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# Exploring Novel Phosphonite Chemistry and New Bioisosteres

A thesis to be submitted to The University of Nottingham for the degree of Doctor of Philosophy

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syngenta

# Table of Contents

**Part 2**

# Acknowledgements

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# Table of Abbreviations

| | |
|---|---|
| ABUTH | Abutilon theophrasti |
| AcOH | acetic acid |
| AIBN | azobisisobutyronitrile |
| AMARE | Amaranthus retroflexus |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| BSA | bis(trimethylsilyl)acetamide |
| BTSP | bis(trimethylsilyl)phosphonite |
| CDI | carbonyldiimidazole |
| coe | cyclooctene |
| CSD | Cambridge Structural Database |
| Cy | cyclohexyl |
| dba | dibenzylideneacetone |
| DIBAL-H | diisobutylaluminium hydride |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| de | diastereomeric excess |
| $[DHQ]_2PHAL$ | hydroquinine 1,4-phthalazinediyl diether |
| DIPAMP | ethylenebis((2-methoxyphenyl)phenylphosphine) |
| DIPAMPO | ethylenebis((2-methoxyphenyl)phenylphosphine oxide) |
| DIPEA | diisopropylethylamine |
| DMF | dimethylformamide |
| DNA | deoxyribonucleic acid |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dr | diastereomeric ratio |
| ECHCG | Echinochloa crus-galli |
| ee | enantiomeric excess |
| er | enantiomeric ratio |

| | |
|---|---|
| FDA | Food and Drug Administration |
| GSK | GlaxoSmithKline |
| HIV | human immunodeficiency virus |
| HMDS | hexamethyldisilazane |
| HPPD | hydroxyphenylpyruvate dioxygenase |
| IPOHE | Ipomoea hederacea |
| LC-MS | liquid chromatography-mass spectrometry |
| LDA | lithium diisopropylamine |
| $L_n$ | ligand |
| NBS | *n*-bromosuccinamide |
| OAc | acetate |
| OTf | triflate |
| PAMPO | 2-methoxyphenylphenylphosphine oxide |
| RNA | ribonucleic acid |
| SEFTA | Setaria faveri |
| SPO | secondary phosphine oxide |
| TES | triethylsilane |
| THF | tetrahydrofuran |
| TMS | trimethylsilane |
| TPO | tertiary phosphine oxide |
| VLCFAs | very-long-chain-fatty acids |
| VLCFAEs | very-long-chain-fatty-acid elongase |
| XantPhos | 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene |
| ZEAMX | Zea mays |

# Part 1

## Abstract

Phosphinic acids are valuable synthetic targets which have many industrial applications. Most notably they have displayed biological activity as herbicides, and as pharmaceutical drugs for the treatment of a range of diseases. Herein, we report a novel *P-C* bond formation reaction for the synthesis of secondary phosphinic acids. This method is underpinned by the generation of a nucleophilic silyl-phosphonite intermediate *via* an unprecedented $B(C_6F_5)_3$-catalysed silylation of primary phosphinic acids. A proposed mechanism for this transformation has been reported, and the scope of the reaction has been explored, with 20 secondary phosphinic acids being synthesised in 44 - 96% yield. Furthermore, the functionalisation of these phosphinic acids has allowed the synthesis of 8 *P*-stereogenic tertiary phosphine oxides. The outlined strategy constitutes a controlled route to tertiary phosphine oxides, which avoids $PCl_3$ and other halophosphines.

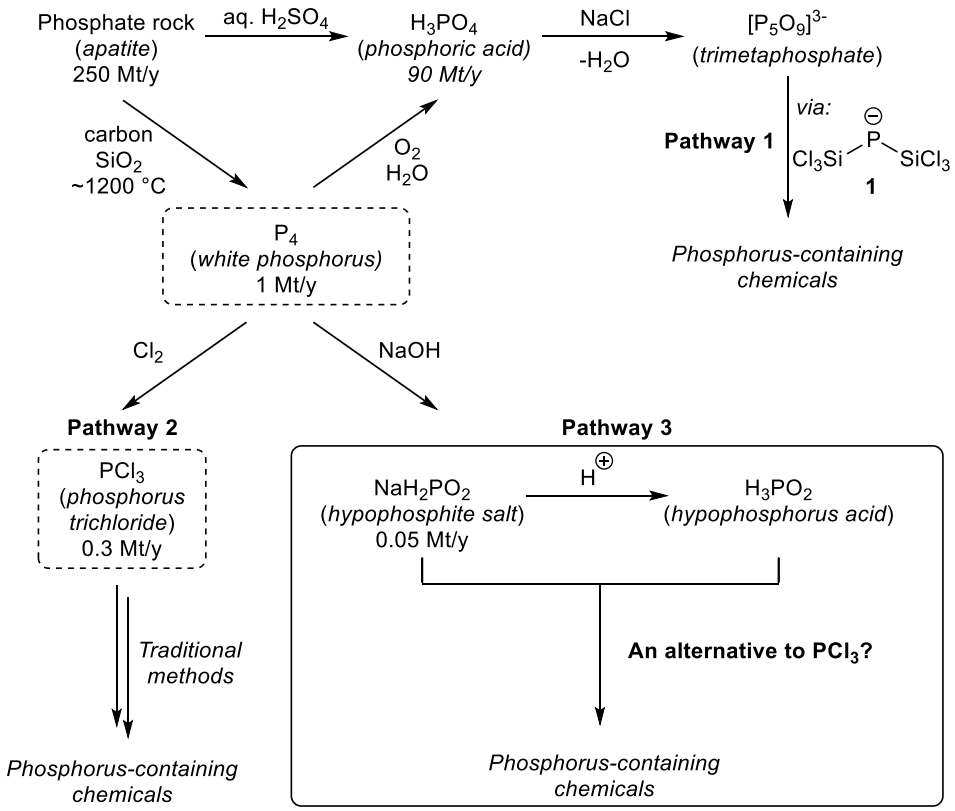
# Chapter 1 – Introduction and Project Aims

## 1.1. Hypophosphorus Compounds – An Alternative to Phosphorus Trichloride

Phosphorus is a fundamental element to society which is often considered essential for the existence of life, as it most notably makes up the backbone of both DNA and RNA.[1] Phosphorus is naturally abundant and is found most commonly in phosphate rock as the mineral, apatite ($Ca_3(PO_4)_2$).[2] A common allotrope of phosphorus, known as white phosphorus, is produced on an industrial scale *via* the high temperature reduction of apatite in the presence of $SiO_2$ and carbon, Scheme 1.[2–4] White phosphorus is toxic and pyrophoric, nevertheless, around one million tonnes are being manufactured per year.[4] It is the main intermediate in nearly all pathways leading to phosphorus-containing chemicals, despite the associated hazards and the intense process for its synthesis, Scheme 1.[4,5] However, Geeson and Cummins recently published work that exploited phosphoric acid ($H_3PO_4$) as an alternative phosphorus source to white phosphorus, Scheme 1 Pathway 1.[4] The synthetic transformations were enabled by the generation of the bis(trichlorosilyl)phosphide species **1**, from trimetaphosphate (which can be synthesised in one-step from phosphoric acid).[4] This was not an industrial process but it did outline an interesting route for the synthesis of phosphorus-containing compounds, which avoided white phosphorus.[4]

The majority of phosphorus-containing compounds, including ligands and organocatalysts, as well as pharmaceutical and herbicidal compounds, are derived from phosphorus trichloride ($PCl_3$), Scheme 1 Pathway 2. Phosphorus trichloride is directly synthesised from white phosphorus *via* a high temperature oxidation with chlorine gas.[2,5,6] It is also highly toxic, and is both air and moisture sensitive.[6] This is

why hypophosphorus acid ($H_3PO_2$), and the corresponding hypophosphite salts, have emerged as viable alternatives to $PCl_3$.




**Scheme 1:** *A summary of three different pathways from naturally occurring phosphate rock to common organophosphorus compounds.*

Hypophosphorus acid is non-toxic and is stable to moisture; to the extent that it is commercially available as a 50 wt% solution in water.[5,7] Moreover, hypophosphite salts are already being produced on a 50,000 tonne per year scale, highlighting its accessibility.[5] Hypophosphorus compounds are synthesised *via* a base hydrolysis of white phosphorus, a process which uses far less toxic reagents than chlorine gas, Scheme 1 Pathway 3.[5,7] Although hypophosphorus compounds may not be as reactive as $PCl_3$, they are still considered versatile building blocks.[7] Over the last 30 years there has been extensive research into *P-C* bond formation reactions using hypophosphorus compounds, and a review of some of the work is presented herein.

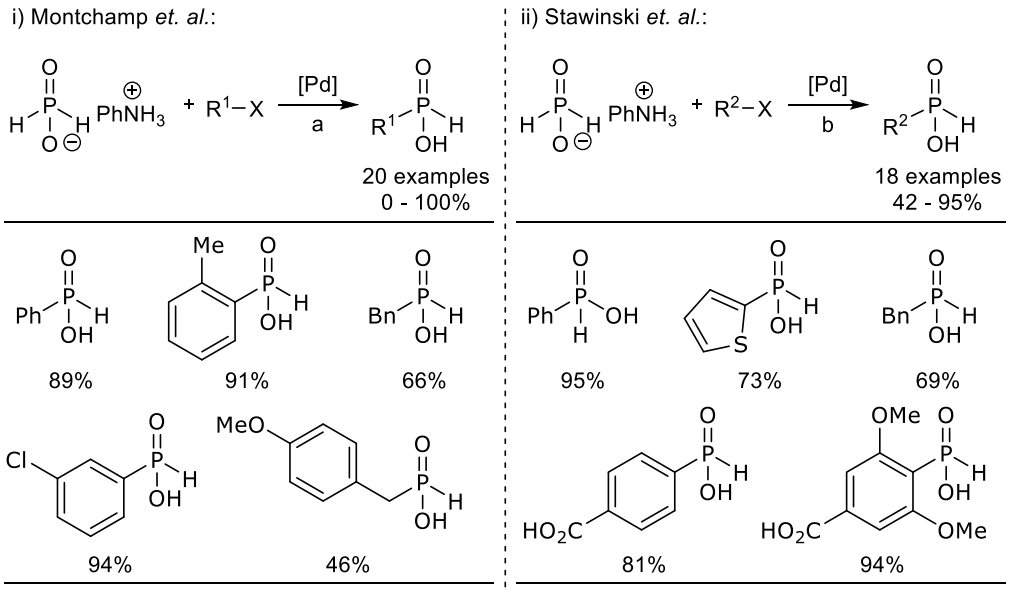
## 1.2. The Synthesis of Phosphinic Acids While Avoiding Phosphorus Trichloride

Hypophosphorus acids and hypophosphite salts can be employed to synthesise a range of phosphinate esters and phosphinic acids *via* an array of *P-C* bond formation reactions.[5,8] A summary of this chemistry can be found in a review by Montchamp and co-workers.[5,8] Herein, a small review on methods to synthesise phosphinic acids from hypophosphite starting materials will be discussed. As well as being versatile building blocks in organophosphorus chemistry, phosphinic acids are prevalent in many industries. They have displayed a wide variety of biological activities against a range of diseases including Alzheimers disease and HIV.[9] Moreover, a number of secondary phosphinic acids have demonstrated herbicidal activity.[10–12] Phosphinic acids are also present in a number of other industries as flame retardant additives,[13,14] photoinitiators,[15] and as agents to aid the separation of cobalt(II) and nickel(II) from aqueous solutions.[16,17] A single functional group, which displays such versatility is an extremely valuable target.

### 1.2.1. Palladium-Catalysed Cross-Coupling Reactions - the Synthesis of Aryl and Benzyl Phosphinic Acids

Palladium-catalysed cross-coupling reactions are the most common approach to synthesise primary and secondary phosphinic acids from hypophosphorus starting materials. The first example of a palladium-catalysed synthesis of primary phosphinic acids was developed by Montchamp and Dumond, in 2001.[18] The reaction between anilinium hypophosphite and various coupling partners was reported, with $Pd(PPh_3)_4$ as the catalyst, Scheme 2i.[18] The reaction was shown to be successful with twenty different coupling partners and complete selectivity for the mono-coupling product over bis-coupling product was observed. For the majority of

the substrates only the $^{31}P$ NMR spectroscopic yield was reported, with yields of between 0 – 100%.[18] Nevertheless, nine of the twenty phosphinic acids were isolated in 34 - 94% yield.[18] Six of the mono-substituted aryl phosphinic acids were obtained in very good yields, and were functionalised with both electron donating and electron withdrawing substituents in the *ortho*-, *meta*- and *para*- position.[18] The remaining three isolated substrates were benzylic phosphinic acids and these were synthesised in lower yields of between 34 – 66%.[18]

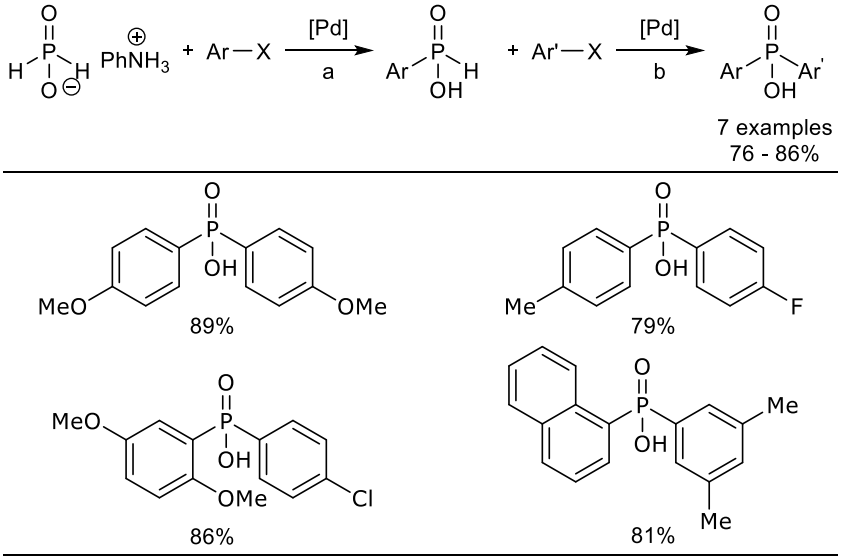



**Scheme 2:** *A summary of palladium-catalysed coupling reactions to synthesise primary phosphinic acids. Reagents and conditions: a) $Pd(PPh_3)_4$, $NEt_3$, DMF or MeCN, 80 – 85 °C, 2 – 24 h. b) $Pd_2(dba)_3{\cdot}CHCl_3$, XantPhos, $NEt_3$, THF, $\mu$W, 120 °C, 10 min.*

In 2009, Stawinski and Kalek published an alternative set of conditions for the synthesis of primary phosphinic acids, Scheme 2ii.[19] The microwave assisted reaction used $Pd_2(dba)_3{\cdot}CHCl_3$ as a pre-catalyst with XantPhos as a ligand.[19] The scope of the reaction was extensive with all mono-substituted phosphinic acids being isolated in moderate to excellent yields.[19] Similar to the work described by Montchamp *et. al.*, complete selectivity for the mono-substituted products was observed.[19] The broad range of isolated phosphinic acids indicated that the new

conditions were an improvement on the work seen previously. In both sets of work the reduced number of *ortho*-functionalised products suggested that this is a challenging moiety to synthesise.

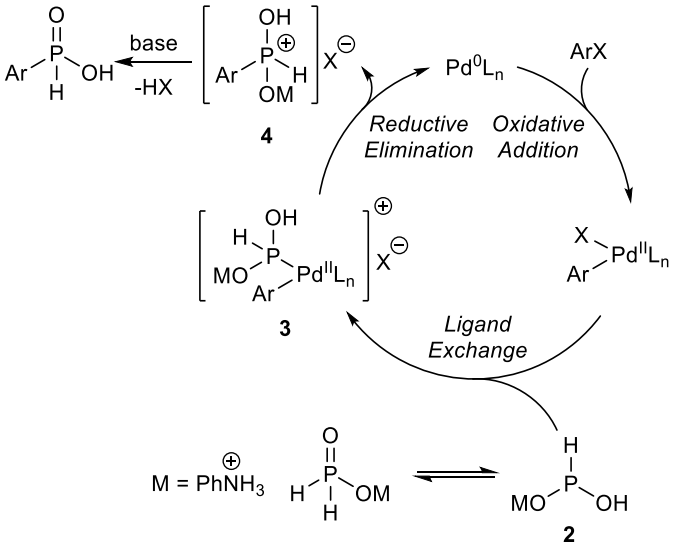
The chemistry described by Stawinski *et. al.* was extended to the synthesis of symmetrical and unsymmetrical di-substituted phosphinic acids in a two-step procedure, Scheme 3.[19] The more challenging second cross-coupling reaction required increased reaction times, higher catalyst loadings and increased equivalents of the aryl halide. Nevertheless, five examples of unsymmetrical phosphinic acids were isolated in good to excellent yields, Scheme 3.[19]




**Scheme 3:** *The synthesis of secondary aryl phosphinic acids. Reagents and conditions: a) $Pd_2(dba)_3{\cdot}CHCl_3$, XantPhos, $NEt_3$, THF, μW, 120 °C, 10 min. b) $Pd_2(dba)_3{\cdot}CHCl_3$, XantPhos, $NEt_3$, THF, μW, 120 °C, 15 min.*

A proposed mechanism for the formation of phosphinic acids *via* a palladium-catalysed cross-coupling reaction was outlined by Montchamp and co-workers.[18] Although the mechanism for corresponding cross-coupling reactions involving phosphonate esters has been investigated, the mechanism with hypophosphite compounds has not been widely studied.[20–22] The proposed catalytic cycle begins

with an oxidative addition between the carbon-halogen bond of the aryl halide, Scheme 4.[18] The subsequent ligand exchange with the trivalent hypophosphorus species **2**, allows for the formation of **3**.[19] A reductive elimination of complex **3** forms the key *P-C* bond and regenerates the active palladium catalyst. Finally, the collapse of salt **4** in the presence of a base gives the desired primary phosphinic acid.

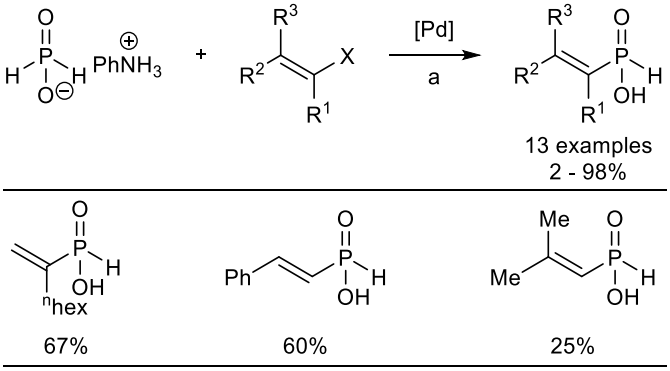



**Scheme 4:** *The proposed catalytic cycle for the formation of primary phosphinic acids.*

### 1.2.2. Palladium-Catalysed Cross-Coupling Reactions - the Synthesis of Alternative Phosphinic Acids

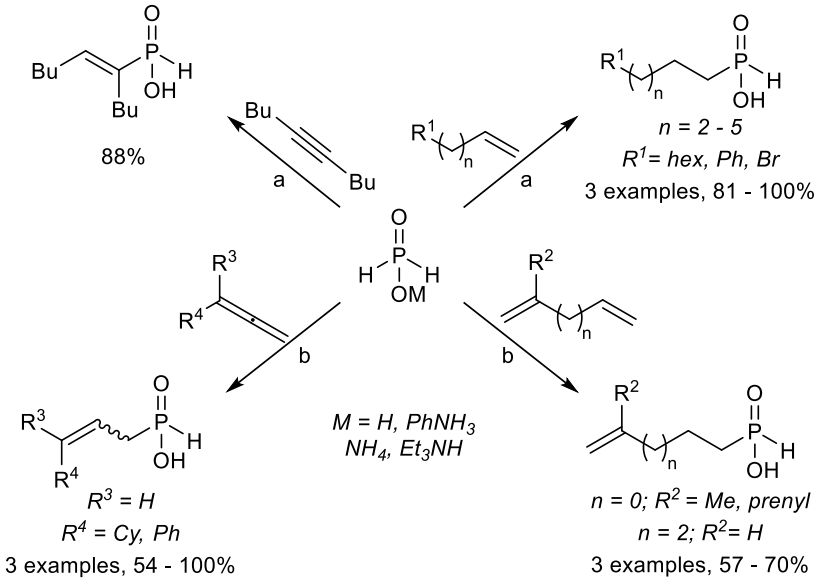
Over a number of publications, Montchamp and co-workers improved the diversity of the coupling partner, for the cross-coupling reaction with hypophosphorus starting materials. Under revised conditions alkenyl phosphinic acids were successfully synthesised from the corresponding alkenyl bromides, iodides and triflates, Scheme 5.[23] For this transformation, $Pd(OAc)_2$ was identified as the optimal pre-catalyst with dppp as the ligand.[23] The reaction was shown to work with numerous alkenyl substrates, with reported $^{31}P$ NMR spectroscopic yields of between 2 – 98%.

However, the scope was limited to only six isolated alkenyl phosphinic acids and yields were inconsistent, Scheme 5.




**Scheme 5:** *The formation of alkenyl phosphinic acids via a palladium-catalysed reaction. Reagents and conditions: a) $Pd(OAc)_2$, dppp, benzene, $NEt_3$, reflux, 18 – 24 h.*

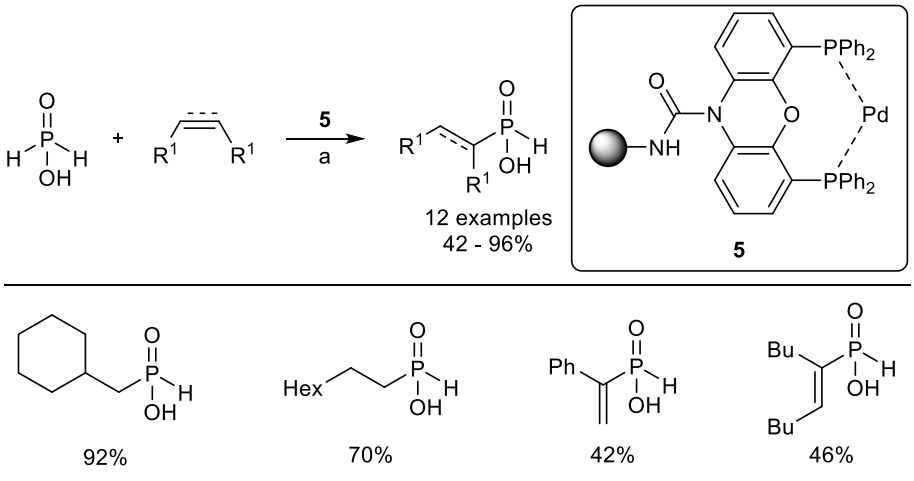
In 2002, Montchamp and Depréle reported the first example of a catalytic hydrophosphination reaction which incorporated hypophosphorus starting materials.[24] Previously, phosphines and phosphonate esters had been reacted in this manner.[25–27]




**Scheme 6:** *A summary of hydrophosphination reactions used to synthesise primary phosphinic acids. Reactions and conditions: a) $Pd_2(dba)_3$, XantPhos, MeCN, reflux, 12 – 16 h. b) $Pd_2(dba)_3$, XantPhos, MeCN or DMF, reflux or 85 °C (respectively), 8 – 14 h.*

Between 2002 and 2008 an assortment of hydrophosphination reactions were published by Montchamp and co-workers, Scheme 6.[24,28] A number of different unsaturated carbon chains were employed as coupling partners, including: alkenes, dienes, allenes and alkynes, Scheme 6.[24,28] In all cases $Pd_2(dba)_3$ and XantPhos were chosen as the optimal catalysts for the reaction.[24,28]

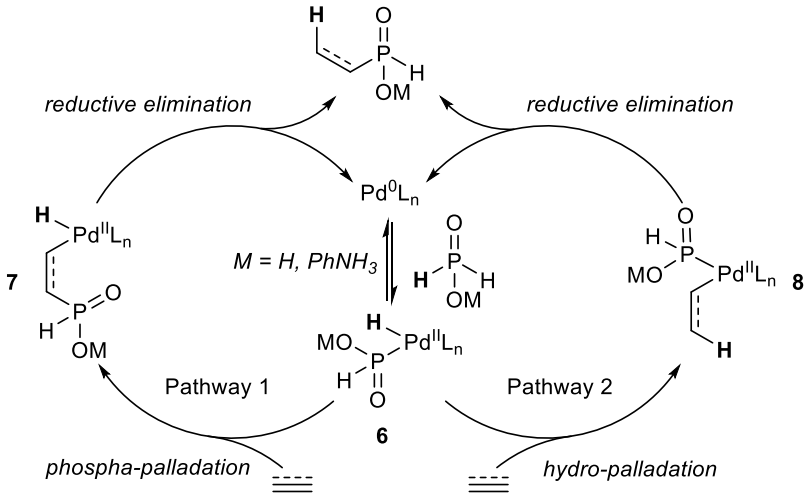
In 2004, an alternative polymer-supported palladium catalyst **5** was designed to catalyse the hydrophosphination of commercially available hypophosphorus acid with alkenes and alkynes, Scheme 7.[29] It was stated that the catalyst was tolerant to air and water, and could be recycled for multiple uses.[29] Through this method, twelve examples of primary phosphinic acids were synthesised in typically good yields, Scheme 7.[29] In general, commercially available hypophosphorus acid (50 wt% solution in water) was used but the alkyne substrates were less reactive and concentrated hypophosphorus acid was required for optimal results.[29]




**Scheme 7:** *The synthesis of primary phosphinic acids using a polymer-supported palladium catalyst. Reagents and conditions: a)* ***5*** *($Pd_2(dba)_3$ precatalyst), $H_3PO_2$ (concentrated or 50 wt% solution in water), MeCN, r.t. - reflux, 3 – 12 h.*

The general mechanism for the hydrophosphination of hypophosphorus compounds with alkenes and alkynes was proposed by Montchamp and co-workers, Scheme 8.[24] The proposed mechanism begins with the oxidative addition of the palladium (0)

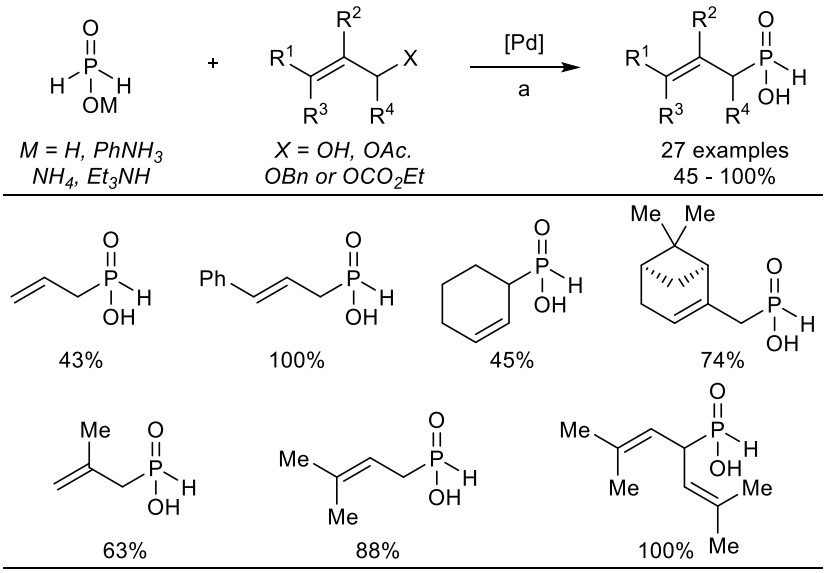
source between the *P-H* bond, of the hypophosphorus compound, to generate the palladium species **6**.




**Scheme 8:** *The proposed catalytic cycle for the hydrophosphination of alkenes and alkynes.*

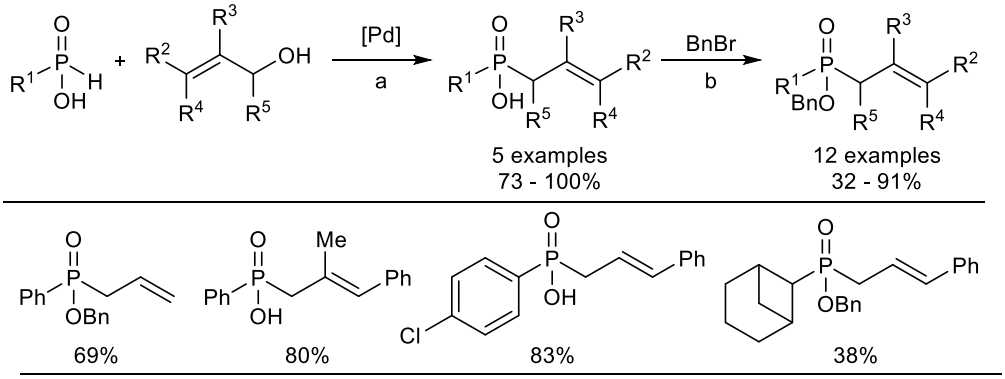
It was suggested that there are two possible routes; either species **6** reacts *via* a phospha-palladation (Scheme 8 Pathway 1) or a hydro-palladation mechanism (Scheme 8 Pathway 2), to give species **7** and **8**, respectively. The final step of both routes was proposed to involve a reductive elimination to generate the desired primary phosphinic acids.

In 2006, Montchamp and Bravo-Altamirano reported the palladium-catalysed allylation to form primary allylic phosphinic acids, Scheme 9.[30] A wide range of allyl alcohol precursors were accommodated under the reaction conditions, Scheme 9.[30] In 2008, an alternative catalytic allylation reaction which used activated allyl alcohol derivatives was also published, Scheme 9.[28] In both reactions, $Pd_2(dba)_3$ and XantPhos were identified as the optimal catalysts for the reaction, and there was no evidence of over-allylation to the corresponding secondary phosphinic acids.[30] It was reasoned that the lower reactivity of the primary phosphinic acids, compared to hypophosphorus acid was responsible for this.[31] Nevertheless, an alternative procedure was reported for palladium-catalysed allylation to obtain secondary phosphinic acid products, Scheme 10.




**Scheme 9:** *The palladium-catalysed allylation of hypophosphorus acids. Reagents and conditions: a) $Pd_2(dba)_3$, XantPhos, MeCN or DMF, reflux or 85 °C, 2 – 8 h.*

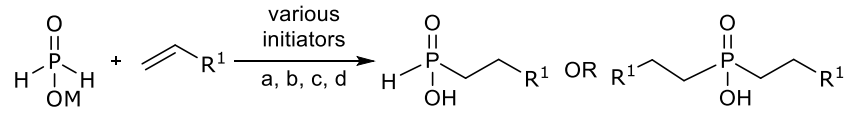
It was found that a change of solvent to *tert*-amyl alcohol and an increase in temperature, as well as more stringent anhydrous conditions, promoted the formation of secondary allylic phosphinic acids, Scheme 10.[31] Even though the majority of substrates required an additional esterification step to aid purification, there were a few examples of secondary phosphinic acids being isolated directly, Scheme 10.[31]




**Scheme 10:** *The palladium-catalysed allylation of primary phosphinic acids. Reagents and conditions: a) $Pd_2(dba)_3$, XantPhos, tert-amyl alcohol, 3 Å MS, 102 °C, 24 h b) BnBr, $Ag_2O$ (portion-wise every 30 min), $CHCl_3$, reflux, 2.5 h.*

### 1.2.3. A Radical Approach to Synthesise Phosphinic Acids

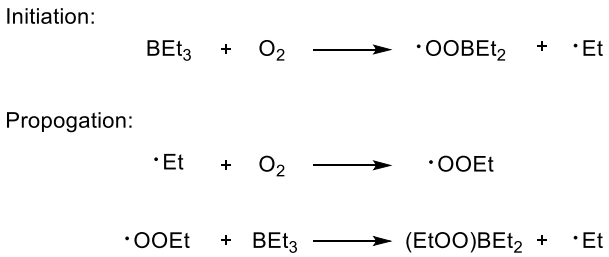
Palladium-catalysed cross-coupling reactions have proved to be an efficient and reliable method for the formation of phosphinic acids. Nevertheless, alternative transition metal free methods have been reported. Radical coupling reactions of olefins have provided a different approach for the synthesis of phosphinic acids. As early as 1955, radical coupling reactions were incorporated into organophosphorus chemistry for the formation of *P-C* bonds.[32] In 1955, Williams and Hamilton prepared various long chain disubstituted phosphinic acids. The reactions between hypophosphorus acid (50% solution in water) and olefins were initiated by dibenzoyl and di-*tert*-butyl peroxide, Scheme 11 (conditions a).[32] The chemistry suffered from low yields and was limited to simple *n*-alkyl olefins with no further functionality.[32]




*M = H, Na*

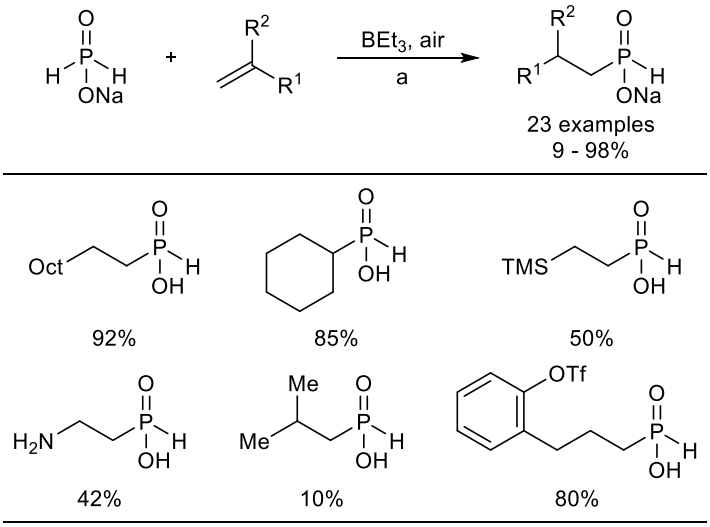
**Scheme 11:** *The general radical method for making primary or secondary phosphinic acids. Reagents and conditions: a) dibenzoyl peroxide, 1,4-dioxane or di-tert-butyl peroxide (neat), 67 – 175 °C, 11 – 24 h. b) $H_2SO_4$, peroxide, $H_2O$/1,4-dioxane. c) t-butyl peroxide, MeOH, 145 °C. d) AIBN, EtOH or $^{i}$PrOH.*

In a report by Montchamp *et al.* it was stated that "Nifant'ev and co-workers were chiefly responsible for the synthetic development of" the reaction between hypophosphorus derivatives and olefins with peroxides.[33] A general depiction of this transformation can be found in Scheme 11 (conditions b and c). The radical approach to phosphinic acids was not limited to just peroxide initiators, examples of azobisisobutyronitrile (AIBN) initiated reactions have also been described, Scheme 11 (conditions d).[34,35]




**Scheme 12:** *Radical generation using triethylborane and oxygen.*

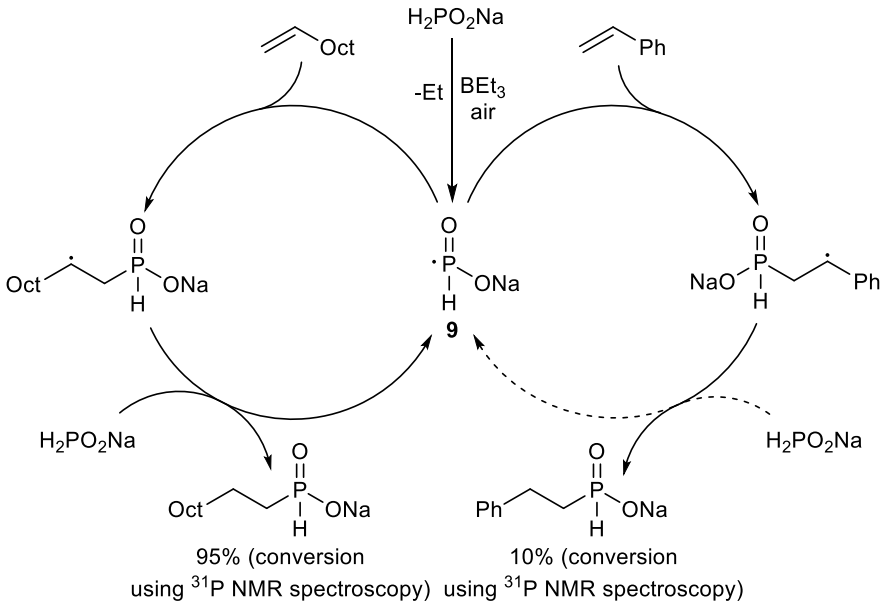
Triethylborane is an alternative radical initiator to both peroxides and AIBN. The generally accepted mechanism for the initiation is suggested to begin with a reaction between triethylborane and triplet oxygen to form an ethyl radical, Scheme 12.[36] To the best of my knowledge, the first example of a triethylborane-initiated radical coupling between sodium hypophosphite and alkenes was described in 2001, by Montchamp and co-workers, Scheme 13.[33]




**Scheme 13:** *The triethylborane-initiated radical reaction with alkenes. Reagents and conditions: a) $BEt_3$ (1.0 M solution in hexane), MeOH, r.t., 2 h.*

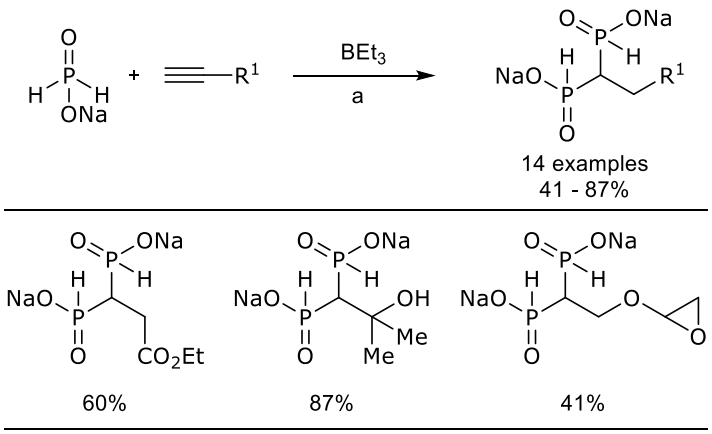
The reaction was reported to proceed at room temperature and therefore showed that the high temperatures, used with other initiators, could be negated.[33] A range of olefins were tolerated under the reaction conditions by $^{31}P$ NMR spectroscopy, however only twelve were isolated as the free acid.[33] It was noted that an alkene

which can form a stable radical suffered from poor conversion to the primary phosphinic acid (10% conversion for styrene compared to 95% conversion with dec-1-ene, Scheme 14).[33] It was proposed that a substrate which can form a stable radical stops the propagation of the reaction by hindering the regeneration of the phosphorus-centred radical **9**, Scheme 14.[33]




**Scheme 14:** *The proposed mechanism of the radical reaction between hypophosphorus acid and alkenes.*

In 2005, alkynes were also shown to react with sodium hypophosphite through a triethylborane-initiated radical process, Scheme 15.[37] Under slightly altered conditions an effective synthesis of bisphosphinates was demonstrated, Scheme 15.[37] Presumably, for ease of isolation the products were isolated as the 1,1-bis-*H*-phosphinate sodium salts rather than the free primary phosphinic acids.[37]




**Scheme 15:** *The triethylborane-initiated radical reaction with alkynes. Reagents and conditions: a) $BEt_3$ (1.0 M solution in hexane), MeOH/1,4-dioxane (5:1), r.t., 4 h.*

### 1.2.4. The Synthesis of Phosphinic Acids Using Silyl-Phosphonites

Bis(trimethylsilyl)phosphonite (BTSP) is a highly reactive, nucleophilic species which can be depicted as synthon **10**, and is therefore an highly valuable intermediate in organophosphorus chemistry, Figure 1.[38] The first synthesis of BTSP was in 1971, by Voronkov and co-workers, and since its discovery the species has been employed in a wide range of addition reactions.[39] Various electrophiles have been used from ketones and imines, to alkyl halides and α,β-unsaturated ketones.[38–46]

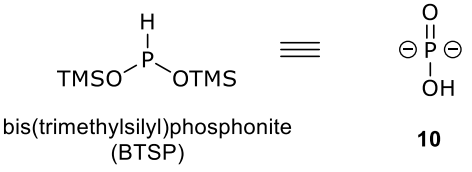
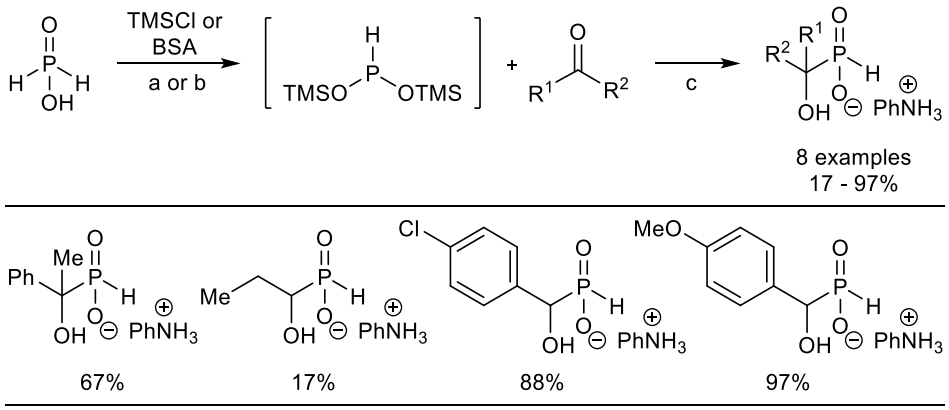



**Figure 1:** *The structure of BTSP with the corresponding synthon.*

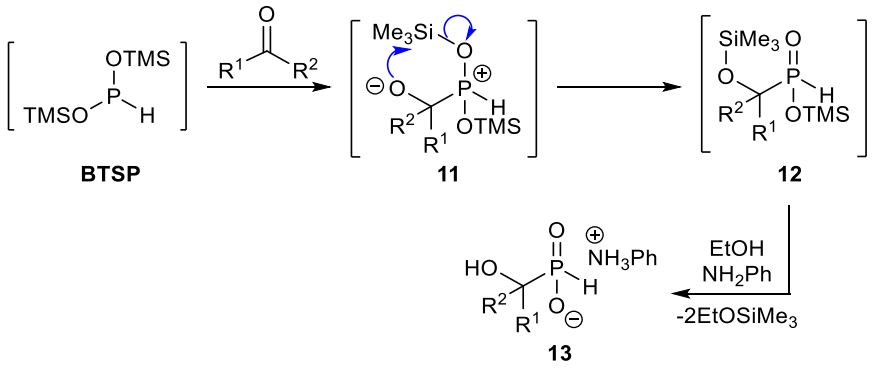
Initially, BTSP was isolated, however, it was discovered that the species was pyrophoric and therefore the *in-situ* generation was preferable.[38,39,41] Hata *et. al.* reported the first *in-situ* generation of BTSP *via* a silylation reaction of

hypophosphorus acid using either chlorotrimethylsilane and triethylamine or bis(trimethylsilyl)acetamide (BSA), Scheme 16.[39]



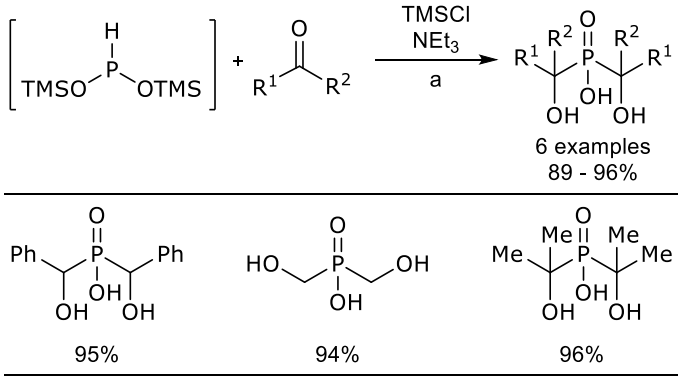

**Scheme 16:** *The first in-situ generation of BTSP and the subsequent reaction with aldehydes and ketones. Reagents and conditions: a) TMSCl, $NEt_3$, THF, r.t., 3 h. b) BSA, THF, r.t., 3 h. c) EtOH, $NH_2Ph$.*

The subsequent reaction of BTSP with ketones and aldehydes was also described, Scheme 16.[39] The α-hydroxyphosphinic acid products were isolated as the anilinium salts in varying yields.[39] Although two separate silylation methods were mentioned (chlorotrimethylsilane and triethylamine or BSA), it was shown that BSA generally produced the higher yielding reactions.[39] The mechanism for the reaction of BTSP with ketones was described by Hata and co-workers, and this can be seen in Scheme 17.



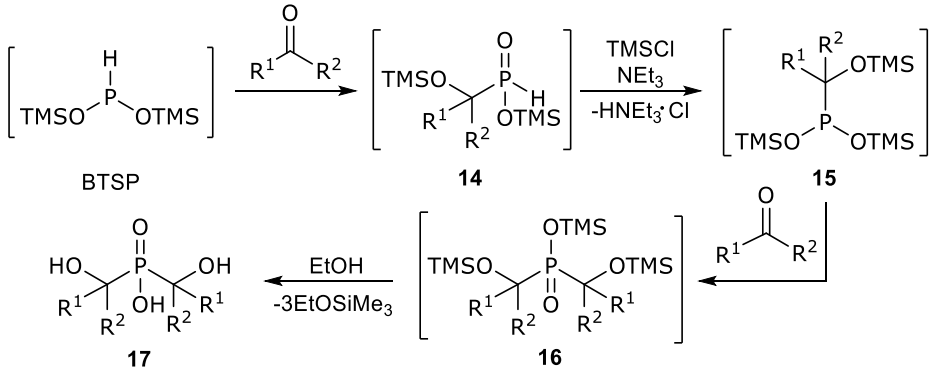

**Scheme 17:** *A general reaction mechanism for the reaction of BTSP with ketones.*

It is suggested that the nucleophilic attack of BTSP with a ketone, generates phosphonium salt **11**.[39] The subsequent silyl-transfer is thought to construct the *P-O* double bond, and then desilylation of **12** would allow the formation of the desired anilinium salt product **13**.




**Scheme 18:** *The reaction of BTSP with ketones and aldehydes. Reagents and conditions: a) $NEt_3$, benzene, 40 – 45 °C, 15 min then reflux, 2 h.*

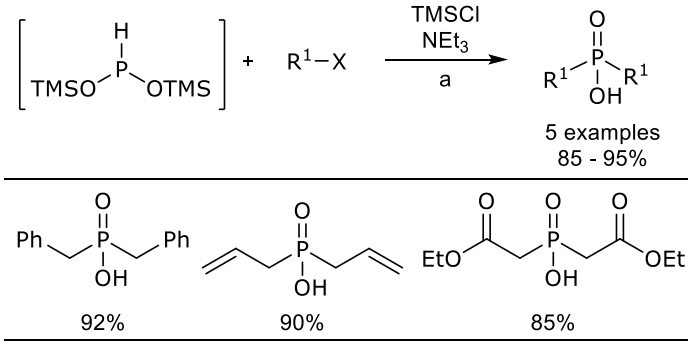
In 1987, Majewski and co-workers reported a similar reaction, which coupled BTSP with ketones and aldehydes to obtain α-hydroxy-phosphinic acid products, Scheme 18.[44] The desired free secondary phosphinic acids were isolated in excellent yields, although the scope of the reaction was somewhat limited to only 6 simple aldehyde and ketone electrophiles. The mechanism for the double alkylation of BTSP was proposed by Majewski and co-workers, Scheme 19.[44]




***Scheme 19:*** *The proposed mechanism for the synthesis of α-hydroxy-phosphinic acids.*

The mechanism for addition of BTSP to either ketones or aldehydes agreed with Hata and co-workers proposal, with silylated phosphinic acid **14** being formed, Scheme 19.[39,44] It was then suggested that a second equivalent of chlorotrimethylsilane and triethylamine regenerates the reactive trivalent species **15**, which undergoes a second addition. The subsequent formation of silylated species **16** was proposed, and following hydrolysis the desired product **17** would be obtained.[44]

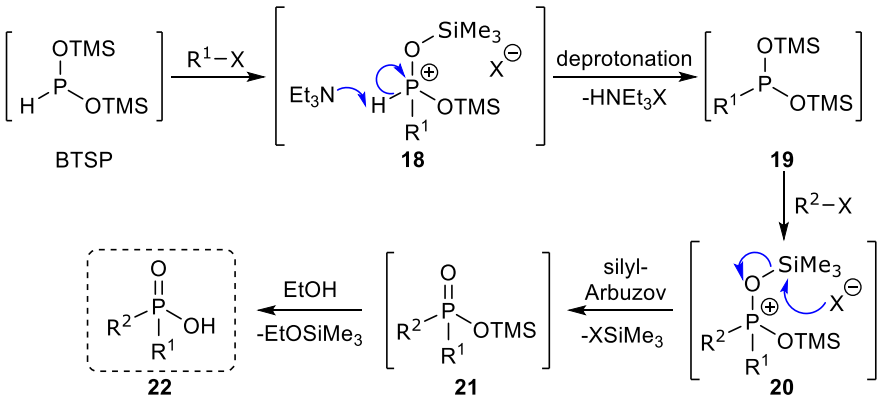
In 1989, Majewski *et. al.* published the one-pot synthesis of symmetrical secondary alkyl phosphinic acids *via* the reaction of BTSP with alkyl halides, Scheme 20.[43] Again the scope of the reaction, with respect to the alkyl halide, was limited to only 5 electrophiles but yields were excellent with all examples isolated in over 85% yield. The mechanism for the double alkylation of BTSP was also proposed by Majewski and co-workers.[43]




**Scheme 20:** *The one-pot synthesis of symmetrical secondary phosphinic acids. Reagents and conditions: a)i) TMSCl, $NEt_3$, benzene, 30 °C, 0.5 h then reflux, 1 h. ii) EtOH, reflux, 5 min.*

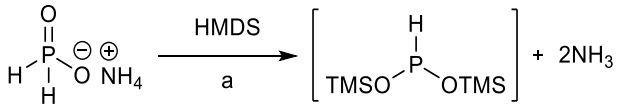
It was suggested that the reaction proceeds *via* a deprotonation of phosphonium salt **18** in order to regenerate the reactive intermediate **19**, Scheme 21.[43] It was then proposed that after a second alkylation, the silylated phosphinic acid **21** would be generated, with the loss of $Me_3SiX$. The generation of $Me_3SiX$ must occur *via* the silyl-Arbuzov collapse of phosphonium salt **20**, and upon desilylation with ethanol

the desired secondary phosphinic acid **22** would be obtained. Although this is a plausible mechanism, it did not explain the need for the additional equivalent of chlorotrimethylsilane during the reaction.




**Scheme 21:** *The suggested mechanism by Majewski and co-workers.*

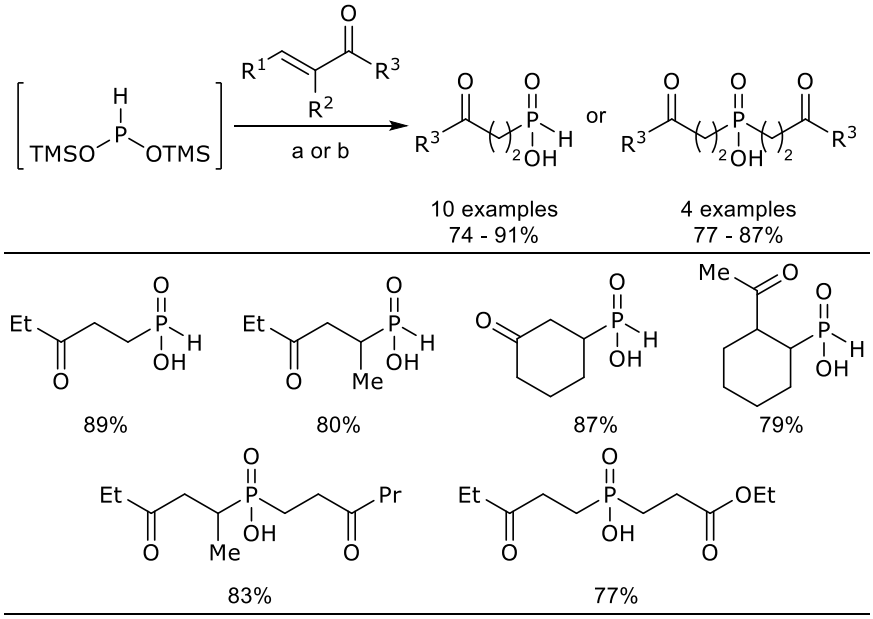
In 1992, Boyd and co-workers reported a novel method to access BTSP *via* the reaction of ammonium hypophosphite with hexamethyldisilazane (HMDS), Scheme 22.[41] The reaction was performed between 100 - 110 °C with the by-product being two equivalents of ammonia.[41]




**Scheme 22:** *The formation of BTSP via a reaction of ammonium hypophosphite with HMDS. Reagents and conditions: a) HMDS, 100 - 110 °C, 1 -2 h.*

Boyd *et. al.* demonstrated that this novel method could be used for the one-pot synthesis of primary or secondary phosphinic acids, Scheme 23 and Scheme 24.[41,42] Initially the use of α,β-unsaturated ketones and esters as electrophiles was demonstrated, with the 1,4-conjugate addition of BTSP synthesising a wide range of primary and secondary phosphinic acids in good yields, Scheme 23.[41] For the synthesis of the primary phosphinic acids only one equivalent of the electrophile and HMDS was required.[41] However, to obtain the secondary phosphinic products a

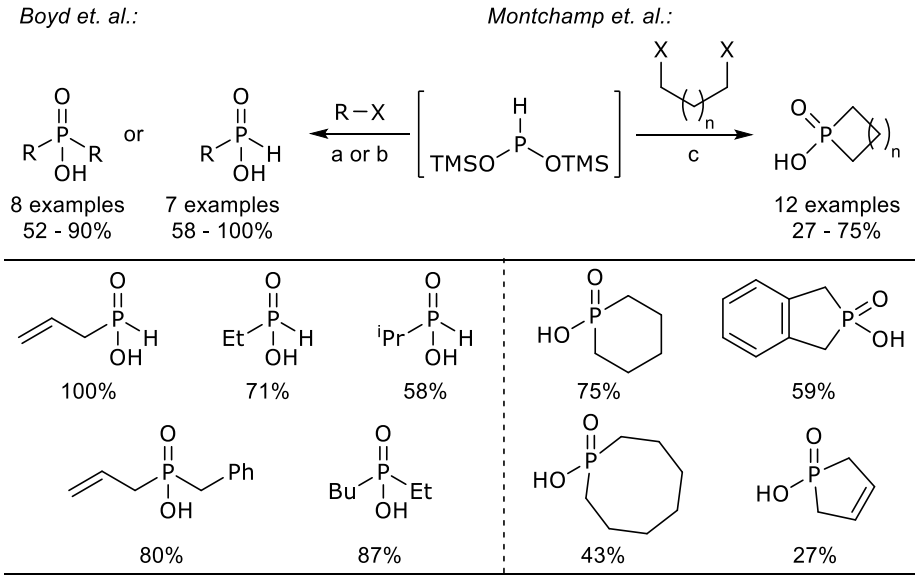
second equivalent of both the electrophile and HMDS was needed.[41] Unsymmetrical secondary phosphinic acids could also be synthesised.[41] Boyd *et. al.* also reported that these products could be formed *via* the more traditional generation of BTSP using chlorotrimethylsilane and triethylamine chemistry.[38] However, using this method the secondary phosphinic acids were obtained over a two-step process.[38]




**Scheme 23**: *The use of* α,β-unsaturated ketones and esters to synthesis primary or secondary phosphinic acids. Reagents and conditions: *a) electrophile, $CH_2Cl_2$, 0 °C – r.t., 16 h. b)i) electrophile, $CH_2Cl_2$, 0 °C – r.t., 16 h. ii) HMDS, 0 °C, 2 h. iii) second electrophile, 0 °C – r.t., 16 h.*

In 1994, Boyd *et. al.* reported the one-pot synthesis of primary and secondary phosphinic acids by the reaction with alkyl halides, Scheme 24.[42] In 1995, Montchamp *et. al.* also demonstrated the synthesis of cyclic phosphinic acids through the reaction of BTSP with dihaloalkanes, Scheme 24.[46] During the work by Boyd and co-workers it was stated that "alkylation reactions involving silyl-phosphonites are generally believed to follow an Arbuzov-type mechanism, where the intermediate phosphonium cation undergoes nucleophilic attack by the halide at silicon".[42] A mechanism was not suggested by Boyd *et. al.*, but this statement could

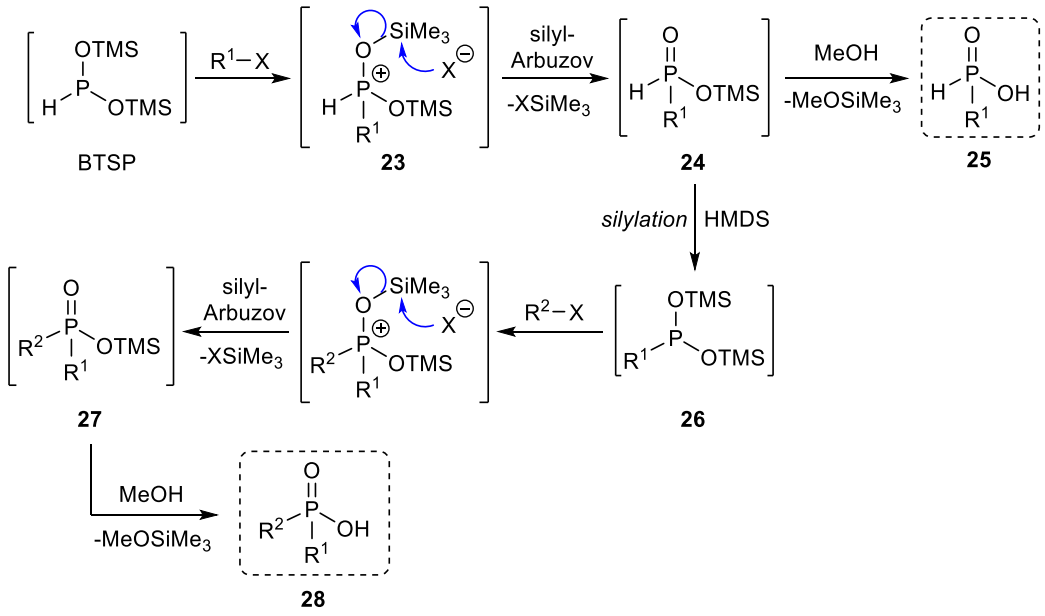
suggest an alternative mechanism, to that proposed by Majewski and co-workers. A mechanism was outlined by Montchamp *et. al.* during the synthesis of the cyclic phosphinic acids.[46] A general depiction for the reaction of BTSP with alkyl halides can be seen in Scheme 25.




**Scheme 24:** *The subsequent reaction of BTSP with alkyl halides. Reagents and conditions:* a*) electrophile, $CH_2Cl_2$, 0 °C – r.t., 16 h b)i) electrophile, $CH_2Cl_2$, 0 °C – r.t., 16 h, ii) HMDS, 0 °C, 2 h iii) second electrophile, 0 °C – r.t., 16 h*. c*) dielectrophile, HMDS, mesitylene, reflux, 16 h.*

The proposed mechanism starts with the alkylation of BTSP with an alkyl halide to generate the phosphonium salt **23**, as suggested by Boyd and co-workers.[42] The subsequent silyl-Arbuzov collapse of **23** would construct the *P-O* bond and give silyl-phosphinic acid **24**. If one equivalent of an alkyl halide and HMDS were used then the subsequent de-silylation of **24** would give primary phosphinic product **25**. However, for the synthesis of secondary phosphinic acids a second equivalent of HMDS was used. Montchamp and co-workers suggested a second silylation reaction occurs to regenerate the trivalent phosphorus species **26**.[46] However, it has not be proposed whether HMDS or $XSiMe_3$ (from the silyl-Arbuzov collapse) perform this silylation. The reactive phosphorus species **26** then undergoes a second

alkylation and silyl-Arbuzov collapse to give silylated secondary phosphinic acid **27**.[46] The de-silylation of **27** completes the synthesis of the desired secondary phosphinic acid **28**.

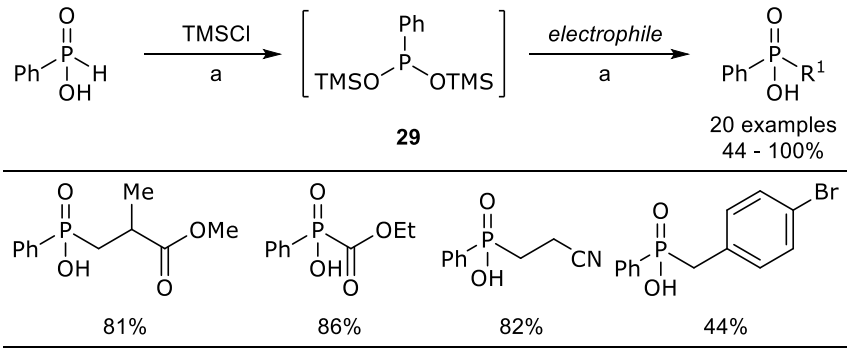



**Scheme 25:** *A proposed mechanism for the formation of primary and secondary phosphinic acids using BTSP and alkyl halides.*

In 1996, Boyd and co-workers published the synthesis of functionalised phenylphosphinic acids *via* the bis(trimethylsilyl)phenyl phosphonite intermediate **29**, Scheme 26.[40] The standard chlorotrimethylsilane and triethylamine conditions were used and twenty functionalised phenylphosphinic acids were isolated in generally good yields.[40] An impressive range of electrophiles were employed, including: acrylates, acrylamides, benzyl bromide, acyl chlorides and α,β-unsaturated cyano functional groups.

Over the last section the versatility of hypophosphorus starting materials for the synthesis of phosphinic acids has been demonstrated. Both palladium catalysed approaches and metal-free strategies were described, with a variety primary and secondary phosphinic acids being synthesised. Of particular importance to this

report was the use of silyl-phosphonites for the synthesis of phosphinic acids, *via* the *P-C* bond formation reaction with a number of electrophiles.

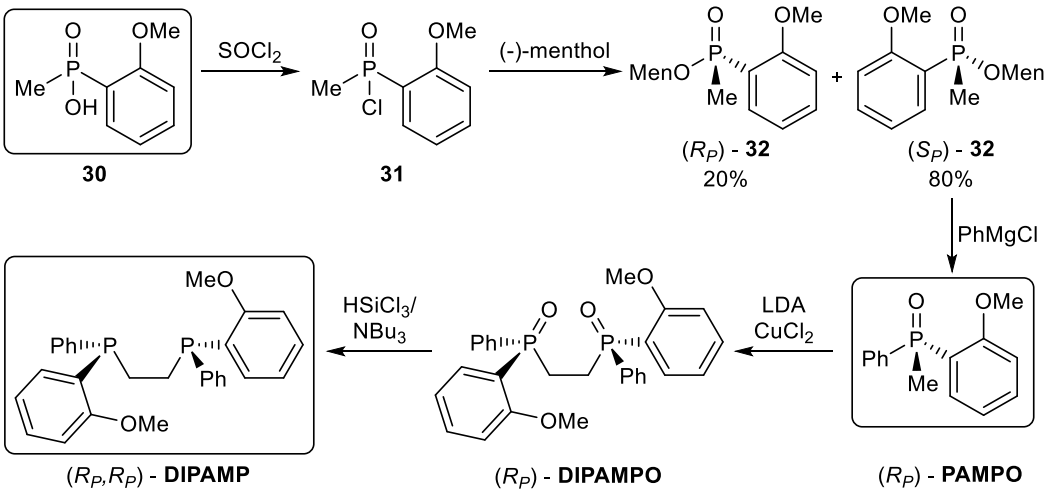



**Scheme 26:** *The synthesis of secondary phenylphosphinic acids via phosphonite* ***29****. Reagents and conditions: ai) $NEt_3$, $CH_2Cl_2$, 0 °C – r.t., 2 – 3 h. ii) electrophile, r.t., 12 – 24 h.*

### 1.3. Phosphinic Acids as Organophosphorus Building Blocks

Phosphinic acids are useful building blocks in organophosphorus chemistry. They can be used to make a range of functional groups, including tertiary phosphine oxides (TPOs). The synthesis of TPOs from phosphinic acids would usually proceed *via* a phosphinic chloride or a phosphinate ester intermediate. A well-known example of this transformation is during the synthesis of DIPAMP, Scheme 27.[47–49] DIPAMP is a enantio-enriched *P*-stereogenic phosphine ligand, which most notably was employed for the enantioselective hydrogenation to make *L*-DOPA.[47–50] DIPAMP is a highly valuable compound which can be synthesised from secondary phosphinic acid **30**, Scheme 27.[48] The synthesis begins with the chlorination to phosphinic chloride **31** which undergoes nucleophilic attack by (-)-menthol. (-)-Menthol is used as a chiral auxiliary which allows the separation of the phosphinate ester diastereomers ($R_P$)-**32** and ($S_P$)-**32**. The auxiliary is later displaced by phenyl magnesium chloride to give ($R_P$)-PAMPO. The subsequent oxidative coupling of ($R_P$)-PAMPO and reduction, with trichlorosilane and tributylamine, completes the

synthesis of ($R_P$,$R_P$)-DIPAMP. This synthesis highlights that phosphine oxides can be used as stable precursors to phosphines.

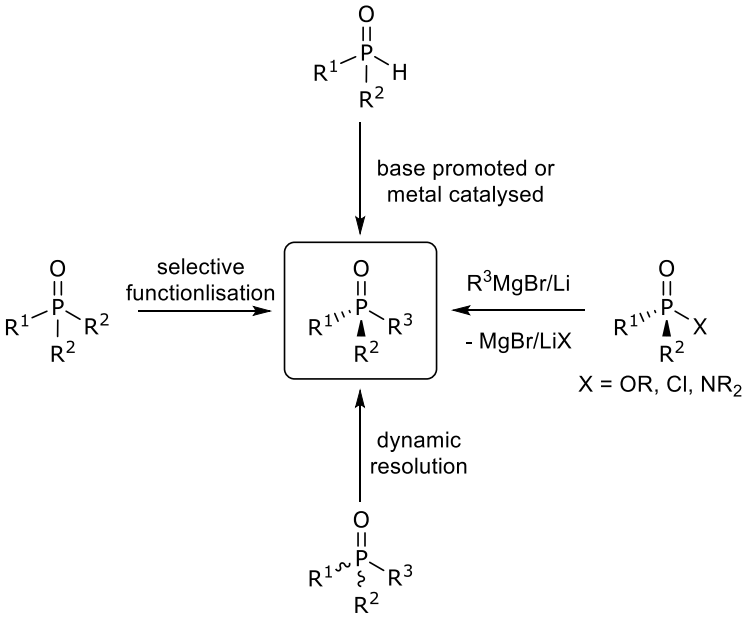



**Scheme 27:** *The synthesis of PAMPO and DIPAMP from secondary phosphinic acid **30**.*

The stereospecific reduction of a *P*-chiral phosphine oxides can give the corresponding *P*-chiral phosphines, which are conformationally stable at room temperature.[51] Tertiary phosphines are often employed as ligands and are essential for metal-catalysed reactions. It is thought that *P*-chiral ligands positively influence the enantioselectivity of metal-catalysed reactions, because the chiral phosphorus centre is closer to the metal.[52] The demand to improve the enantioselectivity of metal catalysed reactions means the need for *P*-stereogenic tertiary phosphine ligands is important.[53] Although the direct synthesis of chiral phosphines is preferable, initially targeting the more stable TPOs can be advantageous. In 2016, Jugé and co-workers published a review on the 'Applications and stereoselective syntheses of *P*-chirogenic phosphorus compounds'.[54] Herein, some select and recent enantioselective syntheses of *P*-stereogenic TPOs are described.

### 1.4. The Synthesis of *P*-Chiral Tertiary Phosphine Oxides

The synthesis of enantio-enriched *P*-stereogenic TPOs can be performed *via* four main approaches (Scheme 28): 1) the use of a chiral auxiliary followed by its displacement with an organometallic group, 2) the dynamic resolution of racemic *P*-stereogenic TPO mixtures, 3) the selective functionalisation and therefore desymmetrisation of TPOs, and 4) the functionalisation of secondary phosphine oxides (SPO), usually *via* a base promoted or metal catalysed reaction.



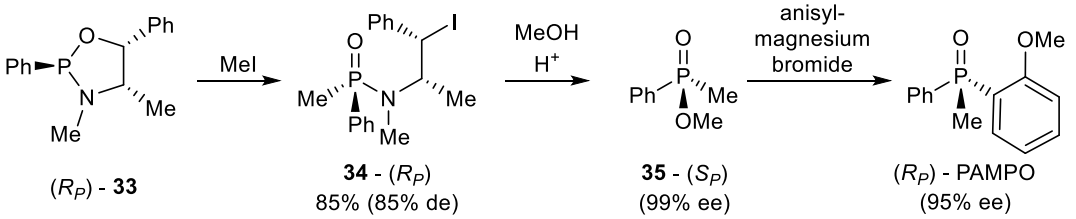

**Scheme 28:** *General strategies for the synthesis of P-chiral TPOs.*

#### 1.4.1. The Use of Chiral Auxiliaries

The classical approach to synthesise enantio-enriched *P*-stereogenic TPOs was to use (-)-menthol as a chiral axillary, as seen in the synthesis of PAMPO (Section 1.3.). This approach was first introduced by Mislow and co-workers in 1967,[59] and since then (-)-menthol has continued to be prominent as a chiral auxiliary in the synthesis of TPOs.[60–64] More recently a number of alternative auxiliaries have been reported, including amino alcohols, oxazolidinones and the adamantyl functional

group.[65–70] Nevertheless, amino alcohols have been heavily employed in the last decade.

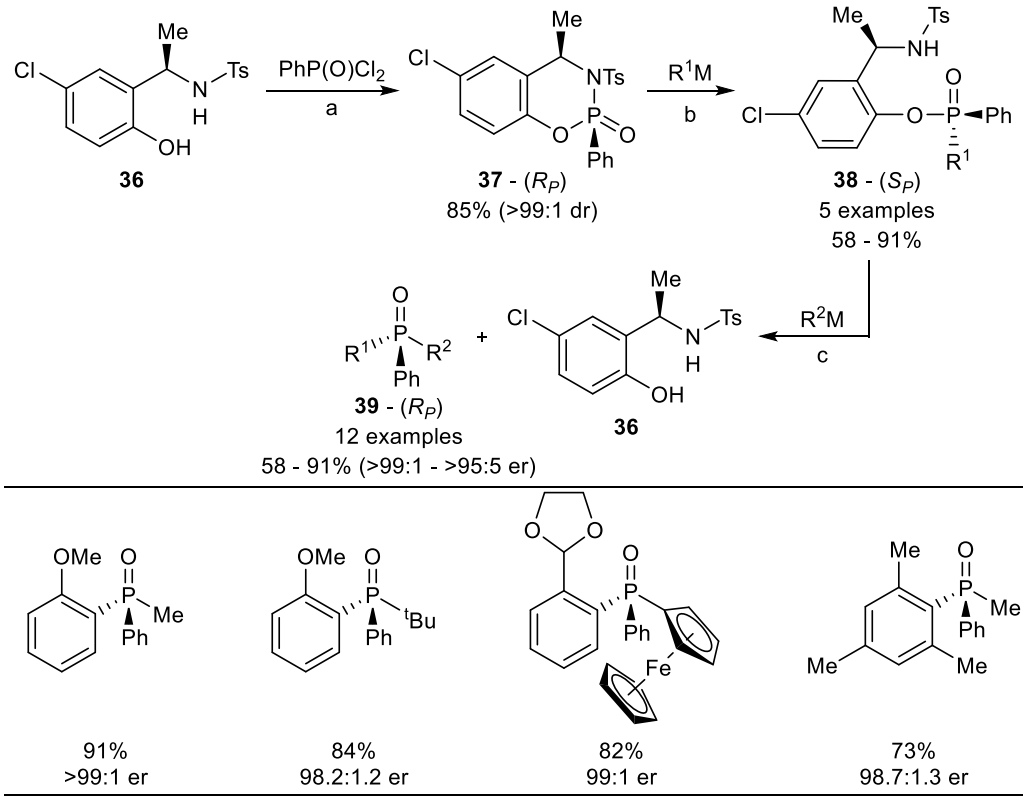
As early as 1987, amino alcohols have been used for the synthesis of enantio-enriched *P*-stereogenic TPOs by Genet *et. al.*.[71] Starting from enantiopure (-)-ephedrine derivative **33**, the synthesis of enantio-enriched PAMPO was demonstrated. First phosphinic amide **34** was made in excellent yields and good diastereoselectivities *via* an Arbuzov-type reaction with methyl iodide, Scheme 29.[71] The hydrolysis of **34** gave phosphinate **35**, and the subsequent organometallic addition gave the desired TPO is high enatioselectivities over three steps, Scheme 29. [71]




**Scheme 29:** *The synthesis of $R_P$-PAMPO with the amino alcohol (-)-ephedrine.*

In 2013, Han and co-workers reported an alternative approach for synthesising enantio-enriched TPOs which used chiral amino phenol **36**, Scheme 30.[65] When amino phenol **36** was reacted with phenylphosphoric dichloride, in the presence of 1-methyl-imidazole, phosphonamidate **37** was isolated, Scheme 30.[65] Phosphonamidate **37** was elegantly designed so that both the *P-O* and *P-N* bonds could be independently broken. It was reasoned that the difference in bond strength between the *P-N* and the *P-O* bonds was responsible for the selective cleavage.[65] The addition of the first organometallic group to **37**, displaced the weaker *P-N* bond, and gave a selection of phosphinates **38** in moderate to good yields, Scheme 30.[65] The reaction with a second organometallic species resulted in the formation of a wide range of enantio-enriched TPOs **39** in generally good yields and excellent

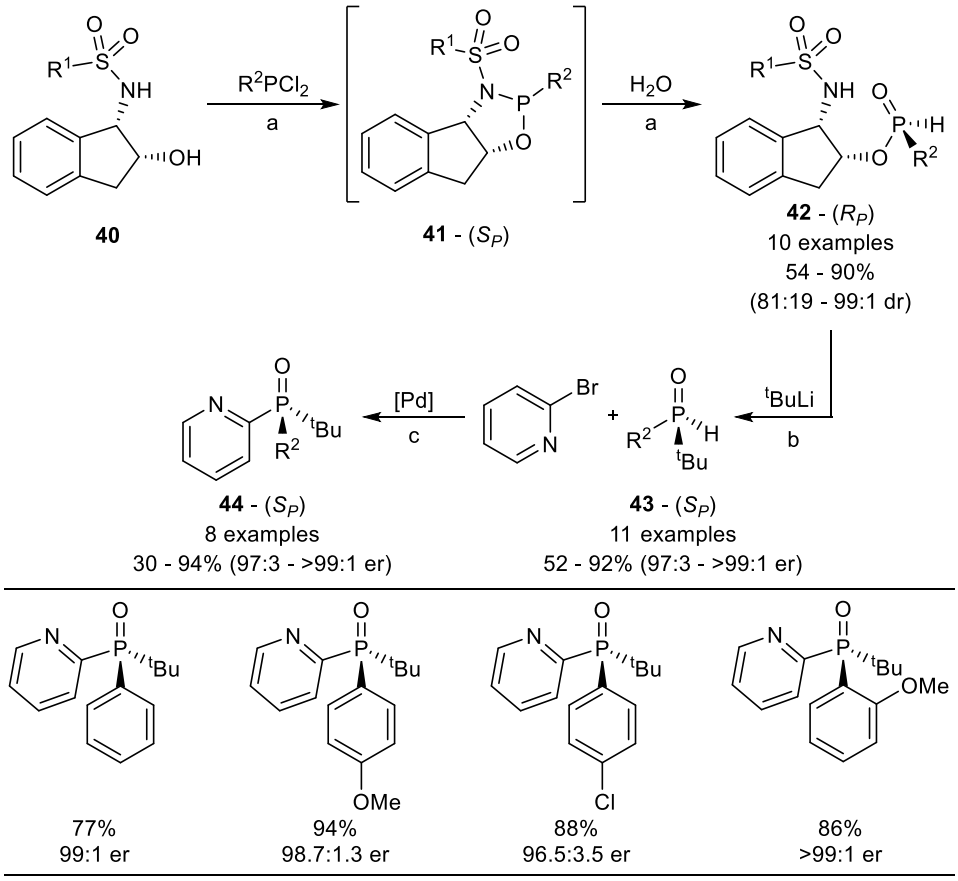
enantioselectivities, with the regeneration of amino phenol **36**, Scheme 30.[65] It is also worth noting that each organometallic addition proceeded *via* a $S_N2$ type mechanism and therefore with inversion at the phosphorus centre. A good range of organometallic reagents were tolerated for the enantioselective synthesis of TPO **39**.[65]




**Scheme 30:** *The synthesis of P-chiral TPOs, using amino phenol auxiliary **36**, via two separate displacement reactions with organometallic reagents. Reagents and conditions: a) 1-Me-imidazole, $CH_2Cl_2$, –10 °C, 30 min, r.t., 1 - 2 h. b) THF or LiCl/1,4-dioxane, –70 - 60 °C, 0.5 – 2 h. c) THF, –70 - –10 °C, 10 – 60 min.*

In 2015, two more amino alcohol auxiliaries, (1S,2S)-2-aminocyclohexanol and D-glucosamine, were reported for the synthesis of enantio-enriched TPOs.[68,69] Again, the sequential addition of two organometallic reagents was used to displace the auxiliary and provided a range of TPOs. However, the most recent example of a chiral auxiliary being used for the synthesis of enantio-enriched phosphorus

compounds was published in 2017, by Han and co-workers, Scheme 31.[67] (1S,2R)-Aminoindanol **40** was employed to synthesise sterically bulky *tert*-butyl secondary phosphine oxides (SPOs) which were functionalised to provide pyridine based TPOs.[67] Initially aminoindanol **40** was reacted with a substituted dichlorophosphine which gave intermediate **41** which was not isolated, Scheme 31.[67] Instead the subsequent hydrolysis of the *P-N* bond gave *H*-phosphinate **42**. The addition of excess *tert*-butyllithium synthesised the desired SPOs **43** in typically high yields and enantiomeric ratios, Scheme 31.



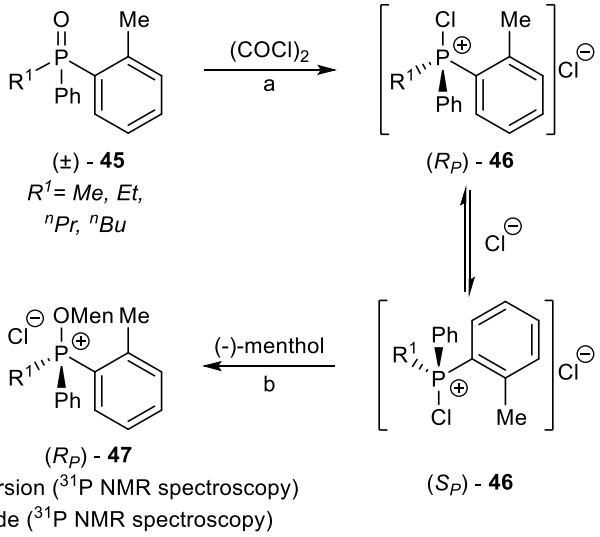

**Scheme 31:** *The synthesis of TPOs **44** via tert-butyl SPOs **43**. Reagents and conditions: a)i) pyridine, THF, –78 °C, 2 – 3 h, –20 - –10 °C, 1 - 2 h. ii) $H_2O$, r.t., 0.17 - 10 h. b) THF, –80°C, 0.5 – 3 h, –20 - –30 °C, 0.5 – 1 h c) $Pd_2(dba)_3$, dppp, toluene, DBU, 110 °C, 18 – 24 h.*

The *P-H* bond is a handle to which further alkylation or cross-coupling chemistry would generate chiral TPOs, and this was also explored by Han and co-workers.

The palladium-catalysed cross-coupling reaction of the SPOs **43** with 2-bromopyridine proceeded with retention of the stereochemistry at phosphorus and gave enantio-enriched TPOs **44** in yields ranging from 30 – 94%, with excellent enantiomeric ratios being achieved, Scheme 31.[67]

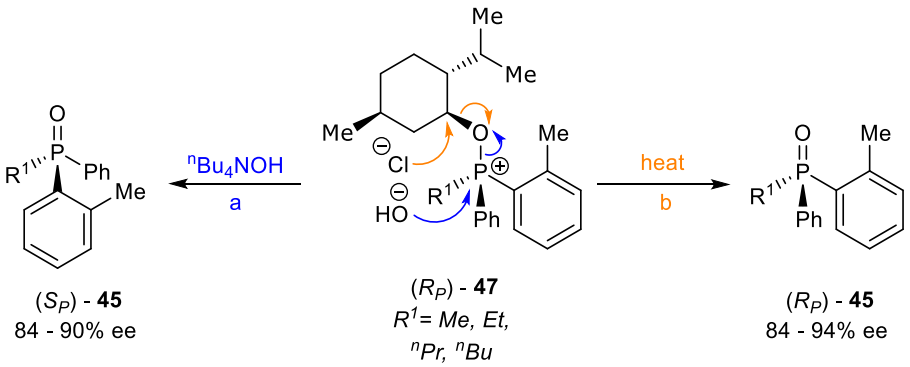
### 1.4.2. The Dynamic Kinetic Resolution of Racemic *P*-Stereogenic TPOs Mixtures

Dynamic kinetic resolutions are a powerful tool in the area of enantioselective phosphorus chemistry. It allows the late stage enantio-enrichment of racemic *P*-stereogenic TPOs. The advantage of this method is that any racemic method to synthesise TPOs can be employed which gives a wider variety of approaches. Furthermore, introducing the chirality at the last stage of synthesis means that the chiral centre does not have to be carried though many steps which reduces the chance of erosion of the enantiomeric excess. In 2014, the resolution of *P*-stereogenic phosphine oxides through a common alkoxy chlorophosphonium salt intermediate **47** was published by Gilheany and co-workers, Scheme 32.[72]




**Scheme 32:** *The resolution of racemic TPOs **45** to form alkoxyphosphonium salt **47**. Reagents and conditions: a) $(COCl)_2$, $CH_2Cl_2$, r.t., 2 h. b) (-)-menthol, toluene, –82 °C, 3 h.*

Initially, racemic phosphine oxide **45** was reacted with oxalyl chloride to give chlorophosphonium salt **46**, Scheme 32. Chlorophosphonium salt **46** is known to rapidly convert between its ($R_P$)- and ($S_P$)- enantiomer. However, in the presence of (-)-menthol the intermediate resolves to form the ($R_P$)-diastereomer of alkoxyphosphosphonium salt **47**, with a diastereomeric excess of between 87 – 97%, Scheme 32.[72] It was found that ($R_P$)-**47** was obtained with greater diastereomeric excess when a larger alkyl chain ($R^1$) was used, Scheme 32.[72] With alkoxyphosphonium salt ($R_P$)-**47** in hand, it was demonstrated that both the ($R_P$)- and ($S_P$)-TPO **45** could be accessed, Scheme 33.[72]

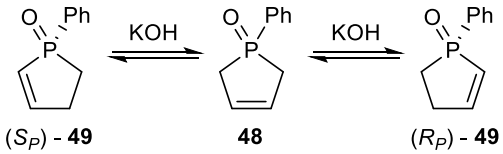



**Scheme 33:** *The formation of each enantiomer of **45** from the same alkoxyphosphonium salt intermediate **47**. Reagents and conditions: a) $^{n}Bu_4NOH$, MeCN, 0°C b) $CH_2Cl_2$/toluene, $^{t}BuOH$ (10%) or $CH(OMe)_3$ (10%) or pyridine (4%), 60 °C, 2 h.*

The optimal conditions for the retention of configuration were to perform the reaction in $CH_2Cl_2$/toluene at 60 °C with substoichometric quantities of either *tert*-butanol, pyridine or trimethylorthoformate present.[72] The preferred conditions for the inversion of stereochemistry were to use tetrabutylammonium hydroxide, as the nucleophilic base, in acetonitrile at 0 °C.[72] The selectivity of both reactions were good with the desired enantiomer being isolated with an enantiomeric excess of between 84 – 94%, Scheme 32.[72] Moreover, the reactions were performed on the gram scale showing the scalability. However, the scope of the reaction was restricted to only four different linear alkyl chains. It was shown that the retention of

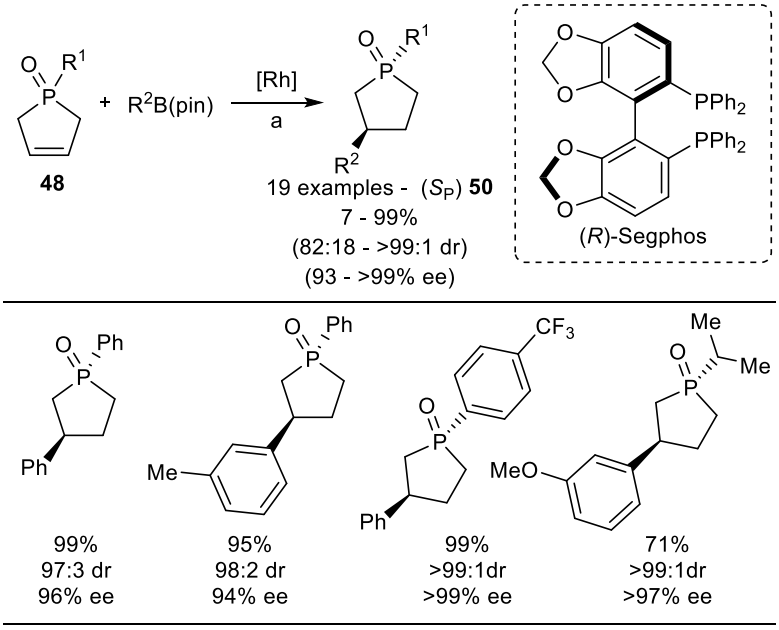
configuration proceeded *via* an Arbuzov-type collapse (Scheme 33 in orange), while the inversion of stereochemistry was demonstrated to follow a $S_N2$ mechanism *via* attack of the hydroxyl group at the phosphorus centre (Scheme 33 in in blue),.[72]

In 2017, Hayashi and Lim reported the dynamic kinetic resolution of phospholene oxide **48**.[73] Achiral 2,5-dihydrophosphole oxide **48** was shown to undergo an isomerisation to the corresponding ($R_P$)- and ($S_P$)-2,3-dihydro species **49** in the presence of a base, Scheme 34.[73] Potassium hydroxide was used and it is stated that after three hours at 80 °C the equilibrium ratio between **48** and **49** was 26:74 by $^{31}$P NMR spectroscopy.[73] The initial 2,5-dihydro-species **48** is reported to be unreactive but the isomerised products **49** are shown to undergo a metal catalysed arylation with aryl boronic esters. The chosen catalyst for the arylation was $[RhCl(coe)_2]_2$ with (*R*)-segphos as the ligand.[73]




**Scheme 34:** *The interconversion of achiral* 2,5-dihydrophosphole oxides **47** *to the* 2,3-dihydrophosphole oxide enantiom*ers via the isomerisation in the presence of KOH.*

The base assisted one-pot asymmetric arylation of 2,5-dihydrophosphole oxide **48** provided arylphospholane oxides **50** in high yields, Scheme 35.[73] Remarkable selectivity for the ($S_P$)-2,3-dihydro species **50** was seen with an enantomeric excess consistently above 90%. Finally, a range of electron withdrawing and donating substituents were tolerated on the aryl rings of both the boronic esters and phosphole oxides, Scheme 35.[73]



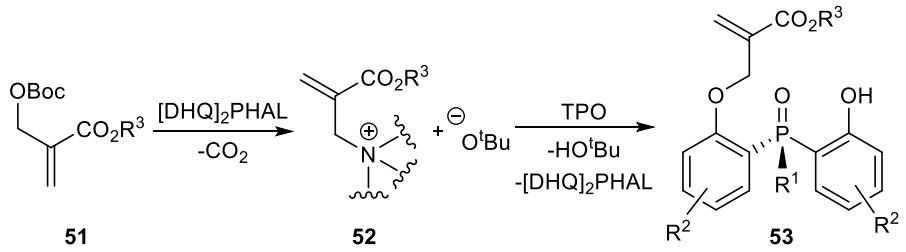

**Scheme 35:** *The rhodium-catalysed asymmetric arylation of 2,5-dihydrophosphole oxide* ***48****. Reagents and conditions: a) [RhCl(coe)$_2$]$_2$, (R)-segphos, KOH, 1,4-dioxane/H$_2$O (10:1), 80 °C, 16 h.*

### 1.4.3. The Selective Functionalisation and Desymmetrisation of TPOs

The selective functionalisation of pro-chiral TPOs is a useful approach for the synthesis of enantio-enriched *P*-stereogenic TPOs. Similar to the dynamic kinetic resolution approach, this strategy consists of introducing the enantio-enriched phosphorus centre at the final stage of the synthesis. An advantage of this route is that the synthesis of the symmetrical TPOs is generally easier than the synthesis of *P*-stereogenic TPOs.

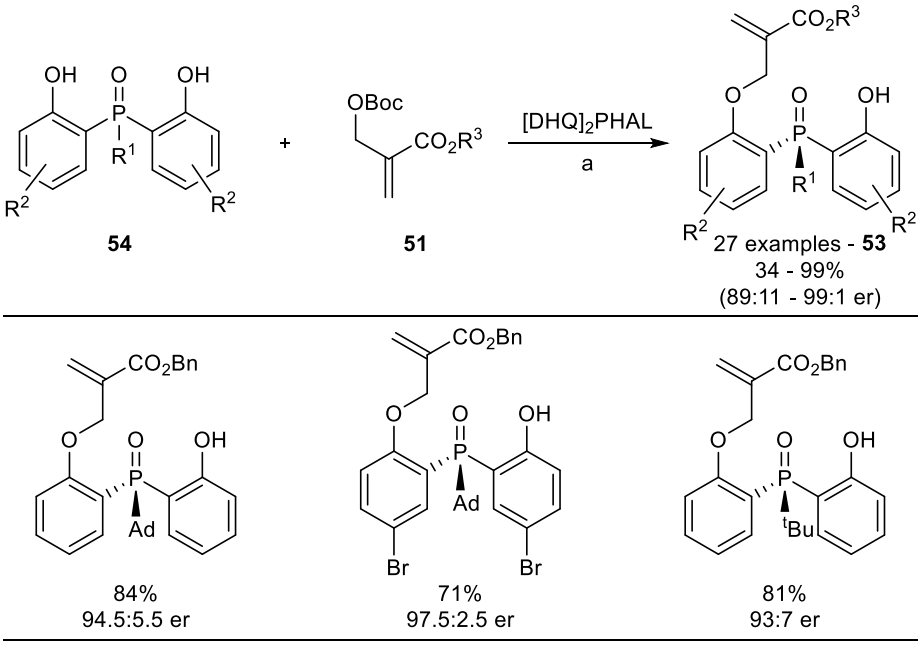
The most recent example of a desymmetrisation of pro-chiral TPOs was published earlier in 2019. Li and co-workers reported the enantioselective asymmetric allylation of bisphenol phosphine oxides **54**, Scheme 37.[74] The reaction was metal-free, with alkaloid [DHQ]$_2$PHAL used as the catalyst. The allylation was performed with Morita-Baylis-Hillman carbonates **51**, and it was suggested that addition of the

tertiary amine catalyst, gave intermediate **52**, with loss *tert*-butoxide and carbon dioxide, Scheme 36.[74]




**Scheme 36:** *The suggested enantioselective allylation pathway via intermediate **52**.*

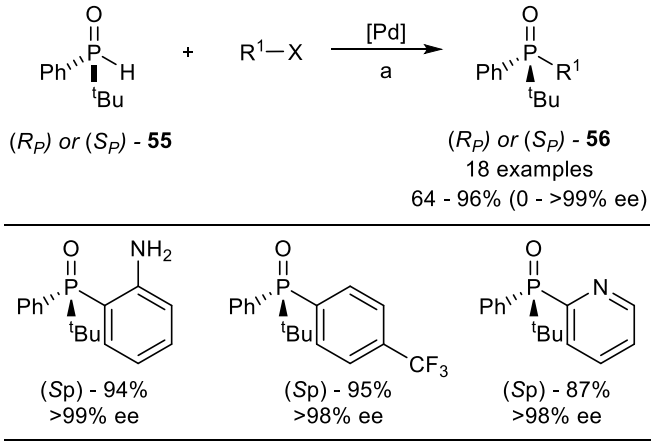
It was proposed that the selective allylation of **54** occurred *via* cationic species **52** generated TPOs **53** in an enantioselective manner, Scheme 36. The selectivity of the reaction was generally high and it was reasoned that a bulky $R^1$ group was essential. The scope of the reaction was shown to accommodate varying functionality on the phenol rings as well as on carbonates.




**Scheme 37:** *The enantioselective allylation of diphenolphosphine oxides **54**. Reagents and conditions: a) [DHQ]$_2$PHAL, CHCl$_3$, –40 °C, 6 days.*

### 1.4.4. The Enantioselective Functionalisation of SPOs

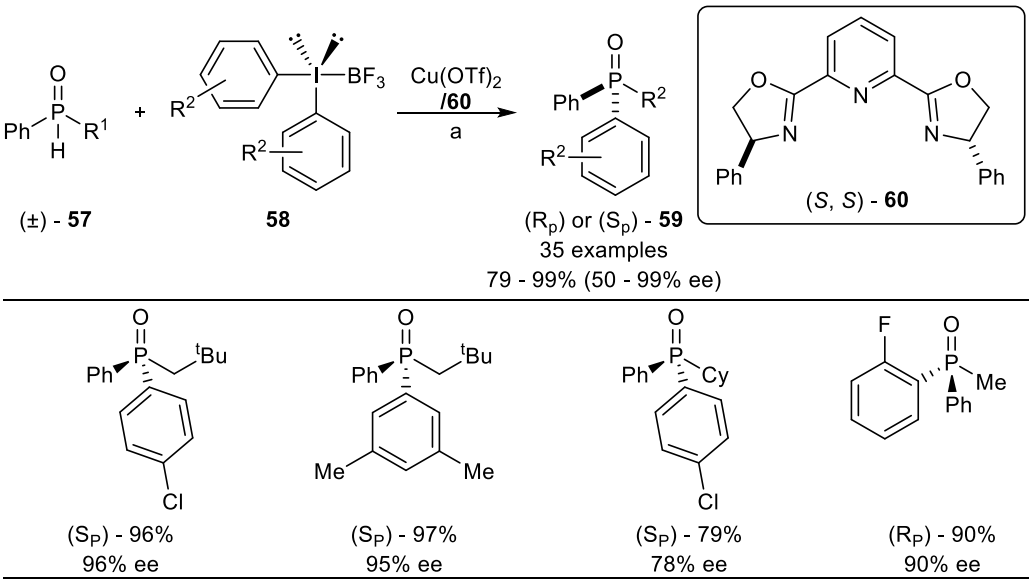
The functionalisation of SPOs is a convenient method to access *P*-chiral TPOs. However, the chirality is usually present in the SPO starting material, which makes their synthesis much more challenging. In 2018, Drabowicz and co-workers reported the palladium-catalysed cross-coupling of enantiopure SPOs with aryl halides, Scheme 38.[76] The reaction was shown to accommodate a range of aryl halides and gave the TPOs **56** in yields of between 64 – 96%.[76] However, the chemistry was solely restricted to phenyl-*tert*-butylphosphine oxides **55**.




**Scheme 38:** *The enantioselective cross-coupling reaction to synthesise TPOs **56**. Reagents and conditions: a) $Pd(PPh_3)_4$, $K_2CO_3$, toluene, 110 °C.*

In 2016, Gaunt and co-workers reported the enantioselective copper-catalysed arylation of secondary phosphinic acids, Scheme 39.[77] The reaction used diaryliodoium salts **58**, as an electrophilic aryl source, and $Cu(OTf)_2$ was chosen as the catalyst with **60** as the ligand.[77] The reaction demonstrated good functional group tolerance with respect to both the SPOs **57** and the diaryliodoium salts **58**.[77] The yields of the reaction were very good to excellent, and the enantio-enriched TPO products were obtained with an enantiomeric excess of between 55 – 90%.[77] This was a very powerful reaction, which allows for the synthesis of enantio-

enriched *P*-stereogenic TPOs from non-chiral SPOs *via* the construction of a *P-C(Sp$^2$)* bond in a one-step process.




**Scheme 39:** *The copper-catalysed enantioselective arylation of SPOs. Reagents and conditions: a) Cu(OTf)$_2$, (S, S) – **60**, K$_2$HPO$_4$, H$_2$O, MeCN, r.t. 12 h.*

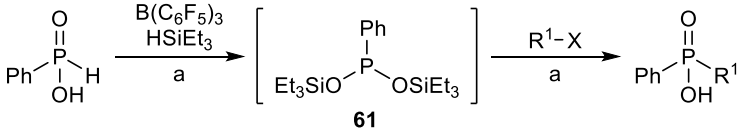
### 1.5. Project Aims

The overall aim of the project was to develop a convenient method to synthesise secondary phosphinic acids from hypophosphorus derived starting materials, *via* a *P-C* bond formation reaction. It was envisaged that a nucleophilic silyl-phosphonite intermediate could be used to construct the desired *P-C* bond. The Denton group had previously discovered that primary phosphinic acids could be converted to secondary phosphinic acids, when reacted with an electrophile, in presence of tris(pentafluorophenyl)borane and triethylsilane. It was suspected that the reaction proceeds *via* a silyl-phosphonite intermediate. The aim of this project was to develop a better understanding of this transformation, as well as, explore the scope of the reaction with respect to the electrophilic coupling partner and the primary phosphinic acid starting material. An additional aim was to investigate the versatility of phosphinic acids as organophosphorus building blocks.

# Chapter 2 – Results and Discussion

## 2.1. Introduction to a Novel *P-C* Bond Formation reaction

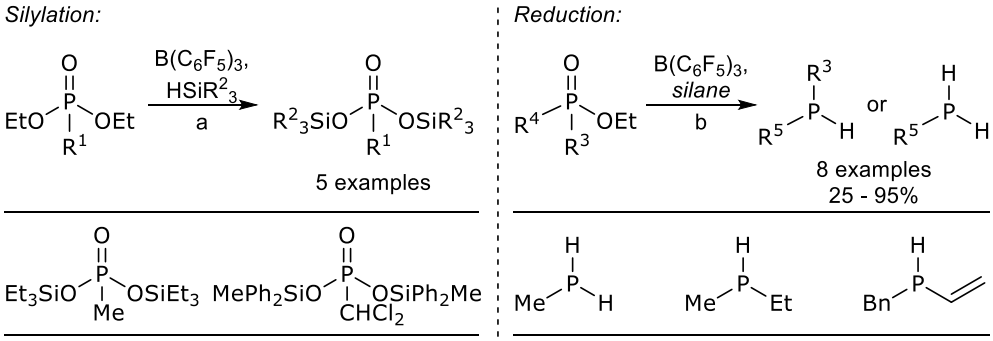
Previous work within the group led to the discovery and development of a *P-C* bond formation reaction, which could synthesise secondary phosphinic acids from phenylphosphinic acid, Scheme 40.[78] It was hypothesised that this reaction proceeded *via* the nucleophilic silyl-phosphonite intermediate **61**. It was therefore proposed that phenylphosphinic acid must undergo a silylation process to access the silyl-phosphonite intermediate. Previous methods to generate silyl-phosphonites have required the use of toxic silylating reagents (HMDS or TMSCl).[38,40–42] Our novel approach overcomes this problem by using less toxic triethylsilane. We settled on the following set of general experimental conditions for the synthesis of secondary phosphinic acids: 3.50 mol% of $B(C_6F_5)_3$, 3.50 equivalents of $HSiEt_3$, 2.50 equivalents of the electrophile, and heating to 100 °C in toluene.




**Scheme 40:** *The novel P-C bond formation method. Reagents and conditions: a) $B(C_6F_5)_3$, $HSiEt_3$, BnBr, toluene, 100 °C.*

Tris(pentafluorophenyl)borane is a commercially available Lewis acid comparable to $BF_3$, in terms of acidity but with greater hydrolytic stability.[79] In combination with silanes, tris(pentafluorophenyl)borane has been reported to promote the catalytic hydrosilylation of imines,[80] olefins,[81] aldehydes and ketones.[82] $B(C_6F_5)_3$ has also been used for the dehydrogenative silylation of alcohols,[83] the dehydrogenative coupling of silanes with thiols,[84] and the fluorine-hydrogen exchange between alkylfluorides and silanes.[85] Furthermore, the reductive amidation between amines

and carboxylic acids was reported in 2015.[86] To the best of our knowledge, there were only two published examples of $B(C_6F_5)_3$-catalysed approaches with silanes, in the area of organophosphorus chemistry, prior to the groups discovery.[87]

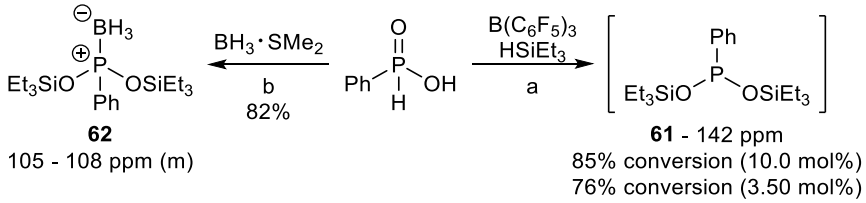



**Scheme 41:** *$B(C_6F_5)_3$-catalysed silylation and the $B(C_6F_5)_3$-catalysed reduction of phosphonate/phosphinate esters. Reagents and conditions: a) $B(C_6F_5)_3$, $HSiEt_3$ or $HSiPh_2Me$, toluene, r.t. b) $B(C_6F_5)_3$, $H_3SiPh$ or $H_2SiPh_2$, toluene, r.t., 2 – 4 days.*

In 2002, Denis and co-workers simultaneously reported the $B(C_6F_5)_3$-catalysed silylation of diethylphosphonates, as well as the $B(C_6F_5)_3$-catalysed reduction of phosphonate and phosphinate esters, Scheme 41.[87] There are very few examples of $B(C_6F_5)_3$ used in organophosphorus chemistry and none for the construction of *P-C* bonds. Herein, the further development and understanding of the novel *P-C* bond formation reaction is explored.

### 2.2. Understanding the New *P-C* Bond Formation Reaction

Our initial goal was to establish that the *P-C* bond formation reaction proceeded *via* the proposed silyl-phosphonite intermediate **61**. A signal in the $^{31}$P NMR spectra was observed at 140 ppm, when the reaction of phenylphosphinic acid with $B(C_6F_5)_3$/$HSiEt_3$ was performed in the absence of benzyl bromide, Scheme 42. This is the expected region for silyl-phosphonites.[88]

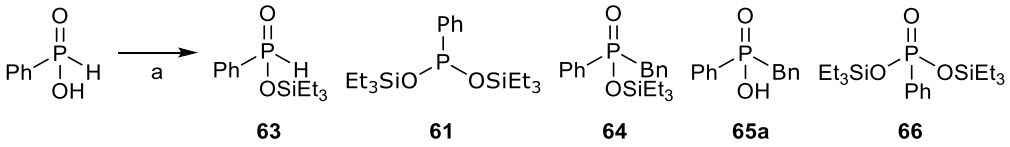



**Scheme 42:** *The generation of silyl-phosphonite **61** and identification via formation of complex **62**. Reagents and conditions: a) $B(C_6F_5)_3$ (10 mol% or 3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene - d8, 100 °C, 5 h. Chemical shift in toluene d8. $^{31}$P NMR experiment: phosdecig, 16 scans, 30 s delay. b)i) $B(C_6F_5)_3$ (10 mol%), $HSiEt_3$ (3.5 eq.), toluene, 100 °C, 16 h ii) $BH_3$•$SMe_2$ (1.5 eq.), 0 °C – r.t., 16 h.*

Better conversion to **61** was seen when the loading of $B(C_6F_5)_3$ was increased to 10 mol%. However, further evidence was required to show that the signal at 140 ppm corresponded to the silyl-phosphonite **61**. It is worth noting, that the same species was observed in small quantities, under the general reaction conditions, with benzyl bromide present. Silyl-phosphonites are generally air sensitive which makes their characterisation very difficult.[5] Nevertheless, when treated with borane dimethylsulfide the stable complex **62** was formed, Scheme 42.[89] This undoubtedly showed that **61** is an intermediate in the newly discovered reaction, and this demonstrates the first example of a $B(C_6F_5)_3$-mediated silylation reaction of phosphinic acids to a silyl-phosphonite.

We next carried out reaction monitoring by $^{31}$P NMR spectroscopy and under the standard conditions, five significant species were observed, Scheme 43.

Unsurprisingly the free phenylphosphinic acid starting material was observed but the benzylphenylphosphinic acid product **65a** was rarely seen *in situ*. It was believed that the complete hydrolysis to the desired product **65a** must occur upon work-up. The silyl-phosphonite intermediate **61** was also identified by the distinct signal at ~140 ppm, in the $^{31}$P NMR spectrum. Silylated intermediates **63** and **64** were proposed to be sensible intermediates during the reaction and were later confirmed to be present.

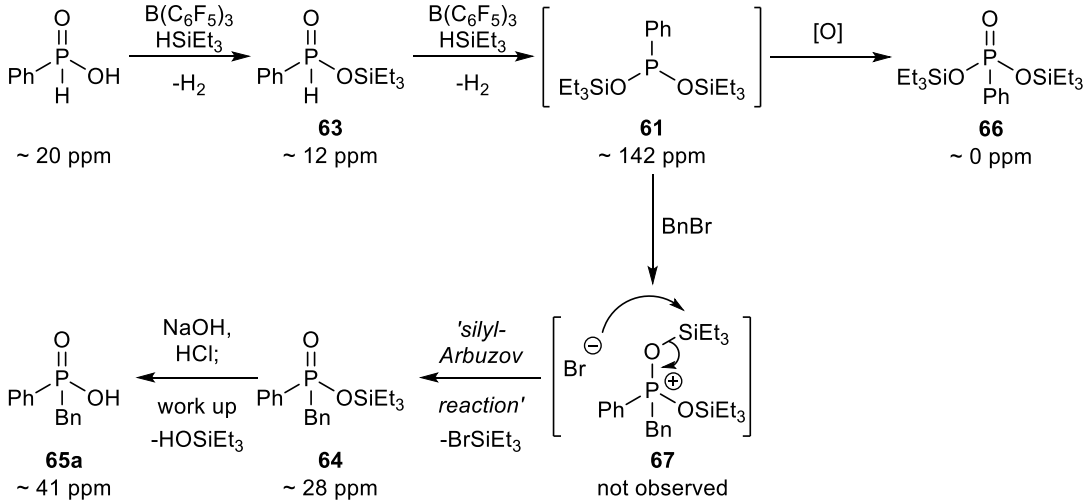



**Scheme 43:** *Reaction monitoring. Reagents and conditions: a) $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), benzyl bromide (2.5 eq.), toluene – $d^8$, 100 °C, 5 h.*

Finally, the silylated-phosphonic acid species **66** was identified and it was reasoned that it was formed *via* the oxidation of intermediate **61**, despite the reaction being performed under an inert atmosphere of argon. Silylated species **63**, **64** and **66** were independently synthesised using TESCl/DIPEA silylation chemistry (*see experimental page 70*). However, compound **63**, **64** and **66** were only observed by $^{31}$P NMR spectroscopy and could not be isolated because they were prone to hydrolysis, even in the presence trace amounts of water. Nevertheless, with all species identified a reaction mechanism was proposed, Scheme 44.

The reaction mechanism begins with the silylation of phenylphosphinic acid to give intermediate **63**. A second silylation is proposed to take place and following a tautomerisation, reactive intermediate **61** is generated. It is reasoned that the formation of **66** occurs *via* an off-cycle oxidation of **61**. The alkylation of **61** with benzylbromide is presumed to generate phosphonium salt **67**, in a similar manner to that suggested by Boyd and co-workers.[42] During the reaction the phosphonium salt

intermediate **67** was not observed by $^{31}$P NMR spectroscopy and therefore it was reasoned that the subsequent collapse to **64** was instantaneous under the reaction conditions. The collapse of the phosphonium salt **67** is suggested to proceed *via* a silyl-Arbuzov mechanism.[42] The final stage of the mechanism was the hydrolysis of **64** to the desired secondary phosphinic acid product **65a**.

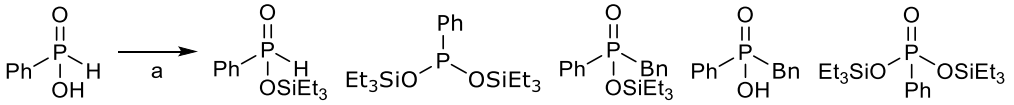



**Scheme 44:** *The proposed reaction mechanism for the formation of **65a**.*

There was a possibility that the TESBr (which was generated during the silyl-Arbuzov collapse) could propagate the *P-C* bond formation reaction. However, when TESCl (a similar silylating agent to TESBr) and phenyl phosphinic acid were heated to 100 °C for 5 hours in the presence benzyl bromide, neither **61**, **64** or **65a** were seen. The phenyl phosphinic acid starting material, the single silylated species **63** and **66** were observed by $^{31}$P NMR spectroscopy in <10%, 92% and <1%, respectively *(see experimental Page 69 for more details)*. The absence of **64** and **65a** suggests that TESCl does not promote the *P-C* bond formation reaction.

To probe the mechanism of the reaction, and to show $B(C_6F_5)_3$ acts as a catalyst, a series of control experiments were performed, Table 1.

**Table 1:** *Control experiments for the novel P-C bond formation reaction.*




**63** **61** **64** **65a** **66**

| Entry | $B(C_6F_5)_3$ / mol% | $Et_3SiH$ / eq. | BnBr / eq. | Time / h | relative % by $^{31}P$ NMR in toluene d8 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | % **SM** | % **63** | % **61** | % **64** | % **65a** | % **66** |
| **1** | 3.50 | 3.50 | 2.50 | 5 | - | 2 | 1 | 95 | - | 2 |
| **2** | 3.50 | 3.50 | 2.50 | 21 | - | - | - | 96 | 2 | 2 |
| **3**[b] | 1.00 | 3.50 | 2.50 | 5 | 9 | 90 | - | - | - | - |
| **4** | 1.00 | 3.50 | 2.50 | 21 | - | - | - | 94 | - | 6 |
| **5** | - | 3.50 | 2.50 | 5 | 86 | 14 | - | - | - | - |
| **6** | - | 3.50 | 2.50 | 21 | 73 | 27 | - | - | - | - |
| **7** | - | 3.50 | - | 16 | 74 | 26 | - | - | - | - |
| **8** | - | - | 2.50 | 16 | 100 | - | - | - | - | - |
| **9** | 3.50 | - | 2.50 | 5 | 100 | - | - | - | - | - |
| **10** | 3.50 | - | 2.50 | 21 | 100 | - | - | - | - | - |
| **11** | 3.50 | - | - | 16 | 100 | - | - | - | - | - |
| **12**[c] | 3.50 | 1.10 | 2.50 | 16 | 67 | 33 | - | - | - | - |

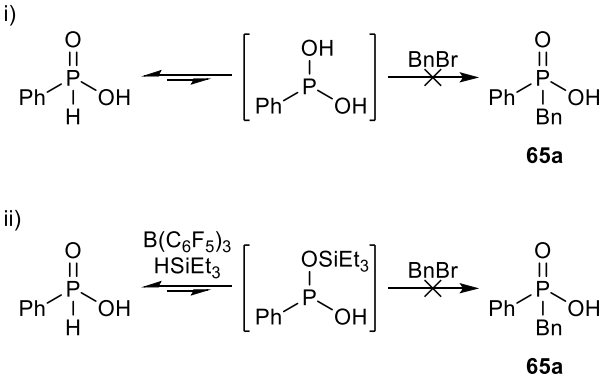
[a] *All reactions were performed under anhydrous conditions, under an argon atmosphere and at 100 °C in distilled dry toluene – d8 for the given time (h), with $B(C_6F_5)_3$ (mol%), $Et_3SiH$ (eq.), BnBr (eq.). NMR experiment: phosdecig, 16 scans, 30 s delay.* [b] *1% of unknown species.* [c] *7% of unknown species but not related to product.*

All reactions were performed in dry deuterated toluene at 100 °C under the conditions stated in Table 1, with each reaction monitored by $^{31}P$ NMR spectroscopy. Initially, a reaction was performed with the standard conditions and it was found that 95% conversion to the product precursor **64** was obtained in 5 hours, Table 1 Entry 1. Extended heating for a further 16 hours, only showed slight improvements in conversion to **64**, Table 1 Entry 2. In order to show that the rate of reaction was dependent on the loading of $B(C_6F_5)_3$, 1 mol% of $B(C_6F_5)_3$ was used. After 5 hours, the reaction only progressed to 90% conversion of **63**, Table 1 Entry 3. The remarkable decrease in conversion demonstrated that the loading of $B(C_6F_5)_3$ is instrumental to the rate of reaction. However, it was still encouraging to observe that the reaction could proceed to 94% conversion with only 1 mol% of $B(C_6F_5)_3$ present, after 21 hours, Table 1 Entry 4. In the total absence of $B(C_6F_5)_3$

the reaction did not generate either **61** or **64**, Table 1 Entry 5 and 6. A similar result was observed without both $B(C_6F_5)_3$ and benzylbromide, Table 1 Entry 7. Unexpectedly, silylated phenylphosphinic acid **63** was observed in the absence of $B(C_6F_5)_3$, with conversion between 14 – 27%, Table 1 Entry 5 - 7.

It has been demonstrated that: 1) sub-stoichiometric quantities of $B(C_6F_5)_3$ allowed the silylation to phosphonite intermediate **61**, indicating that $B(C_6F_5)_3$ is not consumed but instead is regenerated during the reaction, 2) lowering the loading of $B(C_6F_5)_3$ decreased the rate of reaction, and 3) without $B(C_6F_5)_3$ neither **61** or **64** were generated. These experiments are consistent with $B(C_6F_5)_3$ catalysing the silylation of phenylphosphinic acid.

It has been so far assumed that silyl-phosphonite **61** was the only possible intermediate which could undergo the *P-C* bond formation reaction. However, other mechanistic hypotheses were considered, Scheme 45. Phenylphosphinic acid exists in equilibrium with its trivalent tautomer, albeit the equilibrium is heavily in favour of the pentavalent species.[90] The trivalent species, in theory, could react with electrophiles in a similar manner to silyl-phosphonites. Nevertheless, when phenylphosphinic acid was heated in the presence of only benzyl bromide no reaction was observed, Table 1 Entry 8. Even in the presence of $B(C_6F_5)_3$ and benzyl bromide no reaction was seen, Table 1 Entry 9 and 10. Furthermore, only starting material was observed by $^{31}P$ NMR spectroscopy when phenylphosphinic acid was heated with just $B(C_6F_5)_3$ present, Table 1 Entry 11. This demonstrated that the silylation of phenylphosphinic acid was required to promote the *P-C* bond formation reaction therefore showing that triethylsilane was essential.

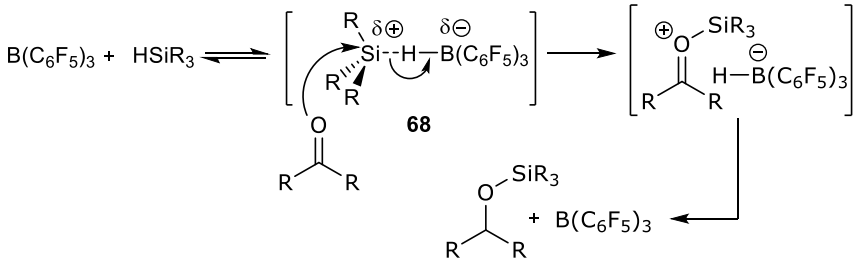



**Scheme 45:** *Alternative P-C bond formation hypotheses.*

It was also reasoned that a single silylation of phenylphosphinic acid could promote the reaction with benzyl bromide to form the *P-C* bond, Scheme 45ii. However, when 1.1 equivalents of triethylsilane were heated, in the presence of $B(C_6F_5)_3$ and benzyl bromide, **64** was not observed, Table 1 Entry 12. This showed that the double silylation of phenylphosphinic acid was required to promote the *P-C* bond formation reaction. The results obtained are consistent with a $B(C_6F_5)_3$-cataysed silylation to access a silyl-phosphonite intermediate, therefore a catalytic cycle for this transformation has been proposed, Scheme 47.

## 2.3. The Proposed Catalytic Cycle for the $B(C_6F_5)_3$-catalysed Silylation Reaction

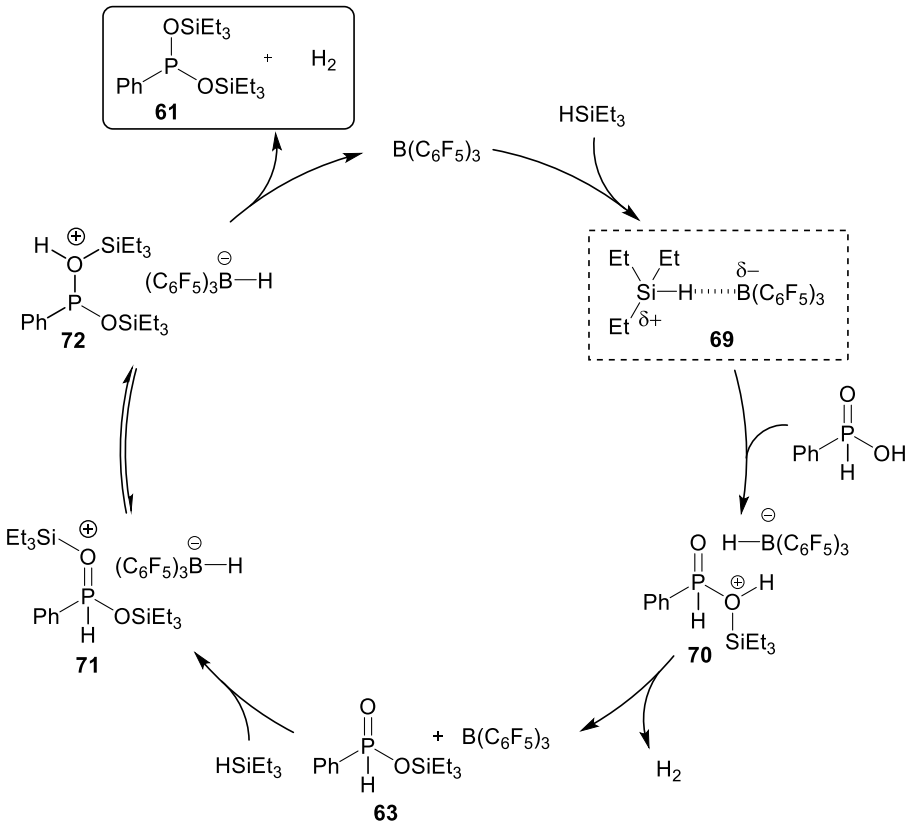
In 2000, Piers and co-workers published work on the mechanistic studies for the $B(C_6F_3)_3$-catalysed hydrosilylation of ketones and esters.[79] It was reported that although $B(C_6F_3)_3$ does co-ordinate the carbonyl moiety, the reaction actually proceeds *via* an unconventional formation of complex **68**, Scheme 46.[79] Complex **68** represents a partial hydride abstraction from the silane, leaving a partially cationic silicon atom.[79] The silane and $B(C_6F_5)_3$ were suggested to be in equilibrium with complex **68**, but the formation of this adduct is limited in the absence of an additional substrate.[79] However, it was suggested that in the presence of a Lewis base (in this case a carbonyl functional group), a nucleophilic attack at silicon occurs in the manner depicted in Scheme 46.[79] This process not only activates the carbonyl substrate but generates a borohydride species, which is thought to be responsible for the reduction of the carbonyl moiety.[79]




**Scheme 46:** *The equilibrium between tris(pentafluorophenyl)borane and trialkylsilanes with as suggested by complex **68**.*

Our mechanistic proposal for generation of silyl-phosphonite **61**, is thought to proceed *via* a similar silyl-borane complex **69**, Scheme 47. It is reasoned that the silylation of phenylphosphinic acid occurs through a nucleophilic attack of complex **69**, which generates silylated intermediate **70**, along with a borohydride species. The subsequent de-hydrogenative deprotonation of **70**, with the borohydride species, regenerates the catalyst and gives silylated phosphinic acid **63**. We have

suggested that a second silylation reaction occurs to generate intermediate **71**, along with another borohydride species. Tautomerisation of **71** is thought to form trivalent phosphorus compound **72** and the subsequent deprotonation of **72** is suggested to complete the cycle by liberating hydrogen, forming the desired silyl-phosphonite intermediate **61** and regenerating the active $B(C_6F_5)_3$ catalyst.



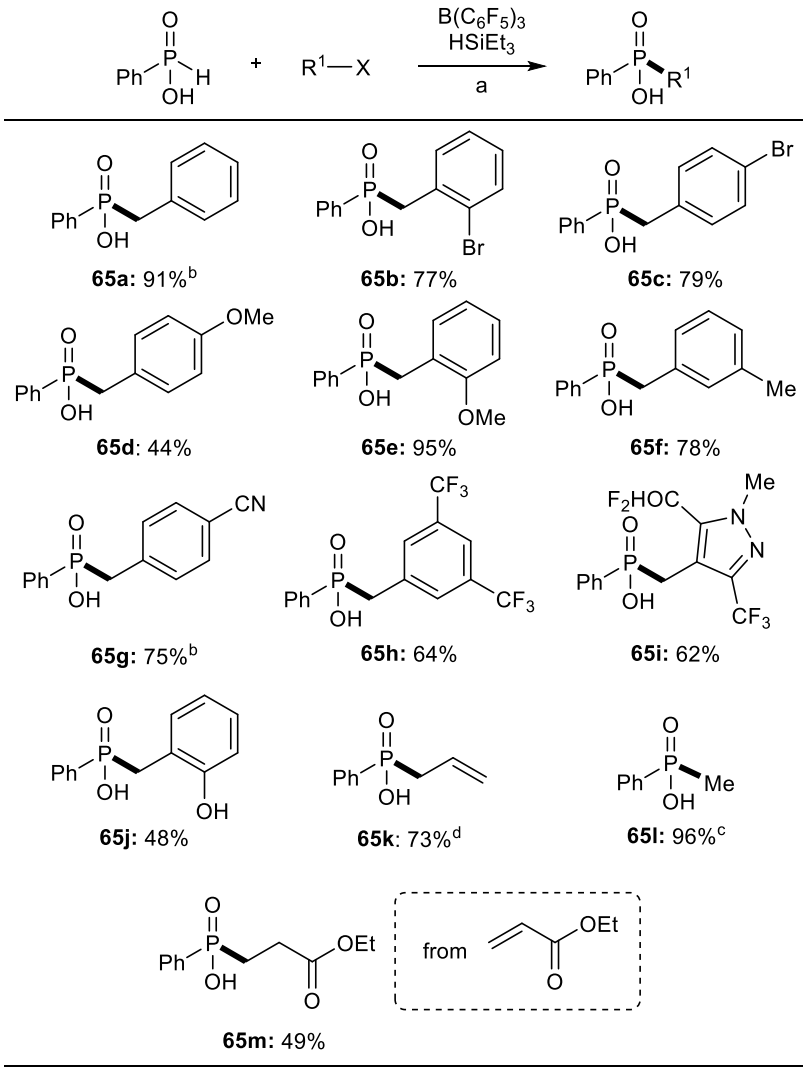

**Scheme 47:** *The proposed catalytic cycle for the formation of silyl-phosphonite **61**.*

To summarise, an unpresented *P-C* bond formation reaction has been discovered for the synthesis of benzylphenylphosphinic acid, from phenyl phosphinic. The evidence that has been reported is consistent with a $B(C_6F_5)_3$-catalysed silylation to access the silyl-phosphonite intermediate **61**. Subsequently, a proposed mechanism for the generation of **61** has been described, as well as, the following reaction with benzyl bromide. Next, we explored the scope of this reaction with respect to the electrophilic coupling partner and the phosphinic acid starting material.

### 2.4. Investigation Into the Scope of the Reaction

The scope of the reaction with respect to the electrophile was investigated, using the standard reaction conditions, unless otherwise stated, Table 2. The reaction times were extended to 16 hours to give a consistent set of convenient conditions for all substrates.

**Table 2:** *The scope with respect to the electrophilic coupling partner.*

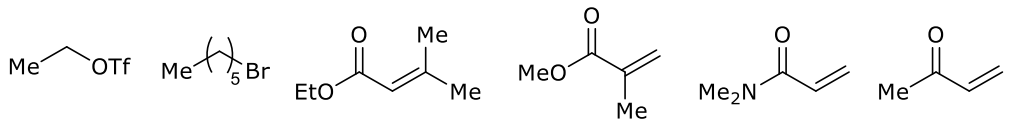



*[a] Reaction and conditions: phenylphosphinic acid (1.0 eq.), electrophile (2.5 eq.), $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene (0.20 M), 100 °C, 16 h. [b] performed on a gram scale (5.0 mmol). [c] MeOTf (3.5 eq.) used. [d] allyl bromide (5.0 eq.) used.*

It was already known that benzyl bromide underwent a successful reaction with phenylphosphinic acid. The resulting product, benzylphenylphosphinic acid **65a**, was isolated in 91% yield. The synthesis of **65a** and **65g** were performed on a gram scale with no operational difficulties. Next, the substituents on the aryl ring of benzyl bromide, were explored, Table 2. It was found that a wide range of functional groups were accommodated. Both *ortho*- and *para*-bromobenzyl bromide were employed and gave products **65b** and **65c** in 77% and 79% yield, respectively. Electron-donating substituents were examined and it was found that *ortho*-methoxy and *meta*-methyl electrophiles were well-tolerated, Table 2. However, the *para*-methoxy moiety only obtained the desired product **65d** in 44% yield. It is suspected that the decomposition of the 4-methoxybenzyl bromide electrophile was responsible for this result. Electron-withdrawing groups ($CF_3$ and CN) were explored and the corresponding secondary phosphinic acids **65g** and **65h** were isolated in moderate to good yields. Even a complex heterocycle was tolerated during under the reaction conditions, **65i**, which may be of interest to the agrochemical industry as this moiety is present in pyroxasulfone, a known herbicide. It was interesting to observe that when an electrophile containing a silyl-protected phenol was used, the free phenol containing phosphinic acid **65j** was isolated. It was reasoned that the silyl-deprotection occurred upon the acid/base work-up rather than happening under the reaction conditions.

Other non-benzylic electrophiles were explored; it was found that reactions with allyl bromide and methyl triflate were successful, and provided **65k** and **65l** in very good yields. The low boiling points of both electrophiles meant that the amount each electrophile used was increased, in order to combat the high temperatures of the reaction. The 1,4-conjugate addition to ethyl acrylate was also successful, and gave **65m** in a moderate yield. The isolation of this compound was difficult and there was

evidence to suggest that the ethyl ester could hydrolyse upon isolation; which contributed to the lower yield of **65m**.



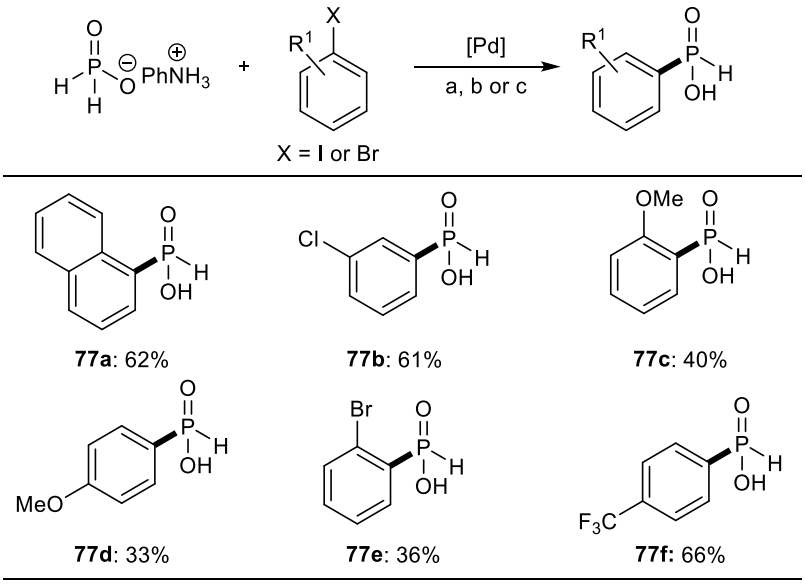

**73** **74** **75** **76**

**Figure 2:** *Examples of other less tolerated electrophiles.*

Unfortunately, other non-benzylic electrophiles were not well-tolerated, Figure 2. When ethyltriflate and 1-bromohexane were employed as electrophiles, although product was observed by $^{31}P$ NMR spectroscopy, full consumption of starting material could not be achieved. The desired product was not observed when acrylate **73** was used and it was reasoned that this was because of the increased steric bulk of the species. Surprisingly acrylate **74** was not well tolerated, and although product was observed, the reaction did not proceed cleanly or to full consumption of the starting material. Attempts to use acylamide **75** or α,β-unsaturated ketone **76** were not successful, and it was reasoned that a competitive reduction of these carbonyl-containing moieties was responsible for this.

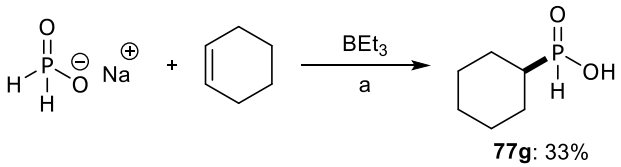
Phenylphosphinic acid had been the only primary phosphinic acid to undergo the *P-C* bond formation reaction so far; therefore an investigation into the use of alternative starting materials was important. The most convenient method to access different phosphinic acids was *via* a one-step synthesis from anilinium hypophosphite, Table 3. The palladium-catalysed approaches developed by Montchamp *et. al*. or Stawinski *et. al*. were employed (*see section 1.2.1.*). Phosphinic acids with a range of electron-donating and electron-withdrawing substituents in the *ortho*-, *meta*- and *para*- positions were synthesised in yields of between 33 – 66%, Table 3.

**Table 3:** *The synthesis of alternative phosphinic acid starting materials.*




*Reagents and conditions: a) $Pd(PPh_3)_4$ (2.0 mol%), $NEt_3$ (3.0 eq.), MeCN, 85 °C, 16 h. b) $Pd(OAc)_2$ (2.0 mol%), dppp (2.2 mol%), $NEt_3$ (3.0 eq.), MeCN, 85 °C, 24 h. c) $Pd_2(dba)_3$ (5.0 or 1.0 mol%), XantPhos (5.0 or 1.0 mol%), $NEt_3$ (2.5 eq.), THF, 120 °C, μW, 10 min.*

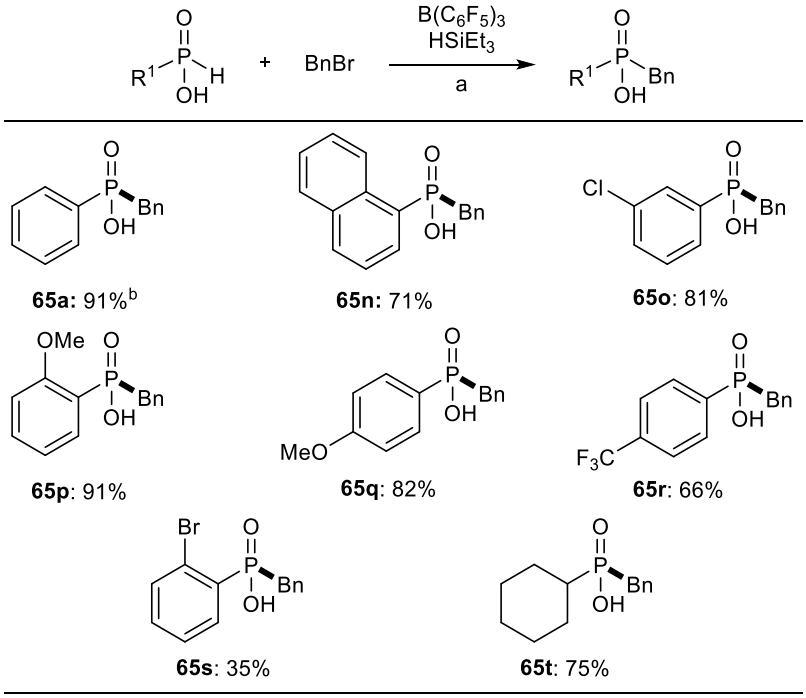
A single example of an alkyl phosphinic acid **77g** was produced *via* the triethylborane-initiated radical coupling between sodium hypophosphite and cyclohexene, Scheme 48, as described by Montchamp and co-workers (*see section 1.2.3.*).[33] The low yield of the reaction was potentially as a result of a competitive radical coupling between cyclohexene and the ethyl radical (generated when triethylborane reacts with oxygen). There was no experimental evidence for this hypothesis because the resulting ethylcyclohexane by-product would be removed upon isolation.




**Scheme 48:** *The synthesis of cyclohexylphosphinic acid **77g**. Reagents and conditions: a) $BEt_3$ (0.20 eq., 1.0 M in hexanes), MeOH, r.t., 4 h.*

The various phosphinic acid starting materials were then reacted with benzyl bromide to investigate if they could be tolerated during the *P-C* bond formation reaction. The reactions were performed under the usual $B(C_6F_5)_3$-catalysed silylation conditions, Table 4.

**Table 4:** *The scope of the primary phosphinic acid starting material.*




[a] *Reaction and conditions: phosphinic acid (1.0 eq.), BnBr (2.5 eq.), $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene (0.20 M), 100 °C, 16 h.* [b] *performed on a gram scale (5.0 mmol).*

Compound **65a** is present as a reference for the success of the reactions. All other aryl phosphinic acids **77a - f**, with the exception of *ortho*-bromo containing compound **77e**, displayed remarkable tolerance for the reaction. The corresponding secondary phosphinic acids **65n** – **65r** were isolated in yields of between 66 – 91%. This demonstrated that electron rich, electron deficient or some sterically hindered silyl-phosphonites were able to undergo the desired *P-C* bond construction. However, when a substrate was both sterically hindered and electron withdrawing, the yield was impacted, for example in the case of *ortho*-bromo compound **65s**. The

cyclohexylphosphinic acid **77g** successfully underwent the *P-C* bond formation reaction and provided **65t** in a good yield. However, a constant flow of argon was required for the duration of heating; otherwise the reaction did not proceed to completion. This suggested that the alkyl silyl-phosphonite was more sensitive or unstable compared to its aryl counterparts.

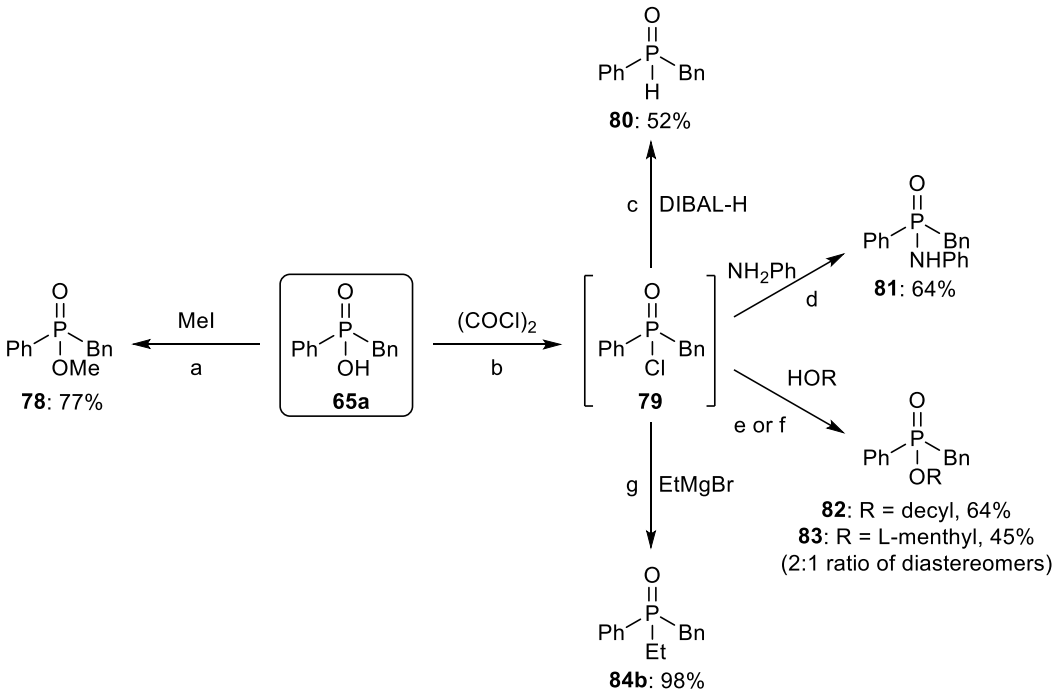
In conclusion, a range of electrophilic coupling partners and primary phosphinic acid starting materials were used in this novel *P-C* bond formation reaction, with 20 secondary phosphinic acids **65a** - **t** being synthesised in 35 – 91% yield.

### 2.5. Phosphinic Acids as Organophosphorus Building Blocks

Phosphinic acids are useful materials in a number of different industries, including as flame retardants,[13,14] photoinitiators,[15] and as agents to separate cobalt and nickel in aqueous solutions.[16,17] They have also displayed a range of pharmacological and herbicidal activities.[9–12] However, this section will demonstrate they can be used as building blocks to access a variety of other organophosphorus compounds.

Secondary phosphinic acids are usually air and moisture stable, which make them convenient compounds. In order to demonstrate their versatility, a number of literature known functional group transformations were performed, Scheme 49.[48,49,98,99,70,91–97] However, the reactions depicted are novel, with the exception of the chlorination reaction. Benzylphenylphosphinic acid **65a** was chosen to investigate these transformations because it can be conveniently synthesised, in high yields, *via* a one-step process from commercially available phenylphosphinic acid. The simplest transformation was the conversion of phosphinic acid **65a** to methylphosphinate **78**. This was achieved in 77% yield by alkylation with methyl iodide in the presence of caesium carbonate. The chlorination of secondary phosphinic acid **65a** to its corresponding phosphinic chloride **79** was also achieved. In the literature, there were three reagents which could convert phosphinic acids to phosphinic chlorides; thionyl chloride, oxalyl chloride or phosphorus pentachloride. For the reaction with **65a**, oxalyl chloride was used, and the reaction underwent clean conversion to phosphinic chloride **79** within an hour, Scheme 49. Phosphinic chloride **79** could be transformed into a variety of different functional groups. The corresponding secondary phosphinic acid **80** was synthesised *via* the reduction of the *P-Cl* bond with DIBAL-H, Scheme 49. The addition of aniline, 1-decanol and (-)-menthol to phosphinic chloride **79** was successful. The corresponding phosphinic amide **81**, and phosphinate products **82** and **83** were isolated in moderate to good

yields, Scheme 49. Moreover, the addition of ethylmagnesium bromide produced tertiary phosphine oxide **84b** in 98% yield, Scheme 49. This result constitutes a method for the synthesis of tertiary *P*-stereogenic tertiary phosphine oxides which completely avoided the use of $PCl_3$, or other halophosphines. *P*-Stereogenic tertiary phosphines are valuable organophosphorus compounds because the subsequent reduction would provide *P*-stereogenic tertiary phosphines, which are desirable as ligands for metal catalysis.

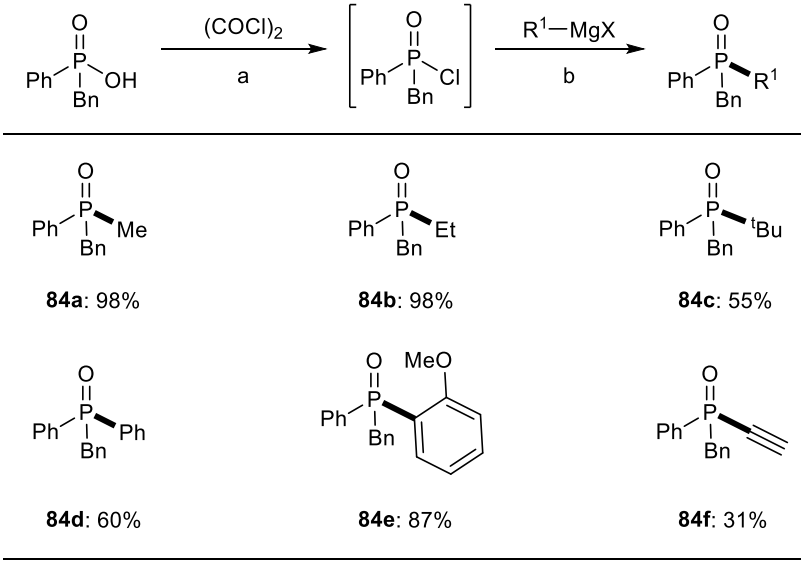



**Scheme 49:** *Secondary phosphinic acids as organophosphorus building blocks. Reagents and conditions: a) MeI (1.0 eq.), $Cs_2CO_3$ (2.0 eq.), MeCN, 90 °C, 16 h. b) $(COCl)_2$ (1.1 eq.), $CH_2Cl_2$, r.t., 30 min. c) DIBAL-H (1.0 M in toluene, 1.1 eq.), $CH_2Cl_2$, –78 °C, 1 h. d) aniline, $CH_2Cl_2$, 0 °C - r.t., 1 h. e) 1-decanol (1.1 eq.), $NEt_3$ (1.1 eq.), $CH_2Cl_2$, r.t., 17 h. f) (-)-menthol (1.1 eq.), $NEt_3$ (2.2 eq.), $CH_2Cl_2$, –78 °C – r.t., 17 h. g) EtMgBr (3.0 M in $Et_2O$, 1.0 eq.), THF, –78 °C - r.t., 17 h.*

The scope for the addition of Grignard reagents to benzylphenylphosphinic chloride **79** was subsequently explored, Table 5. Alkyl nucleophiles with increasing steric bulk were tested. Both the methyl and ethyl products **84a** and **84b** were isolated in

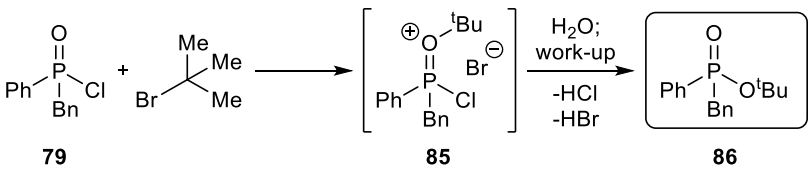
near quantitative yields. However, the synthesis of larger *tert*-butyl tertiary phosphine oxide **84c** was achieved with a significant reduction in yield. Nevertheless, **84c** was synthesised in a moderate 55% yield. A steric argument for the lower yield could be sufficient here; however it was not the only factor responsible.

**Table 5:** *The scope for the reaction with respect to the Grignard reagents.*




*Reagents and conditions: a) $(COCl)_2$ (1.1 eq.), $CH_2Cl_2$, r.t., 30 min. b) Grignard reagent (1.0 eq.), THF, – 78 °C – r.t., 18 h.*

By-product **86** was observed in quantities of 10% (relative to **84c**) by $^1$H NMR spectroscopy, Scheme 50. The structure of the by-product was later confirmed by NMR spectroscopy and HRMS.




**Scheme 50:** *The proposed formation of by-product **85**.*

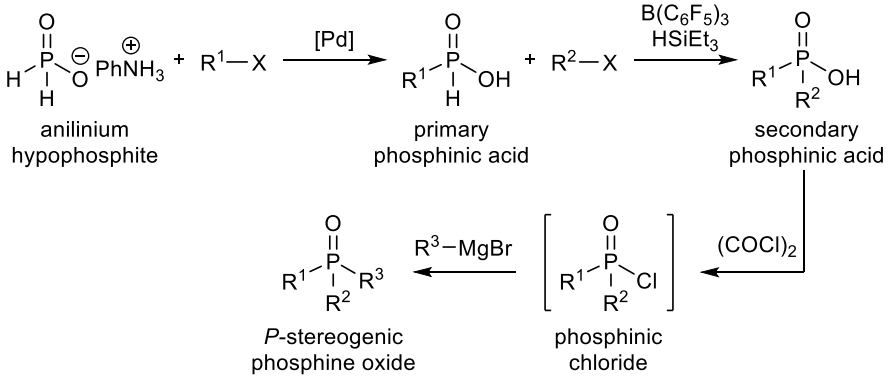
The formation of phosphinate **86** was a contributing factor to the lower yield and was unique to the reaction with *tert*-butylmagnesium bromide. There was a plausible explanation for the formation of **86**, Scheme 50. It could arise from the *O*-alkylation of phosphinic chloride **79** with 2-bromo-2-methylpropane; which would be an impurity present from the synthesis of *tert*-butylmagnesium bromide. The subsequent hydrolysis of the chlorophosphonium salt **85** would then produce the unwanted phosphinate by-product **86**. In hindsight, the solution to this problem was simple, freshly synthesise *tert*-butylmagnesium bromide before use, to ensure the purity of the organometallic reagent.

Two aryl Grignard reagents were also tolerated for the reaction with phosphinic chloride **79**, Table 5. Phenyl magnesium bromide produced the symmetrical tertiary phosphine oxide **84d** in 60 % yield. For this substrate the only explanation for lower yield was a steric argument, although anisyl magnesium bromide gave the corresponding phosphine oxide **84e** in a much improved yield. However, this could be due to the increased nucleophilicity of the anisyl nucleophile due to the electron donating methoxy group. Finally, the successful synthesis of alkyne-containing compound **84f** was achieved, albeit in a low 31% yield, Table 5. It was reasoned that the presence of the relatively acidic alkynyl proton was responsible for the dramatic loss of yield.

The scope of Grignard reagents tolerated for the addition to phosphinic chloride **79** has been shown to be reasonable, with 6 tertiary phosphine oxides **84a** - **f** being synthesised in 31 – 98% yield. Next, the synthesis of more complex *P*-stereogenic tertiary phosphine oxides was attempted.

### 2.6. The Synthesis of *P*-Stereogenic TPOs

The strategy to synthesise the *P*-stereogenic TPOs from anilinium hypophosphite involved four steps, Scheme 51. Initially, it was envisaged that a palladium-catalysed cross-coupling reaction with aryl halides would provide the desired primary phosphinic acids.[18,19]

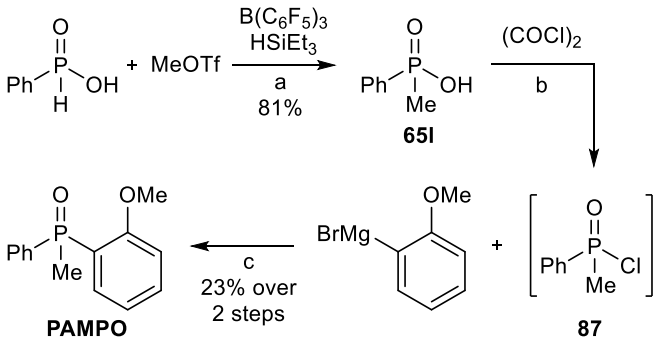



**Scheme 51:** A strategy to *synthesise P-stereogenic tertiary phosphine oxides avoiding $PCl_3$.*

Next, the primary phosphinic acids could be alkylated exploiting the silylation chemistry developed within our group. Finally, it was hoped that the synthesis would be completed with the addition of an organometallic reagent to the corresponding phosphinic chloride. It is worth noting that a thorough purification, *via* column chromatography, could only take place at the final stage of the synthesis. The route would allow for the controlled synthesis of *P*-stereogenic tertiary phosphine oxides *via* the stepwise introduction of $R^1$, $R^2$ and $R^3$; while avoiding the need for $PCl_3$.

Firstly, the synthesis of PAMPO was targeted and the initial methylation of phenylphosphinic acid to **65l** was achieved in 81% yield, Scheme 14. Previously, the yield for this reaction was as high as 96% (*see Section 2.2. Table 2*). However, upon increasing the scale of the reaction from 0.50 mmol (with respect to phenylphosphinic acid) to 10 mmol **65l** could only be isolated in 81% yield. The second and final step of the synthesis was the addition of *ortho*-anisyl magnesium bromide to phosphinic chloride **87**, and the product was obtained in 23% yield.

Compared to the reaction with benzylphenylphosphinic acid **65a** (*see Section 2.3. Table 5*), this result was disappointing.




**Scheme 52:** *The two-step synthesis of PAMPO from phenylphosphinic acid. Reagents and conditions: a) $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene, 100 °C, 16 h. b) $(COCl)_2$ (0.92 eq.), $CH_2Cl_2$, r.t., 30 min. b) ortho-anisyl magnesium bromide (0.90 M, 0.84 eq.), THF, – 78 °C – r.t., 18 h.*

The main difference between the two reactions was the substitution of the benzyl moiety for a methylene group. The protons of the benzyl- and methylphenylphosphinic acid are both acidic, and anisyl magnesium bromide is a strong enough base to deprotonate at these positions, Figure 3.

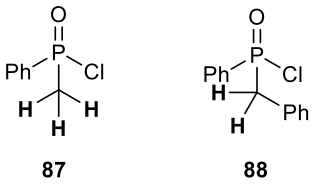
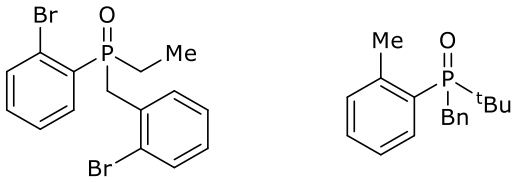



**Figure 3:** *The acidic protons of **87** and **88**.*

The benzylic protons would be expected to be more acidic but vastly more sterically hindered than the equivalent methylene protons. It is not too unreasonable to suggest that if the deprotonation of **87** did occur, unwanted side reactions may occur which could contribute to the loss of material and low yields. Nevertheless, the synthesis of PAMPO was completed in 19% over two-steps from commercially available phenylphosphinic acid, Scheme 52.

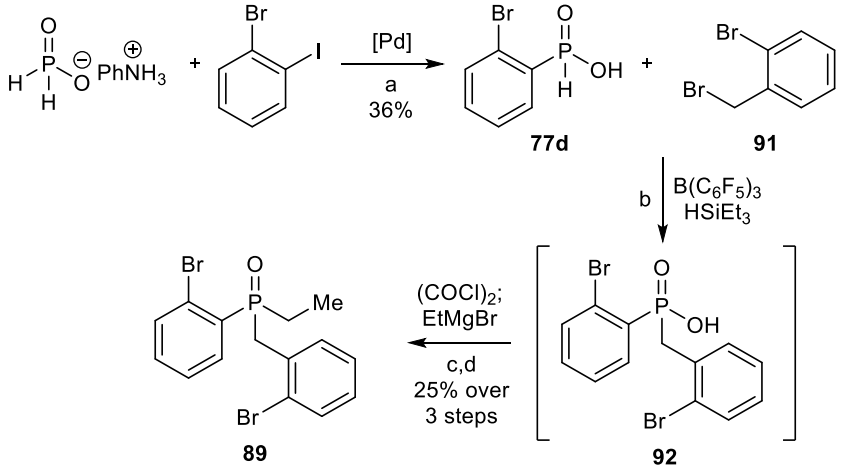
*P*-stereogenic tertiary phosphine oxides **89** and **90** are two novel compounds. They were chosen for their interesting structures, which contain a mixture of substituted aryl rings and sterically bulky alkyl groups. For the following reactions anilinium hypophosphite was synthesised in one-step from the commercially available hypophosphorus acid, in 47% yield




**89** **90**

**Figure 4:** *The structures of the P-stereogenic phosphine oxide targets.*

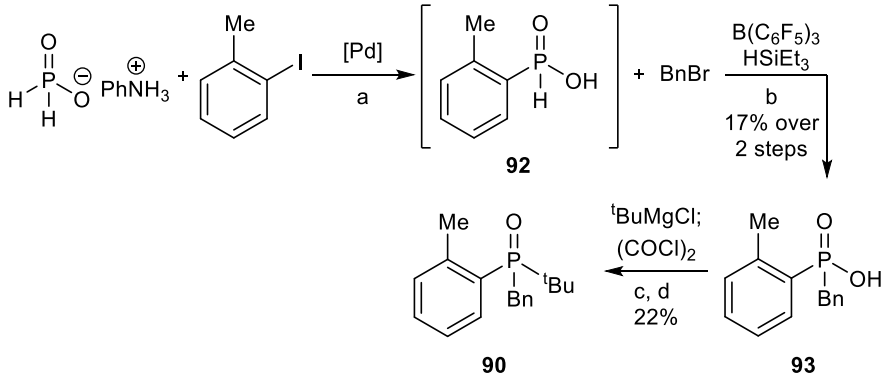
The synthesis of TPO **89** began with formation primary phosphinic acid **77d** *via* a cross-coupling reaction with 2-bromo-1-iodobenzene, and it was isolated in 36% yield, Scheme 53.




**Scheme 53:** *The synthesis of novel phosphine oxide **89**. Reagents and conditions: a) 1-bromo-2-iodobenzene (1.0 eq.), $Pd_2(dba)_3$•$CHCl_3$ (5.0 mol%), XantPhos (5.0 mol%), $NEt_3$ (2.5 eq.), THF, μW, 120 °C, 10 min. b) **91** (2.5 eq.), $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.50 eq.), toluene, 100 °C, 16 h. c) $(COCl)_2$ (1.0 eq.), $CH_2Cl_2$, r.t., 30 min. d) EtMgBr (3.0 M in $Et_2O$, 1.0 eq.), THF, – 78 °C – r.t., 18 h.*

The subsequent alkylation of the electron-deficient, and sterically bulky *ortho*-(bromophenyl)phosphinic acid **77d** was difficult and has already been discussed in Section 2.2. The secondary phosphinic acid **92** could not be cleanly isolated following the reaction between **77d** and **91**, therefore the synthesis needed to be telescoped. However, the chlorination of the phosphinic acid **92** and subsequent addition of ethylmagnesium bromide completed the synthesis of the desired *P*-stereogenic tertiary phosphine oxide **89** in 25% yield over the three steps. Overall phosphine oxide **89** was synthesised in 4% yield over five steps, Scheme 53.

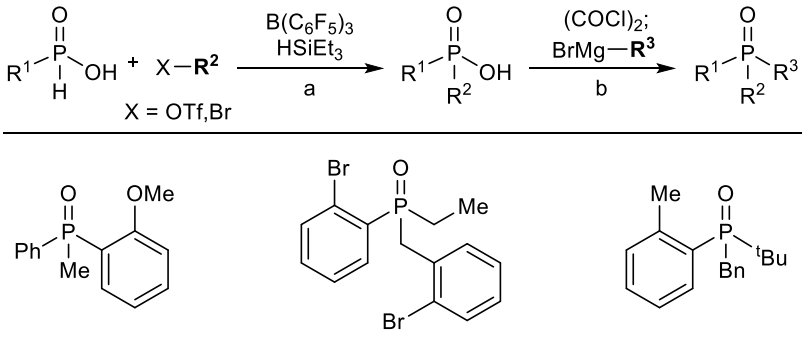
Next, the synthesis of tertiary phosphine oxide **90** was attempted. The first step in the synthesis was the palladium-catalysed arylation of anilinium hypophosphite, with 2-iodotoluene, Scheme 54. The desired primary phosphinic acid **92** was taken through as a crude mixture to the next step. The subsequent reaction of **92** with benzyl bromide gave the secondary phosphinic acid **93** in 17% yield over the two steps. After the final chlorination and organometallic addition TPO **90** was obtained in 22% yield.




**Scheme 54:** *The four step synthesis of P-stereogenic phosphine oxide **90**. Reagents and conditions: a) 1-iodotoluene (1.0 eq.), $Pd_2(dba)_3$•$CHCl_3$ (5.0 mol%), XantPhos (5.0 mol%), $NEt_3$ (2.5 eq.), THF, μW, 120 °C, 10 min. b) BnBr (2.5 eq.), $B(C_6F_5)_3$ (3.50 mol%), $HSiEt_3$ (3.5 eq.), toluene, 100 °C, 16 h. c) $(COCl)_2$ (1.0 eq.), $CH_2Cl_2$, r.t., 30 min. d) tert-butylmagnesium bromide (1.8 M in $Et_2O$, 1.0 eq.), THF, – 78 °C – r.t., 16 h.*

In summary, PAMPO and two novel *P*-stereogenic tertiary phosphine oxides were synthesised in overall yields 2 – 19%, *via* a route which negated the need for $PCl_3$, Table 6. The overall yields for the synthesis of **89** and **90** were lower than desired but this highlights the difficulty of each of the syntheses.

**Table 6:** *The synthesis of complex P-stereogenic phosphine oxides.*




*Reagents and conditions: a) phosphinic acid (1.0 eq.), $R^2$-Br (2.5 eq.) or MeOTf (3.5 eq.), $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene (0.20 M), 100 °C, 16 h. b)i) $(COCl)_2$ (1.1 eq.), $CH_2Cl_2$, r.t., 30 min. ii) Grignard reagent (1.0 eq.), THF, – 78 °C – r.t., 18 h.*

## 2.7. Conclusion

In conclusion, a novel method to access silyl-phosphonites, *via* a convenient $B(C_6F_5)_3$-catalysed silylation of primary phosphinic acids, has been developed. Following the reaction with an appropriate electrophile, it was demonstrated that this was an efficient method to synthesise secondary phosphinic acids. A plausible mechanism for the generation of this intermediate as well as its subsequent reaction with an electrophile was outlined. Various primary phosphinic acid starting materials and electrophilic coupling partners were explored, and 20 secondary phosphinic acids were synthesised in 35 - 91% yield. It was then demonstrated that secondary phosphinic acids could be used as versatile organophosphorus building blocks to access phosphinates, phosphinic chlorides, phosphinic amides and secondary phosphine oxides. A controlled synthesis of *P*-stereogenic tertiary phosphine oxides which avoids $PCl_3$, was also outlined. The newly developed silylation reaction was incorporated into the synthesis of 8 *P*-stereogenic tertiary phosphine oxides.

# Chapter 3 – Experimental Section

### 3.1. General Experimental

Commercially available reagents were used throughout without further purification unless otherwise stated. THF, $Et_2O$ and toluene were obtained from a solvent tower where degassed solvent was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure, then stored over a sodium wire. $CH_2Cl_2$ was either, stirred over calcium hydride, distilled and stored over 4 Å molecular sieves, or obtained from a solvent tower where degassed solvent was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure, and stored over 4 Å molecular sieves. Water refers to deionised water and brine refers to a saturated solution of sodium chloride. Ether represents diethyl ether and light petroleum refers to the fraction with boiling range 40 - 60 °C.

Analytical thin layer chromatography (TLC) was carried out on Merck TLC silica gel 60 $F_{254}$ pre-coated aluminium sheets with fluorescent indicator, and visualised under UV light at 254 nm and/or stained using potassium permanganate. Column chromatography was carried out using Sigma Aldrich or Fluorochem silica gel 60 Å, 40-63 mesh with the eluent specified. Microwave reactions were performed using a Biotage Initator.

Melting points were measured using Stuart SMP3 melting point apparatus or a GallenHamp melting point apparatus. High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF mass spectrometer using Electrospray Spray Ionisation (ESI) or Jeol AccuTOF GCX with Electron Ionisation (GC/EI-TOF). HRMS data were quoted to four decimal places (0.1 mDa). Fourier Transform Infrared Spectrometry (FTIR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of

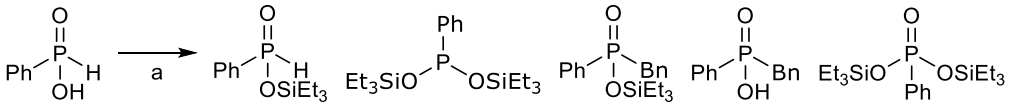
absorption (cm-1). NMR spectra were recorded at the frequencies stated using Bruker DPX300, DPX400, AV400, AV(III)400, or AV(III)500. Chemical shifts are quoted in parts per million (ppm) referenced against the residual protonated solvent as an internal standard. Residual solvent signals are as follows: $CDCl_3$ is referenced at δ 7.26 and 77.16 for 1H and 13C NMR respectively, DMSO-d6 is referenced at δ 2.50 and 39.52 for 1H and 13C NMR respectively, $CD_3OD$ is referenced at δ 3.31 and 49.00 for 1H and 13C NMR respectively and $D_2O$ is reference to δ 4.79 in the $^1H$ NMR. Coupling constants *J* are quoted in Hertz (Hz). Multiplicities for coupled signals are designated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad signal.

### 3.2. Experimental Procedures

Control Experiments:

All reactions were performed on a 0.50 mmol scale (with respect to phenylphosphinic acid). The reactions were done under anhydrous conditions, under an argon atmosphere and at 100 °C in distilled dry toluene – $d_8$, for the given time, with $B(C_6F_5)_3$ (mol%), $Et_3SiH$ (eq.), BnBr (eq.). NMR experiment: phosdecig, 16 scans, 30 s delay.

**Table 7:** *Control experiments for the novel P-C bond formation reaction.*




**63** **61** **64** **65a** **66**

| Entry | $B(C_6F_5)_3$ / mol% | $Et_3SiH$ / eq. | BnBr / eq. | Time / h | relative % by $^{31}P$ NMR in toluene d8 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | % **SM** | % **63** | % **61** | % **64** | % **65a** | % **66** |
| **1** | 3.50 | 3.50 | 2.50 | 5 | - | 2 | 1 | 95 | - | 2 |
| **2** | 3.50 | 3.50 | 2.50 | 21 | - | - | - | 96 | 2 | 2 |
| **3**[b] | 1.00 | 3.50 | 2.50 | 5 | 9 | 90 | - | - | - | - |
| **4** | 1.00 | 3.50 | 2.50 | 21 | - | - | - | 94 | - | 6 |
| **5** | - | 3.50 | 2.50 | 5 | 86 | 14 | - | - | - | - |
| **6** | - | 3.50 | 2.50 | 21 | 73 | 27 | - | - | - | - |
| **7** | - | 3.50 | - | 16 | 74 | 26 | - | - | - | - |
| **8** | - | - | 2.50 | 16 | 100 | - | - | - | - | - |
| **9** | 3.50 | - | 2.50 | 5 | 100 | - | - | - | - | - |
| **10** | 3.50 | - | 2.50 | 21 | 100 | - | - | - | - | - |
| **11** | 3.50 | - | - | 16 | 100 | - | - | - | - | - |
| **12**[c] | 3.50 | 1.10 | 2.50 | 16 | 67 | 33 | - | - | - | - |

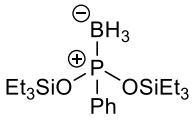
[a] *All reactions were performed under anhydrous conditions, under an argon atmosphere and at 100 °C in distilled dry toluene – d8 for the given time (h), with $B(C_6F_5)_3$ (mol%), $Et_3SiH$ (eq.), BnBr (eq.). NMR experiment: phosdecig, 16 scans, 30 s delay.* [b] *1% of unknown species.* [c] *7% of unknown species but not related to product.*

**TESCl test experiment**:

A stirred solution of solution of phenylphosphinic acid (71 mg, 0.50 mmol), benzyl bromide (60 μL, 0.50 mL), chlorotrimethylsilane (0.17 mL, 1.0 mmol) in toluene - $d_8$ (2.5 mL) was heated to 100 °C for 5 h. NMR experiment: phosdecig, 16 scans, 30 s delay.

| % conversion by $^{31}$P NMR in toluene - d8 | | | | | |
|---|---|---|---|---|---|
| % **SM** | % **63** | % **61** | % **64** | % **65a** | % **66** |
| 8% | 92 | | | - | <1 |

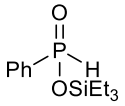
**bis(triethylsilyl)phenyl phosphonite borane (62)**




A stirred solution of phenylphosphinic acid (412 mg, 1.0 mmol), $B(C_6F_5)_3$ (51 mg, 0.10 mmol), $HSiEt_3$ (0.56 mL, 3.5 mmol) in toluene (5 mL) was heated to 100 °C for 17 h. The reaction was cooled to 0 °C then $BH_3$•$SMe_3$ (0.75 mL, 1.5 mmol of a 2.0 M solution in THF) was added. The was warmed to r.t. and stirred for 16 h then the reaction was concentrated *in vacuo* and purified by silica gel column chromatography (1 – 5% $Et_2O$ in petrol) and gave the *title compound* colourless oil (315 mg, 82%).

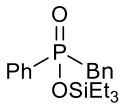
$R_f$: 0.40 (1% $Et_2O$ in petrol); $^1$H NMR (400 MHz, chloroform-*d*) δ 7.86 – 7.76 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 0.97 – 0.88 (m, 17H), 0.73 – 0.65 (m, 12H); $^{13}$C{$^1$H} NMR (75 MHz, chloroform-*d*) δ 137.2 (d, $J_{CP}$ = 72.8 Hz), 131.8 (d, $J_{CP}$ = 2.3 Hz), 129.6 (d, $J_{CP}$ = 13.9 Hz), 128.4 (d, $J_{CP}$ = 11.3 Hz), 6.5 ($CH_3$), 5.7 ($CH_2$); $^{31}$P NMR (162 MHz, chloroform-*d*) δ 107.84 - 105.22 (m); HRMS ($ESI^+$) $C_{18}H_{38}BNaO_2PSi_2^+$ $[M+H]^+$ calcd. 407.2133, found 407.2127.

**triethylsilyl phenylphosphinate (63)**



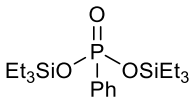
To a stirred solution of phenylphosphinic acid (142 mg, 1.00 mmol) in toluene (8.0 mL) was added DIPEA (0.19 mL, 1.1 mmol) and TESCl (0.19 mL, 1.1 mmol) sequentially, then $CH_2Cl_2$ (2.0 mL) was added. The reaction was stirred at r.t. for 2 h, then an NMR sample was taken and the *title compound* was observed; $^{31}$P NMR (162 MHz, toluene-$d_8$) δ 11.6 (100% conversion).

**triethylsilyl benzyl(phenyl)phosphinate (64)**



To a stirred solution of benzylphenylphosphinic acid (**65a**) (89 mg, 0.38 mmol) in toluene (3.0 mL) was added DIPEA (73 μL, 0.42 mmol) and TESCl (71 μL, 0.42 mmol) sequentially, then $CH_2Cl_2$ (1.00 mL) was added. The reaction was stirred at r.t. for 2 h, then an NMR sample was taken and the *title compound* was observed; $^{31}$P NMR (162 MHz, toluene-$d_8$) δ 28.4 (100% conversion).

**bis(triethylsilyl)phenylphosphonate (66)**



To a stirred solution of phenylphosphinic acid (79 mg, 0.50 mmol) in toluene (4.0 mL) was added DIPEA (0.22 mL, 1.3 mmol) and TESCl (0.21 mL, 1.3 mmol) sequentially. The reaction was stirred at r.t. for 2 h, then an NMR sample was taken

and the *title compound* was observed; $^{31}$P NMR (162 MHz, toluene-$d_8$) δ -0.16 (100% conversion).

**General procedure for the formation of 65a - u:**

A one or two-necked round bottomed flask and condenser was dried under vacuum with a heat gun, the glassware was then backfilled with argon. *Phosphinic acid* (1.0 eq.), $B(C_6F_5)_3$ (3.5 mol%) and *solid electrophile* (2.5 eq.) were, and the reaction was then placed under vacuum and back filled with argon (this was performed three times). Toluene (5.0 mL/mmol), triethylsilane (3.5 eq.) and *liquid electrophile* (2.5 eq.) were added sequentially at room temperature. The reaction mixture was heated to 100 °C for 16 h and the compounds were then purified by either two methods. (Electrophiles that were oils were added as a solution in toluene).

**Method A:**

The reaction mixture was cooled to r.t. and quenched with NaOH (1.0 M aqueous solution). The biphasic mixture was vigorously stirred at r.t. for 1 h then separated. The organic phase was then further extracted with NaOH (1.0 M aqueous solution, × 2). The combined aqueous extracts were acidified to pH 1 with HCl (1.0 M or 3.0 M aqueous solution) and cooled to 0 °C. The precipitate was isolated by filtration, washed with ice cold $H_2O$ and dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 - 24 h and gave the *title compound*.

**Method B:**

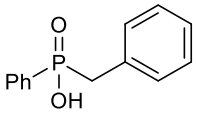
The reaction mixture was cooled to r.t. and quenched with NaOH (1.0 M aqueous solution). The biphasic mixture was vigorously stirred at r.t. for 1 h then separated. The organic phase was then further extracted with NaOH (1.0 M aqueous solution,

× 2). The combined aqueous extracts were acidified to pH 1 with HCl (1.0 M or 3.0 M aqueous solution) and re-extracted with EtOAc (× 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The solid was then titrated with ice cold petrol and gave the *title compound.*

**Method C:**

The reaction mixture was cooled to r.t. and quenched with sat. $Na_2CO_3$. The biphasic mixture was vigorously stirred at r.t. for 1 h then separated. The organic phase was then further extracted with sat. $Na_2CO_3$ (× 2). The combined aqueous extracts were acidified to pH 1 with HCl (2.0 M aqueous solution) at 0 °C and extracted with EtOAc (× 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* and gave the *title compound.*

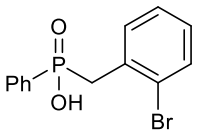
**benzyl(phenyl)phosphinic acid (65a)**[100]




Reaction was performed on a 5.0 mmol scale. Isolation according to method A gave the *title compound* as a white solid (1.05 g, 91%); m.p.: 180 – 182 °C (lit: 187 °C)[100]; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.65 – 7.56 (m, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 7.23 – 7.11 (m, 3H), 7.11 – 7.03 (m, 2H), 3.23 (d, $J_{HP}$ = 17.6 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 133.8 (Cq, d, $J_{CP}$ = 126.4 Hz), 133.1 (Cq, d, $J_{CP}$ = 7.5 Hz), 131.5 (CH, d, $J_{CP}$ = 2.8 Hz), 131.1 (CH, d, $J_{CP}$ = 9.6 Hz), 129.8 (CH, d, $J_{CP}$ = 5.7 Hz), 128.1 (CH, d, $J_{CP}$ = 12.3 Hz), 127.9 (CH, d, $J_{CP}$ = 2.8 Hz), 126.0 (CH, d, $J_{CP}$ = 3.4 Hz), 38.0 ($CH_2$, d, $J_{CP}$ = 92.1 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ

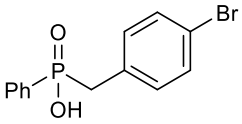
32.7 (m); HRMS (ESI$^-$) $C_{13}H_{12}O_2P$- [M-H]$^-$ calcd. 231.0580, found 231.0604. IR (ATR) $\nu_{max}$ 3085, 3058, 3028, 2980, 2678, 2346, 2107, 1518, 1130, 952 cm$^{-1}$.

**(2-bromobenzyl)(phenyl)phosphinic acid (65b)**




Reaction was performed on a 0.44 mmol scale. Isolation according to method A gave the *title compound* as a white solid (106 mg, 77%); m.p.: 149 – 151 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.63 – 7.39 (m, 6H), 7.36 – 7.22 (m, 2H), 7.16 – 7.06 (m, 1H), 3.41 (d, $J_{HP}$ = 17.8 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 133.6 (Cq, d, $J_{CP}$ = 135.3 Hz), 133.0 (Cq), 132.4 (CH, d, $J_{CP}$ = 2.7 Hz), 131.7 (CH, d, $J_{CP}$ = 4.5 Hz), 131.7 (CH, d, $J_{CP}$ = 2.9 Hz), 131.2 (CH, d, $J_{CP}$ = 9.6 Hz), 128.3 (CH, d, $J_{CP}$ = 3.0 Hz), 128.1 (CH, d, $J_{CP}$ = 12.4 Hz), 127.3 (CH, d, $J_{CP}$ = 2.9 Hz), 124.6 (Cq, d, $J_{CP}$ = 7.4 Hz), 37.9 ($CH_2$, d, $J_{CP}$ = 91.6 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 31.2 (m); HRMS (ESI$^-$) $C_{13}H_{11}{}^{79}BrO_2P^-$ [M-H]$^-$ calcd. 308.9686, found 308.9684; IR (ATR) $\nu_{max}$ 3051, 2959, 2913, 2596, 2218, 1623, 1471, 1295, 1156, 997, 972 cm$^{-1}$.

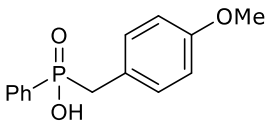
**(4-bromobenzyl)(phenyl)phosphinic acid (65c)**




Reaction was performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a white solid (123 mg, 79%); m.p.: 214 – 216 °C (lit: 214 – 215 °C)[101]; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.69 – 7.57 (m, 2H), 7.57 – 7.48 (m, 1H), 7.48 – 7.41 (m, 2H), 7.41 – 7.36 (m, 2H), 7.08 – 7.01 (m, 2H), 3.23 (d, $J_{HP}$ = 17.6 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 133.5 (Cq, d, $J_{CP}$ = 126.9 Hz), 132.7 (Cq, d, $J_{CP}$ = 7.9 Hz), 132.0 (CH, d, $J_{CP}$ = 5.4 Hz), 131.6 (CH, d, $J_{CP}$ = 2.8 Hz), 131.1 (CH, d, $J_{CP}$ = 9.6 Hz), 130.8 (CH, d, $J_{CP}$ = 2.7 Hz), 128.2 (CH, d, $J_{CP}$ = 12.0

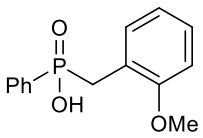
Hz), 119.3 (Cq, d, $J_{CP}$ = 3.8 Hz), 37.3 ($CH_2$, d, $J_{CP}$ = 91.9 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 32.2 (m); HRMS (ESI$^-$) $C_{13}H_{11}{}^{79}BrO_2P^-$ [M-H]$^-$ calcd. 308.9686, found 308.9687; IR (ATR) $\nu_{max}$ 3058, 2936, 2642, 2256, 2098, 1590, 1483, 1145, 1089, 1069, 953 cm$^{-1}$.

**(4-methoxybenzyl)(phenyl)phosphinic acid (65d)**




Reaction was performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a white solid (58 mg, 44%); m.p.: 160 -162 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.65 – 7.56 (m, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 7.03 – 6.95 (m, 2H), 6.82 – 6.70 (m, 2H), 3.68 (s, 3H), 3.15 (d, $J_{HP}$ = 17.3 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 157.7 (Cq, d, $J_{CP}$ = 3.0 Hz), 133.8 (Cq, d, $J_{CP}$ = 125.5 Hz), 131.5 (CH, d, $J_{CP}$ = 2.8 Hz), 131.1 (CH, d, $J_{CP}$ = 9.6 Hz), 130.8 (CH, d, $J_{CP}$ = 5.6 Hz), 128.1 (CH, d, $J_{CP}$ = 12.2 Hz), 124.7 (Cq, d, $J_{CP}$ = 7.9 Hz), 113.5 (CH, d, $J_{CP}$ = 2.8 Hz), 55.0 ($CH_3$), 36.9 ($CH_2$, d, $J_{CP}$ = 93.4 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 33.0 (m); HRMS (ESI$^-$) $C_{14}H_{14}O_3P^-$ [M-H]$^-$ calcd. 261.0686, found 261.0682; IR (ATR) $\nu_{max}$ 3069, 3007, 2968, 2834, 2261, 2056, 1645, 1609, 1505, 1242, 1032, 953 cm$^{-1}$

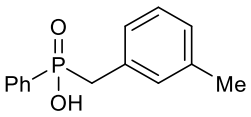
**(2-methoxybenzyl)(phenyl)phosphinic acid (65e)**




Reaction was performed on a 0.50 mmol scale. Isolation according to method B gave the *title compound* as a white solid (118 mg, 95%); m.p.: 114 – 116 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.57 – 7.44 (m, 3H), 7.44 – 7.32 (m, 2H), 7.20 – 7.05 (m, 2H), 6.86 – 6.73 (m, 2H), 3.39 (s, 3H), 3.19 (d, $J_{HP}$ = 18.3 Hz, 2H); $^{13}$C{$^1$H} NMR

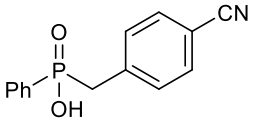
(75 MHz, DMSO-$d_6$) δ 156.7 (Cq, d, $J_{CP}$ = 5.9 Hz), 134.0 (Cq, d, $J_{CP}$ = 127.1 Hz), 131.2 (CH, d, $J_{CP}$ = 2.8 Hz), 131.1 (CH, d, $J_{CP}$ = 9.4 Hz), 130.9 (CH, d, $J_{CP}$ = 5.1 Hz), 127.7 (CH, d, $J_{CP}$ = 12.2 Hz), 127.6 (CH, d, $J_{CP}$ = 3.5 Hz), 121.2 (Cq, d, $J_{CP}$ = 7.5 Hz), 119.9 (CH, d, $J_{CP}$ = 3.3 Hz), 110.6 (CH, d, $J_{CP}$ = 2.7 Hz), 55.0 ($CH_3$), 31.7 ($CH_2$, d, $J_{CP}$ = 93.4 Hz); $^{31}$P NMR (121 MHz, DMSO-$d_6$) δ 32.8 (m); HRMS (ESI$^-$) $C_{14}H_{14}O_3P^-$ [M-H]$^-$ calcd. 261.0686, found 261.0688; IR (ATR) $\nu_{max}$ 3008, 2934, 2831, 2617, 2289, 2098, 1588, 1493, 1248, 1159, 958 cm$^{-1}$.

**(3-methylbenzyl)(phenyl)phosphinic acid (65f)**



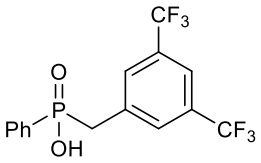

Reaction was performed on a 1.0 mmol scale. Isolation according to method A gave the *title compound* as a white solid (193 mg, 78%); m.p.: 128 – 130 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.66 – 7.56 (m, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.39 (m, 2H), 7.11 – 7.03 (m, 1H), 7.01 – 6.92 (m, 1H), 6.92 – 6.88 (m, 1H), 6.89 (s, 1H), 3.17 (d, $J_{HP}$ = 17.5 Hz, 2H), 2.19 (s, 3H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 136.8 (Cq, d, $J_{CP}$ = 2.9 Hz), 133.8 (Cq, d, $J_{CP}$ = 126.2 Hz), 132.9 (Cq, d, $J_{CP}$ = 7.5 Hz), 131.4 (CH, d, $J_{CP}$ = 3.0 Hz), 131.1 (CH, d, $J_{CP}$ = 9.5 Hz), 130.5 (CH, d, $J_{CP}$ = 5.8 Hz), 128.1 (CH, d, $J_{CP}$ = 12.3 Hz), 127.8 (CH, d, $J_{CP}$ = 2.8 Hz), 126.9 (CH, d, $J_{CP}$ = 5.8 Hz), 126.7 (CH, d, $J_{CP}$ = 3.4 Hz), 37.9 ($CH_2$, d, $J_{CP}$ = 92.2 Hz), 20.9 ($CH_3$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 33.8 (m); HRMS (ESI$^-$) $C_{14}H_{14}O_2P^-$ [M-H]$^-$ calcd. 245.0737, found 245.0736; IR (ATR) $\nu_{max}$ 3019, 2923, 2626, 2315, 1644, 1223, 954 cm$^{-1}$.

**(4-cyanobenzyl)(phenyl)phosphinic acid (65g)**




Reaction was performed on a 5.0 mmol scale. Isolation according to method A gave the *title compound* as a white solid (964 mg, 75%); m.p.: 127 - 130 °C and 160 – 162 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.68 (d, $J_{HH}$ = 8.0 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.58 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 7.28 (dd, $J_{HH}$ = 8.3, $J_{HP}$ = 2.3 Hz, 2H), 3.38 (d, $J$ = 17.9 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 139.6 (Cq, d, $J_{CP}$ = 7.5 Hz), 133.4 (Cq, d, $J_{CP}$ = 127.8 Hz), 131.8 (CH, d, $J_{CP}$ = 3.1 Hz), 131.7 (CH, d, $J_{CP}$ = 2.8 Hz), 131.1 (CH, d, $J_{CP}$ = 9.7 Hz), 130.8 (CH, d, $J_{CP}$ = 5.7 Hz), 128.2 (CH, d, $J_{CP}$ = 12.4 Hz), 118.9 (Cq, d, $J_{CP}$ = 1.9 Hz), 108.9 (Cq, d, $J_{CP}$ = 3.1 Hz), 38.3 ($CH_2$, d, $J_{CP}$ = 89.7 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 31.6 (m); HRMS (ESI$^-$) $C_{14}H_{11}NO_2P^-$ [M-H]$^-$ calcd. 256.0533, found 256.0542; IR (ATR) $\nu_{max}$ 3203, 3064, 2913, 2328, 2222, 2124, 1743, 1154, 1118, 972.

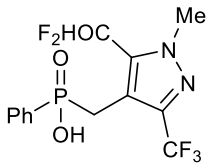
**(3,5-bis(trifluoromethyl)benzyl)(phenyl)phosphinic acid (65h)**




Reaction was performed on a 0.50 mmol scale. Isolation according to method B gave the *title compound* as a white solid (119 mg, 64%); m.p.: 122 – 123 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.90 (br s, 1H), 7.73 (br s, 2H), 7.64 – 7.53 (m, 3H), 7.49 – 7.43 (m, 2H), 3.53 (d, $J_{HP}$ = 17.4 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 137.2 (Cq, d, $J_{CP}$ = 7.9 Hz), 133.0 (Cq, d, $J_{CP}$ = 128.9 Hz), 131.8 (CH, d, $J_{CP}$ = 2.7 Hz), 131.1 (CH, d, $J_{CP}$ = 9.6 Hz), 130.5 (CH), 129.7 (Cq, qd, $J_{CF}$ = 32.7, $J_{CP}$ = 3.1 Hz), 128.2 (CH, d, $J_{CP}$ = 12.4 Hz), 126.0 (Cq, q, $J_{CF}$ = 272.8 Hz), 119.8 (br, CH), 37.4 ($CH_2$, d, $J_{CP}$ = 89.4 Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -61.4; $^{31}$P NMR (162

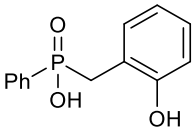
MHz, DMSO-$d_6$) δ 31.4 (m); HRMS (ESI$^-$) $C_{15}H_{10}O_2F_6P^-$ [M-H]$^-$ calcd. 367.0328, found 367.0330; IR (ATR) $\nu_{max}$ 3057, 2908, 2561, 2252, 2109, 1625, 1371, 1371, 1276, 1125 cm$^{-1}$.

**((5-(difluromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)(phenyl)phosphinic acid (65i)**




Reaction was performed on a 1.5 mmol scale. Isolation according to method B gave the *title compound* as an off-white solid (230 mg, 62%); m.p. 108 – 110 °C; $^1$H NMR (500 MHz, methanol-$d_4$) δ 7.76 – 7.65 (m, 2H), 7.65 – 7.57 (m, 1H), 7.55 – 7.45 (m, 2H), 7.08 (t, $J_{HF}$ = 72.4 Hz, 1H), 3.77 (s, 3H), 3.19 (d, $J_{HP}$ = 16.1 Hz, 2H); $^{13}$C{$^1$H} NMR (126 MHz, methanol-$d_4$) δ 145.3 (Cq, d, $J_{CP}$ = 4.7 Hz), 139.9 (Cq, qd, $J_{CF}$ = 36.9, $J_{CP}$ = 3.3 Hz), 133.7 (CH, d, $J_{CP}$ = 2.9 Hz), 132.8 (Cq, d, $J_{CP}$ = 131.3 Hz), 132.5 (CH, d, $J_{CP}$ = 10.1 Hz), 129.6 (CH, d, $J_{CP}$ = 12.8 Hz), 124.5 (Cq, q, $J_{CF}$ = 269.1 Hz), 117.3 (CH, td, $J_{CF}$ = 266.6, $J_{CP}$ = 1.9 Hz), 100.9 (Cq, d, $J_{CP}$ = 8.2 Hz), 36.1 ($CH_3$, d, $J_{CP}$ = 1.7 Hz), 26.2 ($CH_2$, d, $J_{CP}$ = 98.6 Hz); $^{31}$P NMR (162 MHz, methanol-$d_4$) δ 34.2 (m); $^{19}$F NMR (376 MHz, methanol-$d_4$) δ -62.5, -83.0 (d, $J_{FH}$ = 72.4 Hz); HRMS (ESI$^-$) $C_{13}H_{11}F_5O_3N_2P^-$ [M-H]$^-$ calcd. 369.0433, found 369.0426; IR (ATR) $\nu_{max}$ 2940, 2549, 2288, 1731, 1286, 1312, 1067 cm$^{-1}$.

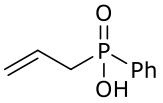
**(2-hydroxybenzyl)(phenyl)phosphinic acid (65j)**




Reaction was performed on a 0.50 mmol scale. The reaction was performed using (2-(bromomethyl)phenoxy)(tert-butyl)dimethylsilane. Isolation according to method B

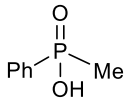
gave the *title compound* as an off white solid (60 mg, 48%); m.p.: 154 – 157 °C: $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.67 – 7.58 (m, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 7.05 – 6.95 (m, 2H), 6.75 – 6.79 (m, 1H), 6.66 (br t, $J_{HH}$ = 7.4 Hz, 1H), 3.22 (d, $J_{HP}$ = 17.5 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 155.4 (Cq, d, $J_{CP}$ = 5.8 Hz), 133.6 (Cq, d, $J_{CP}$ = 126.3 Hz), 131.5 (CH, d, $J_{CP}$ = 2.8 Hz), 131.2 (CH, d, $J_{CP}$ = 5.3 Hz), 131.0 (CH, d, $J_{CP}$ = 10.0 Hz), 128.1 (CH, d, $J_{CP}$ = 12.3 Hz), 127.4 (Cq, d, $J_{CP}$ = 2.9 Hz), 119.5 (CH, d, $J_{CP}$ = 7.4 Hz), 118.9 (CH, d, $J_{CP}$ = 2.7 Hz), 115.8 (CH, d, $J_{CP}$ = 2.2 Hz), 32.1 ($CH_2$, d, $J_{CP}$ = 94.0 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 35.2 (m); HRMS (ESI$^-$) $C_{13}H_{12}O_3P$- [M-H]$^-$ calcd. 247.0530, found 247.0533; IR (ATR) $\nu_{max}$ 3342, 3076, 3053, 2884, 2723, 2326, 1682, 1246, 1128, 940 cm$^{-1}$.

**allyl(phenyl)phosphinic acid (65k)**



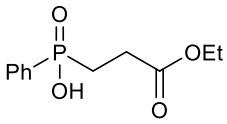

Reaction was performed on a 0.50 mmol scale. The reaction was performed with allyl bromide (5.0 eq.). Isolation according to method B gave the *title compound* as a pale yellow gum (66 mg, 73%); $^{1}$H NMR (400 MHz, methanol-$d_4$) δ 7.87 – 7.70 (m, 2H), 7.65 – 7.55 (m, 1H), 7.55 – 7.43 (m, 2H), 5.85 – 5.62 (m, 1H), 5.15 – 4.98 (m, 2H), 2.77 (dd, $J_{HP}$ = 18.5, $J_{HH}$ = 7.4 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, methanol-$d_4$) δ 133.4 (CH, d, $J_{CP}$ = 2.9 Hz), 133.1 (Cq, d, $J_{CP}$ = 130.5), 132.4 (CH, d, $J_{CP}$ = 10.1 Hz), 129.5 (CH, d, $J_{CP}$ = 13.0 Hz), 128.9 (CH, d, $J_{CP}$ = 9.1 Hz), 120.5 ($CH_2$, d, $J_{CP}$ = 13.1 Hz), 37.3 ($CH_2$, d, $J_{CP}$ = 96.2 Hz); $^{31}$P NMR (162 MHz, methanol-$d_4$) δ 37.9 (m); HRMS (ESI$^-$) $C_9H_{10}O_2P^-$ [M-H]$^-$ calcd. 181.0424, found 181.0429; IR (ATR) $\nu_{max}$ 3059, 3014, 2617, 2260, 2125, 1637, 1438, 1124, 957 cm$^{-1}$.

**methyl(phenyl)phosphinic acid (65l)**



Reaction was performed on a 0.50 mmol scale. The reaction was performed with MeOTf (3.5 eq.) and isolation according to method A gave the *title compound* as an off-white solid (18 mg, 23%). A second batch was obtained when the acidic aqueous washes were extracted with EtOAc (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Trituration with petrol gave the *title compound* as a light brown solid (57 mg, 73%); m.p.: 129 – 131 °C; (lit: 133 – 134 °C)[102]; $^{1}H$ NMR (400 MHz, methanol-$d_4$) δ 9.45 – 9.29 (m, 1H), 9.21 – 9.12 (m, 1H), 9.12 – 8.97 (m, 1H), 3.20 (d, $J_{HP}$ = 14.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, methanol-$d_4$) δ 134.8 (Cq, d, $J_{CP}$ = 132.2 Hz), 133.3 (CH, d, $J_{CP}$ = 2.8 Hz), 131.6 (CH, d, $J_{CP}$ = 10.7 Hz), 129.7 (CH, d, $J_{CP}$ = 12.8 Hz), 16.5 ($CH_3$, d, $J_{CP}$ = 101.1 Hz); $^{31}P$ NMR (162 MHz, methanol-$d_4$) δ 39.9 (m); HRMS ($ESI^-$) $C_7H_8O_2P^-$ $[M\text{-}H]^-$ calcd. 155.0267, found 155.0274; IR (ATR) $\nu_{max}$ 2980, 2818, 2344, 1622, 1250, 1164, 1130, 1028, 959 $cm^{-1}$.

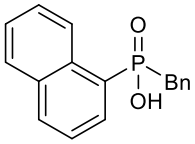
**(3-ethoxy-3-oxopropyl)phosphinic acid (65m)**



Isolation according to method C gave the *title compound* as a colourless oil (118 mg, 49%); $^{1}H$ NMR (500 MHz, methanol-$d_4$) δ 7.88 – 7.71 (m, 2H), 7.66 – 7.59 (m, 1H), 7.59 – 7.49 (m, 2H), 4.05 (q, $J_{HH}$ = 7.2 Hz, 2H), 2.60 – 2.40 (m, 2H), 2.24 – 2.08 (m, 2H), 1.20 (t, $J_{HH}$ = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, methanol-$d_4$) δ 173.7 (Cq, d, $J_{CP}$ = 15.7 Hz), 133.6 (Cq, d, $J_{CP}$ = 2.7 Hz), 133.2 (CH, d, $J_{CP}$ = 129.6 Hz), 132.3 (CH, d, $J_{CP}$ = 10.1 Hz), 129.8 (CH, d, $J_{CP}$ = 12.7 Hz), 62.0 ($CH_2$), 28.1 ($CH_2$, d, $J_{CP}$ = 2.0 Hz), 26.6 ($CH_2$, $J_{CP}$ = 100.9 Hz), 14.4 ($CH_3$); $^{31}P\{^{1}H\}$ NMR (202

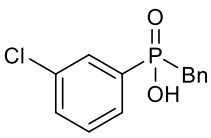
MHz, methanol-$d_4$) δ 40.0; HRMS (ESI$^-$) $C_{11}H_{14}O_4P^-$ [M-H]$^-$ calcd. 241.0635, found 241.0636; IR (ATR) $\nu_{max}$ 3055, 2984, 2638, 2330, 2111, 1734, 1237, 1174, 1126, 968 cm$^{-1}$.

**benzyl(napthalen-1-yl)phosphinic acid (65n)**




Reaction performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a white solid (100 mg, 71%); m.p.: 146 – 148 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.76 – 8.65 (m, 1H), 8.10 (br d, $J_{HH}$ = 8.3, Hz, 1H), 8.04 – 7.98 (m, 1H), 7.90 (ddd, $J_{HP}$ = 13.9, $J_{HH}$ = 7.1, $J_{HH}$ = 1.4 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.53 (ddd, $J_{HH}$ = 8.3, $J_{HH}$ = 7.1, $J_{HP}$ = 2.5 Hz, 1H), 7.17 – 7.08 (m, 3H), 7.02 – 6.95 (m, 2H), 3.33 (d, $J_{HP}$ = = 16.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 133.6 (Cq, d, $J_{CP}$ = 10.2 Hz), 133.4 (Cq, d, $J_{CP}$ = 8.1 Hz), 133.3 (CH, d, $J_{CP}$ = 7.7 Hz), 133.0 (CH, d, $J_{CP}$ = 3.0 Hz), 133.0 (Cq, d, $J_{CP}$ = 11.0 Hz), 130.4 (Cq, d, $J_{CP}$ = 121.6 Hz), 130.2 (CH, d, $J_{CP}$ = 5.7 Hz), 129.3 (CH), 128.3 (CH, d, $J_{CP}$ = 2.8 Hz), 127.4 (CH), 126.9 (CH, d, $J_{CP}$ = 3.6 Hz), 126.6 (CH), 126.5 (CH, d, $J_{CP}$ = 3.6 Hz), 125.1 (CH, d, $J_{CP}$ = 13.1 Hz), 39.5 ($CH_2$, d, $J_{CP}$ = 91.8 Hz); $^{31}$P{$^1$H} NMR (162 MHz, DMSO-$d_6$) δ 32.7; HRMS (ESI$^-$) $C_{17}H_{14}O_2P^-$ [M-H]$^-$ calcd. 281.0737, found 281.0738; IR (ATR) $\nu_{max}$ 3057, 2502, 2256, 2109, 1673, 1240, 1029.

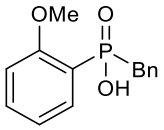
**benzyl(3-chlorophenyl)phosphinic acid (65o)**




Reaction performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a grey powder (108 mg, 81%); m.p.: 151 – 152 °C; $^1$H NMR (400

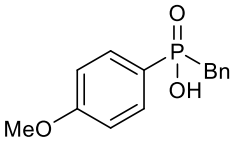
MHz, DMSO-$d_6$) δ 7.63 – 7.51 (m, 3H), 7.51 – 7.43 (m, 1H), 7.26 – 7.12 (m, 3H), 7.12 – 7.05 (m, 2H), 3.27 (d, $J_{HP}$ = 17.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 136.9 (Cq, d, $J_{CP}$ = 123.2 Hz), 133.6 (Cq, d, $J_{CP}$ = 16.1 Hz), 133.2 (Cq, d, $J_{CP}$ = 8.0 Hz), 131.8 (d, $J_{CP}$ = 2.7 Hz, CH), 131.1 (d, $J_{CP}$ = 10.3 Hz, CH), 130.7 (d, $J_{CP}$ = 13.1 Hz, CH), 130.3 (d, $J_{CP}$ = 5.7 Hz, CH), 130.2 (d, $J_{CP}$ = 8.9 Hz, CH), 128.4 (d, $J_{CP}$ = 2.9 Hz, CH), 126.6 (d, $J_{CP}$ = 3.4 Hz, CH), 38.1 (d, $J_{CP}$ = 93.2 Hz, $CH_2$); $^{31}P\{^1H\}$ NMR (162 MHz, DMSO-$d_6$) δ 31.3; HRMS (ESI$^-$) $C_{13}H_{11}{}^{35}ClO_2P^-$ $[M-H]^-$ calcd. 265.0191, found 265.0208. IR (ATR) $\nu_{max}$ 3063, 3032, 2921, 2571, 2251, 2098, 1642, 1112, 957.

**benzyl(2-methoxyphenyl)phosphinic acid (65p)**



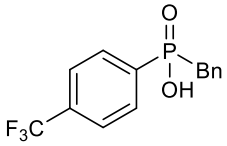

Reaction performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a white solid (78 mg, 91%); m.p.: 214 – 216 °C; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7.61 – 7.43 (m, 2H), 7.20 – 7.05 (m, 6H), 6.95 (ddd, $J_{HH}$ = 7.4, $J_{HH}$ = 2.2, $J_{HP}$ = 0.9 Hz, 1H), 3.90 (s, 3H), 3.32 (d, $J_{HP}$ = 18.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-$d_6$) δ 160.8 (Cq, d, $J_{CP}$ = 4.5 Hz), 134.2 (CH, d, $J_{CP}$ = 3.0 Hz), 134.2 (CH), 133.8 (Cq, d, $J_{CP}$ = 7.9 Hz), 130.1 (CH, d, $J_{CP}$ = 5.9 Hz), 128.4 (CH, d, $J_{CP}$ = 3.1 Hz), 126.4 (CH, d, $J_{CP}$ = 3.3 Hz), 121.5 (Cq, d, $J_{CP}$ = 123.6 Hz), 120.5 (CH, d, $J_{CP}$ = 11.1 Hz), 111.8 (CH, d, $J_{CP}$ = 7.3 Hz), 56.1 ($CH_3$), 38.1 ($CH_2$, d, $J_{CP}$ = 94.5 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, DMSO-$d_6$) δ 31.1; HRMS (ESI$^-$) $C_{14}H_{14}O_3P^-$ $[M-H]^-$ calcd. 261.0686, found 261.0697; IR (ATR) $\nu_{max}$ 3058, 3003, 2838, 2579, 2256, 2091, 1682, 961.

**benzyl(4-methoxyphenyl)phosphinic acid (65q)**




Reaction performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a white solid (107 mg, 82%); m.p.: 165 – 166 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 7.59 – 7.44 (m, 2H), 7.25 – 7.11 (m, 3H), 7.11 – 7.02 (m, 2H), 7.02 – 6.89 (m, 2H), 3.78 (s, 3H), 3.18 (d, $J_{HP}$ = 17.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, DMSO-$d_6$) δ 162.1 (Cq, d, $J_{CP}$ = 2.9 Hz), 133.8 (Cq, d, $J_{CP}$ = 7.4 Hz), 133.5 (CH, d, $J_{CP}$ = 10.9 Hz), 130.3 (CH, d, $J_{CP}$ = 5.8 Hz), 128.3 (CH, d, $J_{CP}$ = 2.8 Hz), 126.4 (CH, d, $J_{CP}$ = 3.4 Hz), 125.5 (Cq, d, $J_{CP}$ = 132.8 Hz), 114.0 (CH, d, $J_{CP}$ = 13.2 Hz), 55.9 ($CH_3$), 38.7 ($CH_2$, d, $J_{CP}$ = 92.8 Hz); $^{31}$P{$^{1}$H} NMR (162 MHz, DMSO-$d_6$) δ 32.9; HRMS (ESI$^-$) $C_{14}H_{14}O_3P^-$ [M-H]$^-$ calcd. 261.0686, found 261.0701; IR (ATR) $\nu_{max}$ 3062, 3005, 2928, 2837, 2542, 2254 2087, 1644, 1098, 955.

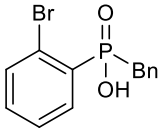
**benzyl(4-(trifluoromethyl)phenyl)phosphinic acid (65r)**




Reaction performed on a 0.50 mmol scale. Isolation according to method A gave the *title compound* as a white solid (99 mg, 66%); m.p.: 157 - 159 °C; $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 7.90 – 7.71 (m, 4H), 7.36 – 6.98 (m, 5H), 3.29 (d, $J_{HP}$ = 17.8 Hz, 2H); $^{13}$C{$^{1}$H} NMR (126 MHz, DMSO-$d_6$) δ 138.8 (Cq, d, $J_{CP}$ = 123.0 Hz), 132.8 (Cq, d, $J_{CP}$ = 8.0 Hz), 132.2 (CH, d, $J_{CP}$ = 9.9 Hz), 131.5 (Cq, dq, $J_{CF}$ = 31.8, $J_{CP}$ = 2.6 Hz), 130.0 (CH, d, $J_{CP}$ = 5.5 Hz), 126.4 (CH, d, $J_{CP}$ = 3.5 Hz), 125.1 (CH, dq, $J_{CF}$ = 11.9, $J_{CP}$ = 3.8 Hz), 124.0 (Cq, d, $J_{CF}$ = 272.7 Hz), 37.8 ($CH_2$, d, $J_{CP}$ = 93.0 Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -61.5; $^{31}$P{$^{1}$H} NMR (162 MHz, DMSO-$d_6$) δ 31.2;

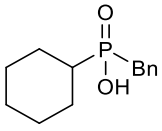
HRMS (ESI$^-$) $C_{14}H_{11}F_3O_2P^-$ [M-H]$^-$ calcd. 299.0454, found 299.0460; IR (ATR) $\nu_{max}$ 3037, 2919, 2641, 2259, 2084, 1650, 1324, 1062.

**benzyl(2-bromophenyl)phosphinic acid (65s)**




Reaction performed on a 0.50 mmol scale. Isolation according to method A but further triturations with distilled pentane (x 9), the minimum amount of EtOAc (x 2), and $Et_2O$ (x 3) were required, and gave the *title compound* as a white solid (54 mg, 35%); m.p.: 136 – 137 °C; $^1$H NMR (400 MHz, methanol-$d_4$) δ 7.77 – 7.67 (m, 2H), 7.45 – 7.31 (m, 2H), 7.19 – 7.09 (m, 5H), 3.58 (d, $J_{HP}$ = 18.3 Hz, 2H); $^{13}$C{$^1$H} NMR (126 MHz, methanol-$d_4$) δ 136.8 (CH, $d_{CP}$, $J$ = 6.5 Hz), 135.4 (CH, $d_{CP}$, $J$ = 10.2 Hz), 134.9 (CH, d, $J_{CP}$ = 2.7 Hz), 133.5 (Cq, d, $J_{CP}$ = 130.1 Hz), 133.0 (Cq, d, $J_{CP}$ = 8.2 Hz), 130.9 (CH, d, $J_{CP}$ = 5.6 Hz), 129.3 (CH, d, $J_{CP}$ = 3.5 Hz), 128.2 (CH, d, $J_{CP}$ = 10.1 Hz), 127.7 (CH, d, $J_{CP}$ = 3.7 Hz), 126.0 (Cq, d, $J_{CP}$ = 6.6 Hz), 37.6 ($CH_2$, d, $J_{CP}$ = 96.5 Hz); $^{31}$P{$^1$H} NMR (162 MHz, methanol-$d_4$) δ 35.2; HRMS (ESI$^-$) $C_{13}H_{11}{}^{79}BrO_2P^-$ [M-H]$^-$ calcd. 308.9686, found 308.9688; IR (ATR) $\nu_{max}$ 3064, 2664, 2297, 2117, 1629, 1139, 968.

**benzyl(cyclohexyl)phosphinic acid (65t)**



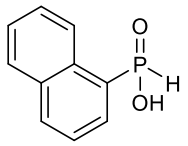

Reaction performed on a 0.50 mmol scale. A constant flow of argon was employed throughout the duration of heating. Isolation according to method A gave the *title compound* as a white solid (89 mg, 75%); m.p.: 154 – 157 °C; $^1$H NMR (400 MHz, methanol-$d_4$) δ 7.40 – 7.17 (m, 5H), 3.13 (d, $J_{HP}$ = 15.8 Hz, 2H), 2.06 – 1.88 (m, 2H), 1.87 – 1.75 (m, 2H), 1.75 – 1.66 (m, 1H), 1.66 – 1.51 (m, 1H), 1.45 – 1.15 (m, 5H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, methanol-$d_4$) δ 133.5 (Cq, d, $J_{CP}$ = 7.9 Hz), 131.0 (CH, d, $J_{CP}$ = 5.2 Hz), 129.5 (CH, d, $J_{CP}$ = 2.9 Hz), 127.7 (CH, d, $J_{CP}$ = 3.3 Hz), 38.3 (CH, d, $J_{CP}$ = 94.5 Hz), 35.3 ($CH_2$, d, $J_{CP}$ = 83.7 Hz), 27.2 ($CH_2$, d, $J_{CP}$ = 14.2 Hz), 27.0 ($CH_2$), 26.3 ($CH_2$, d, $J_{CP}$ = 3.1 Hz); $^{31}P\{^{1}H\}$ NMR (162 MHz, methanol-$d_4$) δ 51.2; HRMS ($ESI^-$) $C_{13}H_{18}O_2P^-$ $[M-H]^-$ calcd. 237.1050, found 237.1057; IR (ATR) $\nu_{max}$ 3063, 2936, 2848, 2309, 2109, 1599, 952.

**General procedure for the formation of 77a, c, e and f:**

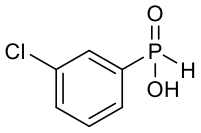
To a pre dried microwave vial anilinium hypophosphite (1.0 eq.), $Pd_2(dba)_3.CHCl_3$ (5.0 mol% or 1.0 mol%), XantPhos (5.0 mol% or 1.0 mol%) and *solid aryl halides* (1.0 eq.) were added. The microwave vial was sealed and cycles of vacuum and argon were performed three times. THF (0.25 M), triethylamine (2.5 eq.) and *liquid aryl halide* (1.0 eq.) were added and the solution was degassed with argon for 20 mins. The reaction mixture was then irradiated to 120 °C in a microwave for 10 min with 20 s pre stirring. The reaction mixtures were concentrated *in vacuo* then partitioned between NaOH (1.0 M aqueous solution) and $Et_2O$. The biphasic mixture was extracted with NaOH (1.0 M aqueous solution, x 3). The combined aqueous extracted were acidified to pH 1 with HCl (conc.), saturated with NaCl then extracted with EtOAc (x 3). The combined organic extracts were then dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to give the crude material which was purified by trituration with the *solvents* given.

**naphalen-1ylphosphinic acid (77a)**



Reaction performed on a 2.5 mmol scale (with respect to anilinium hypophosphite). Isolation according to the general procedure, $Pd_2(dba)_3.CHCl_3$ (1.0 mol%) and XantPhos (1.0 mol%) were used, with no further purification. The *title compound* was isolated as a pale yellow solid (297 mg, 62%); m.p.: 123 – 125 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.49 (d, $J_{HH}$ = 8.4 Hz, 1H), 8.21 – 8.12 (m, 1H), 8.08 – 8.02 (m, 1H), 7.97 (ddd, $J_{HP}$ = 18.4, $J_{HH}$ = 6.9, $J_{HH}$ = 1.2 Hz, 1H), 7.84 (d, $J_{HP}$ = 550.5 Hz, 1H), 7.71 – 7.58 (m, 3H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 133.1 (Cq, d, $J_{CP}$ = 10.0 Hz), 132.7 (CH, d, $J_{CP}$ = 3.1 Hz), 131.7 (Cq, d, $J_{CP}$ = 9.9 Hz), 130.5 (CH, d, $J_{CP}$ = 13.8 Hz), 130.2 (Cq, d, $J_{CP}$ = 125.1 Hz), 128.9 (CH), 127.3 (CH), 126.6 (CH), 125.3 (CH, d, $J_{CP}$ = 7.1 Hz), 125.0 (CH, d, $J_{CP}$ = 15.6 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 18.7 (d, $J_{PH}$ = 550.5 Hz)$^*$; HRMS (ESI$^-$) $C_{10}H_8O_2P^-$ [M-H]$^-$ calcd. 191.0267, found 191.0279; IR (ATR) $\nu_{max}$ 2981, 2421, 2101, 1587, 1507. $^*$*only $J^1$ coupling reported*.

**(3-chlorophenyl)phosphinic acid (77b)**[18]

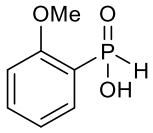


A stirred solution of anilinium hypophosphite (796 mg, 5.0 mmol), 3-chloroiodobenzene (0.31 mL, 2.5 mmol), $NEt_3$ (2.09 mL, 15.0 mmol) in MeCN (12.5 mL) was sparged with argon then $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) was added. The reaction was heated to 85 °C for 6 h then cooled to r.t. and concentrated *in vacuo.* The residue as partitioned between NaOH (1.0 M aqueous solution) and $Et_2O$ then the biphasic mixture was stirred at r.t. for 1 h. The mixture was separated and

further extracted with NaOH (1.0 M aqueous solution, x 2). The combined aqueous extracts were acidified to pH 1 with HCl (3.0 M aqueous solution) and extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude brown solid. The crude material was triturated with $Et_2O$ (x 3) and the excess $Et_2O$ was removed *in vacuo*. The resulting solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 h and the *title compound* was isolated as a beige solid (270 mg, 61%).

m.p.: 87 - 89 °C; $^1$H NMR (500 MHz, chloroform-*d*) δ 12.72 (br s, 1H), 7.77 – 7.71 (m, 1H), 7.68 – 7.62 (m, 1H), 7.57 (d, $J_{HP}$ = 579.1 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.46 – 7.40 (m, 1H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 135.1 (Cq, d, $J_{CP}$ = 18.8 Hz), 133.2 (CH, d, $J_{CP}$ = 2.9 Hz), 132.8 (Cq, d, $J_{CP}$ = 134.6 Hz), 130.8 (CH, d, $J_{CP}$ = 13.1 Hz), 130.2 (CH, d, $J_{CP}$ = 15.3 Hz), 128.9 (CH, d, $J_{CP}$ = 11.6 Hz); $^{31}$P NMR (162 MHz, chloroform-*d*) δ 20.8 (d, $J_{HP}$ = 579.1)$^*$; HRMS (ESI$^-$) $C_6H_5{}^{35}ClO_2P^-$ [M-H]$^-$ calcd. 174.9721, found 174.9733. $^*$*only $J^1$ coupling reported*.

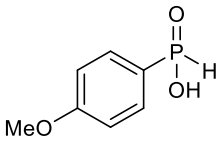
**(2-methoxyphenyl)phosphinic acid (77c)**[19]




Reaction performed on a 2.5 mmol scale (with respect to anilinium hypophosphite). Isolation according to the general procedure, $Pd_2(dba)_3.CHCl_3$ (1.0 mol%) and XantPhos (1.0 mol%) were used. Purification was by trituration with $Et_2O$ (x 1) and EtOAc (x 2). The excess solvent was removed *in vacuo* and the resulting solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 h. The *title compound* was isolated as a yellow solid (170 mg, 40%); m.p.: 101 – 104 °C;$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.66 – 7.52 (m, 2H), 7.49 (d, $J_{HP}$ = 560.6 Hz, 1H), 7.17 – 7.02 (m, 2H), 3.83 (s, 3H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 160.7 (Cq, d, $J_{CP}$ = 4.2 Hz), 134.1 (CH, d, $J_{CP}$ = 1.8 Hz), 131.6 (CH, d, $J_{CP}$ = 7.8 Hz), 121.3 (Cq, d, $J_{CP}$ = 127.6 Hz),

120.3 (CH, d, $J_{CP}$ = 12.5 Hz), 111.5 (CH, d, $J_{CP}$ = 6.6 Hz), 55.7 ($CH_3$); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 11.64 (d, $J_{PH}$ = 560.4 Hz)*. HRMS ($ESI^-$) $C_7H_9O_3P^-$ $[M-H]^-$ calcd. 172.0289, found 172.0214. **only $J^1$ coupling reported*.

**(4-methoxyphenyl)phosphinic acid (77d)**[18]

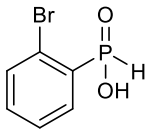



A stirred solution of anilinium hypophosphite (796 mg, 5.00 mmol), 4-methoxyiodobenzene (585 mg, 2.50 mmol), $NEt_3$ (2.09 mL, 15.0 mmol) in MeCN (12.5 mL) was sparged with argon then dppp (45 mg, 0.11 mmol) and $Pd(OAc)_2$ (45 mg, 0.10 mmol) were added. The reaction was heated to 85 °C for 24 h, cooled to r.t. and concentrated *in vacuo.* The residue as partitioned between NaOH (1.0 M aqueous solution) and $Et_2O$ then the biphasic mixture was stirred at r.t. for 1 h. The mixture was separated and further extracted with NaOH (1.0 M aqueous solution, x 2). The combined aqueous extracts were acidified to pH 1 with HCl (3.0 M aqueous solution) and extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude brown solid. The crude material was purified by recrystallisation with EtOAc and washed with EtOAc. The resulting solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 h and the *title compound* was isolated as a beige solid (143 mg, 33%).

m.p.:112 – 115 °C; $^1$H NMR (400 MHz, chloroform-*d*) δ 11.26 (br s, 1H), 7.70 (dd, $J_{HP}$ = 13.5, $J_{HH}$ = 8.8 Hz, 2H), 7.58 (d, $J_{HP}$ = 569.2 Hz, 1H), 6.96 (dd, $J_{HH}$ = 8.8, $J_{HP}$ = 2.7 Hz, 2H), 3.85 (s, 3H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 163.2 (Cq, d, $J_{CP}$ = 3.1 Hz), 132.8 (CH, d, $J_{CP}$ = 13.5 Hz), 122.2 (Cq, d, $J_{CP}$ = 142.8 Hz), 114.2 (CH, d, $J_{CP}$ = 15.1 Hz), 55.4 ($CH_3$); $^{31}$P NMR (162 MHz, chloroform-*d*) δ 23.6 (d, $J_{PH}$ = 569.2

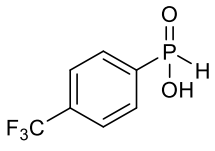
Hz)*; HRMS (ESI-) $C_7H_8O_3P^-$ [M-H]- calcd. 171.0217, found 171.0223. **only $J^1$ coupling reported*.

**(2-bromophenyl)phosphinic acid (77e)**




Isolation according to the general procedure, $Pd_2(dba)_3.CHCl_3$ (5.0 mol%) and XantPhos (5.0 mol%) were used. Purification was by trituration with $Et_2O$ (x 1) and EtOAc (x 2). The excess solvent was removed *in vacuo* and the resulting solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 h. The *title compound* was isolated as a yellow solid (197 mg, 36%); m.p.: 154 – 155 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.80 (ddd, $J_{HP}$ = 13.2, $J_{HH}$ = 7.2, $J_{HH}$ = 2.1 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.63 – 7.47 (m, 2H), 7.50 (d, $J_{HP}$ = 570.7 Hz, 1H); $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$) δ 134.0 (CH, d, $J_{CP}$ = 2.3 Hz), 133.6 (Cq, d, $J_{CP}$ = 130.4 Hz), 133.4 (CH, d, $J_{CP}$ = 7.4 Hz), 133.2 (CH, d, $J_{CP}$ = 8.8 Hz), 127.7 (CH, d, $J_{CP}$ = 11.3 Hz), 123.9 (Cq, d, $J_{CP}$ = 7.3 Hz); $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 14.2 (d, $J_{PH}$ = 576.5)*; HRMS (ESI-) $C_6H_5{}^{79}BrO_2P^-$ [M-H]- calcd. 218.9216, found 218.9218; IR (ATR) $\nu_{max}$ 3081, 2618, 2303, 2127, 1639, 1123, 982. **only $J^1$ coupling reported*.

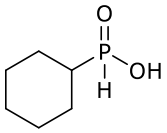
**(4-trifluoromethyl)phenyl)phosphinic acid (77f)**




Performed on a 4.00 mmol scale (with respect to anilinium hypophosphite) and with 4-bromotrifluorotoluene (0.50 eq.). Isolation according to the general procedure, $Pd_2(dba)_3.CHCl_3$ (1.0 mol%) and XantPhos (1.0 mol%) were used. Purification was by trituration with $Et_2O$ (x 3). The excess solvent was removed *in vacuo* and the

resulting solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 h. The *title compound* was isolated as an off-white solid (276 mg, 66%); m.p.: 105 – 107 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.00 – 7.87 (m, 4H), 7.54 (d, $J_{HP}$ = 557.9 Hz, 1H); $^{13}$C{$^1$H} NMR (126 MHz, DMSO-$d_6$) δ 138.6 (Cq, d, $J_{CP}$ = 124.5 Hz), 132.0 (Cq, dq, $J_{CF}$ = 31.8, $J_{CP}$ = 3.0 Hz), 131.1 (CH, d, $J_{CP}$ = 11.9 Hz), 125.5 (CH, dq, $J_{CF}$ = 13.0, $J_{CP}$ =3.7 Hz), 123.8 (Cq, q, $J_{CF}$ = 272.7 Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ -61.6; $^{31}$P NMR (162 MHz, DMSO-$d_6$) δ 14.4 (d, $J_{PH}$ = 557.1 Hz)$^*$; HRMS (ESI$^-$) $C_7H_5F_3O_2P^-$ [M-H]$^-$ calcd. 208.9985, found 208.9987; IR (ATR) $\nu_{max}$ 3049, 2671, 2298, 2111, 1689, 1317, 955. $^*$*only $J^1$ coupling reported*.

**cyclohexylphosphinic acid (77g)**[103]

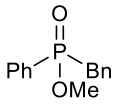



To a solution of sodium hypophosphite (10.1 g, 100 mmol) and cyclohexene (4.05 mL, 40.0 mmol) in MeOH (200 mL) was added $BEt_3$ (20 mL of a 1.0 M solution in hexanes, 20 mmol) at 0 °C, at a rate of 0.5 mL/min. The reaction warmed to r.t. and stirred for 4 h. The reaction was concentrated *in vacuo* to give a white solid which was partitioned between $Et_2O$ and aq. NaOH (1.0 M) and stirred for 30 min. The reaction mixture was separated and further extracted with aq. NaOH (1.0 M, × 2). The aqueous extracts were acidified to pH 1 with aq. HCl (3.0 M) then extracted with $Et_2O$ (× 3). The organic extracts were washed with brine (× 2), dried over $MgSO_4$, filtered and concentrated *in vacuo* and the *title* compound was isolated as a colourless oil (1.98 g, 33 %).

$^1$H NMR (300 MHz, chloroform-*d*) δ 9.97 (br s), 6.82 (d, $J_{HP}$ = 532.3 Hz, 1H), 2.06 – 1.53 (m, 6H), 1.49 – 1.10 (m, 5H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 37.5 (CH, d, $J_{CP}$ = 96.0 Hz), 26.0 ($CH_2$), 25.8 ($CH_2$, d, $J_{CP}$ = 16.0 Hz), 23.9 ($CH_2$, d, $J_{CP}$ =

1.9 Hz); $^{31}$P NMR (162 MHz, chloroform-*d*) δ 43.3 (d, $J_{PH}$ = 532.3 Hz)*; HRMS (ESI$^-$) $C_6H_{12}O_2P^-$ [M-H]$^-$ calcd. 147.0580, found 147.0584. **only $J^1$ coupling reported*.

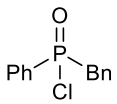
**methyl benzyl(phenyl)phosphinate (78)**[104]




To a solution was of **65a** (116 mg, 0.500 mmol), $CsCO_3$ (326 mg, 1.00 mmol) in MeCN (3.0 mL) at r.t. was added methyl iodide (30 μL, 0.50 mmol). The reaction was heated to 90 °C and stirred for 16 h. The reaction was concentrated *in vacuo* to give a white solid. The crude material was purified by silica gel column chromatography (5% MeOH in $CH_2Cl_2$) and gave the *title compound* as a white solid (94 mg, 77%).

$R_f$: 0.39 (5% MeOH in $CH_2Cl_2$); m.p.: 97 – 99 °C (lit: 94 – 95 °C)[105]; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.63 – 7.55 (m, 2H), 7.55 – 7.49 (m, 1H), 7.46 – 7.36 (m, 2H), 7.25 – 7.16 (m, 3H), 7.13 – 7.05 (m, 2H), 3.64 (d, $J_{HP}$ = 11.0 Hz, 3H), 3.30 (d, $J_{HP}$ = 17.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 132.5 (CH, d, $J_{CP}$ = 2.9 Hz), 132.1 (CH, d, $J_{CP}$ = 9.7 Hz), 131.4 (Cq, d, $J_{CP}$ = 8.0 Hz), 130.1 (CH, d, $J_{CP}$ = 5.8 Hz), 128.9 (CH), 128.6 (CH, d, $J_{CP}$ = 9.0 Hz), 128.5 (CH), 126.9 (CH, d, $J_{CP}$ = 3.6 Hz), 51.6 ($CH_3$, d, $J_{CP}$ = 6.6 Hz), 37.9 ($CH_2$, d, $J_{CP}$ = 95.4 Hz); $^{31}$P NMR (162 MHz, chloroform-*d*) δ 41.9; HRMS (ESI$^+$) $C_{14}H_{15}O_2PNa^+$ [M+Na]$^+$ calcd. 269.0702, found 269.0703; IR (ATR) $\nu_{max}$ 3062, 3027, 2945, 2910, 2843, 1212, 1036 cm$^{-1}$.

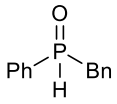
**Benzyl(phenyl)phosphinic chloride (79)**




To stirred solution of **65a** (52 mg, 0.25 mmol) in $CDCl_3$ (1.00 mL) at r.t. was added $(COCl)_2$ (23 μL, 0.275 mmol). The reaction was stirred for 1 h, an NMR sample was

taken and the *title compound* was observed; $^{1}$H NMR (300 MHz, Chloroform-*d*) δ 7.80 – 7.66 (m, 2H), 7.64 – 7.54 (m, 1H), 7.53 – 7.42 (m, 2H), 7.26 – 7.22 (m, 3H), 7.18 – 7.06 (m, 2H), 3.85 – 3.58 (m, 1H); $^{13}$C{$^{1}$H} NMR (75 MHz, Chloroform-*d*) δ 133.4 (CH, d, $J_{CP}$ = 3.0 Hz), 131.7 (Cq, d, $J_{CP}$ = 114.1 Hz), 131.3 (CH, d, $J_{CP}$ = 11.2 Hz), 130.4 (CH, d, $J_{CP}$ = 6.4 Hz), 129.7 (Cq, d, $J_{CP}$ = 9.1 Hz), 128.8 (CH, d, $J_{CP}$ = 5.3 Hz), 128.7 (CH, d, $J_{CP}$ = 5.1 Hz), 127.7 (CH, d, $J_{CP}$ = 4.1 Hz), 44.9 ($CH_2$, d, $J_{CP}$ = 76.4 Hz); $^{31}$P{$^{1}$H} NMR (121 MHz, Chloroform-*d*) δ 52.0.

**benzyl(phenyl)phosphine oxide (80)**[106]

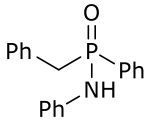



To a stirred suspension of **65a** (116 mg, 0.500 mmol) in $CH_2Cl_2$ (2.0 mL) was added oxalyl chloride (47 μL, 0.55 mmol) at r.t. and stirred for 30 min. The reaction mixture was concentrated *in vacuo* then placed back under an argon atmosphere and re-dissolved in $CH_2Cl_2$ (2.0 mL). The reaction mixture was then cooled to – 78 °C and DIBAL-H (0.55 mL of a 1.0 M solution in toluene, 0.550 mmol) was added dropwise. The mixture was stirred at – 78 °C for 1 h and was quenched with MeOH then citric acid (1.0 M aqueous solution) was added. The biphasic mixture was separated and the aqueous phase was extracted with $CH_2Cl_2$ (×2). The combined organic extracted were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude residue. The crude material was purified by silica gel column chromatography (6% MeOH in $CH_2Cl_2$) and gave *the title compound* as a white solid (56 mg, 52%).

$R_f$: 0.29 (6% MeOH in $CH_2Cl_2$); m.p.: 110 – 116 °C (lit: 112 - 114 °C)[101]; $^{1}$H NMR (400 MHz, chloroform-*d*) δ 7.61- 7.41 (m, 6 H), 7.47 (ddd, $J_{HP}$ = 474.7, $J_{HH}$ = 4.1, $J_{HH}$ = 2.9 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.08 – 7.03 (m, 2H), 3.54 – 3.29 (m, 2H); $^{13}$C{$^{1}$H} NMR (101 MHz, chloroform-*d*) δ 132.7 (CH, d, $J_{CP}$ = 3.2 Hz), 130.6 (Cq, d, $J_{CP}$ = 7.4 Hz), 130.2 (CH, d, $J_{CP}$ = 10.9 Hz), 129.9 (CH, d, $J_{CP}$ = 5.8 Hz), 129.9 (Cq, d, $J_{CP}$ = 97.3 Hz), 129.0 (CH, d, $J_{CP}$ = 3.3 Hz), 128.8 (CH, d, $J_{CP}$ = 12.4 Hz), 127.4 (CH, d,

$J_{CP}$ = 3.7 Hz), 39.0 ($CH_2$, d, $J_{CP}$ = 62.4 Hz); $^{31}P$ NMR (162 MHz, chloroform-*d*) δ 29.5 (d, $J_{PH}$ = 475.0)*; HRMS ($ESI^+$) $C_{13}H_{13}OPNa^+$ $[M+Na]^+$ calcd. 239.0596, found 239.0595. **only $J^1$ coupling reported*.

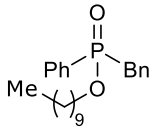
**_P_-benzyl-_N_,_P_-diphenylphosphinic amide (81)**




To a stirred suspension of **65a** (64 mg, 0.28 mmol) in $CH_2Cl_2$ (0.80 mL) was added oxalyl chloride (26 μL, 0.30 mmol) at r.t., and the reaction was stirred for 0.5 h. The reaction mixture was concentrated *in vacuo* then placed back under an argon atmosphere and re-dissolved in $CH_2Cl_2$ (0.80 mL). Aniline (50 μL, 0.55 mmol) at 0 °C then warmed to r.t. for 1h. Additional $CH_2Cl_2$ (2.4 mL) was required and the reaction was stirred at r.t. for 16 h. The reaction was quenched with brine and extracted with $CHCl_3$ (x 3). The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an off-white solid. The crude material was purified by silica gel column chromatography (2% MeOH in $CH_2Cl_2$) and the *title compound* was isolated as a white solid (56 mg, 64%).

$R_f$: 0.23 (2% MeOH in $CH_2Cl_2$); m.p.: 219 – 221 °C (lit: 220 – 222)[105]; $^1H$ NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 2H), 7.55 – 7.49 (m, 1H), 7.45 – 7.37 (m, 2H), 7.32 – 7.21 (m, 2H), 7.17 – 7.08 (m, 4H), 6.94 – 6.85 (m, 3H), 5.06 (d, $J_{HP}$ = 10.1 Hz, 1H), 3.61 – 3.31 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 140.2 (Cq), 132.4 (CH, d, $J_{CP}$ = 3.6 Hz), 132.3 (CH, d, $J_{CP}$ = 3.1 Hz), 131.7 (Cq, d, $J_{CP}$ = 8.0 Hz), 131.1 (Cq, d, $J_{CP}$ = 124.6 Hz), 129.8 (CH, d, $J_{CP}$ = 5.7 Hz), 129.4 (CH), 129.1 (CH, d, $J_{CP}$ = 3.0 Hz), 128.8 (CH, d, $J_{CP}$ = 12.7 Hz), 127.4 (CH, d, $J_{CP}$ = 3.6 Hz), 122.1 (CH), 118.7 (CH, d, $J_{CP}$ = 6.1 Hz), 39.0 ($CH_2$, d, $J_{CP}$ = 84.5 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, Chloroform-*d*) δ 23.6; HRMS ($ESI^-$) $C_{19}H_{17}NOPNa^-$ $[M-H]^-$ calcd. 306.1053, found 306.1050; IR (ATR) $\nu_{max}$ 3204, 3087, 307, 2904, 1499, 1176.

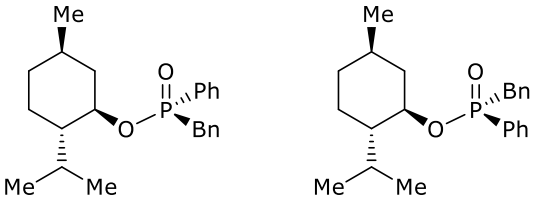
**decyl benzyl(phenyl)phosphinate (82)**




To a stirred suspension of **65a** (116 mg, 0.500 mmol) in $CH_2Cl_2$ (2.0 mL) was added oxalyl chloride (47 μL, 0.55 mmol) at r.t. and stirred for 30 min. 1-decanol (0.11 mL, 0.55 mmol) and triethylamine (77 μL, 0.55 mmol) in $CH_2Cl_2$ (1.00 mL) were pre mixed and added dropwise at r.t. The reaction was stirred at r.t. for 17 h then concentrated *in vacuo* to give a white solid. The crude material was purified by silica gel column chromatography (10% - 50 % EtOAc in petrol) and gave the *title compound* as a white solid (118 mg, 64%).

$R_f$: 0.30 (50% EtOAc in petrol); m.p.: 48 - 50 °C; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.63 – 7.54 (m, 2H), 7.54 – 7.47 (m, 1H), 7.43 – 7.35 (m, 2H), 7.24 – 7.15 (m, 3H), 7.13 – 7.06 (m, 2H), 4.00 (m, 6.7 Hz, 1H), 3.76 (m, 6.7 Hz, 1H), 3.36 – 3.22 (m, 2H), 1.74 – 1.67 (m, 1H), 1.66 – 1.58 (m, 2H), 1.38 – 1.17 (m, 13H), 0.88 (t, $J_{HH}$ = 6.9 Hz, 2H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 132.3 (CH, d, $J_{CP}$ = 2.7 Hz), 132.1 (CH, d, $J_{CP}$ = 9.6 Hz), 131.6 (Cq, d, $J_{CP}$ = 7.6 Hz), 130.3 (Cq, d, $J_{CP}$ = 125.5 Hz), 130.1 (CH, d, $J_{CP}$ = 5.7 Hz), 128.5 (CH, d, $J_{CP}$ = 6.6 Hz), 128.4 (CH, d, $J_{CP}$ = 3.0 Hz), 126.8 (CH, d, $J_{CP}$ = 3.1 Hz), 65.0 ($CH_2$, d, $J_{CP}$ = 6.7 Hz), 38.3 ($CH_2$, d, $J_{CP}$ = 95.4 Hz), 32.0 ($CH_2$), 30.7 ($CH_2$), 30.6 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 25.7 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$); $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 39.5; HRMS (ESI$^+$) $C_{23}H_{33}NaO_2P^+$ $[M+Na]^+$ calcd. 395.2110, found 395.2105; IR (ATR) $\nu_{max}$ 3063, 3027, 2954, 2918, 2850, 1213, 1003 cm$^{-1}$.

**(±)-menthyl benzylphenylphosphinic acid (83)**



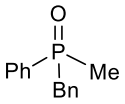
To a stirred solution of **65a** (116 mg, 0.500 mmol) in $CH_2Cl_2$ (2.0 mL) was added oxalyl chloride (47 μL, 0.55 mmol) at r.t. and stirred for 30 min. The reaction mixture was cooled to – 78 °C then L-menthol (86 mg, 0.55 mmol) and triethylamine (0.15 mL, 1.2 mmol) in $CH_2Cl_2$ (1.00 mL) were pre mixed and added dropwise. The mixture was stirred for 17 h then concentrated *in vacuo* and the crude material was purified by silica gel column chromatography (10% - 50 % EtOAc in petrol) and gave the *title compound* as a colourless oil (83 mg, 45%) as a 2:1 mixture of diastereomers.

$R_f$: 0.44 (50% EtOAc in petrol); m.p. 131 – 132 °C; $^1$H NMR (500 MHz, chloroform-*d*) δ 7.68 – 7.59 (m, 3H), 7.52 – 7.45 (m, 1.5H), 7.42 – 7.35 (m, 3H), 7.24 – 7.08 (m, 7.5H), 4.38 - 25 (m, 0.5H, *minor*), 4.08 – 3.98 (m, 1H, *major*), 3.31 (d, $J_{HP}$ = 17.7 Hz, 2H, *major*), 3.23 (dd, $J_{HP}$ = 17.3, $J_{HP}$ = 8.8 Hz, 1H, *minor*), 2.21 – 2.13 (m, 1H), 2.01 – 1.84 (m, 1.5H), 1.75 – 1.67 (m, 1H), 1.66 – 1.53 (m, 3H), 1.39 – 1.20 (m, 3H), 1.14 (q, $J_{HH}$ = 10.8 Hz, 1H), 1.02 – 0.68 (m, 14H), 0.36 (d, $J_{HH}$ = 7.0 Hz, 3H); listed $^{13}$C{$^1$H} NMR (126 MHz, chloroform-*d*) δ 132.0, 132.0, 131.9, 131.9, 131.8, 131.7, 131.7, 131.7, 131.7, 130.3, 130.2, 130.1, 130.1, 128.2, 128.2, 128.2, 128.1, 128.0, 126.6, 126.6, 126.6, 126.5, 48.9, 48.9, 48.8, 48.8, 43.7, 43.1, 39.3, 39.3, 38.4, 38.3, 34.1, 34.1, 31.5, 31.4, 25.4, 25.4, 22.8, 22.6, 21.9, 21.9, 21.2, 21.1, 15.5, 15.2; $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 37.9 (*major*), 37.1 (*minor*); HRMS (ESI$^+$) $C_{23}H_{31}O_2PNa^+$ $[M+Na]^+$ calcd. 393.1954, found 393.1957; IR (ATR) $\nu_{max}$ 3055, 3032, 2937, 2857, 1212, 1015, 986, cm$^{-1}$.

**General Procedure for the formation of 84a - f**

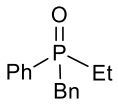
To a stirred solution of **65a** (1.0 eq.) in $CH_2Cl_2$ (0.33 M) was added oxalyl chloride (1.1 eq.) at r.t. and the reaction mixture was held at r.t. for 0.5 h. The solvent was removed *in vacuo* and the **79** was re-dissolved in THF (0.33 M) and the *organometallic reagent* (1.0 eq.) was added dropwise at –78 °C. The reaction mixture was warmed to r.t. and stirred for 18 h. The mixture was quenched with $H_2O$, diluted with brine and extracted with EtOAc (x 3), unless otherwise stated. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude material. The crude material was purified, unless otherwise stated by silica gel column chromatography in the specified solvent system and gave the *titled compound*. All reactions were performed on a 0.50 mmol scale with respect to **65a**.

**benzyl(methyl)phenylphosphine oxide (84a)**[106]



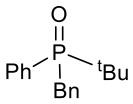

The reaction was performed as stated in the general procedure, with MeMgBr (2.9 M solution in $Et_2O$) and no further purification was required. The *title compound* was isolated as a white solid (113 mg, 98%): m.p.:149 - 150 °C (lit: 146 – 147 °C)[107]; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.68 – 7.57 (m, 2H), 7.57 – 7.49 (m, 1H), 7.49 – 7.39 (m, 2H), 7.30 – 7.18 (m, 3H), 7.14 – 7.06 (m, 2H), 3.41 – 3.22 (m, 2H), 1.67 (d, $J_{HP}$ = 12.7 Hz, 3H); $^{13}$C{$^1$H} NMR (126 MHz, chloroform-*d*) δ 133.2 (d, $J_{CP}$ = 96.5 Hz), 132.0 (d, $J_{CP}$ = 8.0 Hz), 131.9 (d, $J_{CP}$ = 2.7 Hz), 130.5 (d, $J_{CP}$ = 9.1 Hz), 129.9 (d, $J_{CP}$ = 5.4 Hz), 128.8 (d, $J_{CP}$ = 2.7 Hz), 128.6 (d, $J_{CP}$ = 11.2 Hz), 127.1 (d, $J_{CP}$ = 3.6 Hz), 40.6 (d, $J_{CP}$ = 64.5 Hz), 14.8 (d, $J_{CP}$ = 70.8 Hz); $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 35.2; HRMS (ESI$^+$) $C_{14}H_{16}OP^+$ $[M+H]^+$ calcd. 231.0933, found 231.0945; IR (ATR) $\nu_{max}$ 3081, 3059, 3029, 2932, 1177 cm$^{-1}$.

**benzyl(ethyl)phenylphosphine oxide (84b)**




The reaction was performed as stated in the general procedure, with EtMgBr (3.0 M solution in $Et_2O$) and no further purification was required. The *title compound* was isolated as a white solid (119 mg, 98%): m.p.: 116 – 118 °C (lit: 117 – 118 °C)[108]; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.64 – 7.54 (m, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.39 (m, 2H), 7.25 – 7.16 (m, 3H), 7.14 – 7.05 (m, 2H), 3.43 – 3.22 (m, 2H), 2.08 – 1.84 (m, 2H), 1.10 (dt, $J_{HP}$ = 17.0, $J_{HH}$ = 7.7 Hz, 3H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 132.0 (Cq), 131.8 (CH, d, $J_{CP}$ = 2.9 Hz), 131.5 (Cq, d, $J_{CP}$ = 86.2 Hz), 130.9 (CH, d, $J_{CP}$ = 8.7 Hz), 129.9 (CH, d, $J_{CP}$ = 4.9 Hz), 128.6 (CH, d, $J_{CP}$ = 7.2 Hz), 128.6 (CH, d, $J_{CP}$ = 15.8 Hz), 126.9 (CH, d, $J_{CP}$ = 3.0 Hz), 38.7 ($CH_2$, d, $J_{CP}$ = 62.4 Hz), 21.3 ($CH_2$, d, $J_{CP}$ = 70.4 Hz), 5.5 ($CH_3$, d, $J_{CP}$ = 5.1 Hz); $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 39.5; HRMS (ESI$^+$) $C_{15}H_{18}OP^+$ $[M+H]^+$ calcd. 245.1090, found 245.1105; IR (ATR) $\nu_{max}$ 3045, 2964, 2932, 2904, 2876, 1177 cm$^{-1}$.

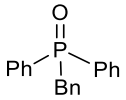
**benzyl(*tert*-butyl)(phenyl)phosphine oxide (84c)**[109]




The reaction was performed as stated in the general procedure, with $^t$BuMgCl (1.8 M solution in $Et_2O$). The compound was purified by silica gel column chromatography (30 - 70% $CH_2Cl_2$ in EtOAc). The *title compound* was isolated as a white solid (75 mg, 55%); $R_f$: 0.15 (70% $CH_2Cl_2$ in EtOAc); m.p.: 185 – 187 °C (lit: 186 - 188)[106]; $^1$H NMR (500 MHz, chloroform-*d*) δ 7.76 – 7.69 (m, 2H), 7.49 – 7.39 (m, 3H), 7.32 – 7.26 (m, 2H), 7.22 – 7.17 (m, 2H), 7.15 – 7.10 (m, 1H), 3.56 – 3.37 (m, 2H), 1.15 (d, $J_{HP}$ = 14.6 Hz, 9H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 132.1

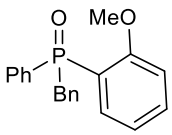
(CH, d, $J_{CP}$ = 7.8 Hz), 131.9 (Cq), 131.4 (CH, d, $J_{CP}$ = 2.9 Hz), 130.2 (CH, d, $J_{CP}$ = 4.8 Hz), 129.8 (Cq, d, $J_{CP}$ = 87.4 Hz), 128.4 (CH, d, $J_{CP}$ = 2.0 Hz), 128.0 (CH, d, $J_{CP}$ = 10.9 Hz), 126.5 (CH, d, $J_{CP}$ = 2.4 Hz), 33.4 (Cq, d, $J_{CP}$ = 67.9 Hz), 31.4 ($CH_2$, d, $J_{CP}$ = 58.9 Hz), 24.8 ($CH_3$); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 46.2; HRMS ($ESI^+$) $C_{17}H_{22}OP^+$ $[M+H]^+$ calcd. 273.1403, found 273.1413.

**benzyl(diphenyl)phosphine oxide (84d)**[110]




The reaction was performed as stated in the general procedure, with PhMgBr (2.7 M solution in $Et_2O$). The compound was purified by silica gel column chromatography (50% $CH_2Cl_2$ in EtOAc). The *title compound* was isolated as a white solid (87 mg, 60%): $R_f$: 0.35 (50% $CH_2Cl_2$ in EtOAc); m.p.: 195 – 197 °C (lit: 192 – 194 °C)[111]; $^1H$ NMR (400 MHz, chloroform-*d*) δ 7.75 – 7.63 (m, 4H), 7.55 – 7.48 (m, 2H), 7.48 – 7.39 (m, 4H), 7.23 – 7.14 (m, 3H), 7.14 – 7.06 (m, 2H), 3.65 (d, $J_{HP}$ = 13.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 132.9 (Cq, s), 131.9 (CH, d, $J_{CP}$ = 2.7 Hz), 131.3 (CH, d, $J_{CP}$ = 9.1 Hz), 131.3 (Cq, d, $J_{CP}$ = 7.9 Hz), 130.3 (CH, d, $J_{CP}$ = 5.1 Hz), 128.6 (CH, d, $J_{CP}$ = 11.7 Hz), 128.5 (CH, d, $J_{CP}$ = 2.3 Hz), 126.9 (CH, d, $J_{CP}$ = 2.9 Hz), 38.3 ($CH_2$, d, $J_{CP}$ = 66.7 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 29.5; HRMS ($ESI^+$) $C_{19}H_{18}OP^+$ $[M+H]^+$ calcd. 293.1090, found 293.1101.

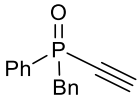
**benzyl(2-methoxyphenyl)(phenyl)phosphine oxide (84e)**




The reaction was performed as stated in the general procedure, with 2-methoxyphenyl magnesium bromide (0.9 M solution in methyl-THF). The compound

was purified by silica gel column chromatography (2% MeOH in EtOAc). The *title compound* was isolated as a white crystalline solid (141 mg, 87%); $R_f$: 0.32 (2% MeOH in EtOAc); m.p.: 157 – 160 °C; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.87 (ddd, $J_{HP}$ = 12.8, $J_{HH}$ = 7.6, $J_{HH}$ = 1.8 Hz, 1H), 7.80 – 7.71 (m, 2H), 7.52 – 7.35 (m, 4H), 7.21 – 7.10 (m, 5H), 7.02 (apparent br t, $J_{HH}$ = 7.6 Hz, 1H), 6.91 (dd, $J_{HH}$ = 8.3, $J_{HP}$ = 5.4 Hz, 1H), 3.85 (s, 3H), 3.93 – 3.70 (m, 2H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 159.6 (Cq, d, $J_{CP}$ = 4.4 Hz), 135.2 (CH, d, $J_{CP}$ = 5.1 Hz), 134.0 (CH, d, $J_{CP}$ = 2.6 Hz), 134.0 (Cq, d, $J_{CP}$ = 100.7 Hz), 132.2 (Cq, d, $J_{CP}$ = 8.5 Hz), 131.4 (CH, d, $J_{CP}$ = 2.8 Hz), 131.0 (CH, d, $J_{CP}$ = 9.5 Hz), 130.1 (CH, d, $J_{CP}$ = 5.2 Hz), 128.4 (CH, d, $J_{CP}$ = 2.9 Hz), 128.2 (CH, d, $J_{CP}$ = 12.1 Hz), 126.7 (CH, d, $J_{CP}$ = 3.5 Hz), 121.3 (CH, d, $J_{CP}$ = 10.9 Hz), 119.9 (Cq, d, $J_{CP}$ = 98.0 Hz), 110.7 (CH, d, $J_{CP}$ = 7.1 Hz), 55.4 ($CH_3$), 37.3 ($CH_2$, d, $J_{CP}$ = 67.8 Hz); $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 29.1; HRMS (ESI$^+$) $C_{20}H_{20}O_2P^+$ $[M+H]^+$ calcd. 323.1195, found 323.1209; IR (ATR) $\nu_{max}$ 3059, 2952, 2895, 1239, 1021.

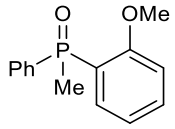
**benzyl(ethynyl)(phenyl)phosphine oxide (84f)**




The reaction was performed as stated in the general procedure, with ethynyl magnesium bromide (0.4 M solution in THF). The compound was purified by silica gel column chromatography (5% petrol in EtOAc). The *title compound* was isolated as a brown solid (37 mg, 31%); $R_f$: 0.35 (5% petrol in EtOAc); m.p.: 94 – 96 °C; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.74 – 7.64 (m, 2H), 7.59 – 7.52 (m, 1H), 7.49 – 7.41 (m, 2H), 7.26 – 7.20 (m, 3H), 7.13 – 7.05 (m, 2H), 3.47 (d, $J_{HP}$ = 16.5 Hz, 2H), 3.18 (d, $J_{HP}$ = 9.5 Hz, 1H); $^{13}$C{$^1$H} NMR (101 MHz, chloroform-*d*) δ 132.7 (CH, d, $J_{CP}$ = 2.9 Hz), 130.9 (CH, d, $J_{CP}$ = 10.2 Hz), 130.3 (Cq, d, $J_{CP}$ = 9.2 Hz), 130.3 (CH, d, $J_{CP}$ = 5.7 Hz), 129.8 (Cq), 128.7 (CH, d, $J_{CP}$ = 8.9 Hz), 128.6 (CH, br s), 127.4

(CH, d, $J_{CP}$ = 3.7 Hz), 93.6 (CH, d, $J_{CP}$ = 24.9 Hz), 78.4 (Cq, d, $J_{CP}$ = 151.8 Hz), 42.01 ($CH_2$, d, $J_{CP}$ = 78.3 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 14.4; HRMS ($ESI^+$) $C_{15}H_{14}OP^+$ $[M+H]^+$ calcd. 241.0777, found 241.0786; IR (ATR) $\nu_{max}$ 3134, 3054, 3028, 2904, 2049, 1202 $cm^{-1}$.

**(2-methoxyphenyl)(methyl)(phenyl)phosphine oxide (PAMPO)**[112]

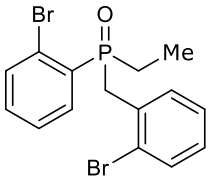



For the synthesis of PAMPO, **65l** was isolated according to general method B, on a 10.0 mmol scale. The *title compound* was azeotroped with $CHCl_3$ and isolated as a light brown gum (1.26 g, 81%).

To a stirred solution of **65l** (186 mg, 1.19 mmol) in $CH_2Cl_2$ (3.0 mL) was added oxalyl chloride (93 μL, 1.1 mmol) at r.t., the reaction was stirred at r.t. for 45 min. The reaction mixture was concentrated *in vacuo* and then re-dissolved in THF (3.0 mL). 2-methoxyphenyl magnesium bromide (1.1 mL of a 0.9 M solution in methyl-THF, 1.0 mmol) was added at –78 °C then the reaction was warmed to r.t. for 16 h. The reaction mixture was quenched with $H_2O$, diluted with brine and extracted with EtOAc (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5% petrol in EtOAc) and the *title compound* was isolated as a white solid (57 mg, 23%): $R_f$: 0.22 (5% MeOH in EtOAc); m.p.: 111 – 115 °C (lit: 131 – 133 °C)[112]; $^1H$ NMR (400 MHz, chloroform-*d*) δ 7.97 (ddd, $J_{HP}$ = 13.1, $J_{HH}$ = 7.5, $J_{HH}$ =1.8 Hz, 1H), 7.77 – 7.69 (m, 2H), 7.54 – 7.37 (m, 4H), 7.09 (apparent br t, $J_{HH}$ = 7.5 Hz, 1H), 6.88 (dd, $J_{HH}$ = 8.3, $J_{HP}$ = 5.3 Hz, 1H), 3.72 (s, 3H), 2.07 (d, $J_{HP}$ = 14.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 160.0 (Cq), 135.1 (Cq, d, $J_{CP}$ = 104.0 Hz), 134.1 (CH, d, $J_{CP}$ = 5.9 Hz), 134.0 (CH, d, $J_{CP}$ = 2.1 Hz), 131.4 (CH, d,

$J_{CP}$ = 2.6 Hz), 130.4 (CH, d, $J_{CP}$ = 10.0 Hz), 128.3 (CH, d, $J_{CP}$ = 11.9 Hz), 121.6 (Cq, d, $J_{CP}$ = 99.9 Hz), 121.2 (CH, d, $J_{CP}$ = 11.5 Hz), 110.0 (CH, d, $J_{CP}$ = 6.7 Hz), 55.4 ($CH_3$), 16.3 ($CH_3$, d, $J_{CP}$ = 75.5 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 29.1; HRMS (ESI$^+$) $C_{14}H_{16}O_2P^+$ $[M+H]^+$ calcd. 247.0882, found 247.0887.

**(2-bromobenzyl)(2-bromophenyl)(ethyl)phosphine oxide (89)**




To pre dried glassware under an inert atmosphere of argon was added (2-bromophenyl)phosphinic acid **77d** (120 mg, 0.543 mmol) and $B(C_6F_5)_3$ (10 mg, 0.019 mmol). The mixture was placed under vacuum and back filled with argon, this was performed three times. At r.t. the solid reagents were dissolved in toluene (2.5 mL) then triethylsilane (0.30 mL, 1.9 mmol) and 2-bromobenzyl bromide (340 mg, 1.36 mmol) were added sequentially. The reaction mixture was heated to 100 °C for 16 h then cooled to r.t. and quenched with NaOH (1.0 M aqueous solution). The biphasic mixture was then stirred at r.t. for 1 h then separated and further extracted with NaOH (1.0 M aqueous solution, × 2). The combined aqueous extracts were acidified to pH 1 with HCl (1.0 M aqueous solution) and cooled to 0 °C, sonication induced precipitation, the solid was filtered and washed with ice cold $H_2O$. The solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16 h and gave (2-bromobenzyl)(2-bromophenyl)phosphinic acid **92** as a white solid (127 mg).

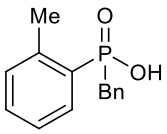
*The material was carried through to the next step with no further purification.*

To a solution of **92** (113 mg, 0.290 mmol) in $CH_2Cl_2$ (0.90 mL) at r.t. was added $(COCl)_2$ (27 μL, 0.32 mmol) dropwise. The reaction was stirred at r.t. for 0.5 h until the gas evolution stopped. The reaction was then concentrated *in vacuo* and re-dissolved in THF (0.90 mL) and cooled to –78 °C. EtMgBr (97 μL of a 3.0 M solution

in $Et_2O$, 0.29 mmol) was added dropwise, the reaction was warmed to r.t. and stirred for 16 h. The reaction mixture was quenched with $H_2O$, diluted with brine and extracted with EtOAc (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude residue. The crude material was purified by silica gel column chromatography (100% EtOAc) and the *title compound* was isolated as a white crystalline solid (55 mg, 25% over the two steps).

$R_f$: 0.34 (100% EtOAc); m.p.: 98 – 100 °C; $^1$H NMR (400 MHz, chloroform-*d*) δ 8.17 (ddd, $J_{HP}$ = 11.4, $J_{HH}$ = 7.6, $J_{HH}$ = 1.8 Hz, 1H), 7.66 (ddd, $J_{HH}$ = 8.0, $J_{HP}$ = 4.0, $J_{HH}$ = 1.2 Hz, 1H), 7.55 (br d, $J_{HH}$ = 8.0 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.44 – 7.36 (m, 1H), 7.25 – 7.20 (m, 1H), 7.14 – 7.06 (m, 1H), 4.16 (dd, $J_{HH}$ = 14.7, $J_{HP}$ = 10.5 Hz, 1H), 3.53 (dd, $J_{HP}$ = 17.2, $J_{HH}$ = 14.7 Hz, 1H), 2.60 – 2.45 (m, 1H), 2.14 – 1.99 (m, 1H), 1.00 (dt, $J_{HP}$ = 18.3, $J_{HH}$ = 7.6 Hz, 3H); $^{13}$C NMR (126 MHz, chloroform-*d*) δ 137.3 (CH, d, $J_{CP}$ = 5.5 Hz), 134.1 (CH, d, $J_{CP}$ = 8.0 Hz), 133.7 (CH, d, $J_{CP}$ = 2.6 Hz), 133.1 (CH, d, $J_{CP}$ = 2.2 Hz), 132.6 (CH, d, $J_{CP}$ = 4.4 Hz), 132.3 (Cq, d, $J_{CP}$ = 89.6 Hz), 132.0 (Cq, d, $J_{CP}$ = 8.0 Hz), 128.7 (CH, d, $J_{CP}$ = 3.3 Hz), 127.7 (CH, d, $J_{CP}$ = 6.7 Hz), 127.7 (CH), 125.0 (Cq, d, $J_{CP}$ = 7.0 Hz), 123.6 (Cq, d, $J_{CP}$ = 7.2 Hz), 36.5 ($CH_2$, d, $J_{CP}$ = 63.5 Hz), 21.4 ($CH_2$, d, $J_{CP}$ = 70.8 Hz), 5.5 ($CH_3$, d, $J_{CP}$ = 6.2 Hz); $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 41.0; HRMS (ESI$^+$) $C_{15}H_{16}{}^{79}Br_2OP^+$ $[M+H]^+$ calcd. 400.9300, found 400.9299; IR (ATR) $\nu_{max}$ 3060, 2931, 2879, 1185, 1044.

**benzyl(*o*-tolyl)phosphinic acid (93)**




To a pre dried flask was added anilinium hypophosphite (398 mg, 2.50 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (129 mg, 0.125 mmol) and XantPhos (72 mg, 0.125 mmol). Three cycles of vacuum and argon were performed then THF (10.0 mL), $NEt_3$ (0.87 mL, 6.25 mmol) and 2-iodotoluene (0.32 mL, 2.50 mmol) were added sequentially. The

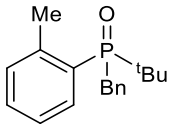
reaction was sparged with argon for 20 min and then irradiated in the microwave at 120 °C for 10 min with 20 s pre-stirring. The reaction mixture was partitioned between NaOH (1.0 M aqueous solution) and $Et_2O$. The biphasic mixture was then separated and further extracted with NaOH (1.0 M aqueous solution, x 2). The combined aqueous extracts were acidified to pH 1 with HCl (conc.) and extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 1), dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to give **92** a brown gum (173 mg). *The material was taken through to the next step crude with no further purification*.

To a stirred solution of **92** (173 mg, 1.11 mmol), $B(C_6F_5)_3$ (20 mg, 0.039 mmol), $HSiEt_3$ (0.62 mL, 3.89 mmol) and BnBr (0.33 mL, 2.78 mmol) in toluene (5.6 mL) was heated to 100 °C for 16 h. The reaction mixture was cooled to r.t. then NaOH (1.0 M aqueous solution) was added and stirred for 1 h. The biphasic mixture was separated and further extracted with NaOH (1.0 M aqueous solution, x 2). The combined aqueous extracts were acidified to pH 1 with HCl (3.0 M aqueous solution) then extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a beige solid. The crude material was purified by trituration with $Et_2O$ (x 2) and pentane (x 3) and gave the *title compound* as a white solid (105 mg, 17% over the two steps).

m.p.: 103 – 105 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.61 (ddd, $J_{HP}$ = 12.3, $J_{HP}$ = 7.6, $J_{HP}$ = 1.5 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.27 – 7.11 (m, 5H), 7.08 – 7.03 (m, 2H), 3.21 (d, $J_{HP}$ = 17.0 Hz, 2H), 2.47 (d, $J_{HP}$ = 1.3 Hz, 3H); $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 140.9 (Cq, d, $J_{CP}$ = 10.7 Hz), 133.0 (Cq, d, $J_{CP}$ = 7.5 Hz), 132.8 (CH, d, $J_{CP}$ = 8.8 Hz), 131.8 (Cq, d, $J_{CP}$ = 122.9 Hz), 131.5 (CH, d, $J_{CP}$ = 2.9 Hz), 131.0 (CH, d, $J_{CP}$ = 12.2 Hz), 129.8 (CH, d, $J_{CP}$ = 5.4 Hz), 127.9 (CH, d, $J_{CP}$ = 2.9 Hz), 126.0 (CH, d, $J_{CP}$ = 3.4 Hz), 125.2 (CH, d, $J_{CP}$ = 11.6 Hz), 38.0 ($CH_2$, d, $J_{CP}$ = 91.0 Hz), 20.9 ($CH_3$, d, $J_{CP}$ = 2.9 Hz); $^{31}$P{$^1$H} NMR (162 MHz, DMSO-$d_6$) δ 33.5; HRMS (ESI$^+$)

$C_{14}H_{14}O_2P^+$ $[M+H]^+$ calcd. 245.0737, found 245.0749; IR (ATR) $\nu_{max}$ 3060, 3033, 2921, 2589, 2251, 2103, 1641, 1453, 1121.

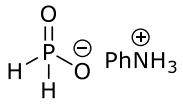
**benzyl(*tert*-butyl)(*o*-tolyl)phosphine oxide (90)**




To a stirred solution of phosphinic acid **93** (40 mg, 0.16 mmol) in $CH_2Cl_2$ (0.50 mL) at r.t. was added $(COCl)_2$ (15 μL, 0.18 mmol) dropwise. The reaction mixture was stirred at r.t. for 0.5 h, until the gas stopped evolving, then was concentrated *in vacuo* and re-dissolved in THF (0.50 mL). The reaction mixture was cooled to – 78 °C and $^t$BuMgCl (91 μL of a 1.8 M solution in $Et_2O$, 0.16 mmol) was added. The reaction mixture was warmed to r.t., stirred for 16 h and quenched with $H_2O$. The mixture was diluted with brine and extracted with EtOAc (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* and gave a crude residue. The crude material was purified by silica gel column chromatography (10 – 30% EtOAc in $CH_2Cl_2$) and the *title compound* was isolated as a white crystalline solid (10 mg, 22%).

$R_f$: 0.20 (30% EtOAc in $CH_2Cl_2$); m.p.: 146 – 148 °C; $^1$H NMR (400 MHz, chloroform-*d*) δ 7.49 – 7.29 (m, 3H), 7.23 – 7.11 (m, 6H), 3.60 – 3.44 (m, 2H), 2.69 (s, 3H), 1.16 (d, $J_{HP}$ = 14.4 Hz, 9H); $^{13}$C{$^1$H} NMR (126 MHz, chloroform-*d*) δ 145.5 (Cq), 132.8 (CH, d, $J_{CP}$ = 10.1 Hz), 132.7 (Cq), 132.5 (CH, d, $J_{CP}$ = 11.1 Hz), 131.3 (CH, d, $J_{CP}$ = 2.7 Hz), 130.5 (CH, d, $J_{CP}$ = 5.4 Hz), 128.4 (CH, d, $J_{CP}$ = 1.9 Hz), 127.1 (Cq, d, $J_{CP}$ = 85.9 Hz), 126.6 (CH, d, $J_{CP}$ = 2.6 Hz), 124.5 (CH, d, $J_{CP}$ = 11.6 Hz), 35.1 (Cq, d, $J_{CP}$ = 66.3 Hz), 32.7 ($CH_2$, d, $J_{CP}$ = 59.8 Hz), 25.1 ($CH_3$), 22.1 ($CH_3$); $^{31}$P{$^1$H} NMR (162 MHz, chloroform-*d*) δ 51.4; HRMS (ESI$^+$) $C_{18}H_{124}OP^+$ $[M+Na]^+$ calcd. 287.1559, found 287.1564; IR (ATR) $\nu_{max}$ 3063, 2947, 2867, 1169.

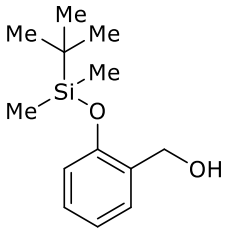
**anilinium hypophosphite**



To a stirred solution of hypophosphorus acid (10.8 mL of a 50 wt% solution in $H_2O$, 100 mmol) at 0 °C was added aniline (9.11 mL, 100 mmol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 1 h. Acetone was added until precipitation began then the mixture was cooled to 0 °C until crystals formed. The crystals were filtered and washed with ice cold acetone and the *title compound* was isolated as off-white crystals (7.39 g, 47%).

m.p.: 116 – 118 °C (lit: 113 – 114 °C)[113]; $^{1}$H NMR (400 MHz, deuterium oxide) δ 7.58 – 7.47 (m, 1H), 7.43 – 7.37 (m, 1H), 7.01 (d, $J_{HP}$ = 518.7 Hz, 1H); $^{13}$C{$^{1}$H} NMR (101 MHz, deuterium oxide) δ 130.0 (CH), 129.9 (Cq), 129.0 (CH), 122.8 (CH); $^{31}$P NMR (162 MHz, deuterium oxide) δ 7.02 (t, $J_{PH}$ = 518.7 Hz).

**(2-((tert-butyldimethylsilyl)oxy)phenyl)methanol**[114]

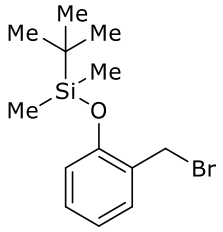


To a stirred solution of TBSCl (1.36 g, 9.00 mmol) in $CH_2Cl_2$ (6.0 mL) was added salicylaldehyde (0.50 mL, 6.0 mmol) and triethylamine (1.25 mL, 9.00 mmol) sequentially. The reaction mixture was stirred at r.t. for 16 h then $H_2O$ was added. The biphasic mixture was stirred for 30 min then was separated. The organic phase was washed with $H_2O$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 2-((*tert*-butyldimetylsilyl)methyl)benzaldehyde as a pale yellow oil (1.06 g). *Taken into the next step crude with no further purification.*

To a stirred solution of 2-((*tert*-butyldimetylsilyl)methyl)benzaldehyde (1.06 g, 4.48 mmol) in THF (30 mL) at cooled to –78 °C was added $NaBH_4$ (339 mg, 8.97 mmol). The reaction was warmed to r.t. and stirred for 2 h, then quenched with sat. $NaHCO_3$ and stirred for a further 30 min. The biphasic mixture was separated and extracted with ether (x 3). The organic extracts were washed with sat. $NH_4Cl$ (x 1) and brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography (10% $Et_2O$ in petrol) to give the *title compound* as a colourless oil (625 mg, 44% over two steps).

$R_f$: 0.10 (10% $Et_2O$ in petrol); $^1H$ NMR (300 MHz, chloroform-*d*) $\delta$ 7.33 (dd, $J_{HH}$ = 8.0, $J_{HH}$ = 1.9 Hz, 1H), 7.18 (ddd, $J_{HH}$ = 8.0, $J_{HH}$ = 8.0, $J_{HH}$ = 1.9 Hz, 1H), 6.96 (ddd, $J_{HH}$ = 8.0, $J_{HH}$ = 8.0, $J_{HH}$ = 1.9 Hz, 1H), 6.83 (dd, $J_{HH}$ = 8.0, $J_{HH}$ = 1.9 Hz, 1H), 4.68 (s, 2H), 2.33 (b s, 1H), 1.04 (s, 9H), 0.28 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, chloroform-*d*) $\delta$ 153.4 (Cq), 131.6 (Cq), 128.8 (CH), 128.6 (CH), 121.4 (CH), 118.4 (CH), 61.8 ($CH_2$), 25.8 ($CH_3$), 18.2 (Cq), -4.2 ($CH_3$).

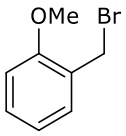
**(2-(bromomethyl)phenoxy)(tert-butyl)dimethylsilane**[115]




To a stirred solution of (2-((*tert*-butyldimetylsilyl)methyl)phenyl)methanol (615 mg, 2.58 mmol) in ether (7.5 mL) at 0 °C. The reaction was warmed to r.t. and stirred for 1.5 h. The reaction was quenched with sat. $NaHCO_3$ and washed with sat. $NaHCO_3$ (x 3). The organic washes were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was passed through a silica plug (5% $Et_2O$ in petrol) and the *title compound* was isolated as a colourless oil (584 mg, 75%).

$R_f$: 0.58 (5% $Et_2O$ in petrol); $^1H$ NMR (300 MHz, Chloroform-*d*) δ 7.35 (dd, $J_{HH}$ = 7.6, $J_{HH}$ = 1.8 Hz, 1H), 7.18 (ddd, $J_{HH}$ = 8.2, $J_{HH}$ = 7.4, $J_{HH}$ = 1.8 Hz, 1H), 6.92 (apparent td, $J_{HH}$ = 7.5, $J_{HH}$ = 0.9 Hz, 1H), 6.81 (dd, $J_{HH}$ = 8.2, $J_{HH}$ = 0.9 Hz, 2H), 4.54 (s, 2H), 1.06 (s, 9H), 0.29 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-*d*) δ 153.9 (Cq), 131.2 (Cq), 129.9 (CH), 128.4 (CH), 121.3 (CH), 118.6 (CH), 29.3 ($CH_2$), 25.8 ($CH_3$), 18.3 (Cq), -4.1 ($CH_3$).

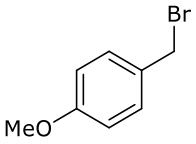
**1-(bromomethyl)-2-methoxybenzene**[116]




Phosphorous tribromide (0.12 mL, 1.3 mmol) was added dropwise to a stirred solution of 4-methoxylbenzyl alcohol (0.33 mL, 2.5 mmol) in diethyl ether (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with sat. $NaHCO_3$ (x 2) and stirred for 1 h. The mixture was the separated and washed with $NaHCO_3$ (x 2). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (5% $Et_2O$ in petrol) and the *title compound* was isolated as a white solid (383 mg, 76%).

$R_f$: 0.39 (5% $Et_2O$ in petrol); $^1H$ NMR (400 MHz, chloroform-*d*) δ 7.36 – 7.27 (m, 2H), 6.93 - 6.89 (m, 2H), 4.58 (s, 2H), 3.90 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, chloroform-*d*) δ 157.6 (Cq), 131.0 (CH), 130.3 (CH), 126.2 (Cq), 120.8 (CH), 111.1 (CH), 55.7 ($CH_3$), 29.2 ($CH_2$).

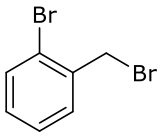
**1-(bromomethyl)-2-methoxybenzene**[117]




Phosphorous tribromide (0.12 mL, 1.3 mmol) was added dropwise to a stirred solution of 4-methoxylbenzyl alcohol (0.31 mL, 2.5 mmol) in diethyl ether (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. The reaction with quenched with sat. $NaHCO_3$, and carefully washed with sat. $NaHCO_3$ (x 3). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (2 % EtOAc in petrol) and the *title compound* was isolated as a orange oil (363 mg, 61 %).

$^1$H NMR (400 MHZ, chloroform-*d*) δ 7.37 (d, *J* = 8.6 Hz, 2H), 6.91 (d, $J_{HH}$ = 8.6 Hz, 2H), 4.55 (s, 2H), 3.85 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, chloroform-*d*) δ 159.7 (Cq), 130.5 (CH), 130.0 (Cq), 55.4 ($CH_3$), 34.0 ($CH_2$). *Additional aromatic peaks observed.*

**1-bromo-2-(bromomethyl)benzene**[118]




Phosphorous tribromide (0.12 mL, 1.3 mmol) was added dropwise to a stirred solution of 2-bromobenzyl alcohol (467 mg, 2.50 mmol) in diethyl ether (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with $H_2O$ and carefully washed with sat. $NaHCO_3$ (x 3). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was passed

through a silica plug (10% $Et_2O$ in petrol), and the *title compound* was isolated as a pale yellow oil (350 mg, 57%).

$R_f$: 0.52 (10 $Et_2O$ in petrol); $^1H$ NMR (400 MHz, chloroform-*d*) δ 7.58 (dd, $J_{HH}$ = 8.0, $J_{HH}$ =1.3 Hz, 1H), 7.46 (dd, $J_{HH}$ = 7.5, $J_{HH}$ = 1.7 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.21 – 7.14 (m, 1H), 4.61 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 137.2 (Cq), 133.5 (CH), 131.4 (CH), 130.3 (CH), 128.1 (CH), 124.6 (Cq), 33.5 ($CH_2$).

# References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