, *J* = 1.6, 7.7 Hz, 1 H), 7.04 (ArH, dd, *J* = 1.3, 7.5 Hz, 1 H), 6.90 (ArH, dd, *J* = 1.0, 8.2 Hz, 1 H), 6.86 (ArH, dt, *J* = 1.1, 7.4 Hz, 1 H), 4.88 (CH_2, s, 2 H), 1.80 (OH, br. s, 2 H) ppm.

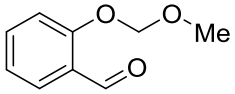
^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.3 (Cq), 129.7 (CH), 127.9 (CH), 124.7 (Cq), 120.2 (CH), 116.7 (CH), 64.9 (CH_2) ppm.

HRMS (ESI+): *m/z* 147.0403 (*m/z* calculated for $C_7H_8O_2Na$ – 147.0417).

IR υ_{max} ($CHCl_3$): 3595, 3410 (br) (O-H), 3010 (O-H), 1589, 1491 (C-Ph), 1375, 1242, 996 cm^{-1}.

Consistent with literature values.[144]

2-(Methoxymethoxy)benzaldehyde (**368**)



368

To a stirred suspension of NaH (60 % w/w) (0.4 g, 10.0 mmol) in THF (8 mL) was added a solution of salicylaldehyde (533 μL, 5.00 mmol) in THF (5 mL). After 1 h methoxymethyl chloride (760 μL, 10.0 mmol) was added dropwise over 5 min. After 20 h the reaction was quenched with H_2O (10 mL). The reaction mixture was then diluted with Et_2O, washed with H_2O (2 x 30 mL), 1 M $NaOH_{(aq.)}$ (2 x 30 mL) and brine (2 x 30 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure to give crude product. Purification by flash chromatography (SiO_2, 9:1, petroleum ether/EtOAc) gave 2-(methoxymethoxy)benzaldehyde as a colourless oil (182 mg, 22%).[145]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.51 (CH, d, *J* = 0.6 Hz, 1 H), 7.84 (ArH, dd, *J* = 7.6, 1.8 Hz, 1 H), 7.56 - 7.50 (ArH, m, 1 H), 7.22 (ArH, d, *J* = 8.4 Hz, 1 H), 7.09 (ArH, t, *J* = 7.6 Hz, 1 H), 5.31 (CH_2, s, 2 H), 3.53 (CH_3, s, 3 H) ppm.

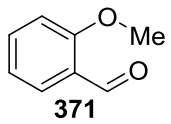
^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.9 (CH), 159.8 (Cq), 136.0 (CH), 128.5 (CH), 125.6 (Cq), 122.0 (CH), 115.2 (CH), 94.7 (CH_2), 56.6 (CH_3) ppm.

HRMS (ESI+): *m/z* 189.0532 (*m/z* calculated for $C_9H_{10}O_3Na$ – 189.0522).

IR υ_{max} ($CHCl_3$): 1687 (C=O), 1600, 1483 (C-Ph), 1283, 1154 (C-O), 991 cm^{-1}.

Consistent with literature values.[145]

2-Methoxybenzaldehyde (**371**)



371

To a stirred suspension of NaH (60 % w/w) (200 mg, 5.00 mmol) in THF/DMF (1:4, 7.5 mL) at 0 °C was added a solution of salicylaldehyde (533 μL, 5.00 mmol) and methyl iodide (623 μL, 10.0 mmol) in THF (5 mL) upon which the solution immediately turned from colourless to yellow. After 17 h the reaction was quenched with H_2O (10 mL). The reaction mixture was then diluted with Et_2O, washed with H_2O (3 x 50 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure to give crude product. Purification by flash chromatography (SiO_2, 9:1, petroleum ether/EtOAc) gave 2-methoxybenzaldehyde as a colourless oil (528 mg, 78%).[146]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.47 (CH, s, 1 H), 7.83 (ArH, dd, *J* = 1.8, 7.7 Hz, 1 H), 7.58 - 7.52 (ArH, m, 1 H), 7.05 - 7.00 (ArH, m, 1 H), 6.99 (ArH, d, *J* = 8.5 Hz, 1 H), 3.93 (CH_3, s, 3 H).

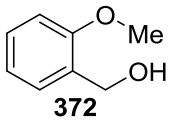
^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.0 (CH), 162.0 (Cq), 136.1 (CH), 128.7 (CH), 125.0 (Cq), 120.8 (CH), 111.8 (CH), 55.8 (CH_3).

HRMS (ESI+): *m/z* 137.0593 (*m/z* calculated for $C_8H_9O_2Na$ – 137.0597).

IR υ_{max} ($CHCl_3$): 1688 (C=O), 1601, 1485, 1468 (C-Ph), 1288, 1248, 1162 (C-O), 1026, 836 cm^{-1}.

Consistent with literature values.[147]

(2-Methoxyphenyl)methanol (**372**)



372

To a stirred solution of 2-methyloxybenzaldehyde (272 mg, 2.00 mmol) in THF/EtOH (14:11, 12.5 mL) was added $NaBH_4$ (83 mg, 2.20 mmol) in portions over 10 min. After 16 h the reaction was quenched with ice water (30 mL). The organic layer was extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give crude alcohol as a colourless oil (238 mg, 86% crude yield.[148]

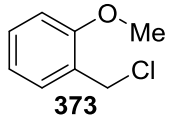
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 - 7.26 (ArH, m, 2 H), 6.95 (ArH, dt, *J* = 7.4, 0.9 Hz, 1 H), 6.89 (ArH, d, *J* = 8.5 Hz, 1 H), 4.69 (CH_2, s, 2 H), 3.87 (CH_3, s, 3 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.6 (Cq), 129.2 (Cq), 129.1 (CH), 128.9 (CH), 120.8 (CH), 110.3 (CH), 62.3 (CH_2), 55.4 (CH_3) ppm.

HRMS (ESI+): *m/z* 161.0578 (*m/z* calculated for $C_8H_{10}O_2Na$ – 161.0573).

IR υ_{max} ($CHCl_3$): 3602, 3011 (O-H), 2965, 2840, 1603, 1494 (C-Ph), 1466, 1440, 1396, 1289, 1244, 1182, 1116 (C-O), 1031, 1008 cm^{-1}.

1-(Chloromethyl)-2-methoxybenzene (**373**)



373

To a stirred solution of 2-methoxybenzyl alcohol (1.33 mL, 10.0 mmol) in CH_2Cl_2 (35 mL) at 0 °C and attached to a Dreschel bottle containing $NaOH_{(aq)}$ (1 M) was added thionyl chloride (1.53 mL, 21.0 mmol) dropwise over 5 min. After 2 h the reaction was quenched with 1 M $NaHCO_{3(aq.)}$ before the organic layer was washed with $NaHCO_3$ (sat. aq.) (30 mL), H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated to

give crude product. Purification by flash chromatography (SiO_2, 9:1, petroleum ether/Et_2O) gave 1-(chloromethyl)-2-methoxybenzene as a colourless oil (1.19 g, 76%).[149]

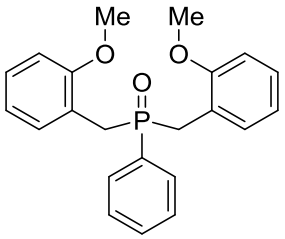
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (ArH, dd, *J* = 7.5, 1.6 Hz, 1 H), 7.32 (ArH, dt, *J* = 8.1, 1.6 Hz, 1 H), 6.95 (ArH, dt, *J* = 7.5, 1.0 Hz, 1 H), 6.90 (ArH, d, *J* = 8.1 Hz, 1 H), 4.67 (CH_2, s, 2 H), 3.89 (CH_3, s, 3 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.5 (Cq), 130.7 (CH), 130.2 (CH), 126.0 (Cq), 120.8 (CH), 110.9 (CH), 55.7 (CH_3), 41.8 (CH_2) ppm.

IR υ_{max} ($CHCl_3$): 2840, 1603, 1495 (C-Ph), 1466, 1252, 1109 (C-O), 1030 cm^{-1}.

Consistent with literature values.[149]

Bis(2-methoxybenzyl)(phenyl)phosphine oxide (**375**)



375

A flask was charged with Mg turnings (1.04 mg, 43.4 mmol) at 0 °C under an Ar atmosphere before dry THF (70 mL) was added. To the stirring mixture was added 1,2-dibromoethane (468 μL, 5.43 mmol). To this mixture was added a solution of crude 1-(chloromethyl)-2-methoxybenzene (5.67 g, 36.2 mmol) in dry THF (10 mL) dropwise over 5 min. The reaction was allowed to warm slowly to r.t. and after 2.5 h the reaction was cooled to 0 °C before phenyldichlorophosphine (2.46 mL, 18.1 mmol) in dry THF (10 mL) was added dropwise over 5 min. After 16 h the reaction was quenched with NH_4Cl (sat. aq.) (20 mL) and the organic solvent was removed. The remains were diluted with H_2O (20 mL) before the organic layer was extracted with CH_2Cl_2 (3 x 30

mL), dried over $MgSO_4$ and concentrated under reduced pressure to give crude phosphine. The crude phosphine was dissolved in THF (90 mL). To the stirred solution was added H_2O_2 (12 % w/w) (24.7 mL, 90.5 mmol). After 3 h the reaction was quenched with $NaHCO_3$ (sat. aq.) (30 mL). The organic solvent was removed and the residue diluted with H_2O (20 mL) before the organic layers were extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 9:1, acetone/MeOH) gave bis(2-methoxybenzyl)(phenyl)phosphine oxide as a yellow oil (4.20 g, 63% over 3 steps).[142]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 36.4 (OPR_3) ppm.

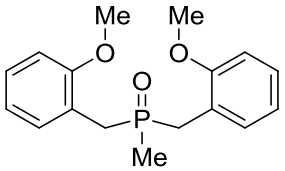
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 - 7.48 (ArH, m, 2 H), 7.41 - 7.36 (ArH, m, 1 H), 7.32 - 7.26 (ArH, m, 4 H), 7.19 - 7.13 (ArH, m, 2 H), 6.86 (ArH, t, *J* = 7.5 Hz, 2 H), 6.72 (ArH, d, *J* = 8.2 Hz, 2 H), 3.59 (CH_3, s, 6 H), 3.47 - 3.41 (CH_2, m, 4 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.0 (Cq, d, *J* = 5.1 Hz, 2 C), 133.3 (Cq, d, *J* = 69.5 Hz), 131.7 (CH, d, *J* = 5.1 Hz, 2 C), 131.2 (CH, d, *J* = 2.9 Hz), 131.2 (CH, d, *J* = 8.0 Hz, 2 C), 128.2 (CH, d, *J* = 2.9 Hz, 2 C), 127.6 (CH, d, *J* = 11.7 Hz, 2 C), 120.8 (CH, d, *J* = 2.2 Hz, 2 C), 120.6 (Cq, d, *J* = 8.0 Hz, 2 C), 110.4 (CH, d, *J* = 2.2 Hz, 2 C), 55.1 (CH_3, 2 C), 31.0 (CH_2, d, *J* = 63.7 Hz, 2 C) ppm.

HRMS (ESI+): *m/z* 367.1464 (*m/z* calculated for $C_{22}H_{24}O_3P$ – 367.1458).

IR υ_{max} ($CHCl_3$): 2974, 1601, 1495 (C-Ph), 1466 (P-Ph), 1250 (P=O), 1030 (C-O) cm^{-1}.

Bis(2-methoxybenzyl)(methyl)phosphine oxide (**377**)



377

A flask was charged with Mg turnings (1.06 mg, 44.2 mmol) at 0 °C under an Ar atmosphere before dry THF (760 mL) was added. To the stirring mixture was added 1,2-dibromoethane (456 μL, 5.29 mmol). To this mixture was added a solution of crude 1-(chloromethyl)-2-methoxybenzene (5.67 g, 36.2 mmol) in dry THF (10 mL) dropwise over 5 min. The reaction was allowed to warm slowly to r.t. and after 3 h the reaction was cooled to 0 °C before methyldichlorophosphine (1.60 mL, 18.1 mmol) was added dropwise over 5 min. After 3.5 h the reaction was quenched with NH_4Cl (sat. aq.) (20 mL) and the organic solvent was removed. The remains were diluted with H_2O (20 mL) before the organic layer was extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give crude phosphine. The crude phosphine was dissolved in THF (90 mL). To the stirred solution was added H_2O_2 (12 % w/w) (24.7 mL, 90.5 mmol). After 2 h the reaction was quenched with $NaHCO_3$ (sat. aq.) (30 mL). The organic solvent was removed and the residue diluted with H_2O (20 mL) before the organic layers were extracted with CH_2Cl_2 (3 x 30 mL), washed with brine (3 x 30 mL), dried over $MgSO_4$ and concentrated to give crude product. Purification by flash chromatography (SiO_2, 9:1, acetone/MeOH) gave bis(2-methoxybenzyl)(methyl)phosphine oxide as a yellow oil (2.44 g, 44% over 3 steps).[142]

^{31}P NMR (162 MHz, $CDCl_3$): δ = 44.8 (OPR_3) ppm.

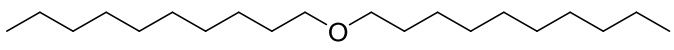
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 - 7.25 (ArH, m, 2 H), 7.24 - 7.19 (ArH, m, 2 H), 6.91 (ArH, t, *J* = 7.4 Hz, 2 H), 6.85 (ArH, d, *J* = 8.2 Hz, 2 H), 3.78 (CH_3, s, 6 H), 3.29 - 3.15 (CH_2, m, 4 H), 1.20 (CH_3, d, *J* = 12.7 Hz, 3 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.9 (Cq, d, *J* = 5.1 Hz, 2 C), 131.5 (CH, d, *J* = 5.1 Hz, 2 C), 128.2 (CH, d, *J* = 3.7 Hz, 2 C), 121.0 (CH, d, *J* = 2.9 Hz, 2 C), 120.9 (Cq, d, *J* = 8.0 Hz, 2 C), 110.5 (CH, d, *J* = 2.2 Hz, 2 C), 55.2 (CH_3, 2 C), 31.5 (CH_2, d, *J* = 62.9 Hz, 2 C), 13.1 (CH_3, d, *J* = 67.3 Hz) ppm.

HRMS (ESI+): *m/z* 305.1319 (*m/z* calculated for $C_{17}H_{22}O_3P$ – 305.1301).

IR υ_{max} ($CHCl_3$): 2961, 1495 (C-Ph), 1465, 1248 (P=O), 1031 (C-O) cm^{-1}.

1-(Decyloxy)decane (**378**)



378

A stirred solution of bis(2-hydroxybenzyl)(phenyl)phosphine oxide (1.18 g, 3.50 mmol) in xylenes (200 mL) under an Ar atmosphere was placed in a Dean-Stark apparatus. The reaction was heated to 170 °C. After 16 h the reaction was cooled and phosphorane formation confirmed by ^{31}P NMR. Decanol (26.6 mL, 140 mmol) and triflic acid (310 μL, 3.5 mmol) were added and the reaction was again heated to 170 °C. After 2.5 h the reaction was cooled and the solvent removed to give crude product, including didecyl ether (19.3 g, 91%) as measured by ^{1}H NMR internal standard.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.39 (CH_2, t, *J* = 6.7 Hz, 4 H), 1.56 (CH_2, tt, *J* = 6.8, 6.8 Hz, 4 H), 1.38 - 1.19 (CH_2, m, 28 H), 0.88 (CH_3, t, *J* = 6.5 Hz, 6 H) ppm.

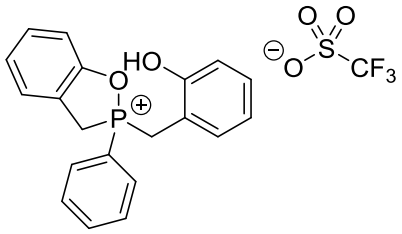
^{13}C NMR (101 MHz, $CDCl_3$): δ = 71.1 (CH_2, 2 C), 32.1 (CH_2, 2 C), 29.9 (CH_2, 2 C), 29.8 (CH_2, 2 C), 29.7 (CH_2, 2 C), 29.7 (CH_2, 2 C), 29.5 (CH_2, 2 C), 26.4 (CH_2, 2 C), 22.8 (CH_2, 2 C), 14.3 (CH_3, 2 C) ppm.

HRMS (ESI+): *m/z* 299.3300 (*m/z* calculated for $C_{20}H_{43}O$ – 299.3308).

IR υ_{max} ($CHCl_3$): 2927, 2855, 1262, 1013 (C-O), 821 cm^{-1}.

Consistent with literature values.[150]

2-(2-Hydroxybenzyl)-2-phenyl-2,3-dihydrobenzo[*d*][1,2]oxaphosphol-2-ium trifluoromethanesulfonate (**379**)



379

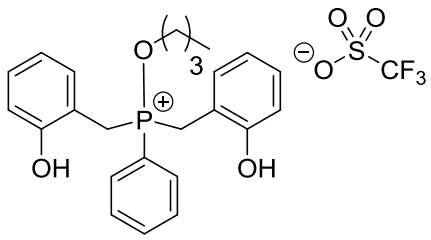
A stirred solution of bis(2-hydroxybenzyl)(phenyl)phosphine oxide (169 mg, 0.500 mmol) in xylenes (10 mL) under an Ar atmosphere was placed in a Dean-Stark apparatus. The reaction was heated to 170 °C. After 16 h the reaction was cooled and the solvent was removed and replaced with $CDCl_3$ (1.4 mL). Triflic acid (44.2 μL, 0.500 mmol) was added. After 5 min the reaction was monitored and 2-(2-hydroxybenzyl)-2-phenyl-2,3-dihydrobenzo[*d*][1,2]oxaphosphol-2-ium trifluoromethanesulfonate was seen to have formed by multinuclear NMR (76% conversion by ^{31}P NMR).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 103.8 (O^+PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (ArH, dd, *J* = 13.4, 7.5 Hz, 2 H), 7.67 (ArH, dd, *J* = 7.7, 6.3 Hz, 1 H), 7.59 - 7.49 (ArH, m, 3 H), 7.38 (ArH, dt, *J* = 3.7, 7.8 Hz, 1 H), 7.10 - 6.86 (ArH, m, 5 H), 6.75 - 6.66 (ArH, m, 1 H), 4.62 - 4.04 (CH_2, m, 4 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.1 (Cq, d, *J* = 5.4 Hz), 136.1 (CH, d, *J* = 3.1 Hz), 134.8 (Cq, d, *J* = 3.1 Hz), 131.8 (CH, d, *J* = 6.1 Hz), 131.1 (CH, d, *J* = 11.5, 2 C), 130.7 (CH), 130.1 (Cq, d, *J* = 93.5 Hz), 130.1 (CH, d, *J* = 13.0 Hz, 2 C), 129.2 (CH, d, *J* = 13.0 Hz), 126.0 (Cq, d, *J* = 24.5 Hz), 121.2 (Cq, d, *J* = 2.3 Hz), 120.1 (CH), 119.1 (CH), 118.1 (CH), 116.2 (CH, d, *J* = 3.1 Hz), 113.7 (CH, d, *J* = 9.2 Hz), 29.1 (CH_2, d, *J* = 60.6 Hz), 28.7 (CH_2, d, *J* = 59.0 Hz) ppm.

(Butoxy)bis(2-hydroxybenzyl)(phenyl)phosphonium trifluoromethanesulfonate (**381**)



381

To a stirred solution of 2-(2-hydroxybenzyl)-2-phenyl-2,3-dihydrobenzo[*d*][1,2]oxaphosphol-2-ium trifluoromethanesulfonate (0.250 mmol) in $CDCl_3$ (0.7 mL) was added butanol (47.7 μL, 0.25 mmol). After 5 min the reaction was monitored and (butoxy)bis(2-hydroxybenzyl)(phenyl)phosphonium trifluoromethanesulfonate was seen to have formed by multinuclear NMR (25% conversion by ^{31}P NMR).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 76.5 (O^+PR_3) ppm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 - 7.47 (ArH, m, 3 H), 7.26 - 7.16 (ArH, m, 4 H), 6.96 - 6.91 (ArH, m, 5 H), 6.69 (ArH, s, 1 H), 3.96 - 3.92 (CH_2, m, 4 H), 1.58 - 1.48 (CH_2, m, 2 H), 1.33 - 1.20 (CH_2, m, 4 H), 0.82 (CH_3, t, *J* = 7.4 Hz, 3 H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (Cq, d, *J* = 4.6 Hz, 2 C), 135.5 (CH, d, *J* = 3.1 Hz, 2 C), 131.3 (CH, d, *J* = 5.4 Hz, 2 C), 131.1 (CH, d, *J* = 10.7 Hz, 2 C), 130.7 (CH), 130.0 (CH, d, *J* = 13.8 Hz, 2 C), 129.8 (Cq, d, *J* = 31.4 Hz), 129.6 (Cq, d, *J* = 13.0 Hz, 2 C), 116.2 (CH, d, *J* = 3.1 Hz, 2 C), 112.9 (CH, d, *J* = 9.2 Hz, 2 C), 72.0 (CH_2, d, *J* = 9.2 Hz), 65.6 (CH_2), 26.6 (CH_2, d, *J* = 58.3 Hz, 2 C), 18.3 (CH_2), 13.4 (CH_3) ppm.

6.3 – Crystallographic information

Bis(2-hydroxybenzyl)(phenyl)phosphine oxide (**346**)

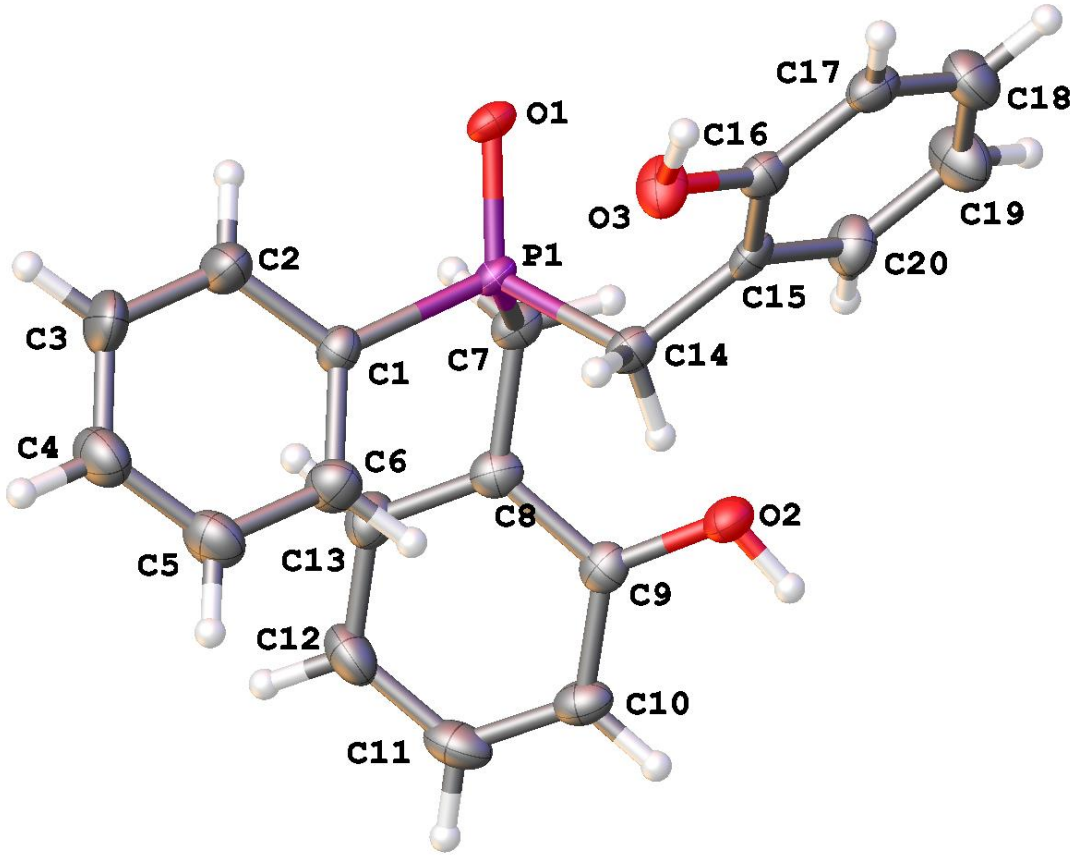


Table 6.1 *– Crystal data and structure refinement for* ***346****.*

Identification code	ASL346
Empirical formula	$C_{20}H_{19}O_3P$
Formula weight	338.32
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.7477(18)
b/Å	14.5336(12)
c/Å	11.7233(17)
α/°	90
β/°	118.915(20)
γ/°	90
Volume/Å^3	1752.1(5)
Z	4
ρ_{calc}g/cm^3	1.283
μ/mm^{-1}	1.507
F(000)	712.0
Crystal size/mm^3	0.2547 × 0.2064 × 0.0625
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.538 to 148.512
Index ranges	$-14 \leq h \leq 12$, $-17 \leq k \leq 17$, $0 \leq l \leq 14$

Reflections collected	3440
Independent reflections	3440 [R_{int} = N/A, R_{sigma} = 0.0508]
Data/restraints/parameters	3440/0/220
Goodness-of-fit on F^2	1.086
Final R indexes [I>=2σ (I)]	R_1 = 0.0916, wR_2 = 0.2858
Final R indexes [all data]	R_1 = 0.0992, wR_2 = 0.2914
Largest diff. peak/hole / e $Å^{-3}$	0.67/-0.72

Table 6.2 *– Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for* ***346****.*

Atom	x	y	z	U(eq)
P1	4141.8(12)	3440.7(8)	7087.3(12)	18.3(4)
O1	5000(4)	2599(2)	7427(3)	21.9(8)
O2	4816(4)	5874(3)	8150(4)	26.7(8)
O3	4984(4)	3226(3)	4466(4)	31.6(9)
C1	2437(5)	3138(4)	6213(5)	22.3(10)
C2	2074(6)	2239(4)	6209(7)	37.8(14)
C3	761(6)	1984(5)	5477(8)	47.4(17)
C4	-156(6)	2637(5)	4763(7)	40.7(15)
C5	200(6)	3539(5)	4773(6)	37.4(14)
C6	1501(6)	3796(4)	5492(6)	32.4(13)
C7	4471(5)	4017(4)	8592(5)	23.1(11)
C8	3559(5)	4767(4)	8516(5)	24.1(11)
C9	3759(5)	5686(4)	8295(5)	23.6(11)
C10	2925(6)	6372(4)	8289(5)	28.4(12)
C11	1915(6)	6159(5)	8521(6)	36.4(14)
C12	1702(6)	5265(5)	8746(6)	36.4(14)
C13	2517(6)	4572(4)	8738(5)	29.8(12)
C14	4406(5)	4252(4)	6074(5)	24.0(11)
C15	5769(5)	4210(3)	6281(5)	23.2(11)
C16	6020(5)	3682(4)	5424(5)	24.8(11)
C17	7251(6)	3630(4)	5549(6)	28.5(12)
C18	8264(6)	4097(5)	6557(6)	38.7(15)
C19	8035(6)	4621(5)	7426(7)	41.8(16)
C20	6806(6)	4673(4)	7278(6)	31.0(13)

U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Table 6.3 *– Anisotropic Displacement Parameters (Å²×10³) for* ***346****.*

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
P1	23.1(7)	12.2(6)	19.0(6)	0.1(4)	9.8(5)	-0.4(5)
O1	29.5(18)	13.9(16)	23.2(17)	2.1(13)	13.3(14)	2.1(14)
O2	31(2)	18.0(18)	33(2)	-0.3(16)	17.3(17)	0.9(15)
O3	37(2)	32(2)	31(2)	-13.7(17)	20.7(18)	-9.3(18)
C1	24(2)	20(2)	22(2)	-2(2)	10(2)	-3(2)
C2	30(3)	26(3)	51(4)	4(3)	14(3)	0(2)
C3	34(3)	32(3)	70(5)	1(3)	20(3)	-12(3)
C4	27(3)	42(4)	47(4)	-7(3)	13(3)	-2(3)
C5	27(3)	44(4)	34(3)	-2(3)	8(2)	2(3)
C6	30(3)	32(3)	29(3)	2(2)	9(2)	1(2)
C7	29(3)	21(3)	18(2)	0.1(19)	10(2)	1(2)
C8	28(3)	24(3)	18(2)	-2.4(19)	10(2)	1(2)
C9	26(3)	24(3)	17(2)	-4.6(19)	7(2)	-3(2)
C10	32(3)	22(3)	26(3)	-3(2)	10(2)	4(2)
C11	29(3)	40(4)	35(3)	-6(3)	12(2)	10(3)
C12	23(3)	45(4)	43(3)	-9(3)	17(3)	-3(3)
C13	34(3)	28(3)	31(3)	-4(2)	18(2)	-5(2)

C14	31(3)	20(2)	21(2)	1(2)	13(2)	0(2)
C15	31(3)	14(2)	22(2)	2.2(19)	12(2)	-4(2)
C16	31(3)	21(3)	24(2)	2(2)	14(2)	1(2)
C17	37(3)	20(3)	33(3)	2(2)	21(2)	3(2)
C18	29(3)	45(4)	45(3)	0(3)	20(3)	1(3)
C19	31(3)	47(4)	40(3)	-14(3)	11(3)	-5(3)
C20	33(3)	30(3)	30(3)	-9(2)	15(2)	-9(2)

The Anisotropic displacement factor exponent takes the form: -

$2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Table 6.4 *– Bond Lengths for* ***346****.*

Atom	Atom	Length/Å
P1	O1	1.511(4)
P1	C1	1.808(5)
P1	C7	1.817(5)
P1	C14	1.804(5)
O2	C9	1.360(7)
O3	C16	1.364(7)
C1	C2	1.374(8)
C1	C6	1.393(8)
C2	C3	1.404(9)
C3	C4	1.375(10)
C4	C5	1.374(10)
C5	C6	1.393(8)
C7	C8	1.501(7)
C8	C9	1.402(8)
C8	C13	1.397(8)
C9	C10	1.396(8)
C10	C11	1.374(9)
C11	C12	1.373(10)
C12	C13	1.392(9)
C14	C15	1.501(8)
C15	C16	1.403(8)
C15	C20	1.388(8)
C16	C17	1.383(8)
C17	C18	1.384(9)
C18	C19	1.399(9)
C19	C20	1.371(9)

Table 6.5 *– Bond Angles for* ***346****.*

Atom	Atom	Atom	Angle/˚
O1	P1	C1	111.5(2)
O1	P1	C7	108.4(2)
O1	P1	C14	113.4(2)
C1	P1	C7	108.7(2)
C14	P1	C1	106.4(2)
C14	P1	C7	108.3(2)
C2	C1	P1	119.4(4)
C2	C1	C6	119.9(5)
C6	C1	P1	120.7(4)
C1	C2	C3	120.0(6)
C4	C3	C2	119.7(6)
C5	C4	C3	120.5(6)
C4	C5	C6	120.0(6)
C1	C6	C5	119.8(6)

C8	C7	P1	117.8(4)
C9	C8	C7	121.6(5)
C13	C8	C7	120.4(5)
C13	C8	C9	117.8(5)
O2	C9	C8	117.3(5)
O2	C9	C10	122.4(5)
C10	C9	C8	120.2(5)
C11	C10	C9	120.5(6)
C12	C11	C10	120.5(6)
C11	C12	C13	119.5(6)
C12	C13	C8	121.5(6)
C15	C14	P1	112.1(4)
C16	C15	C14	118.9(5)
C20	C15	C14	123.3(5)
C20	C15	C16	117.8(5)
O3	C16	C15	116.3(5)
O3	C16	C17	122.1(5)
C17	C16	C15	121.7(5)
C16	C17	C18	119.1(5)
C17	C18	C19	120.0(6)
C20	C19	C18	120.0(6)
C19	C20	C15	121.4(6)

Table 6.6 *– Hydrogen Bonds for* ***346****.*

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O1[1]	0.84	1.81	2.633(5)	165.1
O3	H3	O1[2]	0.84	1.89	2.682(5)	157.8

[1]1-X,1/2+Y,3/2-Z; [2]+X,1/2-Y,-1/2+Z

Table 6.7 *– Torsion Angles for* ***346****.*

A	B	C	D	Angle/°
P1	C1	C2	C3	-176.6(5)
P1	C1	C6	C5	176.8(5)
P1	C7	C8	C9	-89.3(6)
P1	C7	C8	C13	94.3(5)
P1	C14	C15	C16	96.7(5)
P1	C14	C15	C20	-83.7(6)
O1	P1	C1	C2	15.1(5)
O1	P1	C1	C6	-161.6(4)
O1	P1	C7	C8	-168.6(4)
O1	P1	C14	C15	-28.2(4)
O2	C9	C10	C11	-175.9(5)
O3	C16	C17	C18	-178.8(5)
C1	P1	C7	C8	-47.2(5)
C1	P1	C14	C15	-151.1(4)
C1	C2	C3	C4	0.3(11)
C2	C1	C6	C5	0.2(9)
C2	C3	C4	C5	-0.9(12)
C3	C4	C5	C6	1.2(11)
C4	C5	C6	C1	-0.8(10)
C6	C1	C2	C3	0.1(10)
C7	P1	C1	C2	-104.4(5)
C7	P1	C1	C6	79.0(5)
C7	P1	C14	C15	92.2(4)
C7	C8	C9	O2	0.1(7)
C7	C8	C9	C10	-177.1(5)
C7	C8	C13	C12	176.3(5)

C8	C9	C10	C11	1.2(8)
C9	C8	C13	C12	-0.2(8)
C9	C10	C11	C12	-0.8(9)
C10	C11	C12	C13	0.0(9)
C11	C12	C13	C8	0.6(9)
C13	C8	C9	O2	176.6(5)
C13	C8	C9	C10	-0.6(7)
C14	P1	C1	C2	139.2(5)
C14	P1	C1	C6	-37.4(5)
C14	P1	C7	C8	68.0(5)
C14	C15	C16	O3	-1.3(7)
C14	C15	C16	C17	178.8(5)
C14	C15	C20	C19	-179.5(6)
C15	C16	C17	C18	1.1(8)
C16	C15	C20	C19	0.1(9)
C16	C17	C18	C19	-0.7(10)
C17	C18	C19	C20	0.0(11)
C18	C19	C20	C15	0.3(11)
C20	C15	C16	O3	179.2(5)
C20	C15	C16	C17	-0.8(8)

Table 6.8 *– Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for* ***346****.*

Atom	*x*	*y*	*z*	U(eq)
H2	4882	6445	8094	40
H3	5206	2980	3955	47
H2A	2711	1789	6701	45
H3A	507	1363	5476	57
H4	-1042	2464	4258	49
H5	-442	3988	4289	45
H6	1749	4417	5490	39
H7A	4483	3544	9205	28
H7B	5356	4282	8978	28
H10	3056	6992	8122	34
H11	1361	6633	8525	44
H12	1004	5119	8906	44
H13	2361	3954	8886	36
H14A	3788	4121	5147	29
H14B	4228	4881	6270	29
H17	7398	3278	4950	34
H18	9116	4061	6660	46
H19	8731	4942	8118	50
H20	6660	5034	7871	37

Single crystals of $C_{20}H_{19}O_3P$ (**346**) were produced. A suitable crystal was selected and placed in fomblin film on a micromount on a GV1000, Atlas diffractometer. The crystal was kept at 120(2) K during data collection. Using Olex2,[151] the structure was solved with the olex2.solve[152] structure solution program using Charge Flipping and refined with the ShelXL[153] refinement package using Least Squares minimisation.

Crystal structure determination of **346**

Crystal Data for $C_{20}H_{19}O_3P$ (M =338.32 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 11.7477(18) Å, b = 14.5336(12) Å, c = 11.7233(17) Å, β = 118.915(20)°, V = 1752.1(5) Å^3, Z = 4, T = 120(2) K, μ(CuKα) = 1.507 mm^{-1}, $Dcalc$ = 1.283 g/cm^3, 3440 reflections measured (10.538° ≤ 2Θ ≤ 148.512°), 3440 unique (R_{int} = N/A, R_{sigma} = 0.0508) which were used in all calculations. The final R_1 was 0.0916 (I > 2σ(I)) and wR_2 was 0.2914 (all data).

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