HYPOPHOSPHOROUS ACID AS A PRECURSOR TO VARIOUS ORGANOPHOSPHORUS COMPOUNDS

A Thesis

Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in Chemistry

of

Manchester Metropolitan University

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March 2016

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Abstract

Hypophosphorous Acid as a Precursor to Various Organophosphorus Compounds

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The work presented in this thesis is based on the common theme, of the use of hypophosphorous acid as a starting material for the synthesis of functionalised organophosphorus compounds. Hypophosphorous acid and its salts have gained attention as potentially greener precursors, than PCl_3, to a range of organophosphorus compounds.

An investigation into an alternative synthesis of perfluoroalkylphosphorus(V) compounds is presented. The reaction of hypophosphorous acid derived bis(trimethylsilyl)phosphonite [$(Me_3SiO)_2PH$] (BTSP) and bis(trimethylsilyl)-phenylphosphonite [$(Me_3SiO)_2PPh$] (BTSPP) with perfluoroalkyl iodides (R_fI) is investigated. A range of reactions are discussed, including the synthesis of perfluoroalkyl H-phosphinic acids, $R_fPO(OH)H$, perfluoroalkyl phosphonic acids, $R_fPO(OH)_2$ and perfluoroalkyl(phenyl)phosphinic acids, $(R_f)PhPO(OH)H$.

The synthesis and catalytic testing of a new Brønsted acid catalyst is presented. 2,2'-Bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid was targeted, as a stronger (more acidic) Brønsted acid catalyst compared to 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BINOL-phosphoric acid). 2,2'-Bis(difluoromethylene)-1,1'-

binaphthyl phosphinic acid was synthesised in a seven-step procedure from BINOL, including a ring closure reaction in which BTSP is used. The full synthesis of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid is presented with full characterisation data for four novel compounds. The X-ray crystal structures of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid and ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate were determined. Preliminary catalytic testing of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid, on a Nazarov cyclisation, and comparisons to known Brønsted acid catalysts are presented.

An alternative route to Aryl-dichlorophosphines ($ArPCl_2$) is discussed. These were synthesised from stable and easily accessible aryl H-phosphinic acids ($ArPO_2H_2$). A series of aryl-dichlorophosphines are presented, on a multi-gram scale, with two novel aryl-dichlorophosphines synthesised.

Keywords: Jay Anthony Dixon, bis(trimethylsilyl)phosphinate, perfluoroalkyl, H-phosphinic, phosphonic, phenyl H-phosphinic, acids, Brønsted, catalyst, BINOL, difluoromethylene, binaphthyl, aryl, dichlorophosphines, main group halides.

Acknowledgements

I would like to thank my supervisor, Dr. Andrew. J. M. Caffyn, for all the help, guidance, reassurance and patience he has provided me throughout my graduate studies. I would like to thank my colleagues, Sasha Smith, Dr. Nyevero Simbanegavi, Ricard Solà Mestres, James Ryan, Dr. Kinaan Tawfiq and everyone else in the 7th floor labs. Special thanks go to Dr. Vittorio Caprio, Dr. Paul Birkett and Dr. Beatriz Macia-Ruiz for all their support and guidance. I would also like to thank the technicians from both the 6th and 7th floor labs, for all their help (Special thanks to Mrs. Helen Bentley, Mr. Lee Harman, Mr. Paul Warren, Mr. Bill Ellison and Dr. David Smith). I would like to thank the Dalton Research Institute for the funding to attend 20th International Conference on Phosphorus Chemistry Conference in Dublin, July 2014. I would also like to thank the EPSRC UK National Crystallography Service at the University of Southampton for the collection of the crystallographic data. Thanks also to the EPSRC UK National Mass Spectrometry Facility at Swansea University for accurate mass analysis on functionalised aryldichlorophosphines. Special thanks go to my family and friends for their support during my graduate studies. Finally, I would like to thank my partner, Amanda, for her constant support, understanding and encouragement throughout the years.

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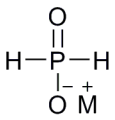
Chapter 1

General Introduction

1.1. Hypophosphorous acid in organophosphorus chemistry

The formation of the P-C bond is one of the main manipulations in synthetic organophosphorus chemistry. The work presented in this thesis is based on the formation of the P-C bond, starting from hypophosphorous acid and its salts.

Both in the chemical industry and the chemical laboratory environments, the starting material for the synthesis of organophosphorus compounds is generally PCl_3. The use of hypophosphorous acid (H_3PO_2) and salts, derived from H_3PO_2, as an alternative to PCl_3, is attractive as "greener" precursor in the synthesis of organophosphorus compounds. The reactions of H_3PO_2 and salts (Figure 1.1) as synthetic precursors have been discussed, in detail, particularly as an alternative to PCl_3.[1, 2] Salts of hypophosphorous acids are stable, readily available and non-hygroscopic, and as such are desirable starting materials for a range of procedures.[3]



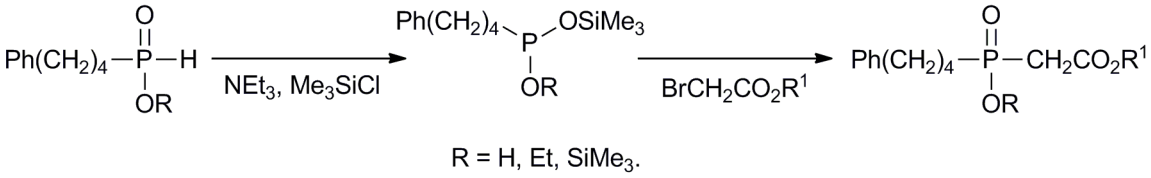
M = Na^+, NH_4^+, $HNEt_3^+$, NH_3Ph^+.

Figure 1.1: Salts of hypophosphorous acid.

The salts of hypophosphorous acids were used extensively in this work. These salts are easy to handle, commercially available and are stable over prolonged periods of time. The two main manipulations of hypophosphite salts used in this work are summarised below.

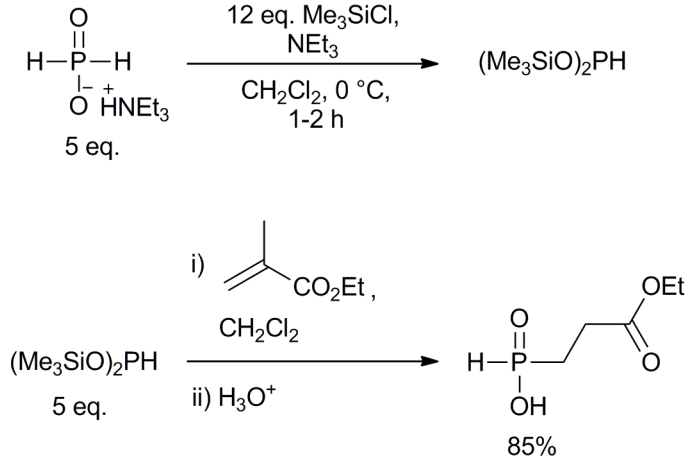
1.2. Generation and reactions of phosphorus(III) silyl ethers

One of the first examples of the synthesis and reactions of phosphorus(III) silyl ethers was published by Thottathil *et al.*[4, 5] Phosphorus(V) acids and silyl ether derivatives were converted to the reactive phosphorus(III) silyl ethers by reaction with triethylamine (NEt_3) and trimethylsilyl chloride (TMSCl) (Scheme 1.1).



Scheme 1.1: The *in situ* formation or phosphorus(III) silyl ethers and reaction with ethyl bromoacetate.

It was noted that the $(Me_3SiO)_2PH$ (BTSP) reacted quicker with ethyl bromoacetate than $Ph(CH_2)_4PH(OSiMe_3)$. A modified reaction was published by Regan and co-workers (Scheme 1.2).[6] BTSP was generated *in situ* and reacted with acrylates to give functionalised H-phosphinic acids.



Scheme 1.2: The reaction of BTSP with ethyl acrylate to give mono-substituted H-phosphinic acids.

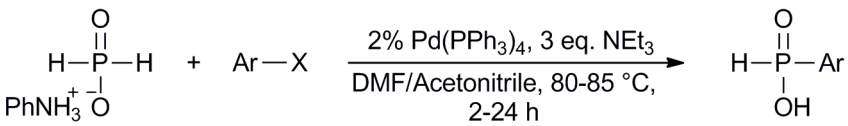
Symmetrical di-substituted phosphinic acids were also prepared by increasing the amount of acrylate added. Non-symmetrical di-substituted phosphinic acids were prepared in a two-step procedure, by isolation and further reaction of a mono-substituted H-phosphinic acid. This reaction, and further reactions of BTSP, allow for the synthesis of a range of H-phosphinic acids from readily available hypophosphite salts under facile conditions (see Introduction, Chapter Two for further reactions of BTSP).

In this work ammonium hypophosphite derived BTSP was used, as a reactive intermediate, in the synthesis of a range of perfluoroalkyl phosphorus (V) compounds (Chapter Two).

BTSP was also used in a ring closure step,[7] in synthesis of 2,2'-bis(difluoro-methylene)-1,1'-binaphthyl phosphinic acid, a new Brønsted acid catalyst (Chapter Three).

1.3. Cross-coupling reactions of hypophosphorous acid and its salts

The first example of a metal catalysed cross-coupling reaction involving a hypophosphite with aryl halides was published by Montchamp and Dumond.[3] The reaction was catalysed by 2 mol % of tetrakis(triphenylphosphine)palladium(0) in the presence of a base. A range of aryl- and benzylic- H-phosphinic acids were synthesised in good yields (55-99%) (Scheme 1.3).



Scheme 1.3: The palladium catalysed synthesis of aryl- and benzylic- H-phosphinic acids.

The cross-coupling reactions of hypophosphite allow for the synthesis of a range of aryl H-phosphinic acids. Since this early method, a substantial amount of research has been performed, to generate more efficient reactions (See introduction Chapter Four).

In this work similar reactions to those described above were used in the synthesis of aryl-H-phosphinic acids, precursors to aryldichlorophosphines (Chapter Four).

Chapter 2

The reactions of phosphorus (III) silylethers with perfluoroalkyl iodides, the synthesis of perfluoroalkyl phosphorus (V) compounds

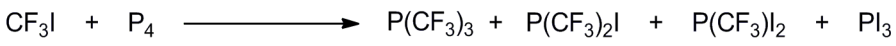
2.1 Introduction

Perfluoroalkylphosphonic, phosphinic and phosphonous acids have been shown to be useful as anti-foaming agents,[8] components in optical gain media,[9] anhydrous proton-exchange membranes,[10] for their water repellent properties and as room temperature ionic liquids.[11] Despite the growing interest, these compounds have historically proven difficult to synthesise.

2.1.1 Previous syntheses of perfluoroalkylphosphorus(V) acids

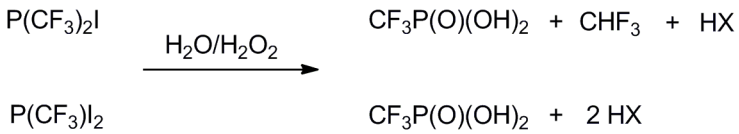
2.1.1.1. The "Emeléus method"

One of the main routes to perfluoroalkylated phosphorus compounds is the reaction of elemental phosphorus with perfluoroalkyl iodides under forcing conditions. This seminal work by Emeléus[12] and co-workers paved the way for research on these compounds (Scheme 2.1).



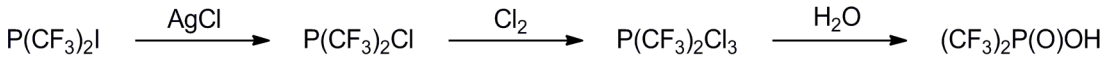
Scheme 2.1: The reaction of trifluoromethyl iodide with elemental phosphorus.

Excess phosphorus was reacted with CF_3I, in an autoclave, to give a mixture of trifluoromethyl halophosphines and phosphorus tri-iodide. The ratio of phosphines was dependant on temperature. At 195 °C, $P(CF_3)_2I$ and $P(CF_3)I_2$ were the main products. Once separated $P(CF_3)_2I$ and $P(CF_3)I_2$ were converted to $CF_3P(O)(OH)_2$ by oxidative hydroylsis[13] (Scheme 2.2).



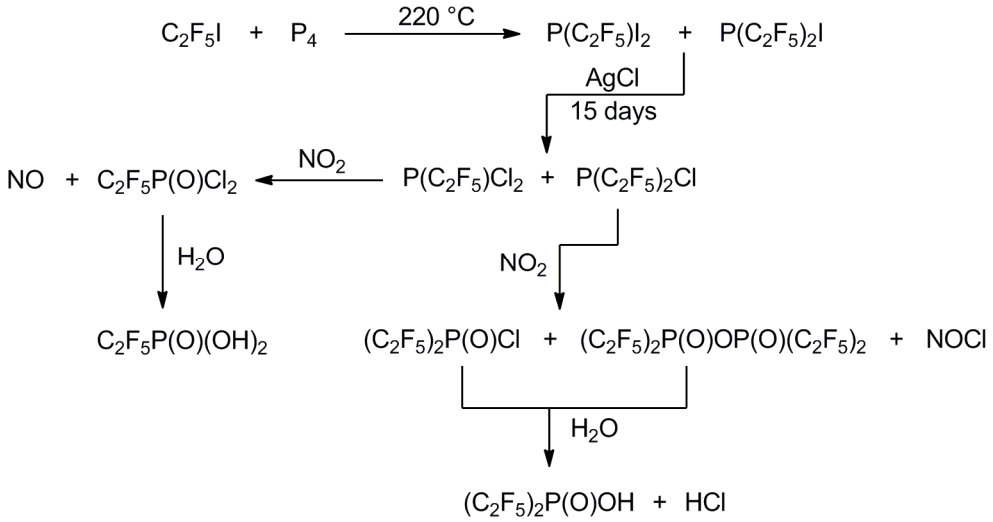
Scheme 2.2: The hydrolysis of trifluoromethyl halophosphines to trifluoromethyl phosphonic acid.

Furthering their research, Emeléus[14] *et al.* synthesised bis(trifluoromethyl)-phosphinic acid from the hydrolysis of bis(trifluoromethyl)phosphorus trihalides (Scheme 2.3)

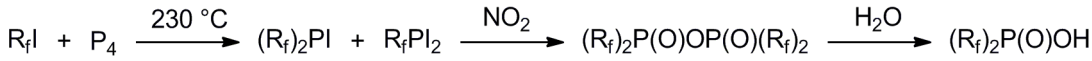


Scheme 2.3: The formation of bis(trifluoromethyl)phosphinic acid.

Higher analogues of acids were synthesised by a similar method. Shreeve *et al.*, extended Emeléus's seminal work, firstly to C_2F_5 (Scheme 2.4) and C_4F_9 derivatives[15] then to C_6F_{13}-, C_7F_{15}- and C_8F_{17}- derivatives[16] (Scheme 2.5).



Scheme 2.4: The formation of tetrafluoroethyl phosphonic and phosphinic acids



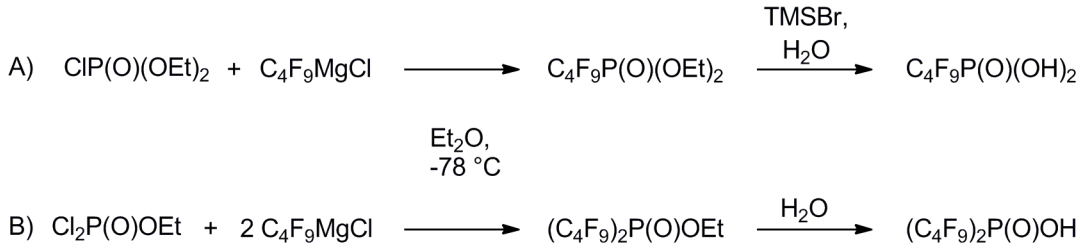
Scheme 2.5: The synthesis of bis(perfluoroalkyl)phosphinic acids.

The seminal Emeléus method opened up the field of research into perfluoroalkylphosphorus compounds. Despite this, the method has several drawbacks. Due to the toxicity and pyrophoricity, the use of white phosphorus is

undesirable. Separation of R_fPI_2 and $(R_f)_2PI$ proved difficult requiring trap-to-trap distillation. The overall yields of perfluoroalkylphosphonic acids, by the Emeléus method, are ≤ 30% (based on perfluoroalkyl iodides).

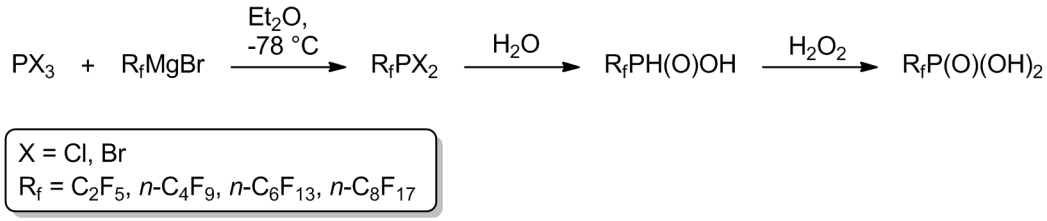
2.1.1.2. Perfluoroalkyl Grignard methods

Perfluoroalkyl phosphorus compounds are accessible by reaction of chlorophosphates and perfluoroalkyl Grignard reagents.[17] From the perfluoroalkyl phosphonates, the relative phosphonic acids can by synthesised. DesMarteau[18] and co-workers synthesised perfluorobutylphosphonic acid (Scheme 2.6 A) and bis(perfluorobutyl)phosphinic acid (Scheme 2.6 B) in yields of 72% and 60% respectively. C_4F_9MgCl was generated *in situ*, from *i*-PrMgCl and C_4F_9I, and reacted with chlorophosphates.



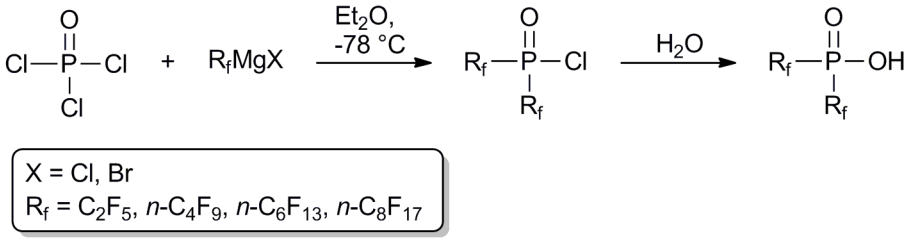
Scheme 2.6: The reaction of chloro and bis(chloro)phosphates with perfluorobutyl Grignard reagent.

Hosein and co-workers synthesised perfluoroalkyl phosphonous acids, starting from the reaction of phosphorus trihalides with perfluoroalkyl Grignard reagents (Scheme 2.7).[19] Equimolar amounts of R_fMgX and PX_3 gave (perfluoroalkyl)-phosphonous dihalides. Hydrolysis of (perfluoroalkyl)-phosphonous dihalides gave perfluoroalkyl H-phosphinic acids and subsequent oxidation gave perfluoroalkylphosphonic acids in yields of 60-78%.



Scheme 2.7: The synthesis of perfluoroalkyl H-phosphinic and phosphonic acids from the reaction of phosphorus (III) halides and perfluoroalkyl Grignard reagents.

Hosein[20] *et al.* expanded this methodology to the formation of bis(perfluoroalkyl)-phosphinic acids (Scheme 2.8).[20] Phosphoryl chloride was reacted with two equivalents of perfluoroalkylmagnesium halide. Hydrolysis of the resulting bis(perfluoroalkyl)phosphonyl halides produced bis(perfluoroalkyl)phosphinic acids in yields of 60-80%.

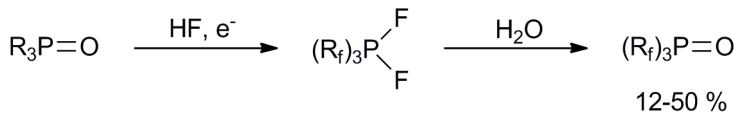


Scheme 2.8: The synthesis of bis(perfluoroalkyl)phosphinic acids by reaction of phosphoryl chloride and perfluoroalkyl Grignard reagents.

The halogen exchange reactions between perfluoroalkyl Grignards and a range of tri and penta-valent phosphorus halides, is a convenient procedure with moderate yields. A disadvantage to these Grignard procedures is the lack of applicability to CF_3 derivatives. This is due to the thermal instability of CF_3MgX, which readily decomposes below -78 °C.

2.1.1.3. Synthesis of perfluoroalkyl phosphorus(V) acids via phosphoranes and phosphines

The formation of tris(perfluoroalkyl)difluorophosphoranes is an alternative route to formation of perfluoroalkylphosphorus(V) acids. Electrochemical fluorination, with nickel electrodes (Simon's process), of $R_3P{=}O$ yields $(R_f)_3PF_2$ (Scheme 2.9).[21]



R_f = C_2F_5, *n*-C_3F_7, *n*-C_4F_9, *i*-C_5F_{11}, *n*-C_5F_{11}, *n*-C_6F_{13}, *n*-C_7F_{15}, *n*-C_8F_{17}

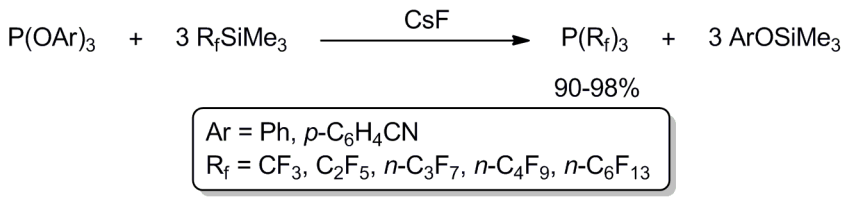
Scheme 2.9: The electrochemical fluorination of trialkylphosphine oxides.

Tris(perfluoroalkyl)difluorophosphanes are hydrolysed to tris(perfluoroalkyl)-phosphine oxide. Further hydrolysis gives bis(perfluoroalkyl)phosphinic acids.[22] Tris(perfluoroalkyl)difluorophosphoranes can be hydrolysed to both bis(perfluoroalkyl)phosphinic acids[23] and perfluoroalkylphosphonic acids.[24]

The Simon's process has also been applied to trialkylphosphines to produce tris(perfluoroalkyl)difluorophosphoranes.[25] The formation of bis(perfluoroalkyl)-phosphinic acids by the Simon's electrochemical fluorination method is not "atom efficient" with respect to the perfluoroalkyl group. Also the use of highly toxic anhydrous HF is undesirable. It should also be noted that the formation of OF_2 in the electrochemical fluorination of trialkylphosphine oxides, can "cause severe explosions".[25]

Perfluoroalkylphosphonic acids can also be formed by controlled alkaline hydrolysis of tris(perfluoroalkyl)phosphines.[26] Murphy-Jolly and co-workers synthesised a range of $P(R_f)_3$ compounds, by reaction of perfluoroalkyltrimethyl-silanes with triphenylphosphite catalysed be CsF (Scheme 2.10). [27] For longer

chain perfluoroalkyl groups (ie C_3F_7, C_4F_9, C_6F_{13}) more reactive $P(O\text{-}p\text{-}C_6H_4CN)_3$ was required.



Scheme 2.10: The reaction of triarylphosphites with perfluoroalkyltrimethylsilanes.

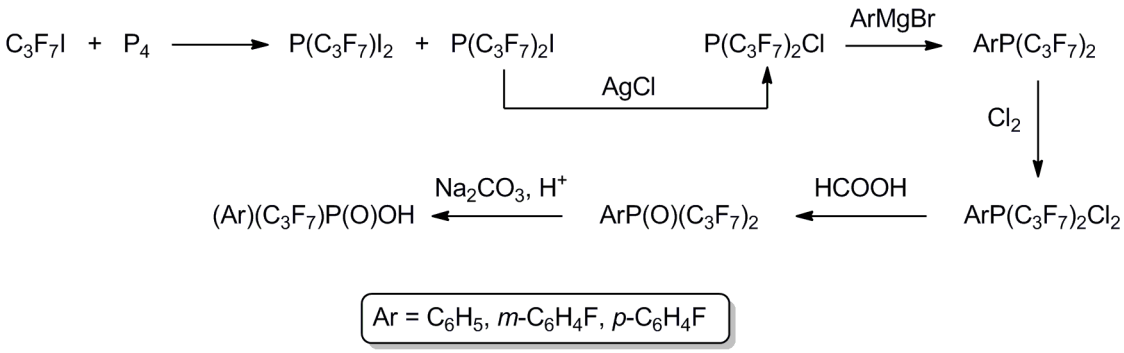
Although this procedure is high yielding, rigorously anhydrous conditions are required due to the very hygroscopic nature of CsF. The use of $P(CF_3)_3$ is undesirable as it's a spontaneously flammable gas.

For further reactions on the synthesis of perfluoroalkyl phosphorus(III) compounds please see the following review.[28]

2.1.2. Previous synthesis of perfluoroalkyl(aryl)phosphinic acids

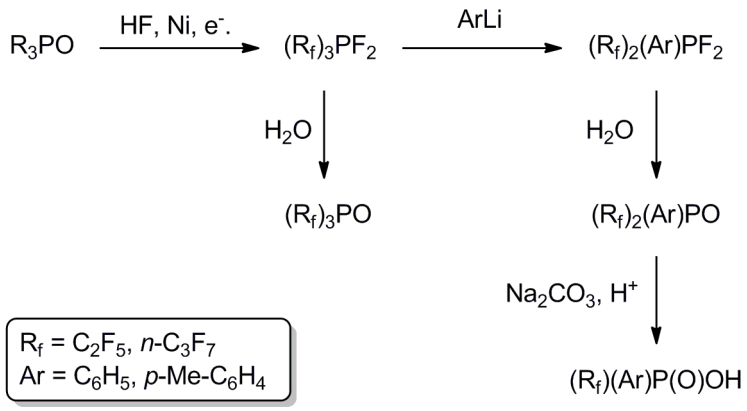
Perfluoroalkyl(aryl)phosphinic acids, like perfluoroalkylphosphorus(V) acids, have historically been difficult to synthesise.

The first example of such compounds was published by Yagupol'skii and co-workers (Scheme 2.11). [29] The initial reaction step is modified from the Emeléus procedure[30], followed by isolation of bis(perfluoropropyl)iodophosphine. Chlorination and subsequent reaction of the phosphine, with aryl Grignard reagents, gave bis(perfluoropropyl)(aryl)phosphine. After several more steps involving cleavage of one perfluoroalkyl group, followed by hydrolysis, perfluoropropyl(aryl)-phosphinic acids were formed.



Scheme 2.11: The synthesis of perfluoropropyl(aryl)phosphinic acids using aryl Grignard reagents.

Several years later Pavlenko and co-workers reacted aryl lithium reagents with tris(perfluoroalkyl) difluorophosphoranes (Scheme 2.12). [31]

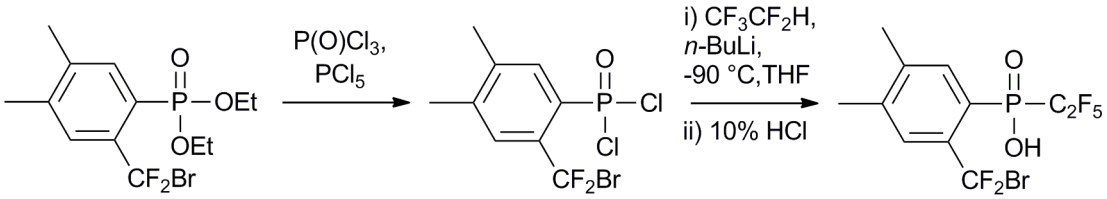


Scheme 2.12: The synthesis of perfluoroalkyl(aryl)phosphinic acids using aryl lithium reagents.

Hydrolysis of the resulting bis(perfluoroalkyl)aryl difluorophosphorane gave bis(perfluoroalkyl)arylphosphine oxides.

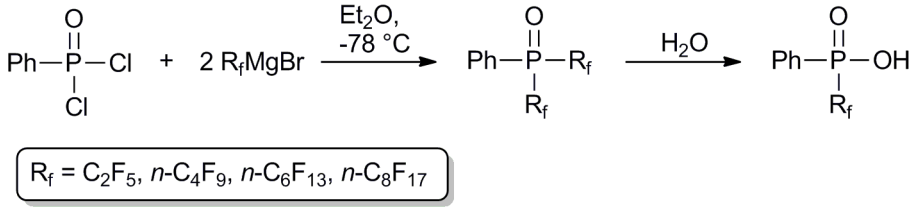
The two methods described above, by Yagupol'skii and Pavlenko, have initial reaction steps based on early methodology, often involving harsh reaction conditions and toxic fluorinating reagents (HF) . The Emeléus method, used in the first procedure, produces a mixture of perfluoroalkyl iodophosphines that are difficult to separate. Electrochemical fluorination, used in the second procedure (Pavlenko *et al.*), uses highly toxic HF, which is difficult to handle and requires specialised reaction vessels.

In 2011 Tverdomed[32] and co-workers reacted pentafluoroethyl lithium with a arylphosphonic dichloride to give, after aqueous work-up, pentafluoroethyl(aryl)-phosphinic acid (Scheme 2.13). The reaction was high yielding (85%), however the full scope of this reaction is unknown as no other fluorinated alkanes were reacted with the arylphosphonic dichloride.



Scheme 2.13: The reaction of perfluoroethyl lithium with a arylphosphonic dichloride.

More recently Hosein *et al*. synthesised perfluoroalkyl(phenyl)phosphinic acids from the reaction of perfluoroalkyl Grignard reagents with phenylphosphonic dichloride (Scheme 2.14).[20] A range of perfluoroalkyl Grignard reagents were generated *in situ* and reacted with phenylphosphonic dichloride to give bis(perfluoroalkyl)phenylphosphine oxides, which were readily hydrolysed to the phosphinic acids in good yields. Trifluoromethyl(phenyl)phosphinic acid was not synthesised by this method due to the thermal instability of trifluoromethyl Grignard reagents.



Scheme 2.14: The synthesis of perfluoroalkyl(phenyl)phosphinic acids using perfluoroalkyl Grignard reagents.

Interestingly no mono-substitution of the perfluoroalkyl groups was observed, only the bis(perfluoroalkyl)phenylphosphine oxides were formed. This method is not "atom efficient" with respect to the perfluoroalkyl group.

To summarise a majority of preparations of perfluoroalkyl phosphorus(V) acids are based on the seminal Emeléus method. This methodology requires harsh reaction conditions and is lower yielding than later methods. Other methods such as those by Hosein *et al*. are higher yielding. This preparation however, cannot be applied

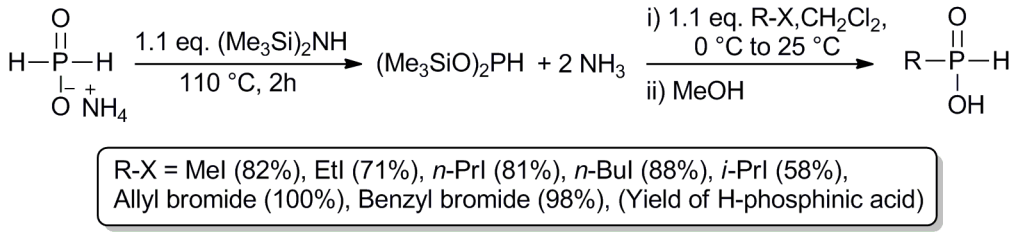
to the trifluoromethyl derivatives. Herein the synthesis of perfluoroalkyl phosphorus(V) compounds was investigated using phosphorus(III)silyl ether intermediates.

2.2. Phosphorus (III) silylethers as reactive intermediates

2.2.1. Previous reactions of bis(trimethylsilyl)phosphonite (BTSP)

A large amount of work has been performed in the synthesis and reactivity of phosphorus(III) silylethers. In particular bis(trimethylsilyl)phosphonite (BTSP) is of interest due to its high reactivity to electron deficient compounds. During the early 1990s Regan *et al.* generated BTSP *in situ* and reacted it with a range of acrylates, giving both the mono and di-substituted phosphorus(V) acids (Scheme 1.2, Chapter One).[6] Triethylammonium hypophosphite was reacted with trimethylsilyl chloride (TMSCl) and NEt_3 to give BTSP, at room temperature. This facile synthesis proved to be an effective method for forming carbon-phosphorus linkages.

Boyd and co-workers simplified their methodology by applying hexamethyldisilazane (HMDS) in place of $TMSCl/Et_3N$ [33,34] (Scheme 2.15) with ammonia being a side product, in the formation of BTSP.

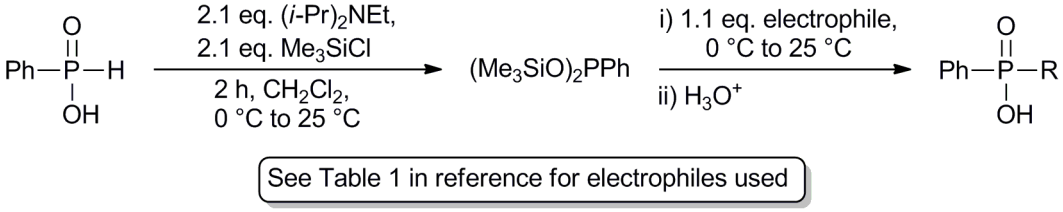


Scheme 2.15: The reaction of BTSP with alkyl halides in the synthesis of functionalised H-phosphinic acids.

Further testing of BTSP has shown high reactivity towards α,β-unsaturated ketones as well as alkyl iodides. Alkyl H-phosphinic acids, symmetrical and unsymmetrical bis(alkyl)phosphinic acids were generated in good yields.

2.2.2. Reactions of bis(trimethylsilyl)phenyl phosphonite (BTSPP)

Boyd and co-workers applied their previous methodology to the formation of functionalised phenylphosphinic acids.[35] The reaction proceeds similar to the formation of BTSP, however the use of phenylphosphinic acid as the starting material gives rise to bis(trimethylsilyl)phenylphosphonite (BTSPP). A solution of BTSPP was generated in situ from TMSCl and a base (NEt_3 Or $EtN(i\text{-}Pr)_2$). A range of functionalised electrophiles were added and acidic work-up gave the corresponding acids (Scheme 2.16).



Scheme 2.16: The synthesis of functionalised phenyl phosphinic acids.

2.3. Rationale

Regan and Boyd have shown that BTSP readily reacts with alkyl iodides to give alkyl H-phosphinic acids.[34] The objective, in this chapter, is to investigate the reactions of BTSP and BTSPP with perfluoroalkyl iodides, as a possible new route to perfluoroalkyl H-phosphinic acids and perfluoroalkyl(phenyl)phosphinic acids respectively.

2.4. Results and discussion

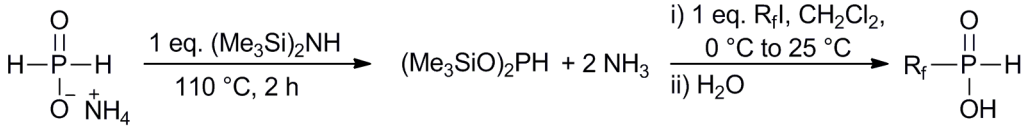
2.4.1. Formation of bis(trimethylsilyl)phosphonite

Similar to previous work by Boyd and Regan,[33, 34] BTSP was synthesised *in situ* and was not isolated. However the reaction of ammonium phosphinate and HMDS was monitored by ^{31}P NMR spectroscopy. In a addition to a triplet at δ -1.1 ($^{1}J_{P-H}$ = 553 Hz), due to remaining $[NH_4][PO_2H_2]$, a doublet centred at δ 142.4 ($^{1}J_{P-H}$ = 174 Hz) was observed. The doublet was assigned as BTSP, as the value agree with that of isolated BTSP.[36, 37]

2.4.2. Reaction of bis(trimethylsilyl)phosphonite with perfluoroalkyl iodides

2.4.2.1. Synthesis of perfluoroalkyl H-phosphinic acids

The reactions of BTSP with perfluoroalkyl iodides (R_fI) have been investigated (Scheme 2.17). Firstly, ammonium phosphinate was heated with HMDS to generate BTSP *in situ*.



Scheme 2.17: The synthesis of perfluoroalkyl H-phosphinic acids by reaction of BTSP with perfluoroalkyl iodides

Then reaction of BTSP with perfluoroalkyl iodides was tested. The perfluoroalkyl iodides (*n*-C_4F_9I, *n*-$C_6F_{13}I$, *n*-$C_8F_{17}I$) were added cautiously to a solution of BTSP in CH_2Cl_2 at 0 ℃. The reactions were then allowed to warm up to room temperature and stirred overnight (Scheme 2.17). The reactions were then worked

up. It should be noted that a significant amount of yellow solid, which has low solubility in a range of solvents (MeOH, $CHCl_3$, DMSO), formed during the reaction. ^{31}P NMR spectroscopy of this partially soluble yellow solid indicates a complex mixture of phosphorus containing compounds, but did not contain any perfluoroalkyl phosphorus compounds. The remaining insoluble yellow solid could be a polyphosphorus material, generated during the reaction.

Typically the reactions were filtered to remove the yellow solid formed during the reaction. Then the solvent was removed under reduced pressure. The resulting residues were then partitioned between diethyl ether and 2M aq. HCl. The organic layer was then washed further with 2M aq. HCl and water. Removal of the solvent *in vacuo*, gave the crude perfluoroalkyl H-phosphinic acids as pale yellow oils/solids. The crude products contained a small amount, by ^{31}P NMR spectroscopy, of oxidised product, perfluoroalkyl phosphonic acid.

For example the ^{31}P NMR spectrum of crude *n*-$C_4F_9PO(OH)H$ (**Figure 2.1**), is shown below. The doublet of triplets at δ 2.1 ($^1J_{P-H}$ = 571 Hz, $^2J_{P-F}$ = 74 Hz) was assigned as the expected product *n*-$C_4F_9PO(OH)H$ and the small triplet at -3.4 ($^2J_{P-F}$ = 79 Hz) was assigned as oxidised product *n*-$C_4F_9PO(OH)_2$.[15] A doublet on the ^{19}F NMR spectrum of crude *n*-$C_4F_9PO(OH)H$ (**Figure 2.2**) was observed at -128.4 ($^2J_{P-F}$ = 75 Hz, 2F).[15] The presence of perfluoroalkyl phosphonic acids indicates that, either during the reaction, of BTSP with perfluoroalkyl iodides, or during work up, oxidation is occurring. Perfluoroalkyl H-phosphinic acids are susceptible to oxidation.[19] The aqueous layer was checked for the presence of any perfluoroalkyl phosphorus compounds, by removal of the solvent *in vacuo* and ^{31}P and ^{19}F NMR spectroscopy screening on the resulting residue (DMSO-d_6). H_3PO_3 was observed as a doublet at δ 2.0 ($^1J_{P-H}$ = 645 Hz). A trace amount of *n*-

$C_4F_9PO(OH)_2$ was observed in the ^{31}P and ^{19}F NMR spectra, however no *n*-$C_4F_9PO(OH)H$ was observed in the aqueous layer.

The crude acids were purified by precipitation of their salts using *p*-toluidine. This isolation technique has been utilsed by Caffyn *et al*.[19]

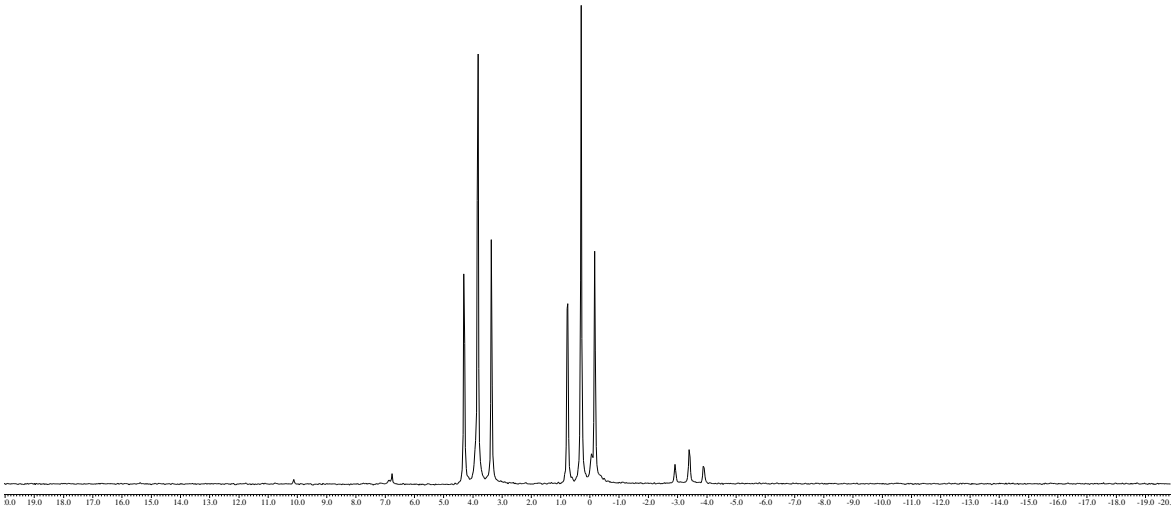


Figure 2.1: ^{31}P NMR spectrum of crude *n*-$C_4F_9PO(OH)H$ (DMSO-d_6).

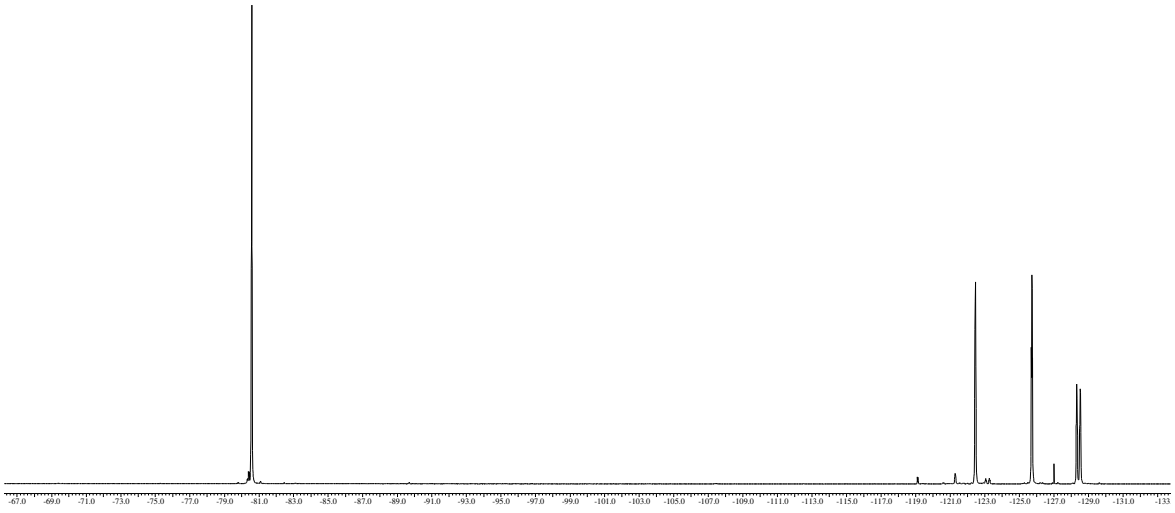


Figure 2.2: ^{19}F NMR spectrum of crude *n*-$C_4F_9P(O)(OH)H$ (DMSO-d_6).

A solution of *p*-toluidine in ether was added slowly to solutions of crude perfluoroalkyl H-phosphinic acids. Removal of the solvent and recrystallisation gave perfluoroalkyl H-phosphinic acids as their toluidinium salts.

Table 2.1: The synthesis of perfluoroalkyl H-phosphinic acids.

Entry	R_fI	Product[a]	Yield (%)[c]
1	*n*-C_4F_9I	*n*-$C_4F_9P(O)(OH)H$	12
2	*n*-$C_6F_{13}I$	*n*-$C_6F_{13}P(O)(OH)H$	23[b]
3	*n*-$C_8F_{17}I$	*n*-$C_8F_{17}P(O)(OH)H$	33

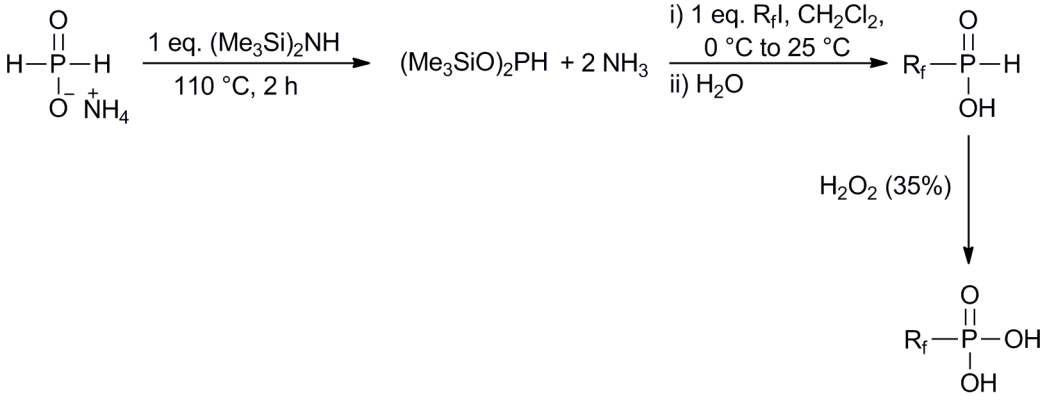
a) Isolated as *p*-toluidinium salts. b) crude yield. c) isolated yields based on perfluoroalkyl iodides.

The yields of perfluoroalkyl H-phosphinic acids (Table 2.1), were low, compared to previous methodology.[19] This could be attributed to the generation of insoluble phosphorus and a complex mixture of phosphorus containing compounds during the reaction. Also, the formation and recrystallisation of salts of perfluoroalkyl H-phosphinic acids, reduced the yield, by loss of compound in the filtrate of the recrystallisation step.

Both the perfluorobutyl- and perfluorooctyl- H-phosphinic acid were successfully isolated, as their salts (Table 2.1, Entries 1 and 3). However, perfluorohexyl H-phosphinic acid, as the *p*-toluidinium salt, was not isolated. [*p*-MeC_6H_4][*n*-$C_6F_{13}P(O)_2H$] co-crystallised with [*p*-MeC_6H_4][*n*-$C_6F_{13}P(O)_2OH$]. Also a peak at δ 0.0 by ^{31}P suggests the formation of phosphoric acid and its toluidinium salt.

2.4.2.2. Synthesis of Perfluoroalkyl phosphonic acids

It has been shown that perfluoroalkyl H-phosphinic acids can easily be converted to their phosphonic acid derivatives by a simple oxidation step.[19] Therefore the synthesis of perfluoroalkyl phosphonic acids by reaction of BTSP with perfluoroalkyl iodides, followed by the oxidation of crude perfluoroalkyl H-phosphinic acids, was tested (Scheme 2.18).



Scheme 2.18: The synthesis of perfluoroalkyl phosphonic acids.

The reactions were performed in the same manner as those previously described (perfluoroalkyl H-phosphinic acids). The crude acids were then subjected to oxidation by 35% H_2O_2. Extraction of the phosphonic acids from the aqueous fraction with ether gave crude perfluoroalkyl phosphonic acids. The acids were then converted to their corresponding *p*-toluidinium salts, which were recrystallised to afford pure perfluoroalkyl phosphonic toluidinium salts.

The results of the synthesis, of perfluoroalkyl phosphonic acids, are summarised in Table 2.2.

Table 2.2: The synthesis of perfluoroalkyl phosphonic acids.

Entry	R_fI	Product[a]	Yield (%)[c]
1	*n*-C_4F_9I	*n*-$C_4F_9PO(OH)_2$[b]	7.3
2	*n*-$C_6F_{13}I$	*n*-$C_6F_{13}PO(OH)_2$	16
3	*n*-$C_8F_{17}I$	*n*-$C_8F_{17}PO(OH)_2$	2.4

a) Isolated as toluidinium salts. b) Isolated as bis(toluidinium) salt. c) yields based on perfluoro-alkyl iodides (1 eq.).

Similar to the results of perfluoroalkyl H-phosphinic acids, the yields of perfluoroalkyl phosphonic acids are very low, compared to previous methodology.[19] The extra oxidation step, has reduced the yields of the perfluoroalkyl- phosphonic acids compared to the H-phosphinic acids. Despite the low yields, pure products (See Figure 2.3 and Figure 2.4) were synthesised as their toluidinium salts.

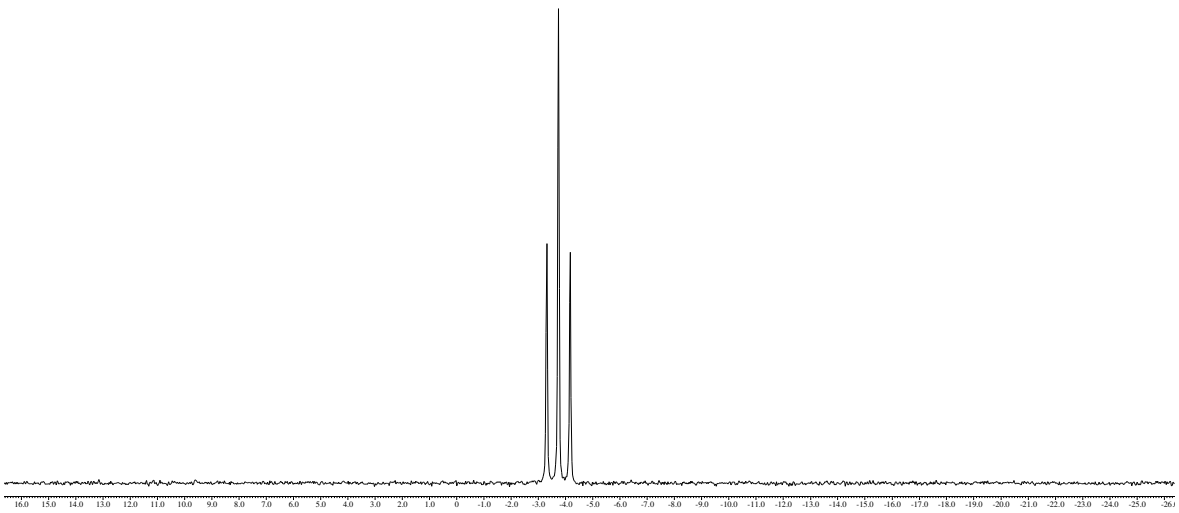


Figure 2.3: ^{31}P NMR spectrum of [*p*-$MeC_6H_4NH_3]_2[n$-$C_4F_9P(O)_3$] (DMSO-d_6).

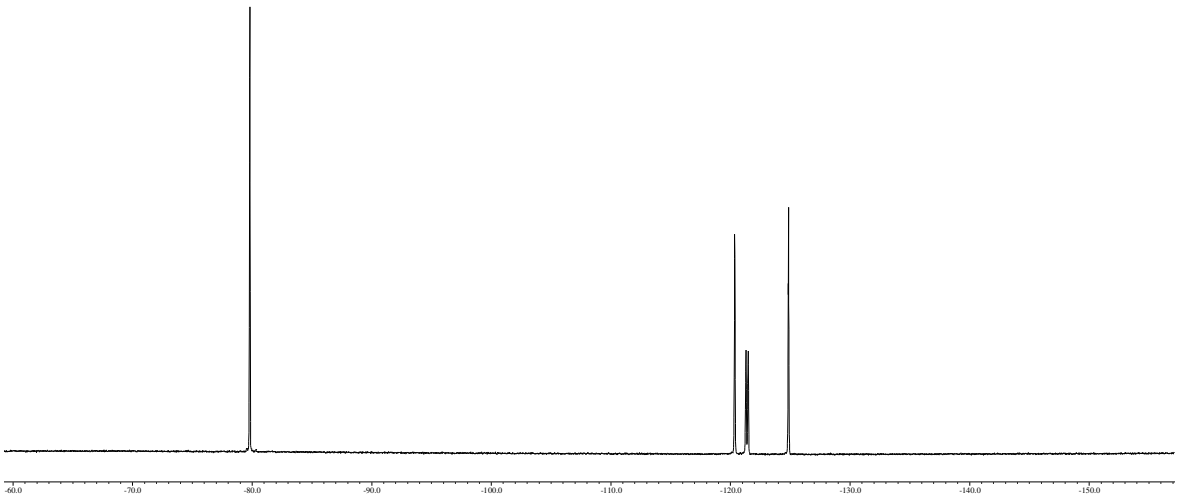


Figure 2.4: ^{19}F NMR spectrum of [*p*-$MeC_6H_4NH_3$]$_2$[*n*-$C_4F_9P(O)_3$] (DMSO-d_6).

The perfluoroalkyl phosphonic acids are observed as triplets on the ^{31}P NMR spectrum. This is due to the CF_2-P group, 2 fluorines in a 2 bond coupling to phosphorus, and a lack of a P-H bond, e.g. the perfluoroalkyl H-phosphinic acids are observed as a doublet of triplets due to the P-H bond and CF_2-P group. The multi-nuclear NMR data of [*p*-$MeC_6H_4NH_3$]$_2$[n-$C_4F_9P(O)_3$], [*p*-$MeC_6H_4NH_3$][n-$C_6F_{13}P(O)_2OH$] and [*p*-$MeC_6H_4NH_3$][n-$C_8F_{17}P(O)_2OH$] agree with the literature.[19]

2.4.2.3. The reactions of BTSP with shorter chain perfluoroalkyl iodides:

Attempted synthesis of $CF_3P(O)(OH)_2$

The simplest perfluoroalkyl iodide, CF_3I, was reacted with BTSP. After 24 hours at room temperature, the reaction was quenched and oxidised, as described previously. The trifluoromethyl phosphonic acid was then converted to the corresponding toluidinium salt.

Attempts to isolate the salt were unsuccessful. This was due to the low solubility of the salt in moderately polar solvents (ether, $CHCl_3$, CH_2Cl_2). The trifluoromethyl phosphonic toluidinium salt was very soluble in MeOH, therefore was difficult to crystallise, as several other non-fluorinated phosphorus compounds co-crystallised with the product (Figure 2.5). Trifluoromethyl phosphonic toluidinium salt was observed as a large quartet, with a $^2J_{P\text{-}F}$ coupling of 96 Hz, by 31P NMR spectroscopy. The coupling was also observed in the ^{19}F NMR spectra as a doublet with a $^2J_{F\text{-}P}$ value of 95 Hz.

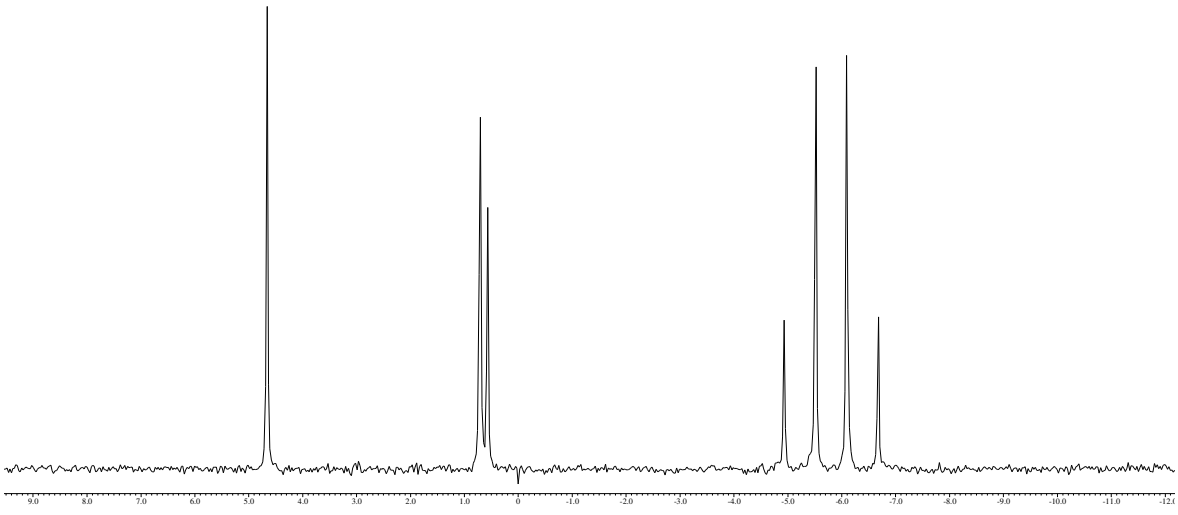


Figure 2.5: ^{31}P NMR spectrum of crude $[p\text{-}MeC_6H_4NH_3]_2[CF_3P(O)_3]$ ($DMSO\text{-}d_6$).

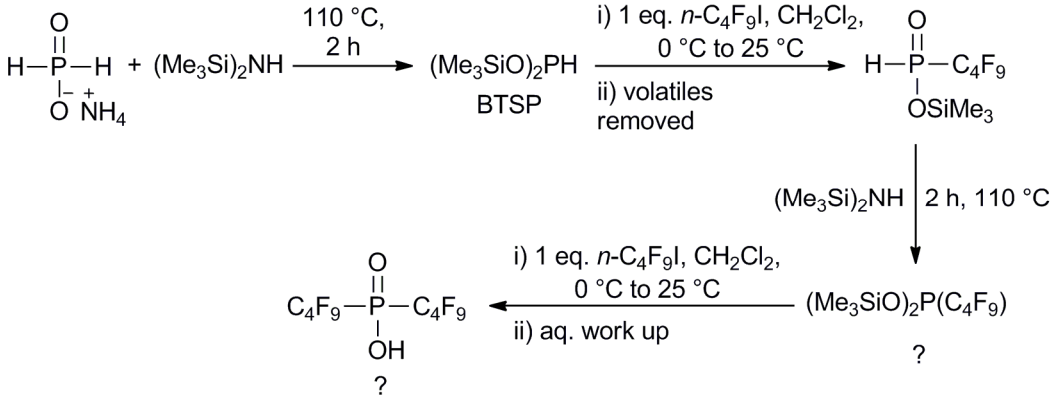
NMR studies of the reaction of BTSP with CF_3I show the presence of the expected product $CF_3PO(OH)_2$ (after oxidation), however isolation of the compound proved challenging due to the solubility of $[p\text{-}MeC_6H_4NH_3]_2[CF_3P(O)_3]$.

2.4.2.4. Attempted synthesis of a bis(perfluoroalkyl)phosphinic acid

The synthesis of $(R_f)_2P(O)OH$ was investigated. Non-fluorinated acids, of the formula $(R)_2P(O)OH$, have previously been synthesised by reaction of BTSP with alkyl iodides in a "one-pot" procedure.[34] This methodology was explored with respect to perfluorobutyl iodide.

Attempted synthesis of $(n\text{-}C_4F_9)_2P(O)(OH)$

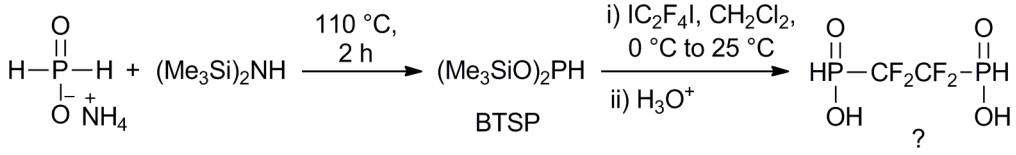
A one pot synthesis of bis(perfluorobutyl)phosphinic acid was attempted (Scheme 2.19). BTSP was formed as previously described and perfluorobutyl iodide was added. After 12 hours, volatiles were removed and another equivalent of HMDS was added and the reaction was heated to 110℃ for 2 hours. Perfluorobutyl iodide was then added at 0℃ and the reaction was stirred at room temperature for 12 hours. The ^{31}P NMR spectrum of the reaction mixture indicated a complex mixture of compounds. The intended product, $(n\text{-}C_4F_9)_2P(O)(OH)$, was not observed, due to the lack of an expected pentet at δ -0.9 with $^2J_{P\text{-}F}$ coupling of 66 Hz.[15] The main phosphorus containing compound observed, in the ^{31}P NMR spectrum, was the mono-perfluoroalkyl H-phosphinic acid $n\text{-}C_4F_9P(O)(OH)H$ as a doublet of triplets. $n\text{-}C_4F_9P(O)(OH)_2$ was also observed by ^{31}P NMR data.



Scheme 2.19: Attempted synthesis of bis(perfluorobutyl)phosphinic acid.

2.4.2.5. Attempted synthesis of tetrafluoroethyl bis(H-phosphinic acid)

The reaction of BTSP with 1,2-diiodotetrafluoroethane was tested, in an attempt to synthesis a bis(H-phosphinic acid) with a perfluoroethylene linkage. IC_2F_4I (0.5 eq.) was added to a solution of BTSP, generated *in situ* (Scheme 2.20). The volatiles were removed *in vacuo* and the resulting residue was quenched with a methanol solution. NMR screening of the quenched reaction indicated that the reaction was unsuccessful. A trace amount of fluorinated compound was observed on the ^{19}F NMR spectrum, which agrees with a genuine sample of ICF_2CF_2I. No fluorine phosphorus coupling was observed in the ^{19}F NMR spectrum. No fluorinated- phosphorus compounds were observed in the ^{31}P NMR spectrum.

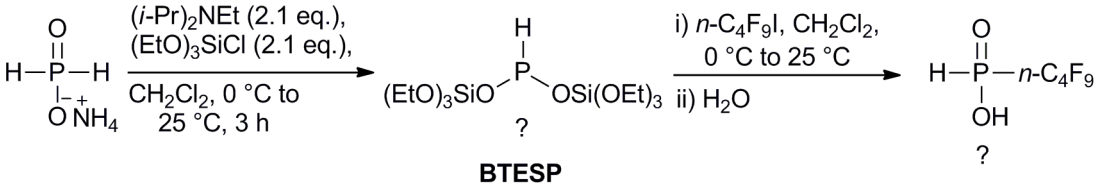


Scheme 2.20: Attempted synthesis of H(O)(OH)P-CF_2CF_2-P(O)(OH)H.

2.4.2.6. Attempted synthesis and reaction of bis(triethoxysilyl)phosphonite (BTESP) with perfluorobutyl iodide

As an expansion to this research, the formation and reactivity of bis(triethoxysilyl)-phosphonite [$(EtO)_3SiO)_2PH$] (BTESP) towards perfluoroalkyl iodides was investigated. Ammonium phosphinate was stirred at room temperature with *i*-Pr_2NEt and $(EtO)_3SiCl$ in CH_2Cl_2 (Scheme 2.21). After 2 hours perfluorobutyl iodide was added. The reaction was quenched with methanol and solvent was removed *in vacuo*. ^{31}P NMR spectroscopy of the resulting material indicated ammonium phosphinate was the only phosphorus containing compound δ -4.2 (t, $^1J_{P-H}$ = 475 Hz). The ^1H NMR data δ 7.0 (d, $^1J_{P-H}$ = 472 Hz) agreed with the ^{31}P

NMR data observation. No peaks were observed in the ^{19}F NMR spectrum. To conclude, no reaction was observed.

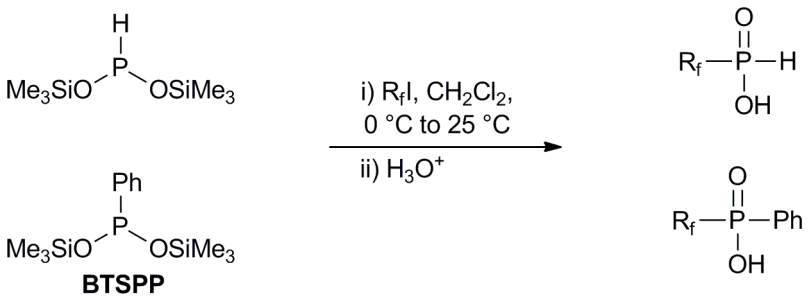


BTESP

Scheme 2.21: Attempted synthesis of BTESP and reaction with *n*-C_4F_9I.

2.4.3. Reactions of bis(trimethylsilyl)phenyl phosphonite with perfluoroalkyl iodides

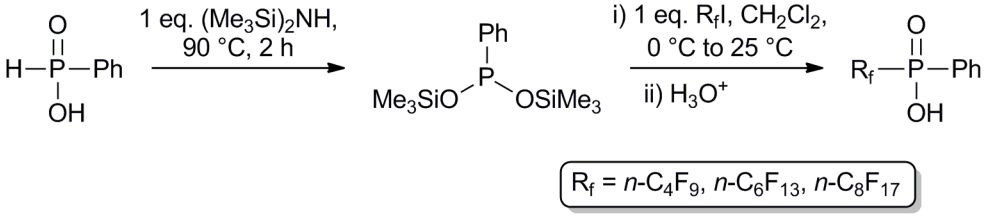
In addition to the formation of perfluoroalkyl H-phosphinic $R_fP(O)(OH)H$ and phosphonic acids $R_fP(O)(OH)_2$, the formation of perfluoroalkyl(phenyl)phosphinic acids $(R_f)PhP(O)OH$ was also investigated (Scheme 2.22). Boyd and co-workers have shown that bis(trimethylsilyl)phenylphosphonite (BTSPP) react with a range of electrophiles to give the corresponding mixed phosphinic acids.[35] It was envisaged that the reaction of BTSPP with R_fI would give perfluoroalkyl(phenyl)-phosphinic acids $(R_f)PhP(O)(OH)$.



Scheme 2.22: The formation of perfluoroalkyl H-phosphinic acids and perfluoroalkyl(phenyl)phosphinic acids.

2.4.3.1. The formation of (R_f)PhP(O)OH by the "HMDS Method"

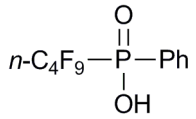
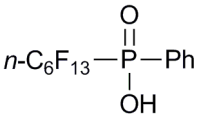
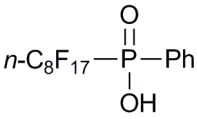
The reaction of bis(trimethylsilyl)phenylphosphonite and perfluoroalkyl iodides were tested. Equimolar amounts of PhP(O)(OH)H and HMDS were heated neat followed by addition of CH_2Cl_2 and R_fI at 0 °C (Scheme 2.23)



Scheme 2.23: The formation of perfluoroalkyl(phenyl)phosphinic acids.

When the reaction was complete (24 h) the solvent was removed under vacuum. The resulting residue was dissolved in ether and washed with aq. HCl. The solvent was removed from the organic fraction to afford the crude perfluoroalkyl(phenyl)-phosphinic acids. These were then purified as their toluidinium salts. Ethereal solutions of crude perfluoroalkyl(phenyl)phosphinic acids and *p*-toluidine were mixed. The solvent was removed and the residue was recrystallised using chloroform/acetone mixtures, to give pure perfluoroalkyl(phenyl)phosphinic toluidinium salts.

Table 2.3: Results of perfluoroalkyl(phenyl)phosphinic acid synthesis.

Entry	R_fI	Product [a]	Yield (%) [b]
1	*n*-C_4F_9I		40
2	*n*-$C_6F_{13}I$		35
3	*n*-$C_8F_{17}I$		43

a) Isolated as toluidinium salts. b) Yields based on perfluoroalkyl iodides.

Perfluoro -butyl, -hexyl and -octyl derivatives were successfully isolated by this method (Table 2.3). Multi-nuclear NMR of the salts agree with the previous literature values.[20] High resolution mass spectrometry (HRMS), on these compounds, is in agreement with calculated values.

This is the first reported example of the formation of BTSPP from the reaction of phenyl H-phosphinic acid and HMDS. Also this is the first example of the reaction of BTSPP with perfluoroalkyl iodides.

2.4.3.2. Attempted synthesis of $(CF_3)PhP(O)OH$

As an extension to the reaction of BTSPP with long chain perfluoroalkyl iodides, trifluoromethyl iodide was also tested. CF_3I was added to BTSPP. CF_3I was condensed over a solution of BTSPP in CH_2Cl_2. ^{31}P NMR screening of the crude reaction mixture (Figure 2.6) is shown below.

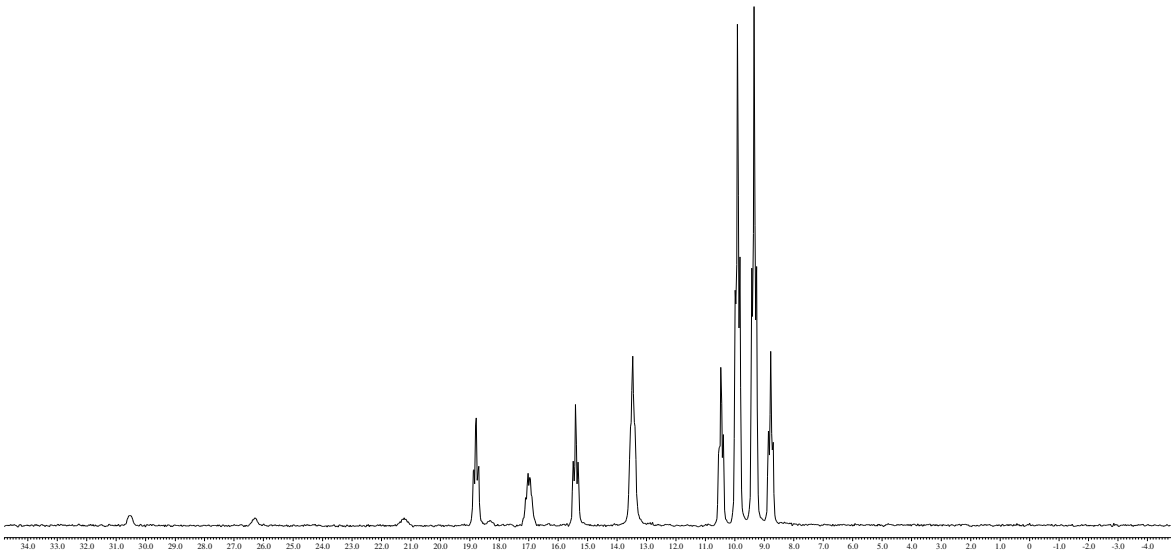


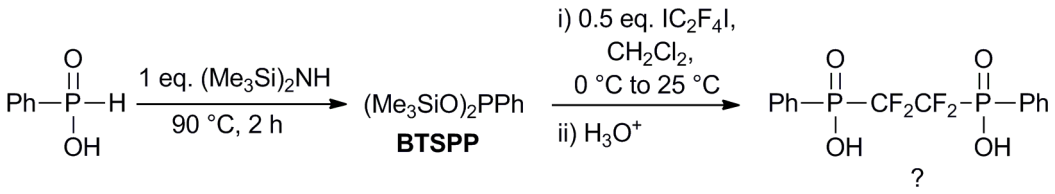
Figure 2.6: ^{31}P NMR spectrum of crude PhP(O)(OH)CF_3 (DMSO-d_6).

The quartet of triplets centred at δ 9.6 was assigned as the expected product CF_3(Ph)P(O)OH. The quartet arises from the 3 fluorine atoms through a 2 bond coupling. The smaller coupling appears to be a 3 bond P-H coupling from the aromatic protons ortho to the phosphorus-carbon linkage. The doublet of triplets centred at δ17 was assigned as unreacted PhP(O)(OH)H. The triplet centred at δ17 suggests the presence of PhP(O)$(OH)_2$. The ^{19}F NMR contained a single doublet with a coupling value of 91 Hz which agrees with the coupling observed for the resonance in the ^{31}P NMR spectrum.

Attempts to isolate CF_3(Ph)P(O)OH were unsuccessful, despite it being the main phosphorus containing compound in the crude reaction mixture. The crude product was transformed to its toluidinium salt. Attempts to recrystallise the resulting residue were unsuccessful, owing to its low solubility in moderately polar solvents (insoluble in ether, THF, $CHCl_3$, CH_2Cl_2). More polar solvents such as ethanol and acetone did dissolve the crude sample however, impure compound formed from recrystallisation in these solvents.

2.4.3.3. Attempted synthesis of PhP(O)(OH)-CF_2CF_2-PhP(O)(OH)

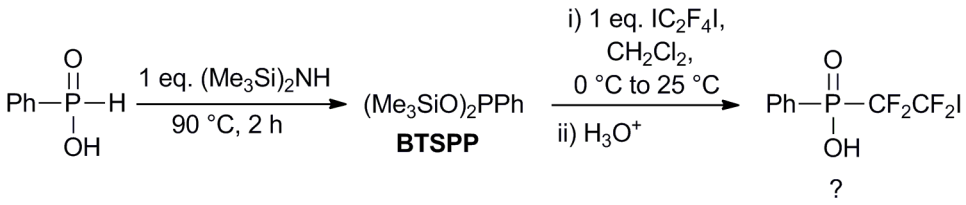
The reaction of BTSPP with ICF_2CF_2I (Scheme 2.24) was investigated as a possible route to tetrafluoroethylene bis(phenylphosphinic acid). BTSPP, formed in situ from HMDS, was stirred with 0.5 equivalents of ICF_2CF_2I in CH_2Cl_2. ^{31}P NMR of the reaction revealed a mixture of phosphorus compounds. However, no $^2J_{P\text{-}F}$ coupling was observed. Similarly no coupling was observed on the ^{19}F NMR spectrum. The ^{19}F spectrum contained only one peak (δ -60, s) which is almost identical to a genuine sample of ICF_2CF_2I in DMSO-D6 (δ -60.5, s). No product was observed.



Scheme 2.24: The attempted synthesis of PhP(O)(OH)-CF_2CF_2-P(O)(OH)Ph.

2.4.3.4. Attempted synthesis of PhP(O)(OH)C_2F_4I

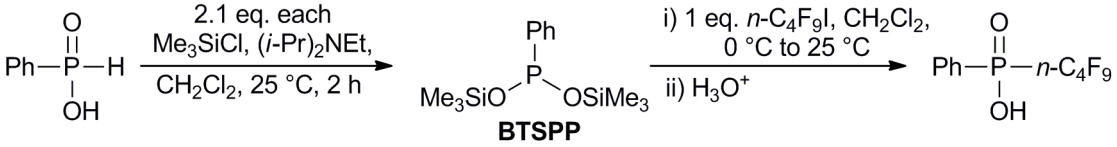
The reaction above was repeated with 1 equivalent of ICF_2CF_2I in an attempt to synthesise PhP(O)(OH)C_2F_4I (Scheme 2.25), which could be reacted further with BTSPP in a two-step procedure. However, similar to the previous reaction no $^2J_{P\text{-}F}$ coupling was observed in both ^{31}P and ^{19}F NMR spectra. No reaction with ICF_2CF_2I was observed.



Scheme 2.25: The attempted synthesis of PhP(O)(OH)-CF_2CF_2I.

2.4.4. The formation of (*n*-C_4F_9)PhP(O)OH using *i*-Pr_2NEt and Me_3SiCl ("Hunig's base/TMSCl method")

The reaction of BTSPP, formed *in situ* with *i*-Pr_2NEt , Me_3SiCl and PhP(O)(OH)H,[33, 35] with perfluorobutyl iodide was tested (Scheme 2.26). Acidic work-up gave crude (*n*-C_4F_9)PhP(O)OH (63%). A portion of crude product was transformed to the toluidinium salt (55% conversion). A triplet ($^2J_{P-F}$ = 61 Hz), with some unresolved fine structure ($^3J_{P-H}$ = 13 Hz), was observed in the ^{31}P NMR spectrum (Figure 2.7) which was assigned as the anion (*n*-C_4F_9)$PhPO_2^-$. The ^{19}F NMR spectrum (Figure 2.8) of the salt confirms the presence of (*n*-C_4F_9)$PhPO_2^-$ with the CF_2-P group visible as a doublet at δ -122 ($^2J_{P-F}$ = 64 Hz). The ^{31}P and ^{19}F NMR specra of (*n*-C_4F_9)$PhPO_2^-$ agrees with the literature.[20]



Scheme 2.26: The synthesis of (*n*-C_4F_9)PhP(O)OH by "Hunig's base/Me_3SiCl method".

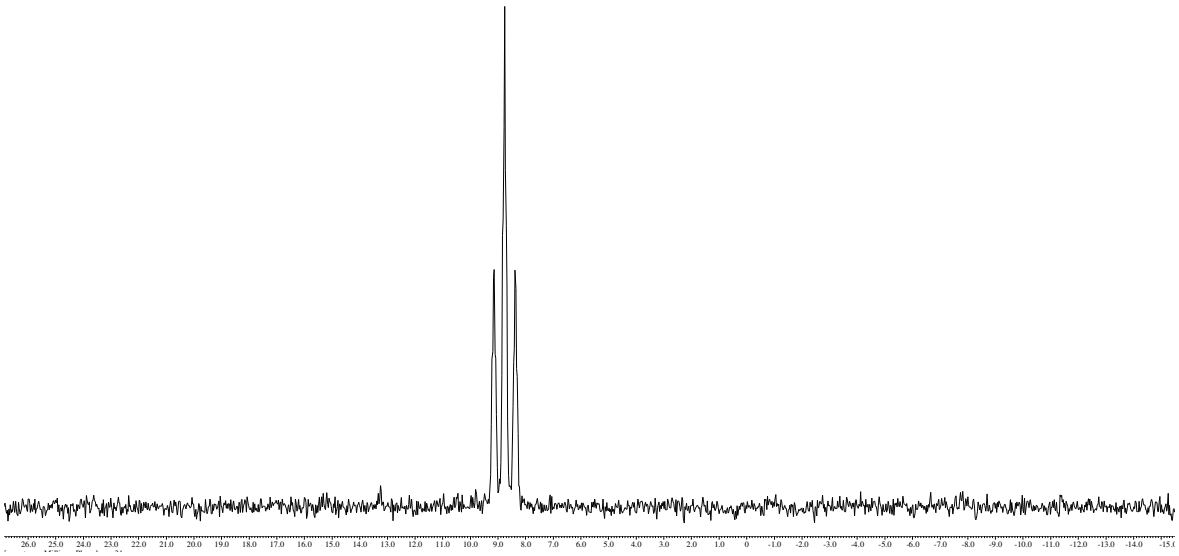


Figure 2.7: ^{31}P NMR spectrum of [*p*-$MeC_6H_4NH_3$][(*n*-C_4F_9)$PhPO_2$] (DMSO-d_6).

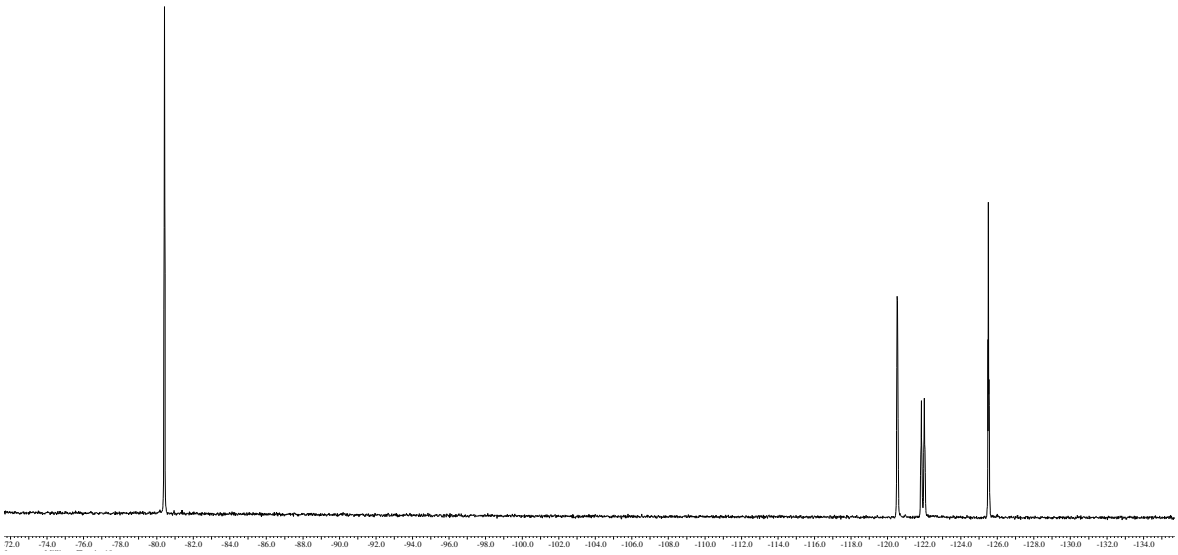


Figure 2.8: ^{19}F NMR spectrum of [*p*-$MeC_6H_4NH_3$][(*n*-C_4F_9)$PhPO_2$] (DMSO-d_6).

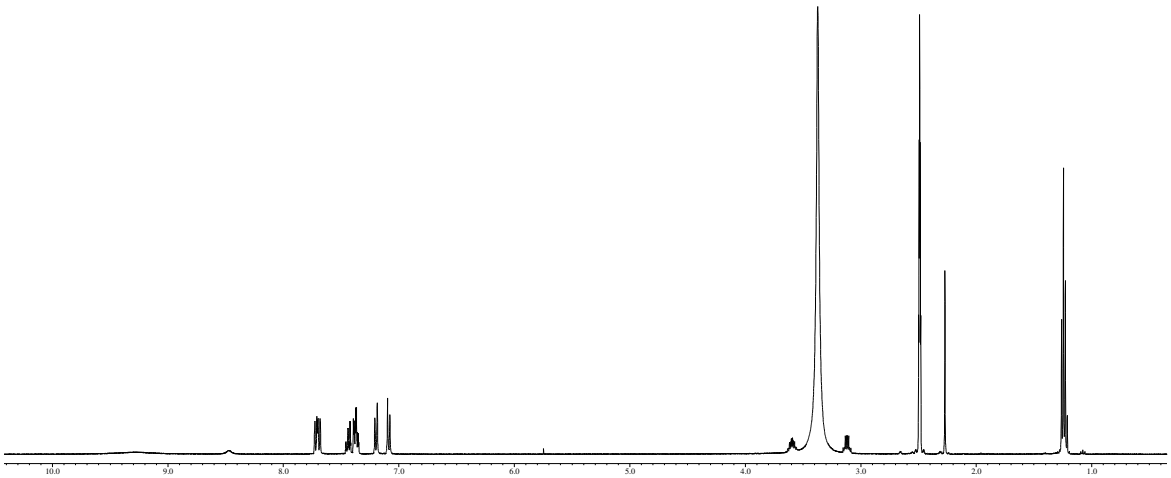


Figure 2.9: ^{1}H NMR spectrum of [*p*-$MeC_6H_4NH_3$][(*n*-C_4F_9)$PhPO_2$] (DMSO-d_6).

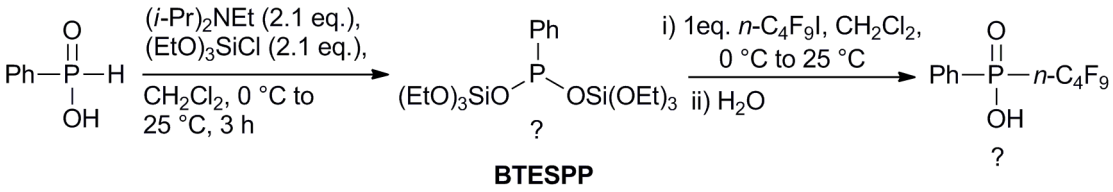
Several extra peaks were observed in the ^{1}H NMR that did not match the peaks expected for [*p*-$MeC_6H_4NH_3$][(*n*-C_4F_9)$PhPO_2$] (Figure 2.9). The extra peaks observed were assigned as a [*i*-$Pr_2N(Et)H]^+$ group, as the single protons on the *i*-Pr groups are visible as multiplets at δ 3.1 and 3.6. Also an additional broad singlet is visible downfield δ 8.5 suggesting the presence of an extra NH_X^+ group. This was confirmed by mass spectrometry of M^+, in which two peaks were observed, 108.1 (*p*-$MeC_6H_4NH_3)^+$ and 130.2 which agrees with the presence of [*i*-$Pr_2N(Et)H]^+$. The reaction was repeated, using *i*-Pr_2NEt in the purification step of

crude (*n*-C_4F_9)PhP(O)OH. No solid formed when mixing the crude (*n*-C_4F_9)PhP(O)OH and *i*-Pr_2NEt . The sample formed as a crude oil.

2.4.4.1. Attempted synthesis of (*i*-C_3F_7)PhP(O)(OH)

The reaction of BTSPP and *i*-C_3F_7I was tested to see the tolerance of secondary perfluoroalkyl groups. The reaction was performed in a similar procedure to the previous reaction. No PF coupling was observed in both the phosphorus and fluorine NMR. It is possible that the bulky CF_3 groups prevented successful formation of the P-C bond.

2.4.5. Attempted synthesis of bis(triethoxysilyl)phenylphosphonite (BTESPP) and reactivity towards *n*-C_4F_9I



Scheme 2.27: The possible formation of BTESPP and reaction with perfluorobutyl iodide.

The formation of perfluorobutyl(phenyl)phosphinic acid, via BTESPP was investigated (Scheme 2.27). The reaction was performed in a similar manner to the non-phenyl derivative (Scheme 2.21). Phenyl phosphinic acid was observed as the main compound in the ^{31}P NMR spectrum. (*n*-C_4F_9)PhP(O)OH was not observed in the ^{31}P NMR spectrum. No peaks were obseved in the fluorine spectrum.

2.5. Conclusions

The reactions of BTSP with perfluoroalkyl iodides is not an efficient method for the formation of perfluoroalkyl- H-phosphinic and phosphonic acids, compared to previous methodology.[19] Most of the reactions attempted indicated the presence of crude perfluoroalkyl- H-phosphinic and phosphonic acids by NMR studies. However, due to low yields and the presence of side products, isolation proved difficult. The low yields of these reactions could be attributed to the electronic nature of the perfluoroalkyl group. Due to the high electron-withdrawing properties of fluorine, perfluoroalkyl iodides are weaker electrophiles compared to alkyl iodides, which could hinder the nucleophilic attack of BTSP on the perfluoroalkyl iodides.

It was found that for the synthesis of perfluoroalkyl(phenyl)phosphinic acids, the formation of BTSPP via HMDS was more advantageous than formation of BTSPP via *i*-Pr_2NEt /Me_3SiCl. The synthesis of $(R_f)PhP(O)OH$ (where R_f = *n*-C_4F_9-, *n*-C_6F_{13}-, *n*-C_8F_{17}-) is lower yielding than previous methods.[20] Interestingly the reaction was compatible with CF_3I giving the expected product with a mixture of side products of which isolation was unsuccessful. The reaction did not tolerate *i*-C_3F_7I similar to previous reactions with BTSP. The formation of a bis(phenylphosphinic) acid by reaction of BTSPP with ICF_2CF_2I was also unsuccessful.

Chapter 3

The Synthesis of 2,2’-Bis(difluoromethylene)-1,1’-binaphthyl phosphinic acid, a New Brønsted Acid Catalyst.

3.1. Introduction

Interest in organocatalysis has grown considerably over the past decade.[38-41] The use of small organic compounds in catalysis is desirable, compared to metal-based complexes, which tend to be more expensive and in some cases more toxic.

One such group of organocatalysts are binaphthol-phosphoric acids (Figure 3.1). The presence of a chiral binaphthyl group allows for the possibility of enantioselective bond formation.

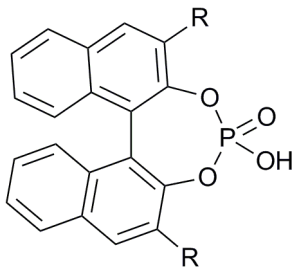
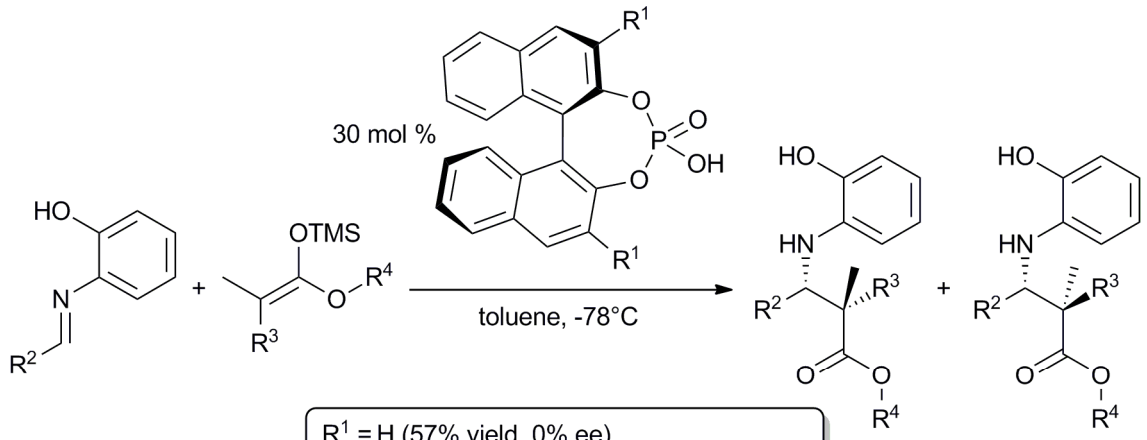


Figure 3.1: BINOL-phosphoric acid.

1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BINOL-phosphoric acid) (Figure 3.1) (where R = H) was first synthesised by Marschalk in 1928 by reaction of phosphoryl chloride and binaphthol followed by hydrolysis of the resulting acid chloride.[42]

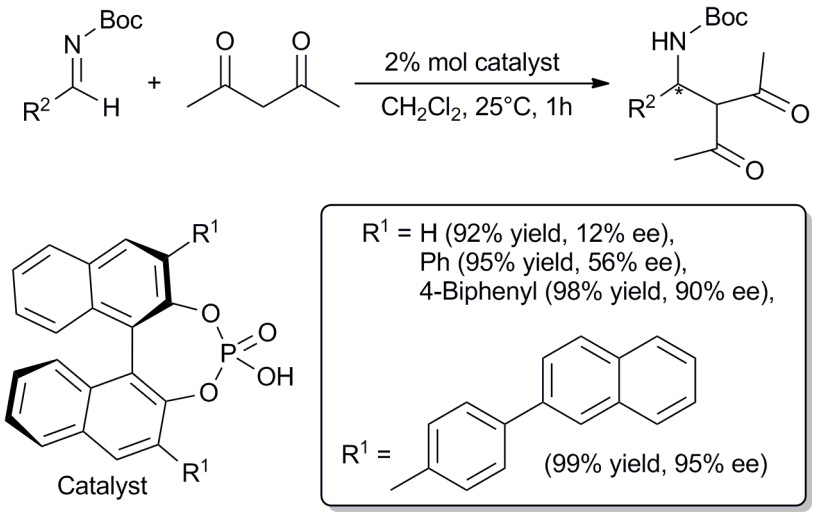
However, it was not until 2004 that BINOL-phosphoric acid and its derivatives were applied as chiral Brønsted acids catalysts in asymmetric synthesis. Akiyama and co-workers applied BINOL-phosphoric acids to catalyse a series of Mannich-type reactions of aldimines with ketene silyl acetals to give β-aminoesters.[43] A range of (*R*)-3,3'-disubstitued BINOL-phosphoric acids were tested for optimum reaction conditions (Scheme 3.1). The BINOL-phosphoric acid catalyst where R^1 =

4-$NO_2C_6H_4$ was found to give the highest selectivity and shortest reaction time (96% yield, 87% ee). The parent acid, where R^1 = H, gave 57% yield and 0% ee. The 4-$NO_2C_6H_4$ acid derivative was then used to synthesise a series of β-aminoesters, in yields ranging from 65 to 100% and ee from 81 to 96%, by changing the R^2, R^3 and R^4 groups.



Scheme 3.1: Optimisation of Mannich-type reactions of aldimines with ketene silyl acetals catalysed by (*R*)-BINOL-phosphoric acids.

Terada *et al.* independently reported a similar Mannich-type reaction catalysed by (*R*)-BINOL-phosphoric acids.[44] The group reacted protected-imines with acetyl acetone using 2 mol % loading of BINOL-phosphoric acid (and its derivatives) to give a range of β-amino ketones (Scheme 3.2). Of the BINOL-phosphoric acid catalysts tested, R^1 = 4-(β-Naph)-C_6H_4 gave a yield of 99% and 95% ee compared to the parent acid, R^1 = H, which gave 92% yield and 12% ee, where R^2 = Ph.



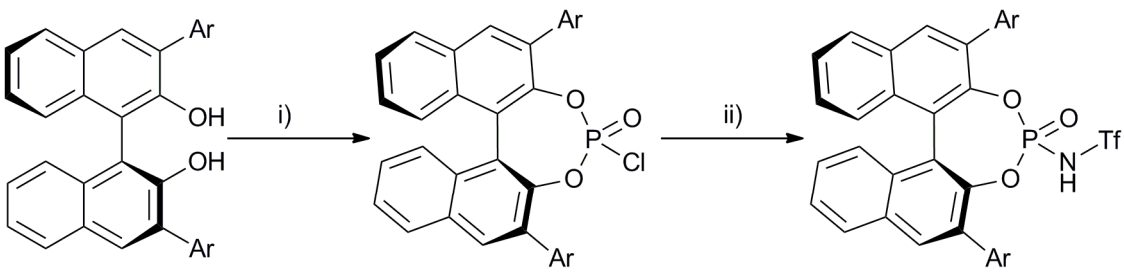
Scheme 3.2: Mannich-type reaction of imines with actyl acetone catalysed by (*R*)-BINOL-phosphoric acids.

These seminal works by Akiyama and Terada showcased the effectiveness of BINOL-phosphoric acids as chiral Brønsted acid catalysts. Since these reactions, a vast amount of research has been performed on BINOL-phosphoric acid derivatives as chiral Brønsted acid catalysts.[45-47] However, the work was limited to reactive substrates, such as imines, due to the moderate acidity of the phosphoric acid. In order to increase reactivity, to groups such as carbonyls, stronger-Brønsted acid catalysts were required.

3.1.1. Stronger Brønsted acid catalysts

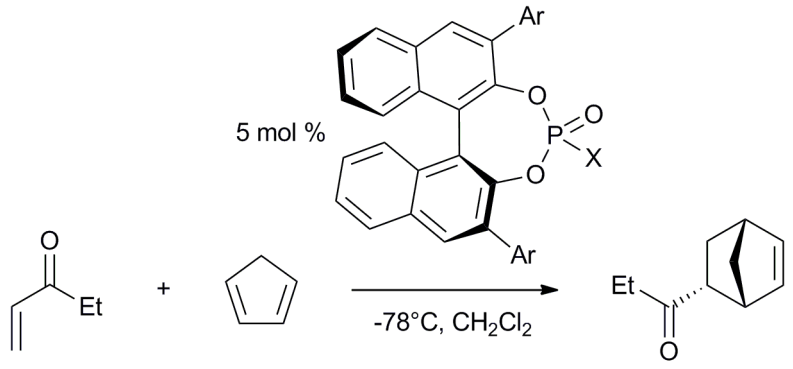
There has been a range of compounds synthesised incorporating the BINOL group, which were envisaged to be stronger Brønsted acid catalysts.

Yamamoto *et al.*[48] set out to create a stronger Brønsted acid catalyst by incorporating an *N*-triflylamide group. The *N*-triflyl phosphoramides were synthesised from the respective (*S*)-BINOL-phosphoryl chlorides and 2 equivalents of $TfNH_2$ (where Tf = SO_2CF_3) (Scheme 3.3). The *N*-triflyl phosphoramides were shown to activate the asymmetric Diels-Alder reactions of ethyl vinyl ketone (Scheme 3.4), unlike 3,3'-diphenyl-BINOL-phosphoric acid.



Conditions: i) $POCl_3$ (1.2 eq.), DMAP (2 eq.), NEt_3 (7 eq.), CH_2Cl_2, 0 °C to 25 °C, 2h
ii) $TfNH_2$ (2 eq.), EtCN, reflux (DMAP = 4-dimethylaminopyridine)

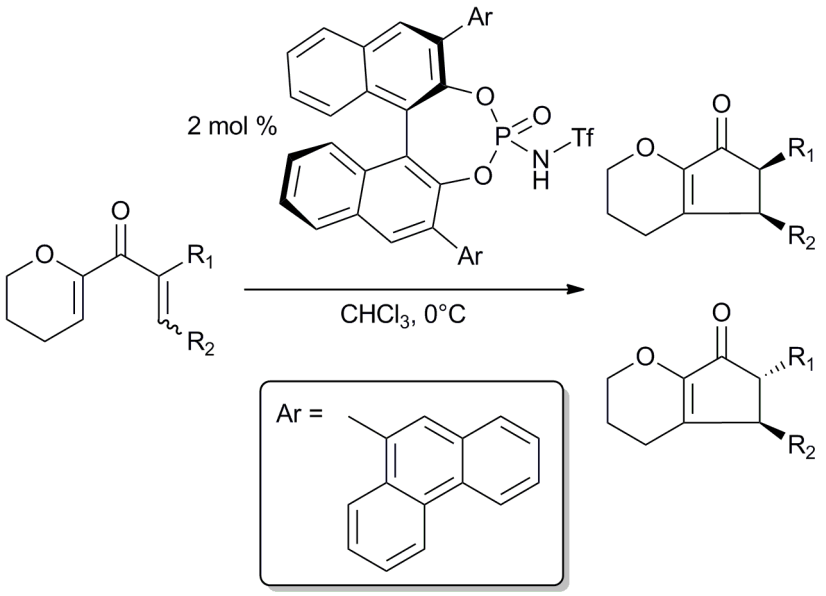
Scheme 3.3: The synthesis of BINOL *N*-triflyl phosphoramides.



1) Ar = Ph, X = OH (0% yield),
2) Ar = Ph, X = NTf (91% yield, (*S*) 9% ee)
3) Ar = 1,3,5-(*i*-Pr)$_3$C$_6$H$_2$, X = NTf (86% yield, (*R*) 32% ee)

Scheme 3.4: The Diels-Alder reaction of ethyl vinyl ketone and pentadiene, catalysed by BINOL- phosphoric acids and *N*-triflylphosphoramides.

Rueping[49] and co-workers applied BINOL *N*-triflyl phosphoramides to the formation of 5-membered ring systems. A range of divinyl ketones were transformed to cyclopentenones, via a Nazarov cyclisation reaction, using 2 mol % of a BINOL *N*-triflyl phosphoramide (Scheme 3.5,Table 3.1).



Scheme 3.5: The Nazarov cyclisation of divinyl ketones to cyclopentanones catalysed by BINOL *N*-triflylphosphoramide.

Table 3.1: Reuping *et al*. results of the Nazarov cyclisation of divinyl ketones to cyclopentanones catalysed by BINOL *N*-triflylphosphoramide

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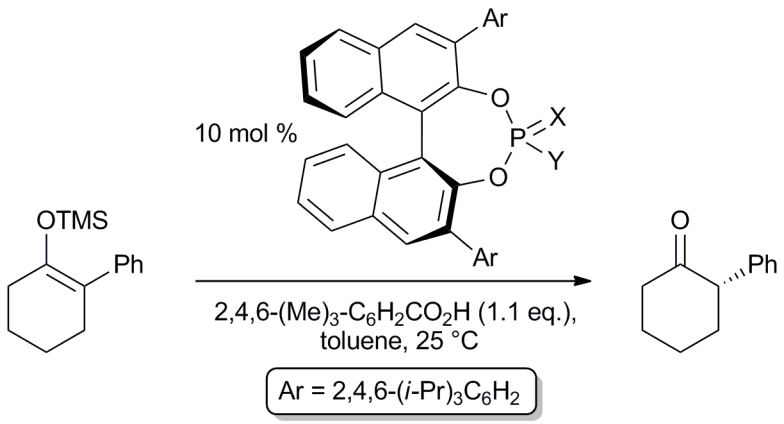
Entry	R_1	R_2	Yield (%)	*cis/trans*	*ee* (*cis*), ee (*trans*)
1	Me	Ph	88	6:1	87, 95
2	*n*-pentyl	Ph	78	3.2:1	91, 91
3	Me	2-naphthyl	92	9.3:1	88, 98
4	Et	Ph	61	4.3:1	92, 96
5	propyl	Ph	85	3.2:1	93, 91

See reference for further examples.

Since their first example of BINOL *N*-triflyl phosphoramides, Yamamoto *et al.* have continued their investigations into stronger Brønsted acid catalysts based on the *N*-triflyl phosphoramide moiety.[50] The group synthesised a range of chiral *N*-triflyl thio- and selenophosphoramides. Several of these catalysts were tested in the protonation of silylenol ethers (Scheme 3.6). The parent acids did not produce any product (Table 3.2 entries 1 and 2), where as the *N*-triflyl- derivates gave almost quantitative yields (Table 3.2, entries 3-5). However, the thio- and seleno-derivatives resulted in higher reactivity and improved enantioselectivity.

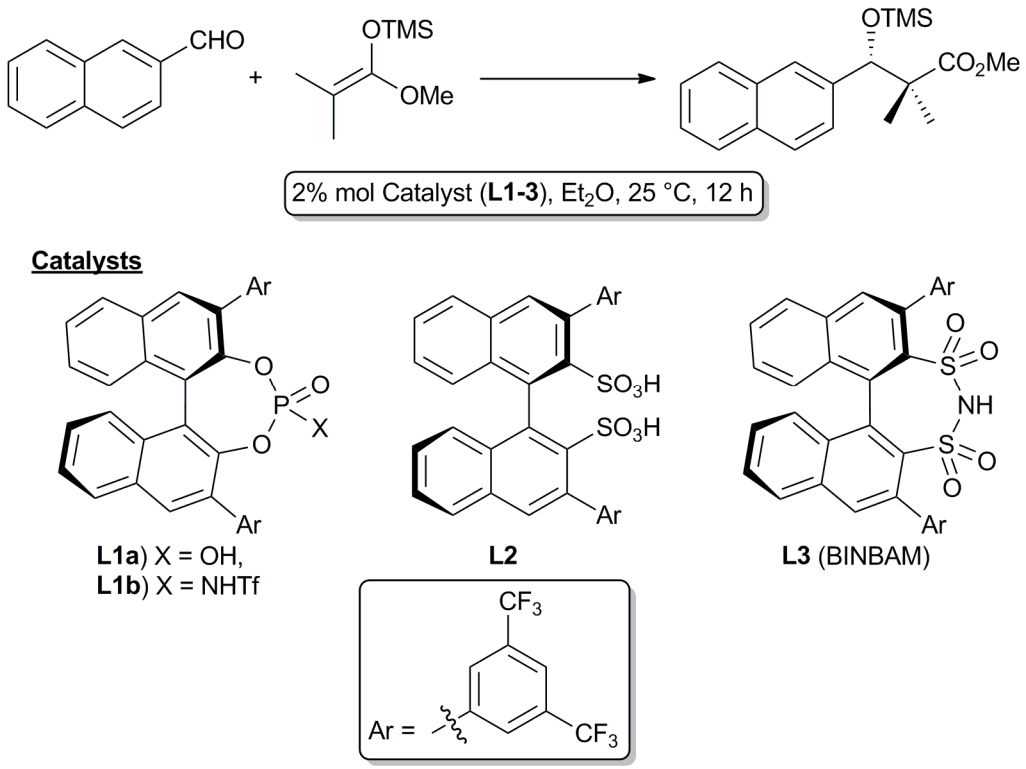


Scheme 3.6: Catalytic screening of the protonation of a silylenol ethers to its cyclohexanone.

Table 3.2: Results of the enantioselective protonations catalyst (*S*)-BINOL-phosphoric acids and its sulphur, selenium and *N*-triflylphosphoramide derivatives (Scheme 3.6)

	Catalyst functionalities				
Entry	**X**	**Y**	**Time (h)**	**Yield (%)**	***er* (*S*:*R*)**
1	O	OH	96	0	-
2	O	SH	96	trace	-
3	O	NHTf	4.5	98	77:23
4	S	NHTf	3.5	97	89:11
5	Se	NHTf	3.5	97	86:14

Continuing the search for stronger chiral Brønsted acid catalysts, Treskow and co-workers synthesised (*R*)-1,1'-binaphthyl-2,2'-bis(sulphon)-amide (BINBAM).[51] List *et al*. tested (*R*)-3,3'-di(trifluoromethyl)phenyl BINBAM (**3**, Scheme 3.7) in the activation of naphthlaldehyde with 1-methoxy-1-trimethylsiloxyethene.[52] 3,3'-di(trifluoromethyl)phenyl BINBAM gave near quantitative product (Table 3.3) with high enantioselectivity, compared to the parent acid (**1a**, Scheme 3.7), *N*-triflyl phosphoramide (**1b**, Scheme 3.7) and disulphoninic acid (**2**, Scheme 3.7), which all gave <2% yield (Table 3.3).



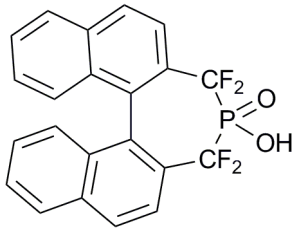
Scheme 3.7: Catalytic screening of the Mukaiyama aldol reaction of 2-naphthaldehyde with a ketene acetal.

Table 3.3: Results of the catalytic screening of the Mukaiyama aldol reaction of 2-naphthaldehyde with a ketene acetal

Entry	Catalyst (Scheme 3.7)	Yield (%)	*er* (*S*:*R*)
1	**L1a**	<2	-
2	**L1b**	<2	-
3	**L2**	<2	-
4	**L3**	>99	90:10

3.2. Rationale

Continuing the development of potentially stronger and more active binaphthyl based Brønsted acid catalysts, 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) was targeted.



1: 2,2-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid.

It was hypothesised that new **1** would be a stronger Brønsted acid than the parent BINOL-phosphoric acids, due to the electron withdrawing properties of the difluoromethylene groups.

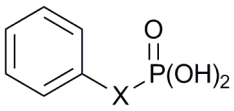


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Table 3.4: pK_a2 values for phenyl phosphate **2** and related benzylic phosphonic acids.

Compound	X	pK_a2
2a	O	6.20
2b	CH_2	7.72
2c	CHF	6.60
2d	CF_2	5.71

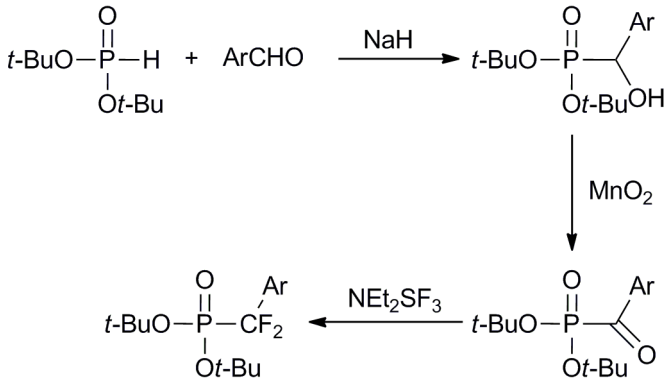
A previous study supports this postulate. Smyth *et al.* reported the pK_a2 values for phenyl phosphate **2a** and related benzylic phosphonic acids **2b-d**.[53] As can be seen from the data obtained (Table 3.4), α,α-difluorobenzyl phosphonic acid **2d** is more acidic than both benzyl phosphonic acid **2b** and phenyl phosphate **2a**.

3.3. Synthetic Challenges

The main synthetic challenge in this work is the formation of the P-CF_2-aryl linkages, which is well documented in the literature.[54]

3.3.1. Literature methods

An early example in the formation of benzylic α,α-difluoromethylphosphonates was performed using (diethylamino)sulphur trifluoride (DAST)[53] (Scheme 3.8).

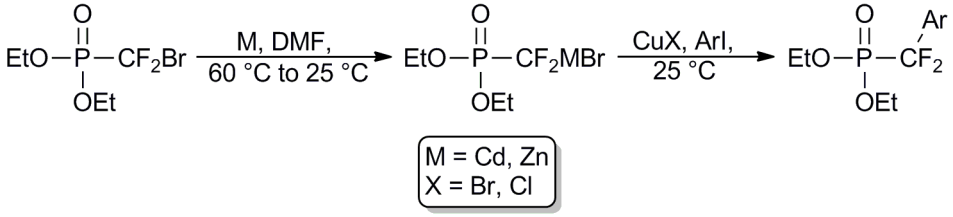


Scheme 3.8: The formation of benzylic α,α-difluoromethylphosphonates using DAST via a benzylketophosphonate.

The authors noted that the reaction was suitable for *tert*-butyl phosphate esters and that methyl- and benzyl- hydroxyphosphonates reverted back to the aldehyde. The reaction was run in neat DAST, with yields of 43% (Ar = Naphthyl) and 79% (Ar = Phenyl) of aryl α,α-difluoromethylphosphonates. This reaction is limited to O*t*-Bu groups and requires a large excess of expensive and hazardous DAST. Yokomatsu[55] also reported "an unpredictable exothermic reaction" when DAST was used on a multi-gram scale.

In another method a range of aryl iodides were reacted, via a CuBr-mediated coupling reaction, with (diethylphosphonyl)difluoromethylcadmium[56] bromide and

(diethylphosphonyl)difluoromethylzinc[55] bromide to give aryl α,α-difluoromethyl-phosphonates and aryl bis(α,α-difluoromethylphosphonates) (Scheme 3.9).

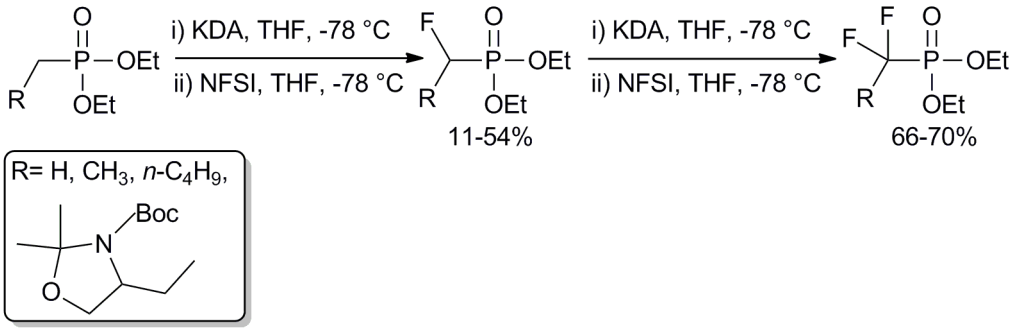


Scheme 3.9: The copper mediated coupling of (diethylphosphonyl)difluoromethylcadmium/zinc bromides with aryl iodides.

The reaction shows good functional group tolerance on the aryl group (-NO_2, -OMe, -Cl, -CO_2R).

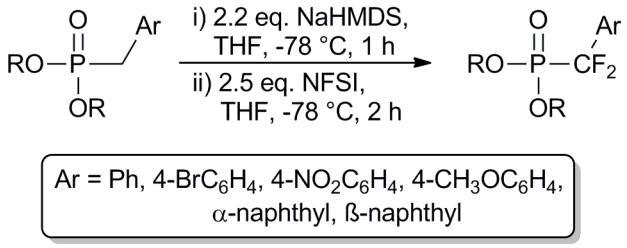
3.3.2. Electrophilic fluorination of alkyl- and benzylic phosphonates

Electrophilic fluorination has been applied to a series of alkyl phosphonates.[57] The reaction proceeds via deprotonation using potassium diisopropylamine (KDA) at reduced temperature followed by the addition of the fluorinating agent *N*-fluorobenzenesulphonimide (NFSI) (Scheme 3.10). This reaction allows for selective mono-fluorination, subsequent to which further fluorination can be performed to give alkyl α,α-difluorophosphonates. The difluoro derivatives could be synthesised from a "one-pot" method however, the yield was reduced (R = Me, 20 % yield) compared to the two stage synthesis (R = Me, 66 % yield).



Scheme 3.10: The electrophilic fluorination of alkyl phosphonates.

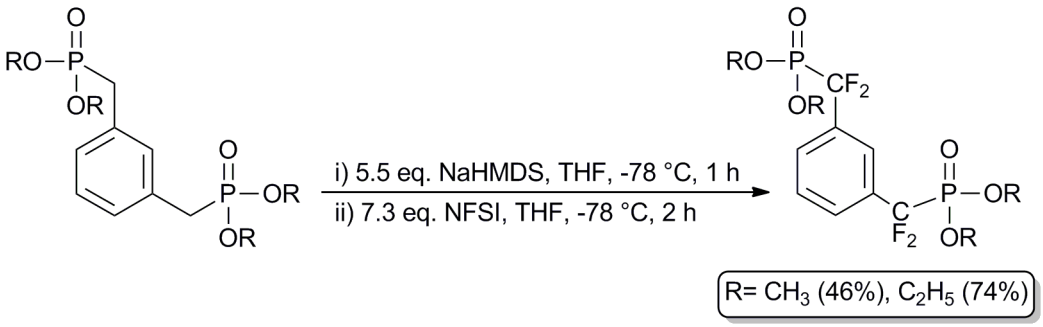
This methodology was then applied to a range of benzylic phosphonates (Scheme 3.11).[58] Taylor and co-workers first studied a range of bases for the initial deprotonation step and found that sodium bis(trimethylsilyl)amide (NaHMDS) consistently gave the highest yields and LDA producing the lowest yields.



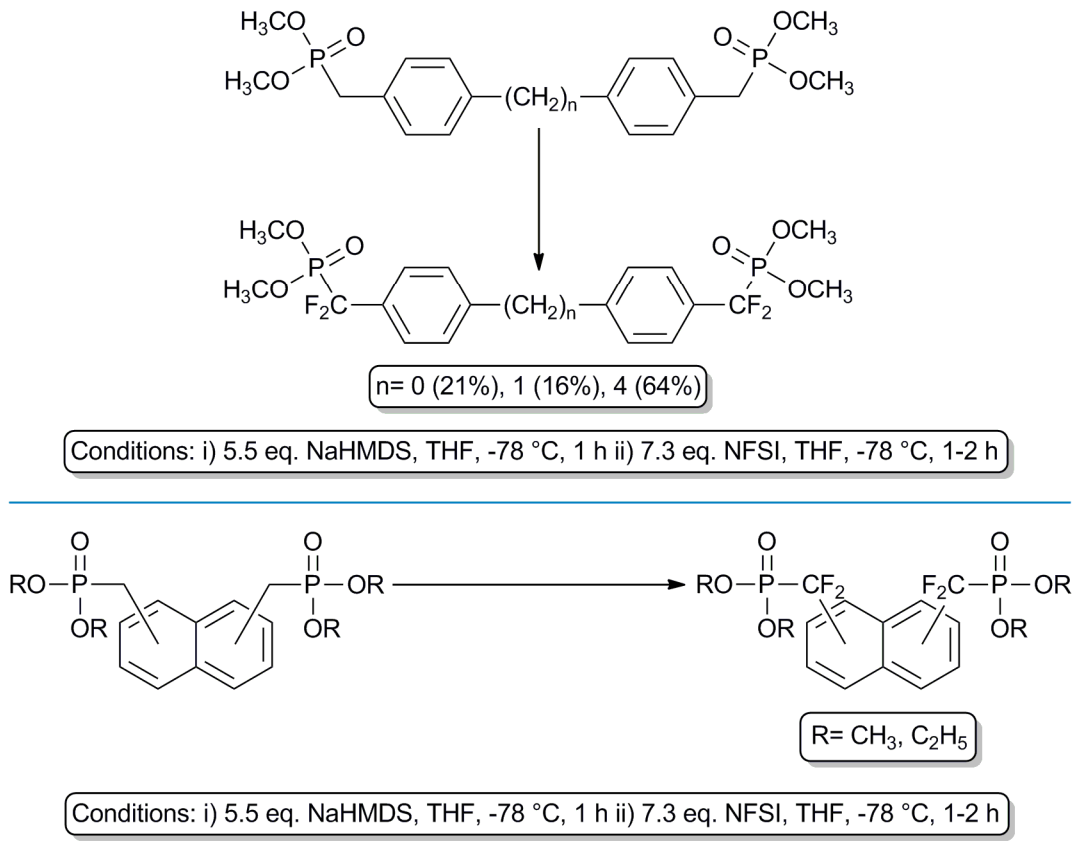
Scheme 3.11: The electrophilic fluorination of benzylic phosphonates.

A range of benzylic mono(α,α-difluoromethylphosphonates) (Scheme 3.11) were synthesised, in good yields, using 2.2 equivalents of NaHMDS and 2.5 equivalents of NFSI. The mono-derivative (where Ar = Ph) was accessed in good yield by using 1.1 equivalents NaHMDS and NFSI. Interestingly the group noticed no change in yields between a one-pot synthesis of benzylic α,α-difluorophosphates and isolation of benzylic α-monofluorophosphates followed by further fluorination, unlike in Differding's research (Scheme 3.10).

Taylor and co-workers extended their method to the formation of a range of benzylic bis(difluoromethylphosphonates) in modest to good yields (Scheme 3.12 and Scheme 3.13).



Scheme 3.12: The synthesis of 1,3-bis[(diethylphosphono)difluoromethyl]-benzene and 1,3-bis[(dimethylphosphono)difluoromethyl]benzene.

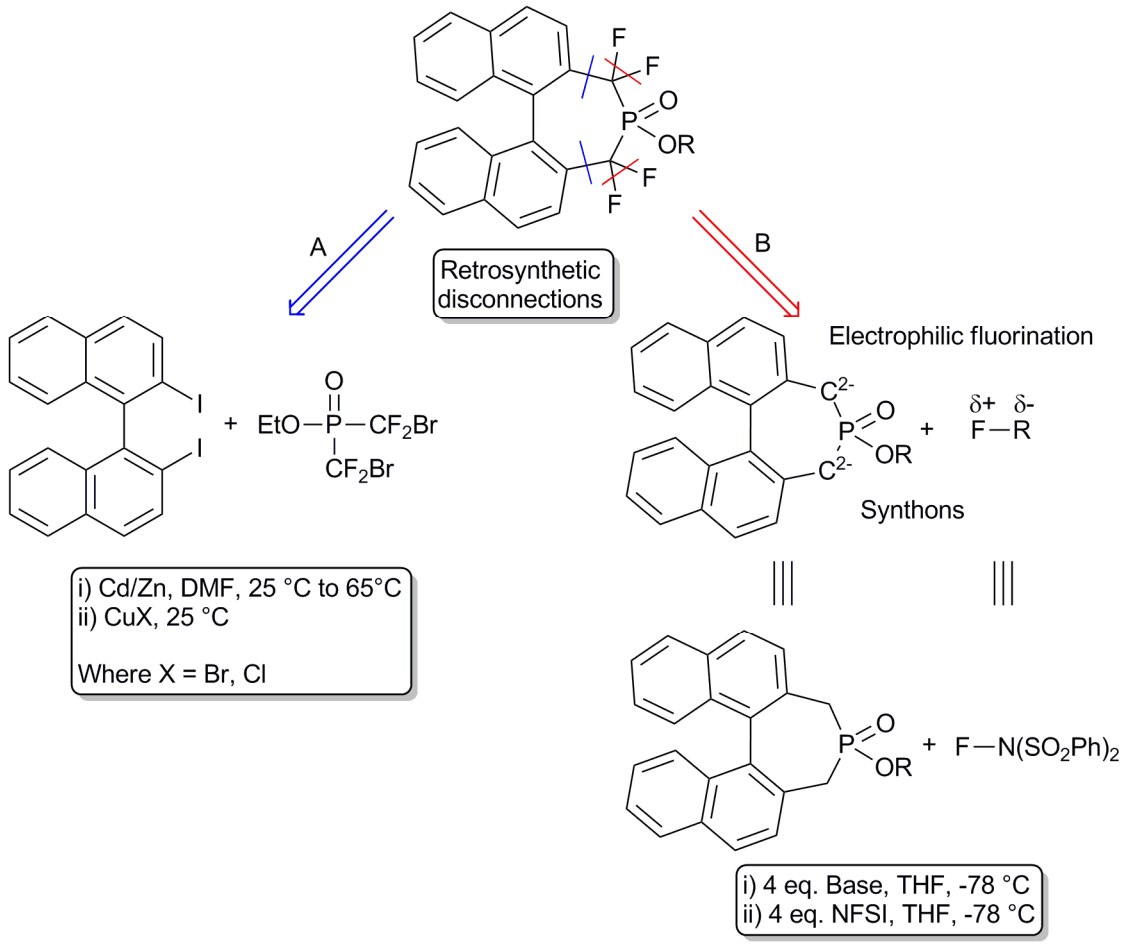


Scheme 3.13: The fluorination of diphenyl bis(phosphonates) and naphthyl bis(phosphonates).

The electrophilic fluorination of benzylic phosphonates is a more desirable route to benzylic α,α-difluoromethylphosphonates compared with the previous methods described for several reasons. NFSI is commercially available, cheaper and less hazardous than DAST. The work described above shows a good tolerance of functional groups. Multiple fluorinations, such as with bis(phosphonates), can be performed in a one-pot method.

3.4. Possible Synthetic routes to 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid

Based on the previous literature, described in the previous section, there appears to be two reasonable routes in the synthesis of **1** (Scheme 3.14 routes A and B).



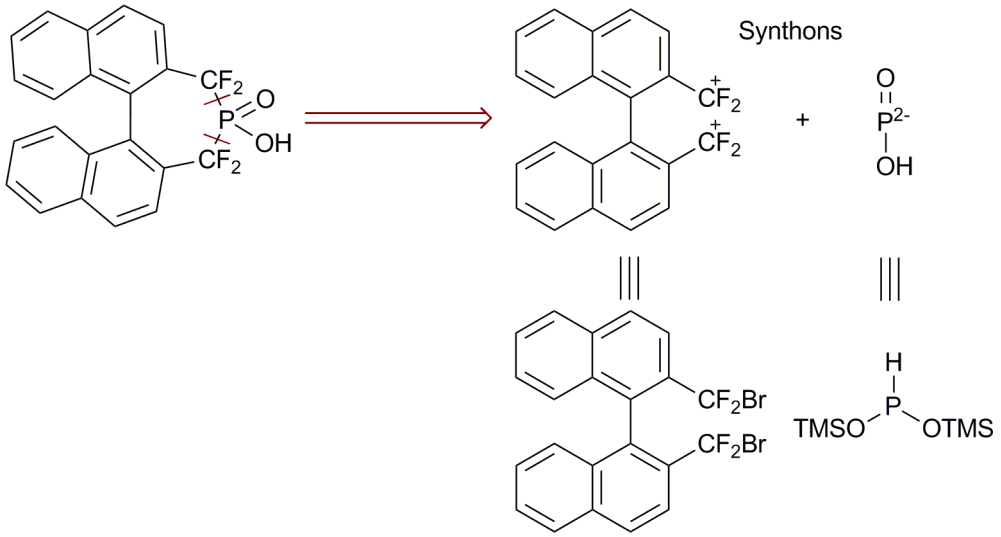
Scheme 3.14: Retrosynthetic analysis for the synthesis of **1**.

Route A is based on the Cu-halide mediated coupling reaction of group 12 metal-bromodifluoromethylphosphonates with aryl halides. In this case ethyl bis(bromodifluoromethyl)phosphonate would be required with 2,2'-diiodo-1,1'-binaphthalene. The reaction would need to proceed via a ring closure step at the 2,2' positions on the binaphthalene with the difluorobromomethyl groups.

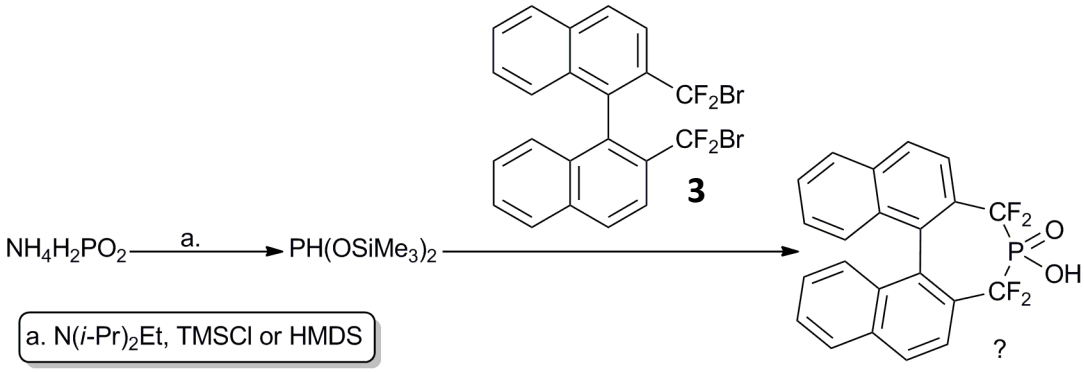
Route B is based on work by Taylor *et al.* on the electrophilic fluorination of benzylic phosphonates. In route B the deprotonation of the methylene linkage of 2,2'-bis(methylene)-1,1'-binaphthyl phosphinate followed by fluorination with NFSI could give 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate, which after deprotection of the phosphinate ester group would give **1**. It has been previously shown that four simultaneous fluorinations could be performed, on a range of benzylic phosphonates (Scheme 3.12 and Scheme 3.13) in a one pot procedure. However, no examples are present in the literature on the fluorination of benzylic phosphinates $(ArCH_2)_2$-P(O)OEt by this method.

Route B was selected over route A, in the synthesis of **1**, as the fluorination is selective to the benzylic moiety. Also it has previously been shown that two benzylic groups can be fluorinated in a one-pot procedure, under facile conditions. Also there appears to be no examples of the synthesis of phosphinates by route A.

A third option is presented in Scheme 3.15 and is based on the work mentioned in chapter one. However, due to the results (low yields) in Chapter One, this method did not seem a viable option (Scheme 3.16). Also the synthesis of 2,2-bis(difluorobromomethyl)1,1'-binaphthalene (**3**) was investigated, by electrophilic fluorination with NFSI, but no product was observed. This method would require the reaction between 2,2'-bis(difluorobromomethyl)-1,1'-binaphthyl and BTSP (Scheme 3.16).

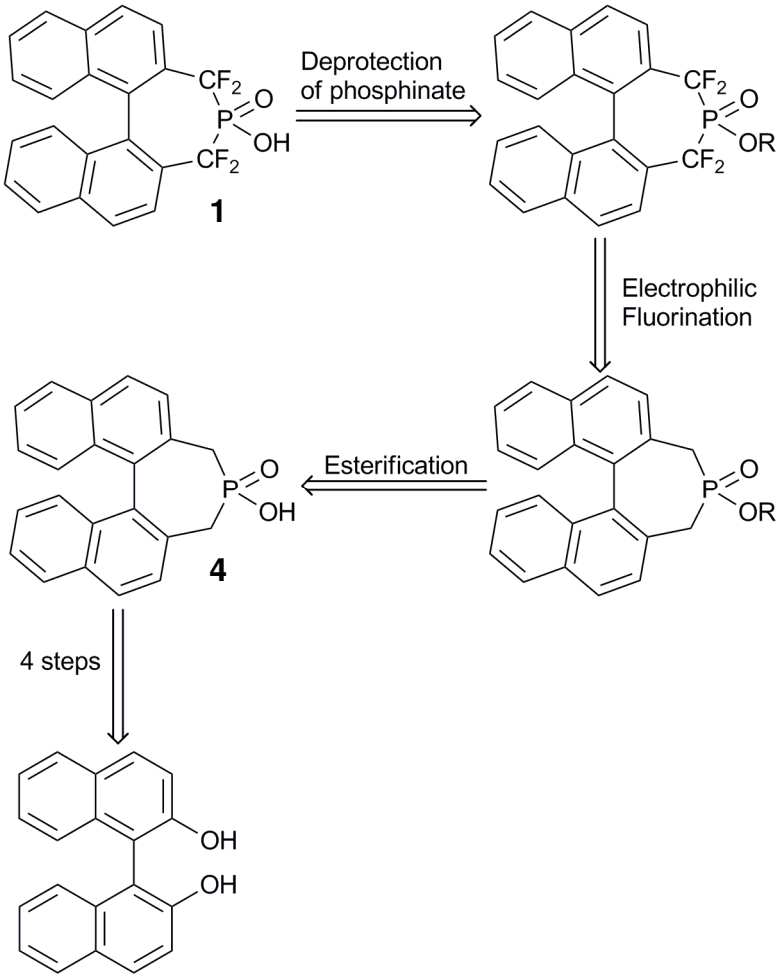


Scheme 3.15: Retrosynthetic scheme of acid **1** based on Regan/Boyd methodology.



Scheme 3.16: Possible reaction scheme for Regan/Boyd procedure to acid **1**.

Scheme 3.17 shows the retrosynthetic analysis, by means of electrophilic fluorination, of **1**. As can be seen phosphinic acid **4** is an excellent starting point in this synthesis.[7]

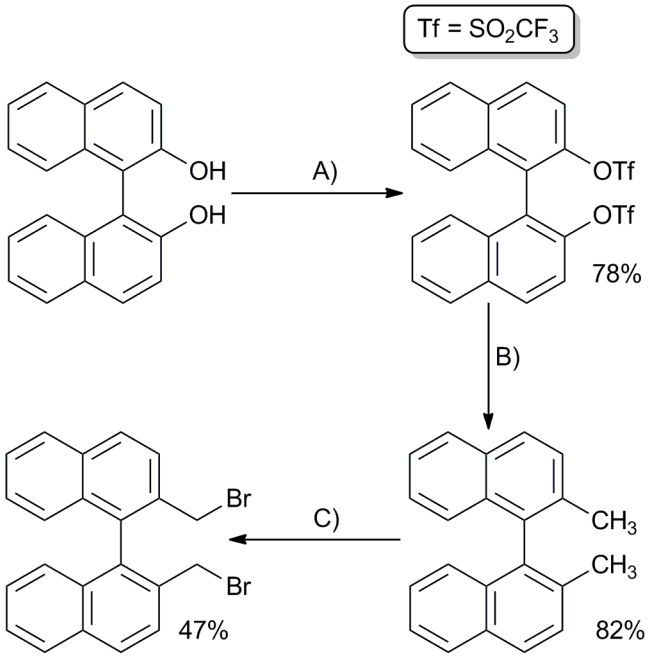


Scheme 3.17: Retrosynthetic scheme for the total synthesis of target compound **1**

3.5. Results and Discussion

3.5.1. The synthesis of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid

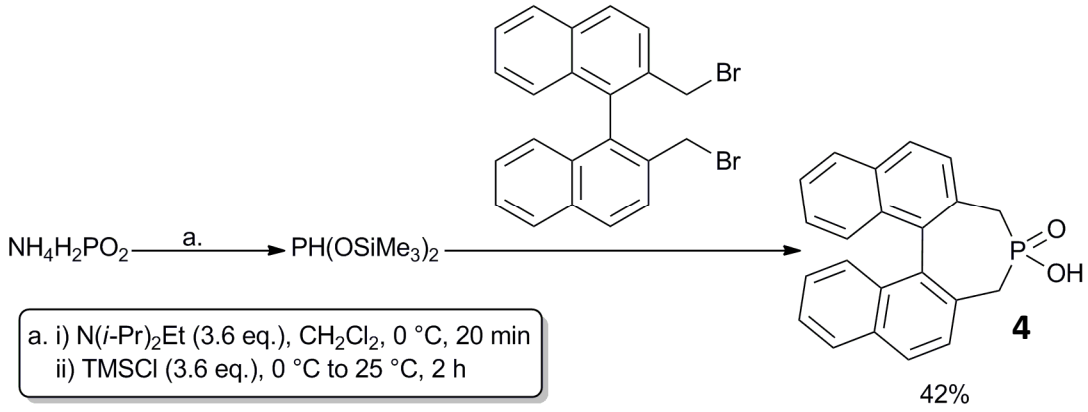
Moberg and co-workers have previously synthesised 2,2'-bis(methylene)-1,1'-binaphthyl phosphinic acid (**4**).[7] This was synthesised from 2,2'-di(bromomethyl)-1,1'-binaphthyl, which was accessed from commercially available BINOL in three steps (Scheme 3.18). Racemic BINOL was transferred to 2,2'-bis(trifluoro-methanesulfonate)-1,1'-binaphthyl.[59] 2,2'-dimethyl-1,1'-binaphthyl was synthesised from bis(trifluoromethanesulfonate)-1,1'-binaphthyl with methyl magnesium iodide in the presence of a nickel catalyst.[60]



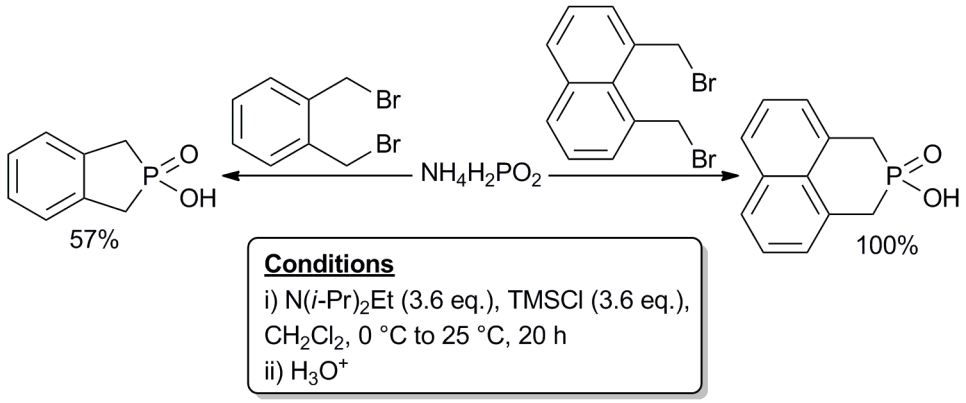
Scheme 3.18: The synthesis of di(bromomethyl)-1,1'-binapthalene from racemic BINOL.

2,2'-di(bromomethyl)-1,1'-binaphthalene was synthesised by a modified procedure.[61] The radical bromination of 2,2'-dimethyl-1,1'-binaphthyl with *N*-bromosuccinimide was carried out in tetrachloroethylene, in place of CCl_4. The reaction proceeded with the aid of a UV lamp and heating, to give 2,2'-di(bromomethyl)-1,1'-binaphthalene in a yield of 47%.

The reaction to produce 2,2'-bis(methylene)-1,1'-binaphthyl phosphinic acid (**4**) (Scheme 3.19)[7] is an extension of the methodology of Boyd and co-workers previous work on the formation of cyclic phosphinic acids from the reactive intermediate BTSP (Scheme 3.20).[62]

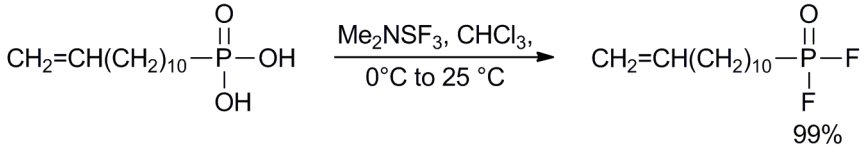


Scheme 3.19: The synthesis of bis(methylene)-1,1'-binapthyl phosphinic acid.



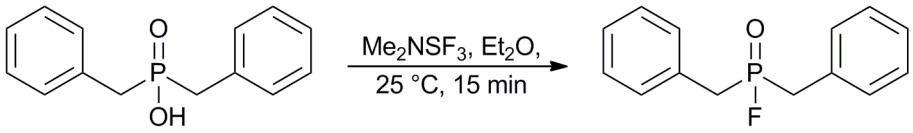
Scheme 3.20: Previous cyclo-phosphinic acids synthesised by Boyd *et al*.

Protection of the phosphinic acid group of **4** was required as phosphonic and phosphinic OH functionalities can be susceptible to fluorination, generating P-F bonds. For example, the reaction of a straight chain phosphonic acid with DAST proceeds at room temperature giving the corresponding difluorophosphonate in quantitative yield (Scheme 3.21).[63]



Scheme 3.21: Fluorination of a phosphonic acid to its difluorophosphonate.

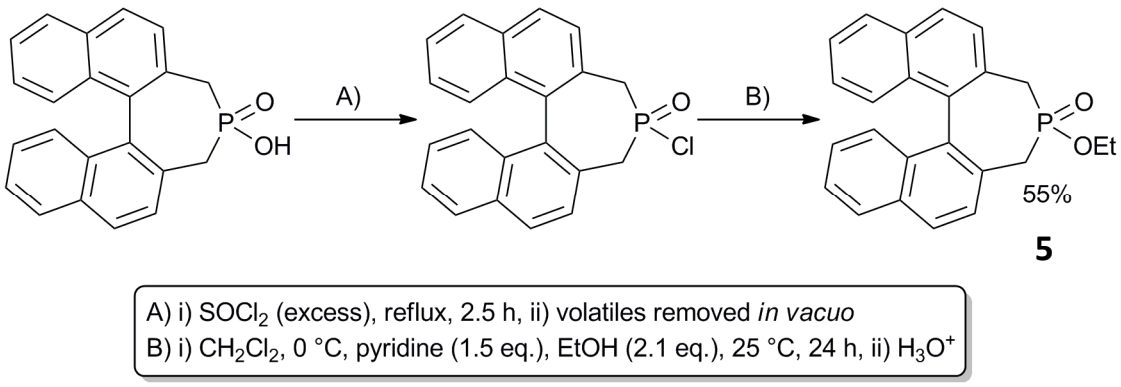
Another example includes the fluorination of dibenzyl phosphinic acid to dibenzyl fluorophosphinate (Scheme 3.22).



Scheme 3.22: Fluorination of dibenzyl phosphinic acid to dibenzyl fluorophosphinate.

In order to protect the OH group, the phosphinic acid was esterified, in a one-pot procedure (Scheme 3.23). The acid **4** was converted to the acid chloride derivative by refluxing in neat $SOCl_2$. The remaining $SOCl_2$ was removed under reduced pressure. The resulting acid chloride was stirred with absolute ethanol in the presence of pyridine to give crude phosphinate ester. Purification by silica gel

chromatography afforded ethyl 2,2'-bis(methylene)-1,1'-binaphthyl phosphinate (**5**) in 55% yield.



Scheme 3.23: The esterification of 2,2'-bis(methylene)-1,1'-binaphthyl phosphinic acid.

The proton NMR spectrum of **5** (Figure 3.2) shows the POEt group as a multiplet situated at δ 4.13 and a triplet at δ 1.31. The methylene linkages are also observed in the form of a multiplet at δ 3.2. However, a more complex multiplet, compared to **4** could indicates non-equivalency of the methylene protons. This is likely due to the lack of tautomerisation of the phosphinate moiety compared to the phosphinic acid group.

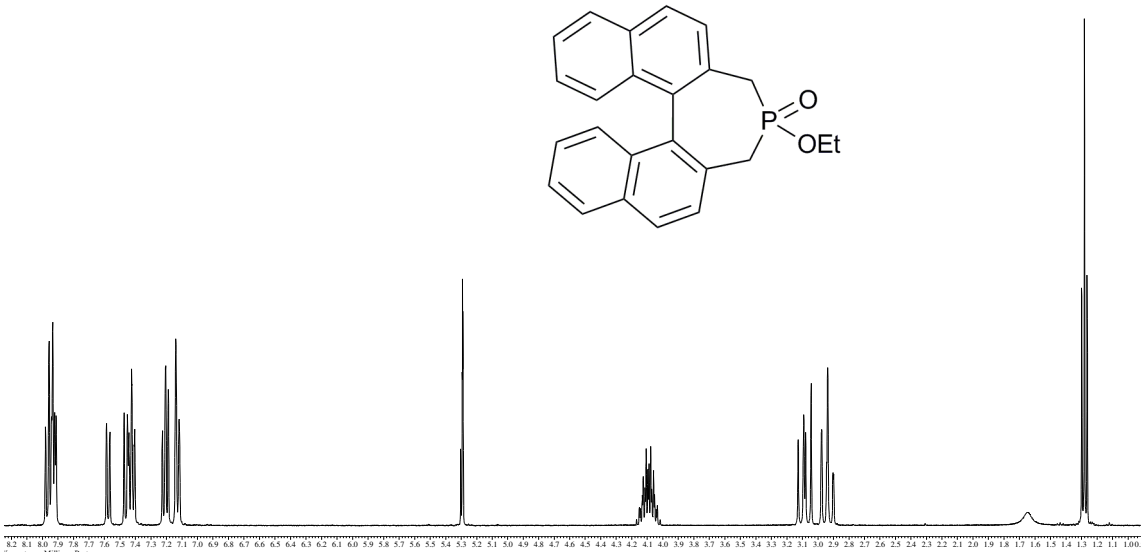
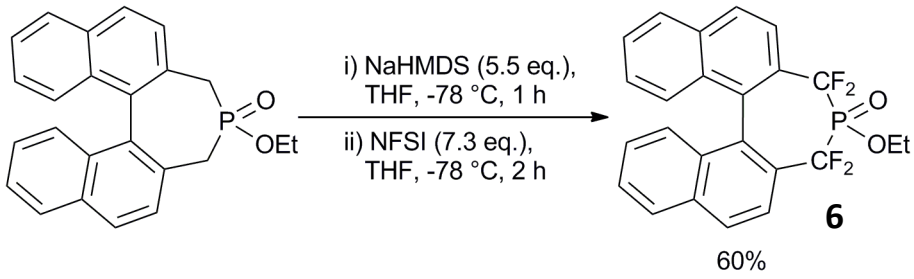


Figure 3.2: ^{1}H NMR spectrum of **5** (CD_2Cl_2).

Phosphinate **5** was then subjected to electrophilic fluorination. First the methylene linkages were deprotonated with NaHMDS at -78℃ in THF for 1 hour. NFSI was then added over a period of 3 minutes to the deep red solution and stirred for 2 hours (Scheme 3.24). An aqueous quench and extraction with EtOAc gave crude 2,2-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**). Trace amounts of partially fluorinated side products were observed by ^{31}P NMR data, but were not isolated. Purification by column chromatography gave **6** in 60% yield.



Scheme 3.24: The fluorination of ethyl 2,2'-bis(methylene)-1,1'-binapthyl phosphinate.

The ^{1}H NMR spectrum of **6** (Figure 3.3) was similar to the of the non-fluorinated phosphinate **5**, with the expected lack of methylene protons.

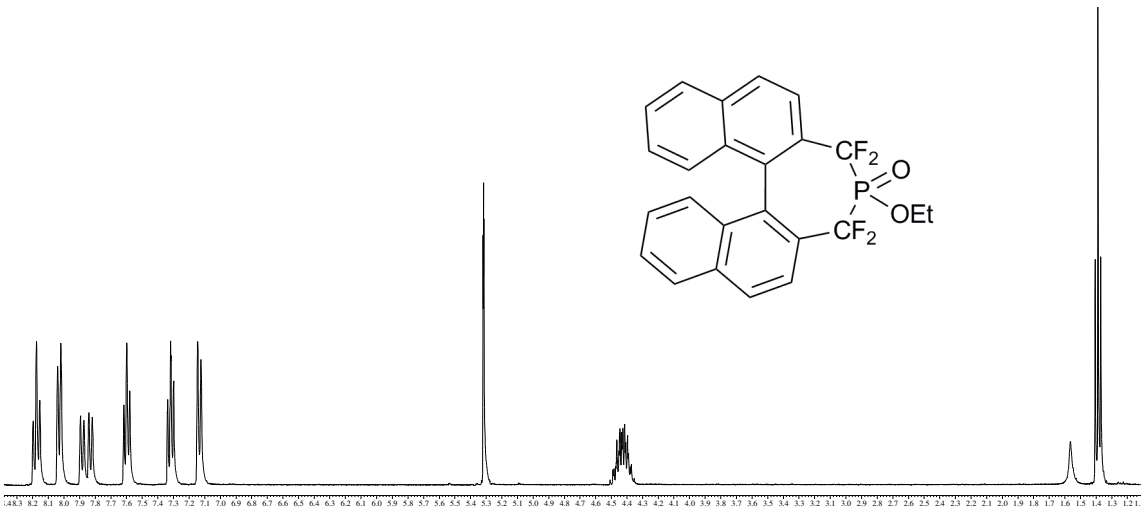


Figure 3.3: ^{1}H NMR spectrum of **6** (CD_2Cl_2).

The fluorine NMR spectrum for **6** (Figure 3.4) suggested that the fluorine atoms are non-equivalent. This again is likely due to the lack of tautomerisation of the phosphinate moiety and also due to the lack of rotation of the CF_2 groups. Each fluorine is split into a doublet of doublets with a J values of 87-115 Hz for the two bond P-F coupling and 280-290 Hz for two bond F-F coupling.

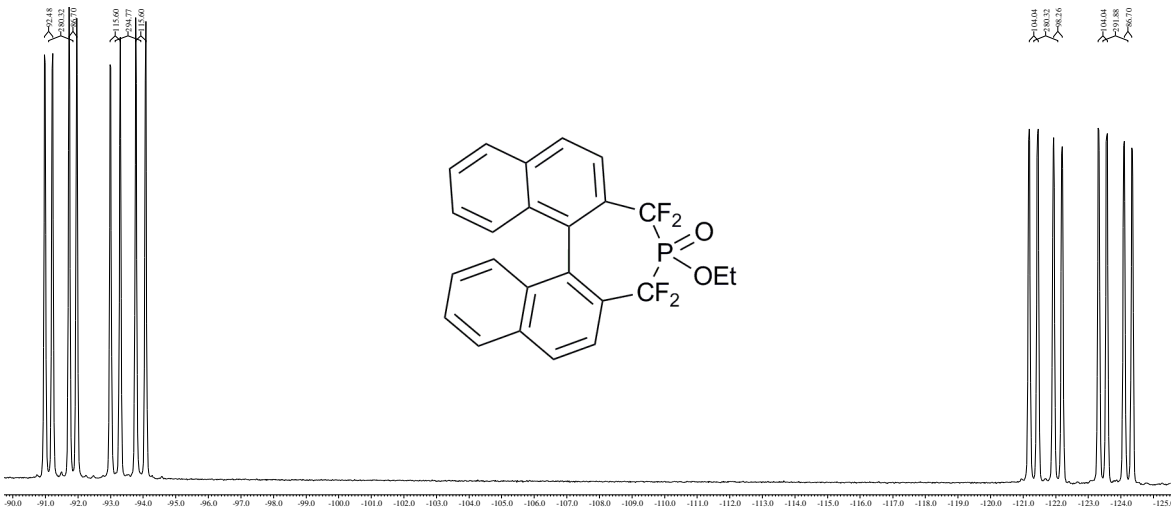


Figure 3.4: ^{19}F NMR spectrum of **6** (CD_2Cl_2).

The phosphorus NMR spectrum of **6** (Figure 3.5) suggests that the compound has non-equivalent groups present. A multiplet is observed with some un-resolved fine structure present, which could be due to coupling from the ethoxy protons over three bonds.

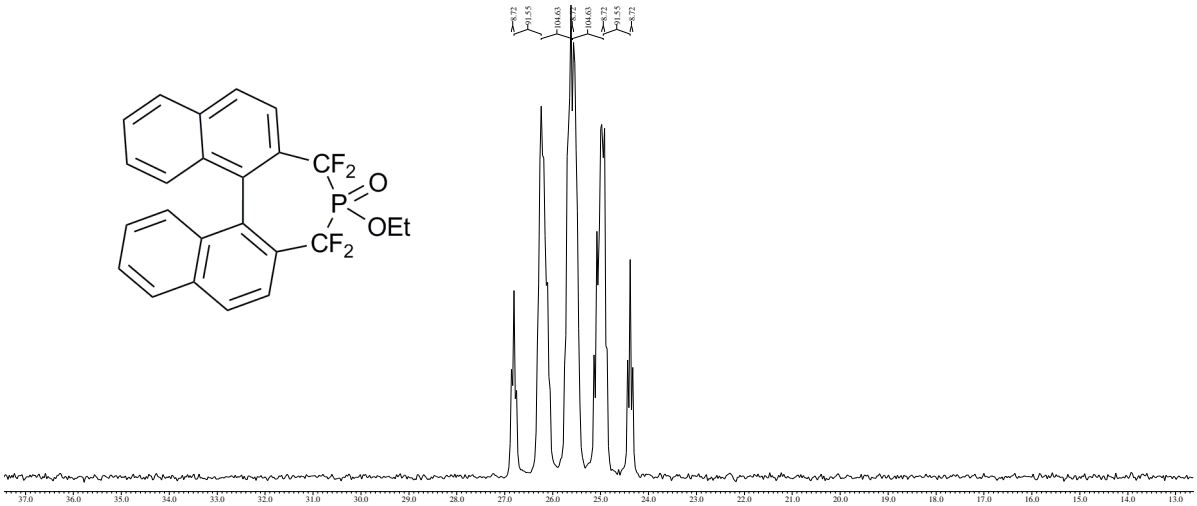


Figure 3.5: ^{31}P NMR spectrum of **6** (CD_2Cl_2).

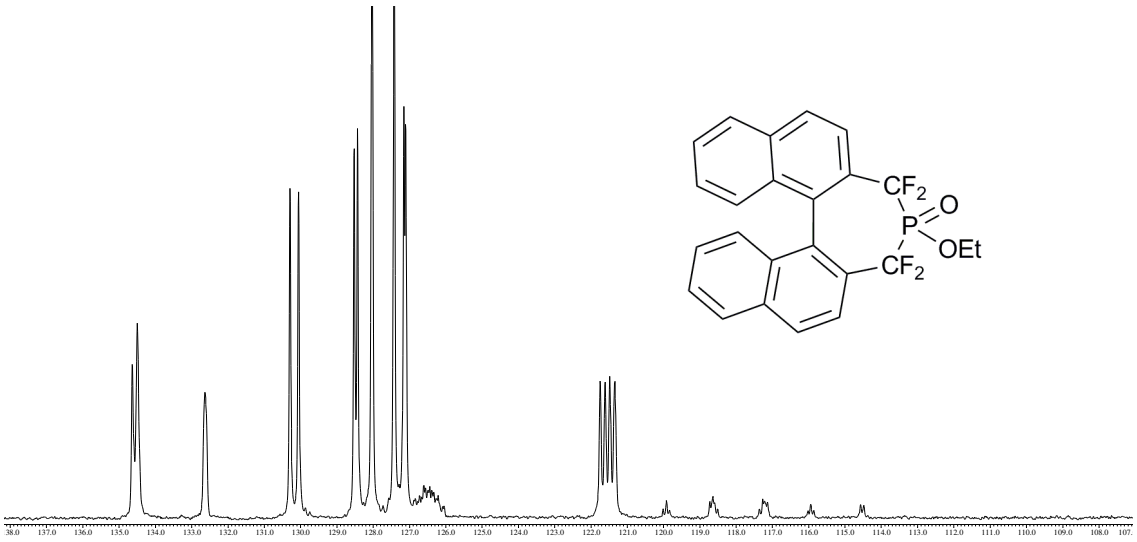
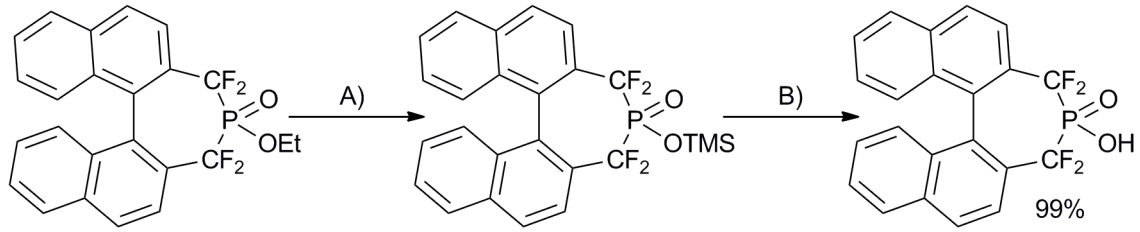


Figure 3.6: ^{13}C NMR spectrum of **6** (CD_2Cl_2).

A doublet of triplets, at δ 118, are observed in the ^{13}C NMR spectrum of **6** (Figure 3.6), for the CF_2 groups with a C-P coupling of 138 Hz and C-F of 271 Hz.

The final stage in the step-wise synthesis of **1**, was the de-protection of the phosphinate moiety to the phosphinic acid. Typically this can be performed by alkaline or acid hydrolysis. However, fluorinated alkyl groups can be susceptible to cleavage in harsh basic or acidic conditions. Therefore the method of McKenna *et al.* is used, which is utilised for sensitive functionalties.[64, 65] The de-protection involves the transfer of the phosphinate to its trimethylsiloxy derivative, by reaction with trimethylsilyl bromide (TMSBr), followed by hydrolysis with water or an alcohol to give the acid.

Refluxing **6** with TMSBr in CH_2Cl_2, followed by hydrolysis with methanol gave bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid **1** in quantitative yield (Scheme 3.25).



A) i) TMSBr (2.1 eq), CH_2Cl_2, reflux, 4 d, ii) volatiles removed *in vacuo,*
B) MeOH, 25 °C, 24 h

Scheme 3.25: De-protection of ethyl 2,2-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**) to 2,2-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) via a trimethylsilyl ester.

In the ^{1}H NMR spectrum of **1**, the P-OH moiety was observed as a broad singlet (δ 11, integration of 1H) (Figure 3.7).

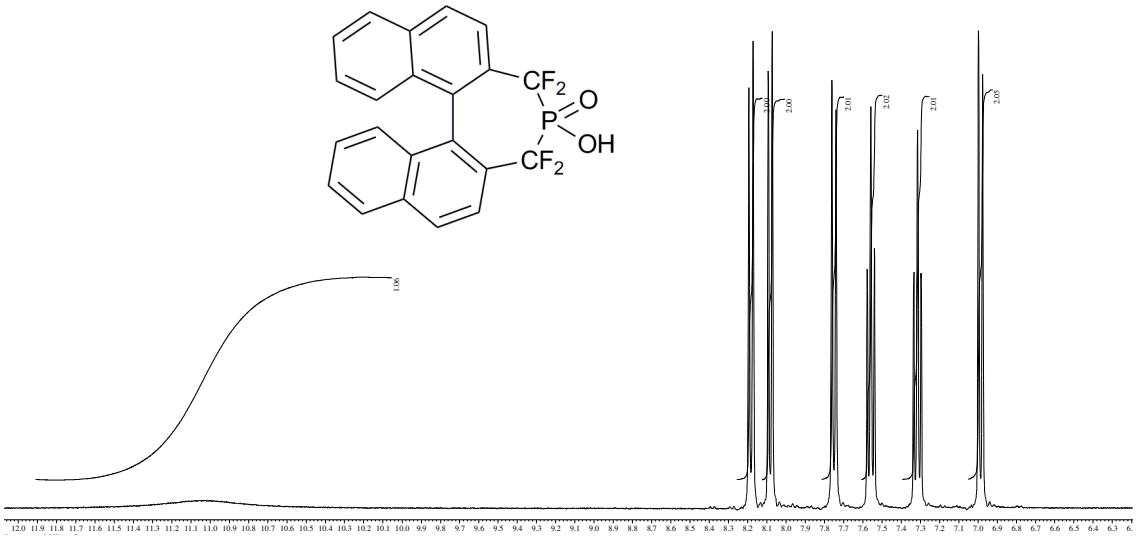


Figure 3.7: ^{1}H NMR spectrum of **1** (DMSO- d_6).

The aromatic protons appear as 6 peaks, in the aromatic region with an integration of 12. A peak at δ 5.75 is residual CH_2Cl_2 remaining in the sample.

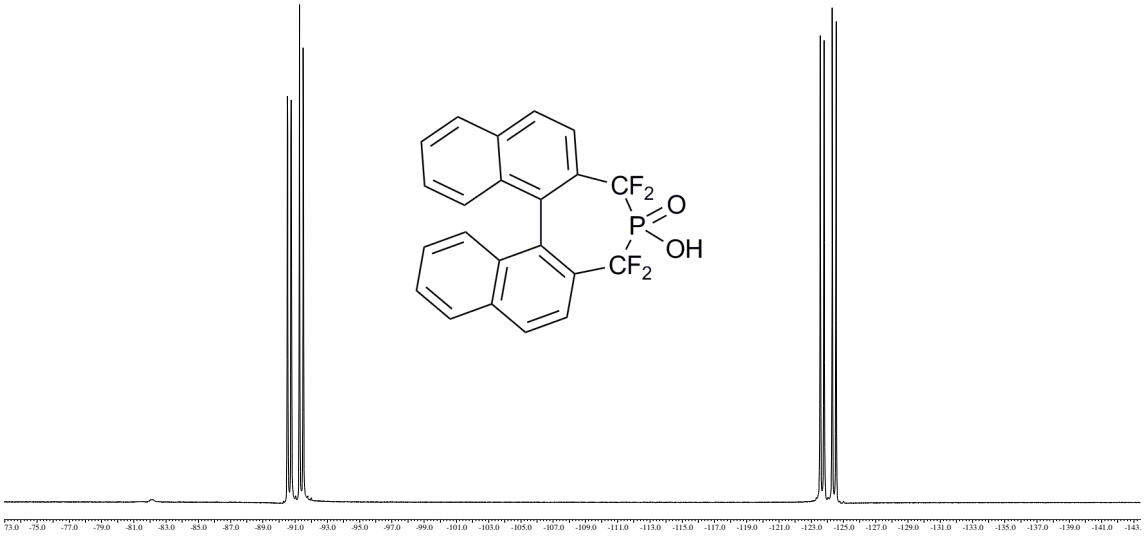


Figure 3.8: ^{19}F NMR spectrum of **1** (DMSO- d_6).

The ^{19}F NMR spectrum of **1** (Figure 3.8) shows a simpler splitting pattern than the observed peaks in the ^{19}F NMR data of **6**. This suggests that a layer of non-equivalency has been removed from **6** to **1**. This is likely due to the tautomerisation of the phosphinic acid group compared to the fixed phosphinate functionality.

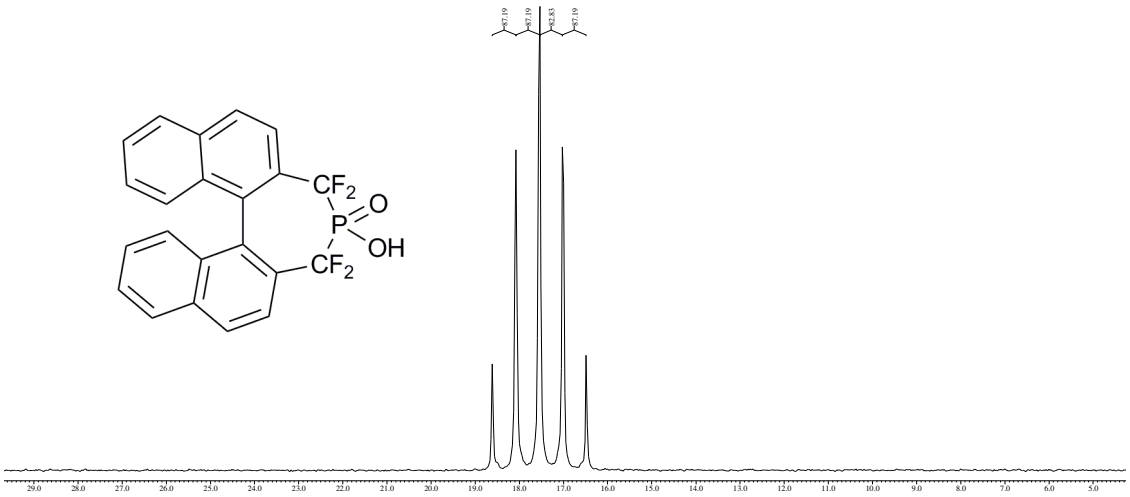


Figure 3.9: ^{31}P NMR spectrum of **1** (DMSO- d_6).

A pentet is observed in the ^{31}P NMR spectrum of **1** (Figure 3.9).

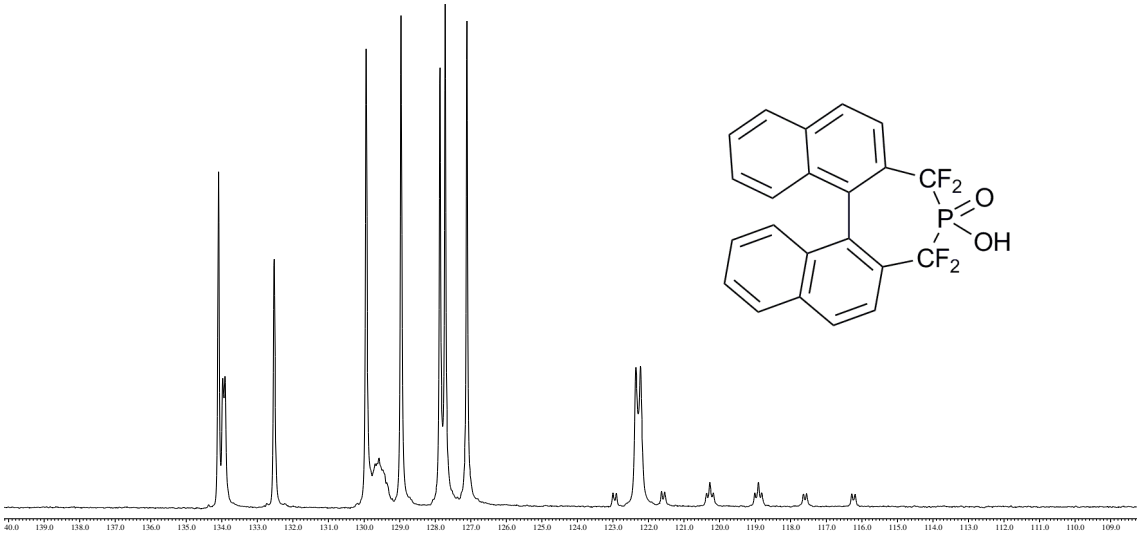


Figure 3.10: ^{13}C NMR spectrum of **1** (DMSO- d_6).

A doublet of triplets, at δ 119, is observed in the ^{13}C NMR spectrum of **1** (Figure 3.10), similar to that observed for the ^{13}C NMR spectrum of **6**. Both the C-P coupling and C-F coupling (137 Hz and 269 Hz respectively) are similar to that of **6** (138 Hz and 271 Hz respectively).

In summary the target compound **1** was successfully synthesised and isolated in a seven-step procedure starting from commercially available racemic BINOL. Full characterisation has been performed on new compounds formed in this synthesis. The X-ray crystal structures of **1** and **6** have been determined and are presented below (Section 3.5.2).

3.5.2 X-ray structures of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid and ethyl 2,2'-bis(difluoro-methylene)-1,1'-binaphthyl phosphinate

X-ray structure determination of both the phosphinate ester **6** and target acid **1**, is of interest due to its potential use in asymmetric catalysed reactions. Selected parameters for the crystal structures can be found in Table 5.1, page 163.

3.5.2.1. 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid

Two independent molecules (**A** and **B**) were observed in the crystal structure of **1**. The two independent molecules differ in the orientation of the binaphthyl group and in the orientation of the CF_2 linkages to the P=O and P-OH moieties (See Figure 3.11 and Figure 3.12). However, bond lengths and bond angles are very similar in **A** and **B**. Therefore the molecules are discussed as one compound, using average bond lengths and bond angles.

The phosphorus centre is not tetrahedral. The O-P=O angle (117.71°, Table 3.5, entry 1) is more acute than the CF_2-P-CF_2 angle (105.41, Table 3.5, Entry 6). The difluoromethylene groups are not tetrahedral. The F-C-F angle (105.89°, Table 3.5, Entries 8 and 14) is more accute than the P-C-C(naphthyl) angle (112.63°, Table 3.5, Entries 7 and 13). The CF_2 functional groups appear to by non-equivalent. The F-C-P angles vary by 5° (Table 3.5, Entries 11 and 12, 17 and 18).

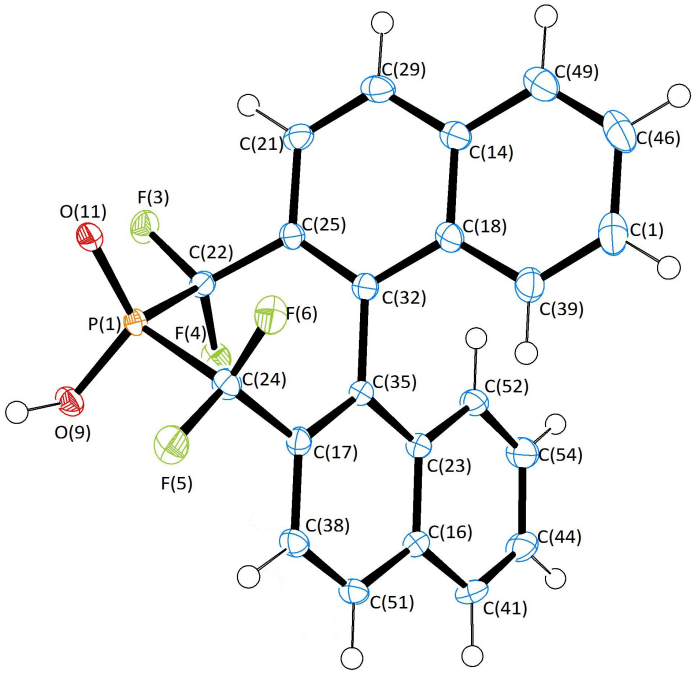


Figure 3.11: Labelled molecular structure of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) molecule **A**. Ellipsoids are drawn at 50% probability.

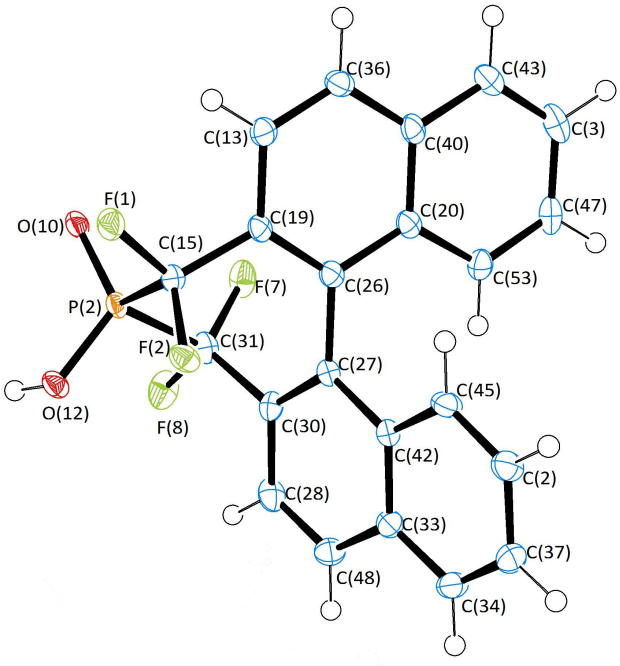


Figure 3.12: Labelled molecular structure of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) molecule **B**. Ellipsoids are drawn at 50% probability.

Table 3.5: Selected bond angles and dihedral angles between naphthyl groups in molecules **A** and **B** of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**)

Entry	Molecule A Bond angles (°)		Molecule B Bond angles (°)	
1	O(11)-P(1)-O(9)	117.64(8)	O(10)-P(2)-O(12)	117.77(8)
2	O(11)-P(1)-C(22)	110.90(8)	O(10)-P(2)-C(15)	110.71(8)
3	O(9)-P(1)-C(22)	104.90(8)	O(12)-P(2)-C(15)	105.70(8)
4	O(11)-P(1)-C(24)	110.86(8)	O(10)-P(2)-C(31)	110.93(8)
5	O(9)-P(1)-C(24)	105.94(8)	O(12)-P(2)-C(31)	105.81(8)
6	C(22)-P(1)-C(24)	105.79(8)	C(15)-P(2)-C(31)	105.03(8)
7	C(25)-C(22)-P(1)	110.97(12)	C(19)-C(15)-P(2)	111.37(12)
8	F(3)-C(22)-F(4)	105.60(14)	F(2)-C(15)-F(1)	106.03(13)
9	F(3)-C(22)-C(25)	111.44(15)	F(2)-C(15)-C(19)	112.66(15)
10	F(4)-C(22)-C(25)	112.41(15)	F(1)-C(15)-C(19)	110.85(15)
11	F(3)-C(22)-P(1)	105.90(12)	F(2)-C(15)-P(2)	109.85(12)
12	F(4)-C(22)-P(1)	110.20(12)	F(1)-C(15)-P(2)	105.72(12)
13	C(17)-C(24)-P(1)	113.62(13)	C(30)-C(31)-P(2)	114.54(13)
14	F(6)-C(24)-F(5)	105.99(14)	F(7)-C(31)-F(8)	105.93(14)
15	F(6)-C(24)-C(17)	112.23(15)	F(7)-C(31)-C(30)	112.35(16)
16	F(5)-C(24)-C(17)	111.14(15)	F(8)-C(31)-C(30)	111.09(16)
17	F(6)-C(24)-P(1)	108.90(12)	F(7)-C(31)-P(2)	107.47(13)
18	F(5)-C(24)-P(1)	104.42(12)	F(8)-C(31)-P(2)	104.84(12)
Dihedral angles between naphthyl moieties (°)				
Entry	**Molecule A**		**Molecule B**	
19	70.7		68.8	

The longest bonds in compound **1** are the P-CF_2 linkages. The average length is 1.870 Å (Table 3.6, Entries 3 and 4). The CF_2-C(naphthyl) linkages are considerably shorter, than the P-CF_2 linkages at 1.502 Å. A full list of bond lengths are shown in Table 3.6 below.

Table 3.6: All bond lengths in molecules **A** and **B** of 2,2'-bis(difluoro-methylene)-1,1'-binaphthyl phosphinic acid (**1**)

	Molecule A		Molecule B	
Entry	**Bond**	**Bond distance (Å)**	**Bond**	**Bond distance (Å)**
1	P(1)-O(11)	1.4818(13)	P(2)-O(10)	1.4864(13)
2	P(1)-O(9)	1.5437(14)	P(2)-O(12)	1.5382(14)
3	P(1)-C(22)	1.869(2)	P(2)-C(15)	1.8651(19)
4	P(1)-C(24)	1.8720(19)	P(2)-C(31)	1.871(2)
5	F(3)-C(22)	1.369(2)	F(1)-C(15)	1.371(2)
6	F(4)-C(22)	1.370(2)	F(2)-C(15)	1.368(2)
7	F(5)-C(24)	1.373(2)	F(7)-C(31)	1.366(2)
8	F(6)-C(24)	1.366(2)	F(8)-C(31)	1.370(2)
9	C(17)-C(24)	1.502(2)	C(30)-C(31)	1.504(3)
10	C(22)-C(25)	1.504(3)	C(15)-C(19)	1.497(3)
11	C(21)-C(25)	1.419(3)	C(13)-C(19)	1.414(3)
12	C(21)-C(29)	1.367(3)	C(13)-C(36)	1.363(3)
13	C(14)-C(29)	1.413(3)	C(36)-C(40)	1.416(3)
14	C(14)-C(49)	1.421(3)	C(40)-C(43)	1.419(3)
15	C(46)-C(49)	1.365(3)	C(43)-C(3)	1.361(3)
16	C(46)-C(1)	1.410(3)	C(47)-C(3)	1.410(3)
17	C(39)-C(1)	1.367(3)	C(47)-C(53)	1.368(3)
18	C(18)-C(39)	1.420(3)	C(20)-C(53)	1.424(3)
19	C(14)-C(18)	1.428(3)	C(20)-C(40)	1.425(3)
20	C(18)-C(32)	1.433(3)	C(20)-C(26)	1.434(3)

21	C(25)-C(32)	1.385(2)	C(19)-C(26)	1.389(3)
22	C(32)-C(35)	1.501(2)	C(26)-C(27)	1.495(3)
23	C(23)-C(35)	1.431(2)	C(27)-C(42)	1.431(2)
24	C(23)-C(52)	1.430(3)	C(42)-C(45)	1.420(3)
25	C(52)-C(54)	1.372(3)	C(45)-C(2)	1.370(3)
26	C(44)-C(54)	1.411(3)	C(37)-C(2)	1.409(3)
27	C(41)-C(44)	1.363(3)	C(34)-C(37)	1.367(3)
28	C(16)-C(41)	1.421(3)	C(33)-C(34)	1.422(3)
29	C(16)-C(23)	1.420(3)	C(33)-C(42)	1.418(3)
30	C(16)-C(51)	1.416(3)	C(33)-C(48)	1.416(3)
31	C(38)-C(51)	1.367(3)	C(28)-C(48)	1.368(3)
32	C(17)-C(38)	1.411(3)	C(28)-C(30)	1.410(3)
33	C(17)-C(35)	1.387(3)	C(27)-C(30)	1.389(3)

3.5.2.2. Comparison of 2,2'-bis(difluoro-methylene)-1,1'-binaphthyl phosphinic acid with BINOL-phosphoric acid

The crystal structure of BINOL-phosphoric acid was published by Fujii and Hirayama in 2002.[66] The P-O linkages have an average bond length of 1.587 Å. The O-C(naphthyl) linkages have an average bond length of 1.403 Å. These bonds lengths are shorter than the methylene linkages in **1**, which have average bond lengths of 1.870 Å for P-CF_2 (Table 3.6, entries 3 and 4) and 1.502 Å CF_2-C(naphthyl) (Table 3.6, entries 9 and 10). The longer bonds of the difluoromethylene-phosphinic acid moiety could affect both the orientation of the phosphorus and binaphthyl groups.

The average dihedral angle between the naphthyl moieties in **1** (Table 3.5) is 69.8° which is more acute than the corresponding dihedral angle between the naphthyl

moieties in BINOL-phosphoric acid [61.1(1)°].[66] This could be due to the longer bond lengths in the P-CF_2-C(naphthyl) linkages, compared to the shorter bonds in the P-O-C(naphtyl) linkages.

3.5.2.3. Ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (6)

In the crystal structure of **6** two independent molecules (**A** and **B**) were observed. Similar to the crystals of **1**, the two independent molecules differ in the orientation of the binaphthyl group and in the orientation of the CF_2 linkages to the P=O and P-OEt moieties (See Figure 3.13 and Figure 3.14). However, the main features of each molecule, such as bond lengths and bond angles are very similar. Therefore, the molecules are discussed as one compound, using average bond lengths and bond angles. A full list of bond lengths (Table 3.8) and selected bond angles (Table 3.7), for molecules **A** and **B** are shown below.

The phosphorus centre of **6** is not tetrahedral, with a O=P-O angle of 119.74° (Table 3.7, entry 1) and a more acute C-P-C angle of 104° (Table 3.7, entry 6). The difluoromethylene groups are also not tetrahedral in orientation. The average F-C-F angle is 105.2° (Table 3.7, Entries 8 and 14), F-C-C(naph) of 111.4° (Table 3.7, Entries 9, 10, 15,16) and P-C-C(naph) of 112.1° (Table 3.7, Entries 7 and 13). However, the bond angles observed for P-C-F are non-equivalent. A range of 105.3° to 110.6° (Table 3.7, Entries 11-12 and 17-18). This non-equivalency in the fluorine atoms agrees with the structure observed in solution (^{19}F NMR of **6**, Figure 3.4).

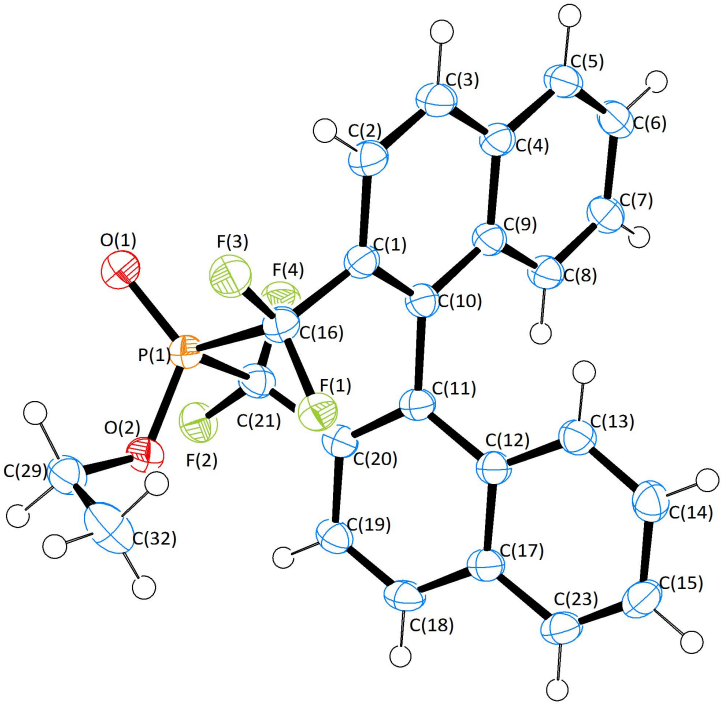


Figure 3.13: Labelled molecular structure of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**) molecule **A**. Ellipsoids are drawn at 50% probability.

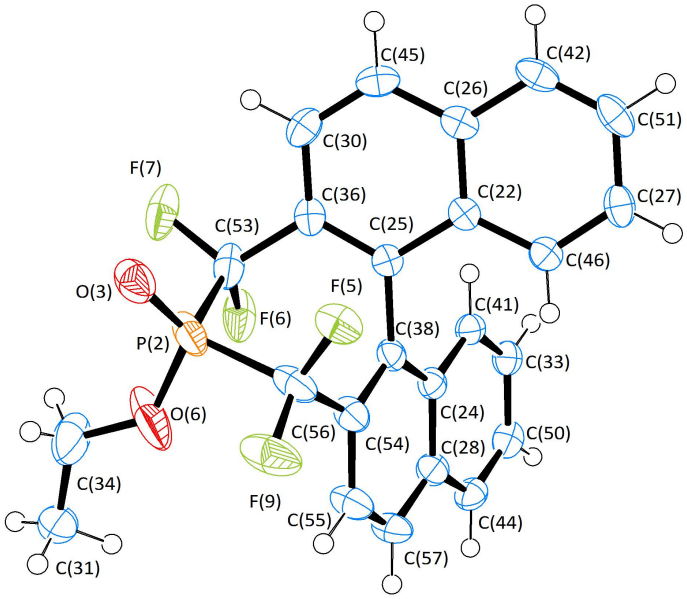


Figure 3.14: Labelled molecular structure of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**) molecule **B**. Ellipsoids are drawn at 50% probability.

Table 3.7: Selected bond angles and dihedral angles between naphtyl groups in molecules **A** and **B** of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)

Entry	Molecule A Bond angles (°)		Molecule B Bond angles (°)	
1	O(1)-P(1)-O(2)	119.76(10)	O(3)-P(2)-O(6)	119.71(13)
2	O(1)-P(1)-C(21)	114.54(11)	O(3)-P(2)-C(56)	116.32(13)
3	O(2)-P(1)-C(21)	99.17(10)	O(6)-P(2)-C(56)	97.44(16)
4	O(1)-P(1)-C(16)	110.66(11)	O(3)-P(2)-C(53)	111.45(13)
5	O(2)-P(1)-C(16)	106.89(10)	O(6)-P(2)-C(53)	106.17(17)
6	C(21)-P(1)-C(16)	104.23(11)	C(56)-P(2)-C(53)	103.78(12)
7	C(1)-C(16)-P(1)	112.36(16)	C(36)-C(53)-P(2)	112.15(18)
8	F(1)-C(16)-F(3)	105.30(18)	F(7)-C(53)-F(6)	105.3(2)
9	F(1)-C(16)-C(1)	111.28(19)	F(7)-C(53)-C(36)	110.7(2)
10	F(3)-C(16)-C(1)	111.59(19)	F(6)-C(53)-C(36)	111.6(2)
11	F(1)-C(16)-P(1)	110.60(15)	F(7)-C(53)-P(2)	105.93(18)
12	F(3)-C(16)-P(1)	105.33(16)	F(6)-C(53)-P(2)	110.8(2)
13	C(20)-C(21)-P(1)	112.65(16)	C(54)-C(56)-P(2)	111.4(2)
14	F(4)-C(21)-F(2)	105.33(18)	F(5)-C(56)-F(9)	105.0(2)
15	F(2)-C(21)-C(20)	111.50(19)	F(5)-C(56)-C(54)	112.7(2)
16	F(4)-C(21)-C(20)	112.0(2)	F(9)-C(56)-C(54)	111.2(2)
17	F(2)-C(21)-P(1)	106.79(16)	F(5)-C(56)-P(2)	109.32(19)
18	F(4)-C(21)-P(1)	108.16(15)	F(9)-C(56)-P(2)	106.9(2)
Dihedral angles between naphthyl moieties (°)				
Entry	**Molecule A**		**Molecule B**	
19	70.2		65.1	

The bond lengths in molecules **A** and **B** are almost identical (Table 3.8). The P=O bond is shorter than P-OEt bond (P=O 1.465 Å, P-OEt 1.563 Å). The phosphorus to difluoro-methylene bonds (P-CF_2) are the longest bonds present in the compound, 1.880 Å (Table 3.8, Entries 5 and 6). The difluoromethylene to binaphthyl linkages, have an average bond length of 1.509 Å (Table 3.8, Entries 11 and 12).

Table 3.8: All bond lengths in molecules **A** and **B** of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)

	Molecule A		Molecule B	
Entry	**Bond**	**Bond distance (Å)**	**Bond**	**Bond distance (Å)**
1	P(1)-O(1)	1.4645(18)	P(2)-O(3)	1.465(2)
2	P(1)-O(2)	1.5644(17)	P(2)-O(6)	1.561(2)
3	O(2)-C(29)	1.483(3)	O(6)-C(34)	1.303(4)
4	C(29)-C(32)	1.500(4)	C(34)-C(31)	1.445(4)
5	P(1)-C(16)	1.890(3)	P(2)-C(53)	1.883(3)
6	P(1)-C(21)	1.874(3)	P(2)-C(56)	1.871(3)
7	F(1)-C(16)	1.375(3)	F(5)-C(56)	1.374(3)
8	F(2)-C(21)	1.375(3)	F(6)-C(53)	1.375(3)
9	F(3)-C(16)	1.376(3)	F(7)-C(53)	1.373(3)
10	F(4)-C(21)	1.375(3)	F(9)-C(56)	1.376(3)
11	C(21)-C(20)	1.506(3)	C(56)-C(54)	1.510(4)
12	C(16)-C(1)	1.508(3)	C(53)-C(36)	1.511(4)
13	C(1)-C(2)	1.426(3)	C(36)-C(30)	1.407(4)
14	C(2)-C(3)	1.363(4)	C(30)-C(45)	1.368(4)
15	C(3)-C(4)	1.417(4)	C(45)-C(26)	1.420(4)
16	C(4)-C(5)	1.422(3)	C(26)-C(42)	1.427(3)
17	C(5)-C(6)	1.367(4)	C(42)-C(51)	1.365(4)

18	C(6)-C(7)	1.414(3)	C(51)-C(27)	1.409(4)
19	C(7)-C(8)	1.367(3)	C(46)-C(27)	1.381(3)
20	C(8)-C(9)	1.425(4)	C(46)-C(22)	1.421(3)
21	C(9)-C(4)	1.429(3)	C(22)-C(26)	1.423(3)
22	C(9)-C(10)	1.438(3)	C(22)-C(25)	1.436(3)
23	C(10)-C(1)	1.387(3)	C(25)-C(36)	1.391(3)
24	C(10)-C(11)	1.505(3)	C(25)-C(38)	1.507(3)
25	C(11)-C(12)	1.442(3)	C(38)-C(24)	1.429(3)
26	C(12)-C(13)	1.419(3)	C(24)-C(41)	1.427(3)
27	C(13)-C(14)	1.373(4)	C(41)-C(33)	1.372(3)
28	C(14)-C(15)	1.413(4)	C(33)-C(50)	1.408(4)
29	C(15)-C(23)	1.363(4)	C(50)-C(44)	1.373(4)
30	C(23)-C(17)	1.429(3)	C(44)-C(28)	1.417(4)
31	C(17)-C(12)	1.431(3)	C(28)-C(24)	1.431(3)
32	C(17)-C(18)	1.417(4)	C(28)-C(57)	1.425(4)
33	C(18)-C(19)	1.364(4)	C(57)-C(55)	1.366(4)
34	C(19)-C(20)	1.419(3)	C(55)-C(54)	1.415(4)
35	C(20)-C(11)	1.391(3)	C(54)-C(38)	1.387(4)

Summary

The crystal structure of **1** has been determined, in which two independent molecules (**A** and **B**) were observed. Comparisons have been made between **1** the parent BINOL-phosphoric acid. The crystal structure of the phosphinate ester **6** has also been determined.

3.5.3 Catalytic testing of Brønsted acid catalysts

Despite the vast amount of research performed on chiral Brønsted acid catalysts, there are limited numbers of direct acidity and catalytic activity comparisons on a range of catalysts.

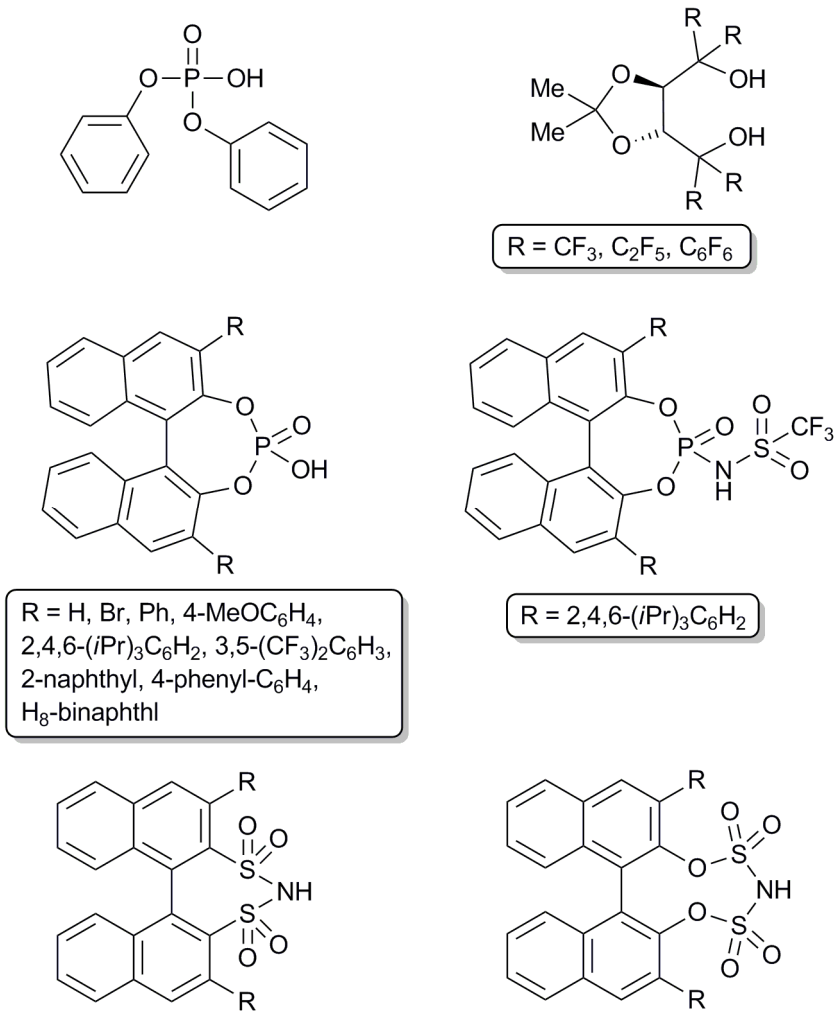


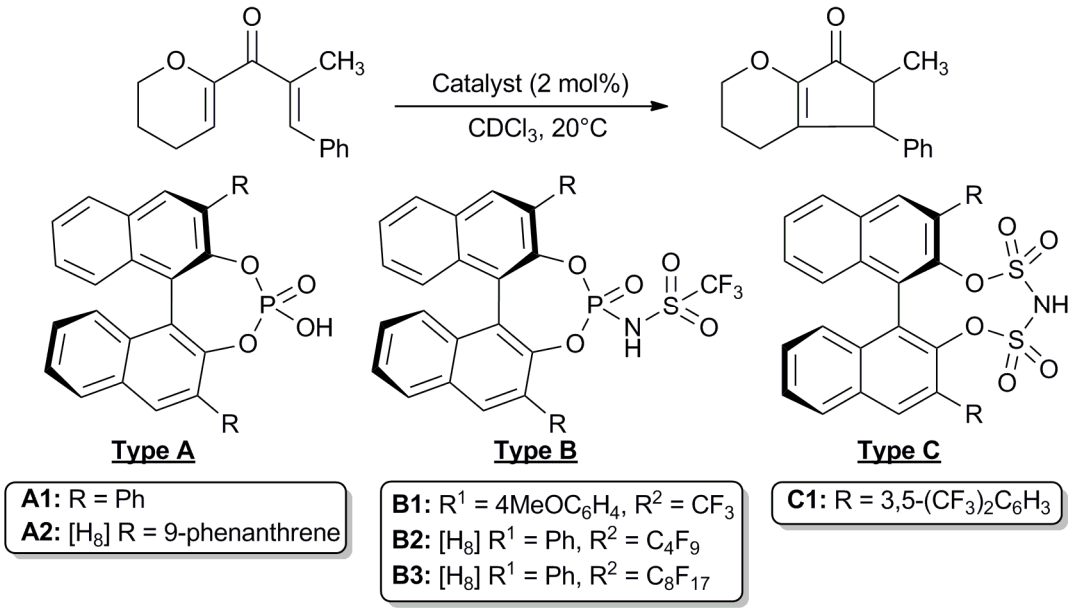
Figure 3.15: A range of Brønsted acids tested by Christ *et al*.

Christ and co-workers screened a range of Brønsted acids (Figure 3.15) in DMSO solutions by spectrophotometric methods.[67] This involves the determination of the equilibrium constant, K_{eq}, in the reaction of phenol or naphthol indicator and the Brønsted acids via UV/Vis spectrophotometry. From the K_{eq} values and the known pKa values of the indicators, the pKa of the Brønsted acids can be determined by

the following equation: pKa(HA) = $\log_{10} K_{eq}$ + pKa(HIn), where HA = Brønsted acids and HIn = Indicator. Their results suggested that the different series of acids (Figure 3.15) were similar in pKa values, as most acids fell into a narrow experimental range of 2-4 pKa units. As such, the group concluded that relative pKa values, of the acids, may not be the only leading factor that contributes to the catalytic activity of the acids tested.

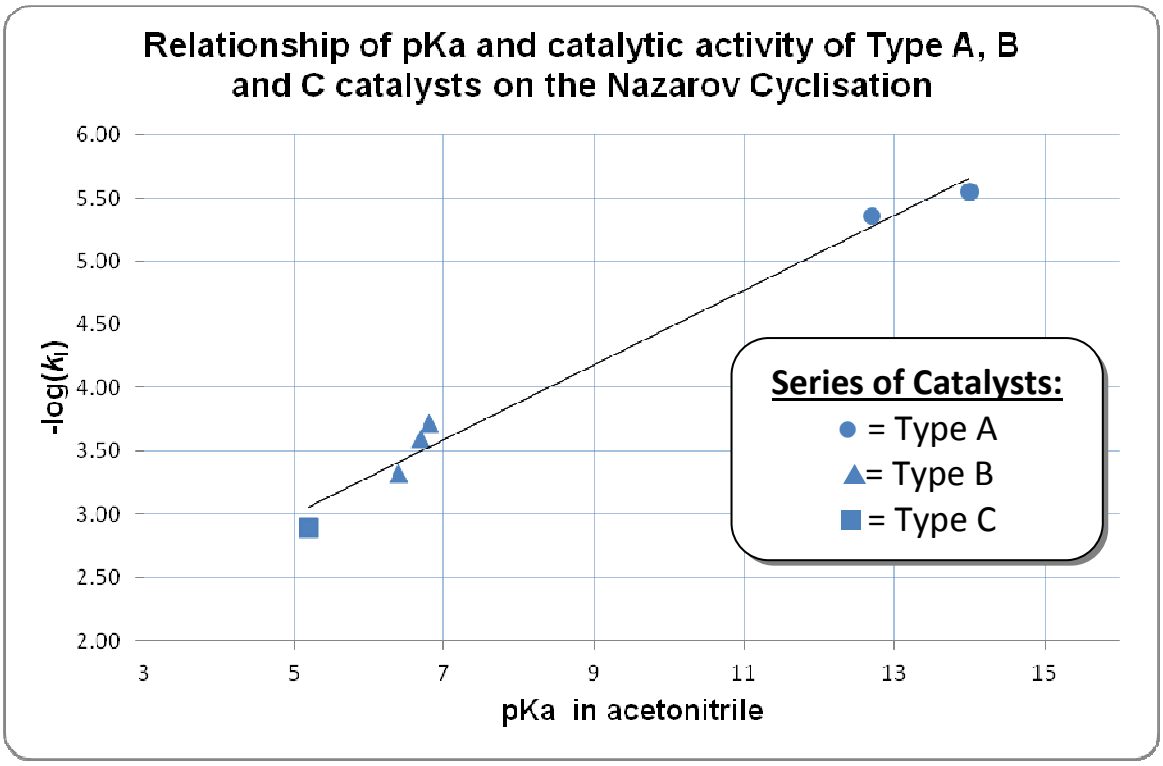
More recently Kaupmees and co-workers measured the pKa values of a similar series of Brønsted acid catalysts in acetonitrile solutions.[68] The values of weaker acids (BINOL-phosphoric acids) agreed with the previous study by Christ *et al*.. However, when stronger acids were screened (e.g. *N*-trifylphosphoramides) there was a discrepancy between the two studies. In acetonitrile the pKa range between the series of acids differed by nearly 9 pKa units, compared to the 2-4 pKa units in DMSO. As surmised by Kaupmees *et al.* this is likely due to the self-dissociation of the acid, being greater in the more basic DMSO than acetonitrile. For the weaker acids i.e. BINOL-phosphoric acids this is not an issue, as fully protonated acids can be formed by the addition of triflic acid. However, with the stronger acids tested (*N*-triflyl phosphoramides) protonation of the anion of *N*-triflyl phosphoramides was not achieved and no changes are observed in the UV/Vis spectra upon the addition of triflic acid (7 fold excess). Most likely the solvent, DMSO, is being protonated instead of the anion of the acids tested and the measurements taken by Christ *et al*. was likely recording the pKa of the solution rather than the acids.

In the same study Kaupmees and co-workers also screened the potential of the acids as catalysts for the Nazarov cyclisation of a dienone (Scheme 3.26).



Scheme 3.26: The catalytic activity testing of a series of (*R*)-BINOL based Brønsted acids on the Nazarov cyclisation of a divinylketone to a cyclopentanone.

^{1}H NMR spectra monitoring allowed for the rate of conversion, of the dienone to the corresponding cyclopentanones, to be measured. Three types of acids were tested. Type A, the Binol Phosphoric Acids, were found to have the lowest catalytic activity (-log(k_l) **A1** = 5.36, **A2** = 5.55). The reaction proceeded significantly faster when Type B catalysts, *N*-triflylphosphoramides, were used (-log(k_l) **B1** = 3.72, **B2** = 3.60, **B3** = 3.32). However, the Type C catalyst, bis(sulfuryl)imide, catalysed the cyclisation in the shortest amount of time (-log(k_l) **C1** = 2.89). When these results are tabulated against the experimental pKa values (in acetonitrile) the acid catalysts, a trend is observed (Graph 1).[68] The more acidic the Brønsted acid catalysts (lower pKa values) the faster the reaction proceeds (lower –log(k_l) values).

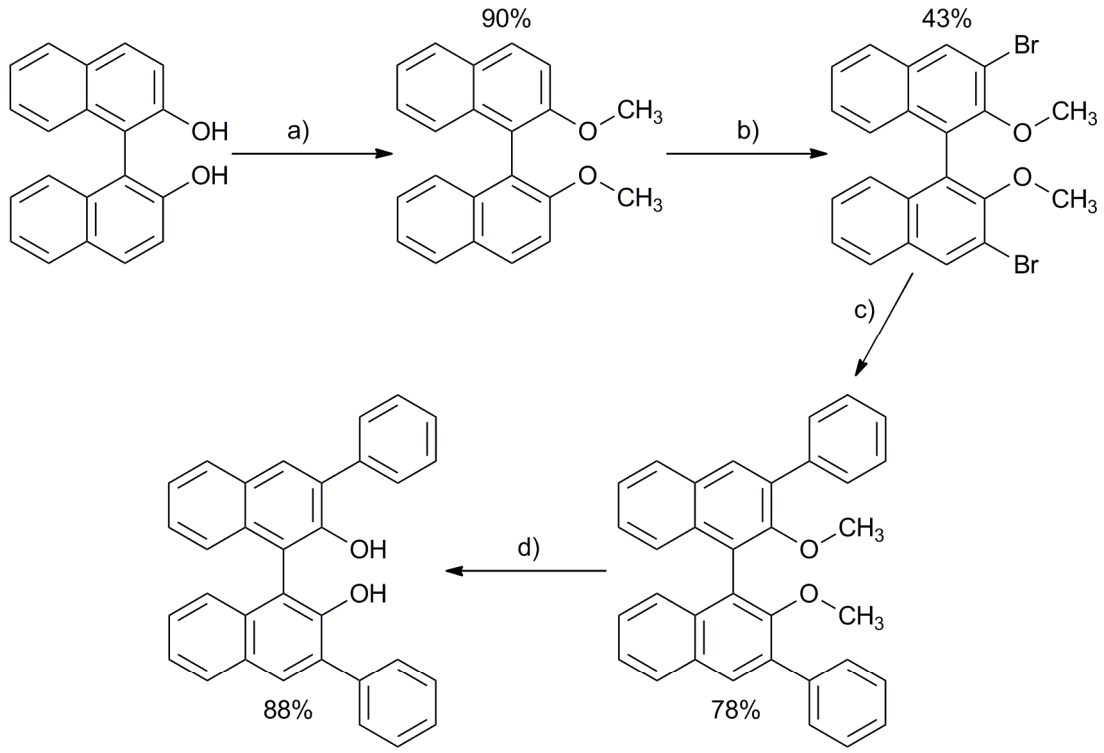


Graph 1: -log(k_I) vs pKa of a series of Brønsted acid catalysts.

Thus Kaupmees *et al.* have developed a simple kinetics study, which would allow for direct comparison of catalytic activity and pKa values of new chiral Brønsted acid catalysts against known chiral Brønsted acid catalysts. In this work the plan was then to test 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) in the Nazarov cyclisation from Kaupmees study.

3.5.4 Results of the catalytic testing of 2,2'-bis(difluoro-methylene)-1,1'-binaphthyl phosphinic acid

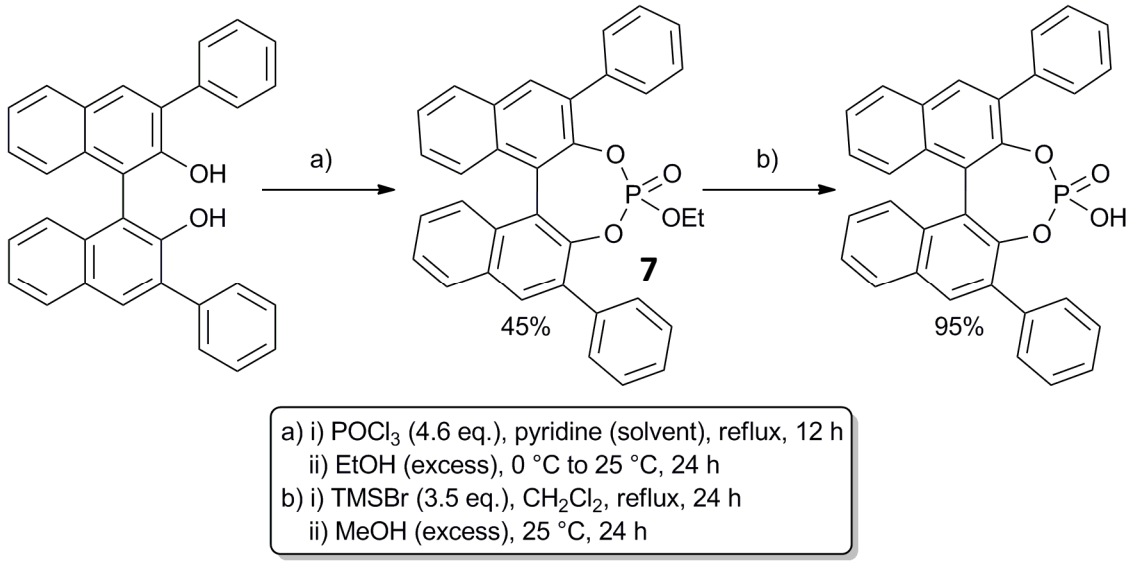
3,3'-diphenyl-1,1'-binaphthyl phosphoric acid was chosen as a control, as both the pKa testing and catalytic testing were previously performed by Kaupmees and co-workers. This compound was synthesised from 3,3'-diphenyl-BINOL, which was synthesised from BINOL in 4 steps (Scheme 3.27).[8, 69, 70]



a) i) K_2CO_3 (3.3 eq.), CH_3I (5 eq.), acetone, reflux, 24 h,
ii) CH_3I (2.5 eq.), reflux, 12h
b) *n*-BuLi (2.3 eq.), TMEDA (2.1 eq.), ether, 25 °C to -78 °C, Bromine (9.2 eq.)
c) $Ni(PPh_3)_2Cl_2$ (6 mol %), PhMgBr (2.8 eq.), ether, reflux 20 h
d) BBr_3 (7.3 eq.), CH_2Cl_2, 25 °C, 24 h

Scheme 3.27: The synthesis of (*rac*)-3,3'-diphenylBINOL.

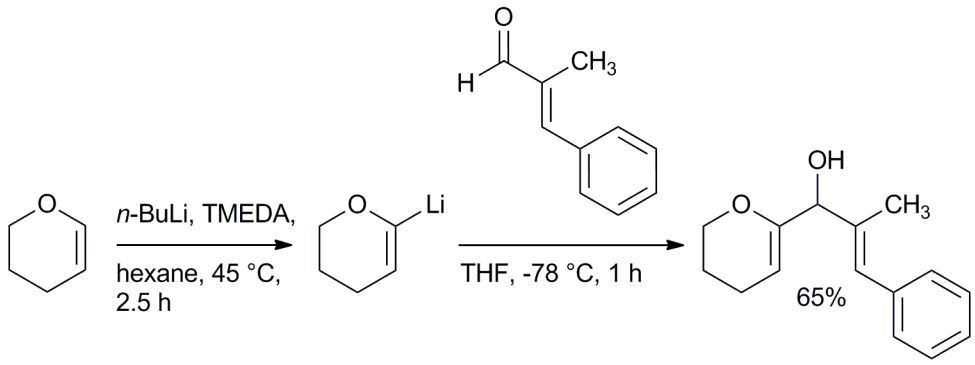
3,3'-diphenyl-BINOL phosphoric acid can be synthesised from 3,3'-diphenyBINOL with $POCl_3$ followed by quenching with water.[70] In this work however, 3,3'-diphenyl-BINOL phosphoric acid was synthesised via the phosphinate ester **7** (Scheme 3.28) in a similar manner to **5**. This route was chosen to ensure that the de-protection step had no effect on the performance of the resulting acid e.g. if any trace amounts of TMSBr or its side products were to remain, this could affect the rate of reaction of the catalytic testing.



Scheme 3.28: The synthesis of (*rac*)-3,3'-diphenyl-BINOL phosphoric acid.

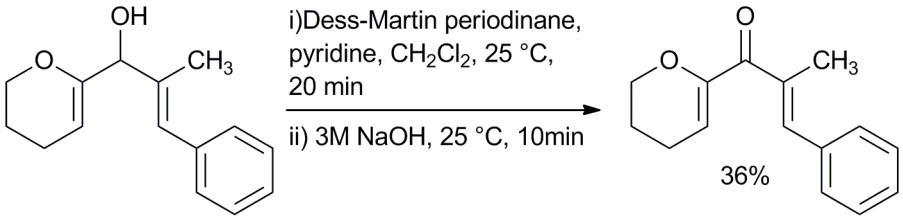
The parent acid, BINOL-phosphoric acid was also synthesised by this method, however this was not tested, by the Nazarov cyclisation, as its solubility was too low (in $CDCl_3$) for the concentrations needed in the catalytic testing.

The divinyl ketone required for this testing was synthesised in a modified procedure to the previous methodology.[68] Firstly the divinyl alcohol was synthesised (Scheme 3.29). 3,4-dihydro-2H-pyran was lithiated *in situ*[71] and a solution of α-methyl-*trans*-cinnamaldehyde was added drop-wise at -78 °C.



Scheme 3.29: The synthesis of 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-prop-2-en-1-ol.

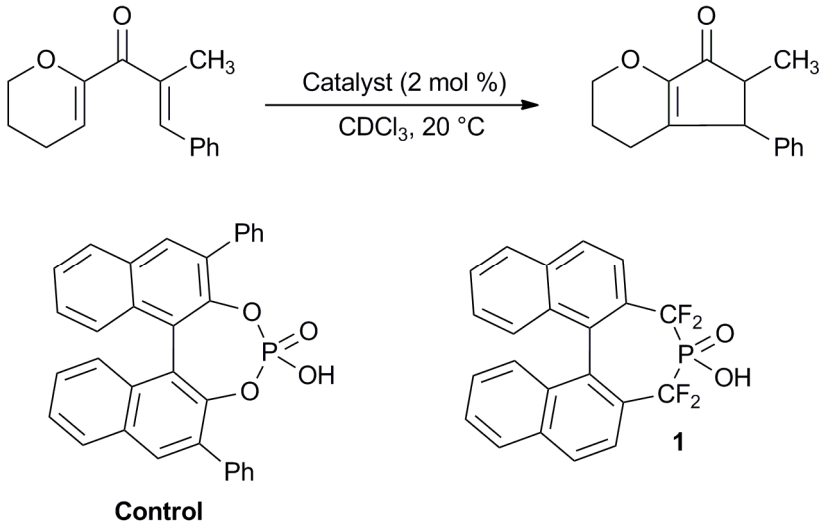
1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-prop-2-en-1-ol was the oxidised using Dess-Martin periodinane ($C_{13}H_{13}IO_8$) (Scheme 3.30).



Scheme 3.30: The synthesis of 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone.

^{1}H and ^{13}C NMR spectra of 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone are in agreement with the literature.[68]

The catalytic testing of 2,2-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid and 3,3'-diphenyl-1,1'-BINOL phosphoric acid, on the Nazarov cyclisation (Scheme 3.31), was perfomed by the mixing of stock solutions of the catalysts and the ketone in NMR tubes.



Scheme 3.31: The catalytic activity testing of **1** on the Nazarov cyclisation of a divinylketone to a cyclopentanone.

Stock solutions of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**), 3,3'-diphenyl-BINOL phosphoric acid and 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-

3-phenyl-propenone were made up in anhydrous $CDCl_3$ (See Section 5.7, page 164). The reaction was monitored by ^1H NMR and the rate of the reaction was determined from the percentage conversion of the divinyl ketone to the cyclopentanone (Scheme 3.31).

The percentage conversion was calculated from the difference in integral values of a C-H from the divinyl ketone [δ5.82 (t, J = 4 Hz, 1H)] and from a CH_3 signal from the cyclopentanone [δ0.68 (d, J = 8 Hz, 3H)].[68] An example of a test ^1H NMR spectrum is shown below in Figure 3.16.

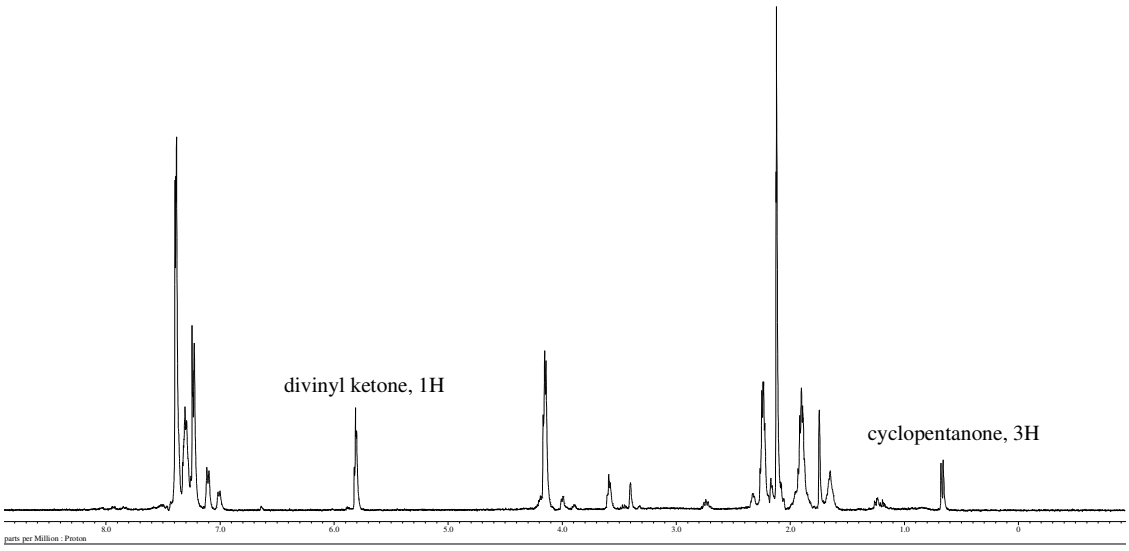


Figure 3.16: An example ^1H NMR spectrum of the conversion of the divinyl ketone to the cyclopentanone.

The testing of the control (3,3'-diphenyl-BINOL-phosphoric acid) and **1** were run in triplicates (Table 5.2 and Table 5.3 in Section 5.7, page 164. See appendices 21 and 22 for rate plots). The rate constants were then calculated using a first order rate plot, Ln[Ketone] vs. time (seconds), where the gradient = k_1. (See Appendix for rate plots).

The -log(k_i) values for the control were 5.52, 5.34, 5.36 with an average value of 5.41, which is in agreement with the literature value, 5.36.[68] The three -log(k_i) values for **1** were 3.52, 3.48 and 3.40 with an average -log(k_i) value of 3.48.

These experimental values show that **1** is a more active catalyst in the Nazarov cyclisation (Scheme 3.31) than 3,3'-diphenylBINOL phosphoric acid **A1** (Figure 3.17). When compared to the *N*-triflylphosphoramide derivates (**B1, B2** and **B3**, Figure 3.17), **1** falls within the same activity range (See Graph 2). Addition of the average –log(k_i) value of **1** to Kaupmees and co-workers data of pKa vs. –log(k_i) gives an estimated pKa value (in acetonitrile) of 6.6 (Table 3.9).

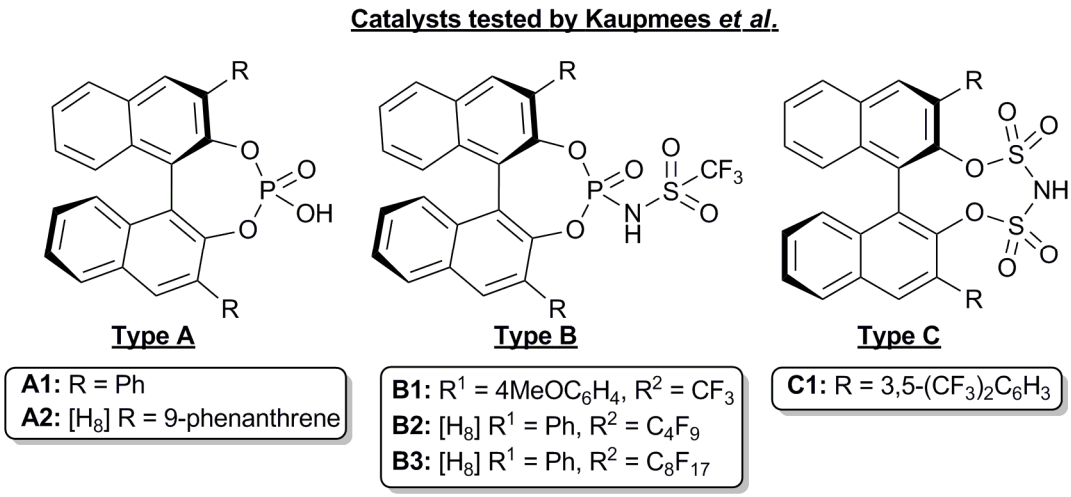
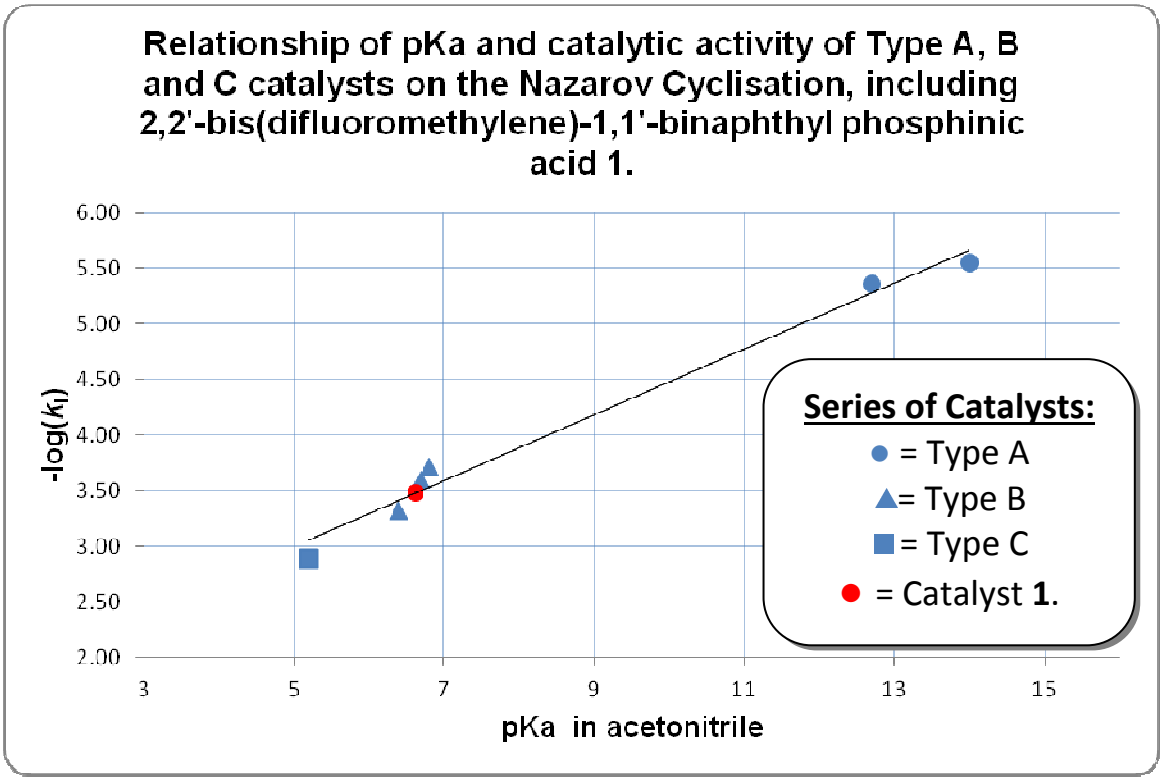


Figure 3.17: Catalysts corresponding to **Graph 2**.



Graph 2: -log(k_I) vs pKa of a series of Brønsted acid catalysts, with 2,2-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid.

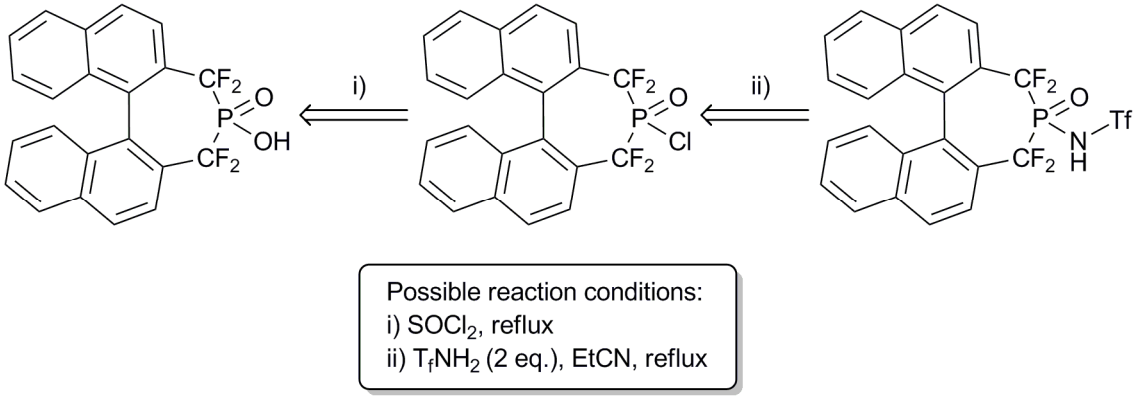
Table 3.9: Experimental data for Graph 2.

Entry	Catalyst[a]	-log(k_I)[b]	pKa[c]
1	A2	5.55	14.0
2	A1	5.36	12.7
3	B3	3.72	6.8
4	B2	3.60	6.7
5	B1	3.32	6.4
6	C1	2.89	5.2
7	1	3.48	6.6 (estimated)

a) See Figure 3.17. b) experimentally determined (See Scheme 3.26 and Scheme 3.31) c) pKa in acetonitrile.

3.5.5 Future work

It could be possible to increase the activity and acidity of **1** further by changing the acidic OH group for the *N*-triflylphosphoramide group. Kaupmees *et al* have shown that *N*-triflylphosphoramides are stronger acids than BINOL-phosphoric acids.[68] One possible route to the formation of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl-*N*-triflylphosphoramide is via the acid chloride (Scheme 3.32).



Scheme 3.32: A possible route to 2,2-bis(difluoromethylene)-1,1'-binaphthyl-*N*-triflylphosphoramide from **1**.

It would be of interest to see how much stronger the acidity of 2,2-bis(difluoro-methylene)-1,1'-binaphthyl-*N*-triflylphosphoramide would be compared to **1** and the previous catalysts (Type A, B and C, **Figure 3.17**).

3.6 Conclusions

In conclusion a new type of Brønsted acid catalyst has been synthesised in a seven step procedure from commercially available racemic BINOL. Full characterisation has been collected on the novel compounds synthesised in this procedure. The X-ray crystal structures of **1** and **6** have been determined and comparisons between **1** and the parent BINOL-phosphoric acid have been discussed.

The catalytic activity of **1**, in the Brønsted acid catalysed Nazarov cyclisation of a divinyl ketone (Scheme 3.31) has been determined. This allowed for comparisons, in catalytic acitivity, to be made between **1** and a series of known Brønsted acid catalysts. It has been shown that exchanging the oxy linkages, in BINOL-phosphoric acid, with CF_2 linkages can increase catalytic activity more than BINOL-phosphoric acids and to the same extent as BINOL *N*-triflylphosphor-amides (See Graph 2). From this data the estimated pKa (in acetonitrile) has been determined as 6.6, however the experimental pKa has not been determined.

Chapter 4

A New Route to Aryl-dichlorophosphines, the Reductive Chlorination of Aryl-H-phosphinic Acids.

4.1. Introduction

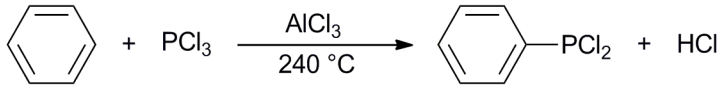
Aryl- and alkyl-dichlorophosphines are an important class of compounds. They are used as synthetic precursors to a vast amount of organophosphorus compounds[72, 73] as well as more elaborate compounds, such as aryl phosphonium salts[74] and as precursors to compounds of biological importance.[75] Aryldichlorophosphines are particularly useful as precursors to ligands, especially in enantioselective catalytic cycles, including the synthesis of drug candidates.

4.1.1. Previous synthesises of Alkyl- and Aryl-dichlorophosphines

The synthesis of aromatic dichlorophosphines dates back to the late 19th century.[76-79] As such, methodologies in the formation of aryl-dichlorophosphines are extensive, However there are several main routes that are frequently used; reaction of PCl_3 with organometallic reagents, reaction of PCl_3 with aromatics (Friedel-Crafts) and chlorination of primary phosphines.[72, 73]

4.1.1.1. The Friedel-Crafts formation of Aryl-dichlorophosphines

The first example of the Friedel-Crafts synthesis of an aryl-dichlorophosphine, was published by Michaelis (Scheme 4.1).[78]

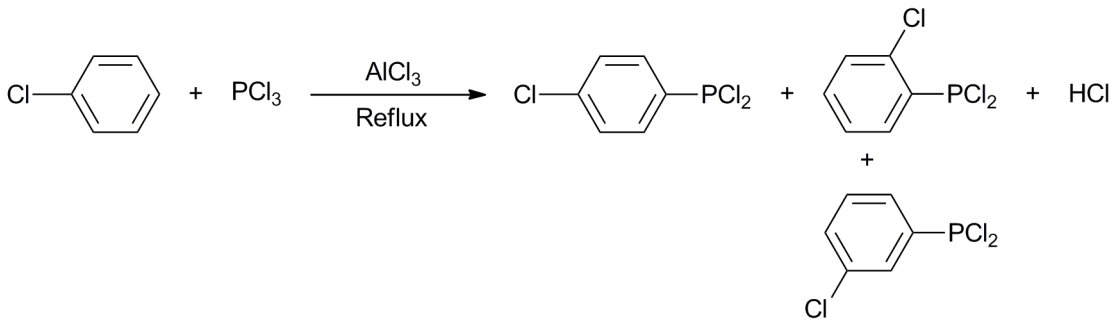


Scheme 4.1: Friedel-Crafts synthesis of $PhPCl_2$.

There are some disadvantages with this procedure. The first is low yields due to the complexation of aluminium trichloride and product.[80] The addition of

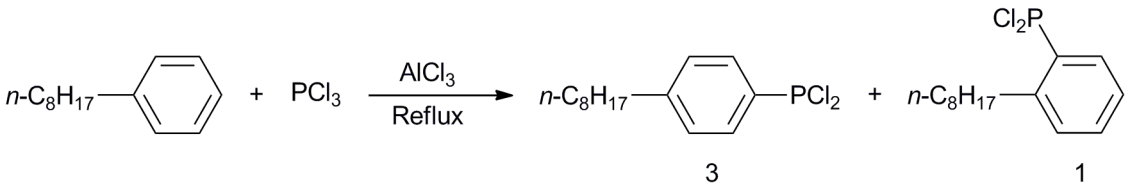
phosphoryl chloride to the reaction mixture forms a complex with aluminium chloride, freeing up the product.[81]

The second disadvantage is the formation of isomers, when using functionalised aromatics. For example the reaction of chlorobenzene with PCl_3 in the presence of $AlCl_3$ gives, after isolation, mainly *para*-chlorophenyldichlorophosphine however, *ortho*- and *meta*-chlorophenyldichlorophosphine are also present, which were visible by FT-IR spectroscopy (Scheme 4.2).[82]



Scheme 4.2: Formation of isomers in the reaction of chlorobenzene and PCl_3.

The reaction of *n*-octylbenzene with PCl_3 in the presence of $AlCl_3$ generates both the para and ortho isomers which are difficult to separate (Scheme 4.3).[83]



Scheme 4.3: Formation of *para*- and *ortho*- *n*-octylphenyldichlorophsphines.

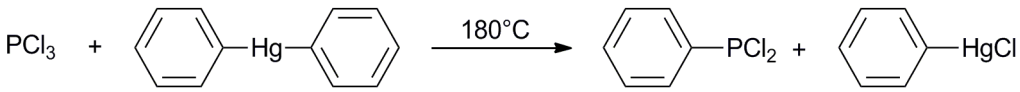
It was reported that after vacuum distillation, ^1H NMR data showed approximately 3:1 of the para and ortho isomers.

4.1.1.2. Reaction of Phosphorus(III) Chlorides with Organometallics

Aryl-dichlorophosphines are also accessible from phosphorus(III) with a range of organometallics such as, Grignard reagents,[84] organo- mercury,[77] lithium[85] and zinc.[86] Examples of reactions of PCl_3 with organo- cadmium[87] and lead[88] reagents are also present in the literature, but are not as commonly used.

Organomercury reagents

The earliest example was the reaction of PCl_3 with diphenylmercury performed by Michaelis *et al* in 1875.[77] The reaction proceeded at 180 °C in sealed glassware to give phenyldichlorophosphine, after distillation (Scheme 4.4).

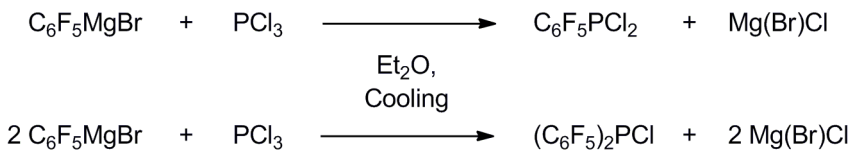


Scheme 4.4: Synthesis of phenyldichlorophosphine from diphenylmercury and trichlorophosphine.

Similarly aryl mercury chloride can be used with PCl_3 to give aryldichloro-phosphines.[89] Typically an excess of PCl_3 is used to suppress the formation of diarylchlorophosphine. However, the use of mercury compounds is not desirable due to their associated toxicity.

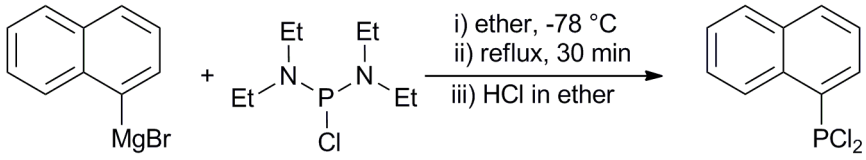
Grignard Reagents

The reaction of aryl Grignard reagents and PCl_3 has been known since 1904[90] and is an established method for the synthesis of trialkylphosphines.[91] The reaction is not generally selective to the mono- and di- aryl chlorophosphines. Certain reactions do undergo selective mono- and di- arylation, for example Magnelli and co-workers[92] synthesised pentafluorophenyldichlorophosphine and bis(pentafluorophenyl)chlorophosphine in respective yields of 55% and 66% (Scheme 4.5).



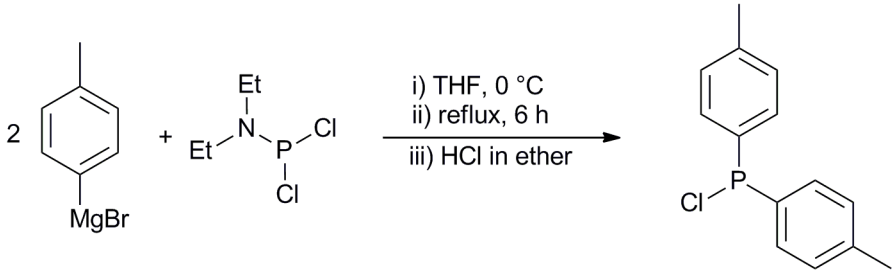
Scheme 4.5: The synthesis of pentafluorophenyldichlorophosphine and bis(pentafluorophenyl)chlorophosphine.

However, in order to achieve mono- or di- aryl chlorophosphines mono- or bis(dialkylamino) chlorophosphines are used. As an example, Duff *et al*.[93] synthesised 1-napthyldichlorophosphine in 55% yield from the reaction of bis(diethylamino)chlorophosphine with 1-naphthylmagnesium bromide (Scheme 4.6). HCl was used to cleave the diethylamino protecting groups.



Scheme 4.6: The synthesis of 1-naphthyldichlorophosphine by Grignard reagent.

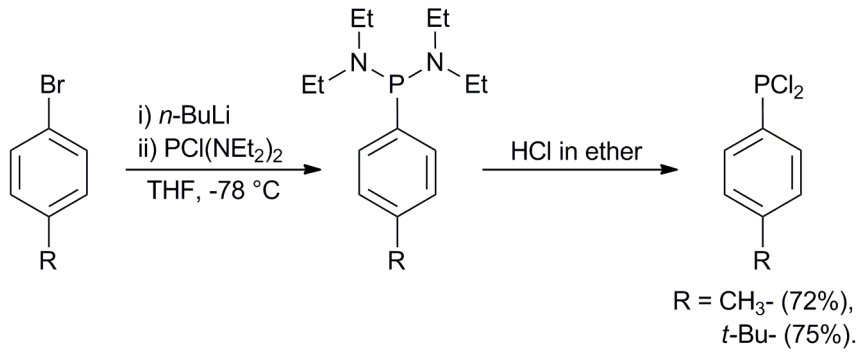
To prepare diarylchlorophosphines using Grignard reagents, diethylamino-dichlorophosphine is used. For example, bis(4-methylphenyl)chlorophosphine was synthesised in 51% yield by the reaction of 4-methyphenyl Grignard reagent and diethylaminodichlorophosphine (Scheme 4.7).[84]



Scheme 4.7: The synthesis of bis(4-methylphenyl)chlorophosphine.

Organolithium reagents

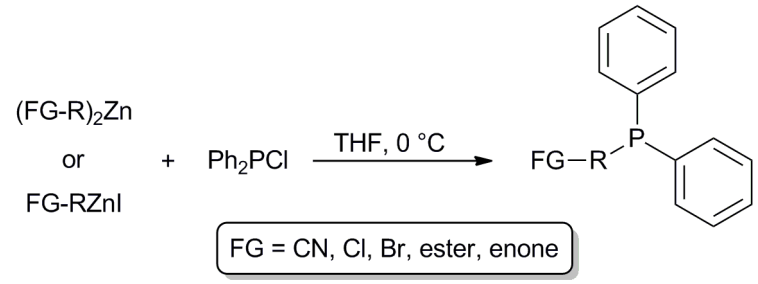
Arylchlorophosphines are also accessible from the reaction of aryl-lithium reagents and PCl_3. For example Jordan and co-workers synthesised 4-$CH_3C_6H_4$-PCl_2 and 4-*t*-BuC_6H_4-PCl_2 by lithiation of the related aryl bromide followed by reaction with bis(diethylamino)chlorophosphine followed by the addition of HCl (Scheme 4.8).[85]



Scheme 4.8: The synthesis of aryldichlorophosphines using organo-lithium reagents.

Organozinc reagents

The use of organozinc reagents in the synthesis of aryl-phosphines, allows for better functional group tolerance, compared to the previously mentioned Grignard reagents. Langer and Knochel synthesised a range of multi-functional phosphines by reaction of either di-organozinc or organo-zinc iodide with diphenylchlorophosphine (Scheme 4.9).[94]



Scheme 4.9: The synthesis of multi-functional phosphines by organo-zinc reagents.

Functionalised organo-zinc halides are prepared *in situ*, e.g. arylzinc halides are accessed by lithiated aromatics (*n*-BuLi and aryl bromides) and zinc halides at reduced temperatures.[86]

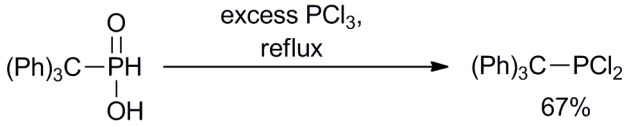
Summary

Both the Friedel-Crafts and organometallic routes to aryldichlorophosphines rely heavily on the use of PCl_3. The formation of ortho, meta and para isomers in the Friedel-Crafts reaction is not desirable. These isomers are often very difficult to separate from one another. Also separation of product from the Lewis acid can be difficult. Additives, such as phosphoryl chloride are required to complex to the Lewis acid, to free-up the product.

The use of organometallic reagents in the synthesis of aryldichlorophosphines limits the use of sensitive functional groups. For example carbonyl groups and other Grignard and organolithium sensitive groups are not tolerated. Also the reactions of chlorophosphines and organometallic reagents, are not selective for mono- or di- substituted products. Therefore the use of “protected” chlorophosphines, such as bis(diethylamino)chlorophosphine and diethylaminodichlorophosphine are often required to achieve selective mono- and di- arylation.

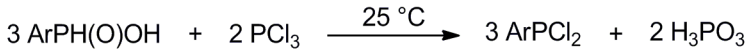
4.1.2. The Reductive Chlorination of Alkyl- and Aryl- H-Phosphinic acids

The reductive chlorination of phosphorus (V) compounds has previously been used in the synthesis of alkyl- and aryl- dichlorophosphines. In the early 1930s Hatt discovered that heating tri(phenyl)methyl H-phosphinic acid, to reflux, with 5.6 equivalents of PCl_3 gave tri(phenyl)methyl dichlorophosphine in 67% yield (Scheme 4.10).[95] The evolution of HCl and the formation of elemental phosphorus and H_3PO_3 was observed.



Scheme 4.10: Hatt's synthesis of tri(phenyl)methyldichlorophosphine.

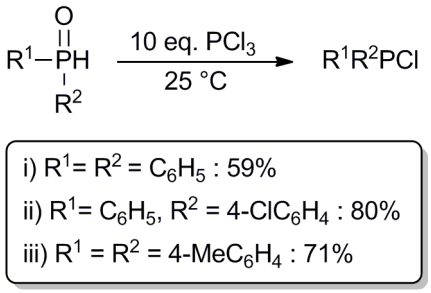
In the 1960s Frank discovered that treatment of phenyl H-phosphinic acid with PCl_3 at room temperature gave phenyldichlorophosphine in 70% yield (Scheme 4.11).[96]



Scheme 4.11: Reaction scheme proposed by Frank.

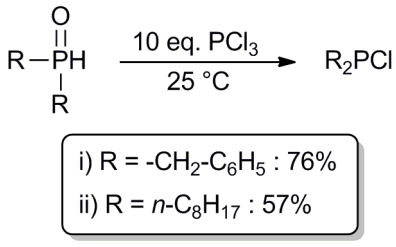
A ten-fold excess of PCl_3 was used, with and without the presence of benzene, giving 70% yield of $PhPCl_2$. It was noted that as the ratio of $PhPO_2H_2$ to PCl_3 was decreased to 1:1.2, the yield of $PhPCl_2$ was reduced to 54%. At a ratio of 3:1 there was no $PhPCl_2$ detected. Unlike the previous reaction by Hatt, no HCl and elemental phosphorus was observed.[96] Montgomery and Quin extended this work to the chlorination of diarylphosphine oxides.[97] Under the same conditions as

Frank's previous methodology, three diarylchlorophosphines were synthesised in moderate yields (Scheme 4.12).



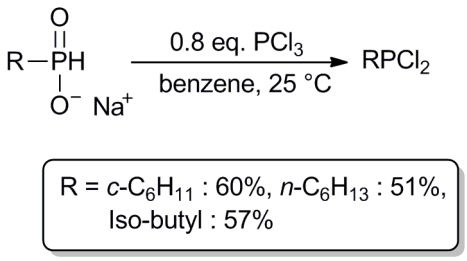
Scheme 4.12: The formation of symmetrical and unsymmetrical diarylchlorophosphines.

Quin and Anderson further extended this reaction to form dialkylchlorophosphines from dialkylphosphine oxides.[98] Dibenzyl and di-*n*-octyl chlorophosphines were isolated in respective yields of 76% and 57% (Scheme 4.13).



Scheme 4.13: The formation of dibenzyl- and di-*n*-octyl-dichlorophosphine.

In the same year Nifant'ev and Koroteev published a method of synthesising alkyl dichlorophosphines from the relevant sodium hydrogen alkylphosphonites and PCl_3.[99] The reaction was performed at room temperature in benzene using 1.2 equivalents of sodium hydrogen alkylphosphonite and 0.8 equivalents of PCl_3 (Scheme 4.14).

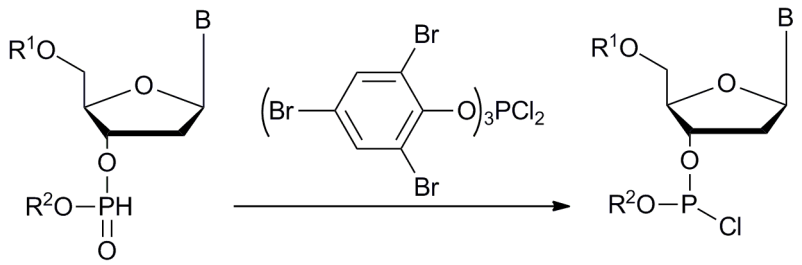


Scheme 4.14: The formation of alkyldichlorophosphines.

Nifant'ev and Koroteev also stated that alkyldichlorophosphines are accessible from the relevant sodium hydrogen alkylphosphonites with thionyl chloride, however no experimental information is given.[99]

4.1.2.1. Non-oxidative chlorination of alkyl/aryl phosphonates:

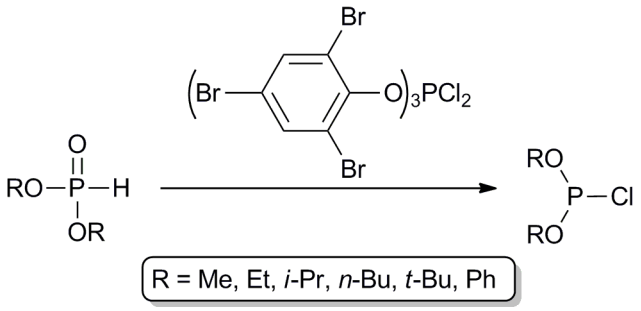
The non-oxidative chlorination of disubstituted phosphonates was described by Hata *et al.* in which a series of disubstituted phosphorochloridites were formed.[100]



Scheme 4.15: The chlorination of alkylnucleoside 3'-phosphonates to their phosphorochloridites.

The reaction, with tris(2,4,6-tribromophenoxy)dichlorophosphorane, allowed for a new and simplified route to the synthesis of oligonucleotides (Scheme 4.15).

Hata and co-workers extended the scope of this reaction to the chlorination to diphenyl- and dialkyl- phosphonates (Scheme 4.16).[100, 101]



Scheme 4.16: The formation of diphenyl- and dialkyl-phosphorochloridites.

The reaction was also applied to the chlorination of RP(O)(OR)H.[102] Modified chlorinating agents have also been used, such as dichloro(2,4,6-tribromophenoxy)(1,2-diphenoxy)phosphorane, limiting side products upon further reaction of *in situ* generated dialkyl phosphorochloridites.[103] The chlorinating agents used in the reactions described above, are not commercially available.

Summary

Despite these early advances, very little research has been performed on the chlorination of aryl H-phosphinic acids to aryl dichlorophosphines, especially without the use of PCl_3. This route however, has several advantages over the previous methods mentioned (Friedel-Crafts and organometallics). Purification of the products appears to be simpler compared to the Friedel-Crafts route, as no additive is necessary. Also there is no issue with regioselectivity as the P-C bond is already present.

No organometallics are needed in this preparation, therefore it is possible that the functional group tolerance could be better than previous methods, allowing for carbonyl groups like ketones and esters, and other Grignard sensitive functionalities to be used.

4.2. Aims

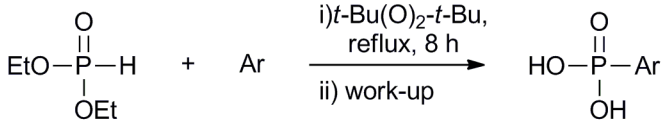
The aims of this project are to test, develop and optimise a new reaction in the synthesis of aryldichlorophosphines. It is envisaged that the reaction will;

- Use stable aromatic phosphorus (V) precursors, incorporating functionality.
- Allow for a “one pot” synthesis of aryl- dichlorophosphines.
- Use mild reaction conditions.
- Allow for a greater functional group tolerance, compared to previous methodology (See above).
- Use readily available chlorinating agents (e.g. $SiCl_4$).

4.3. Previous methodology for the synthesis of Aryl H-phosphinic acids

A series of aryl H-phosphinic acids were required as the starting material in the synthesis of functionalised aryldichlorophosphines. Aryl H-phosphinic acids are readily accessible and throughout the duration of this work were found to be stable over prolonged periods of time, making them an ideal starting material.

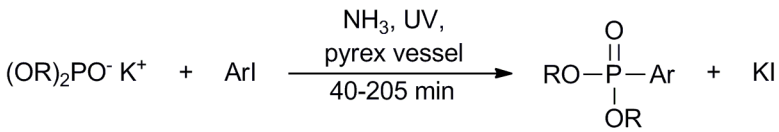
A vast amount of research has been performed on the generation of P-C (Aryl) bonds. Early methods in the formation of aryl phosphorus(V) compounds[104] included the free radical phosphonation of aromatics (Scheme 4.17)[105], the UV mediated reaction of aryl iodides with potassium dialkyl phosphites in liquid ammonia (Scheme 4.18)[106] and the UV mediated reaction of aryl iodides with trialkly phosphites[107, 108].



Products: Ar = 9-anthacene (96%), 9-phenanthene (60%), 1-, 2-napthalene (51%), dibenzofuran* (69%), carbazole* (80%)

*Position of phosphonic group on aromatics not known

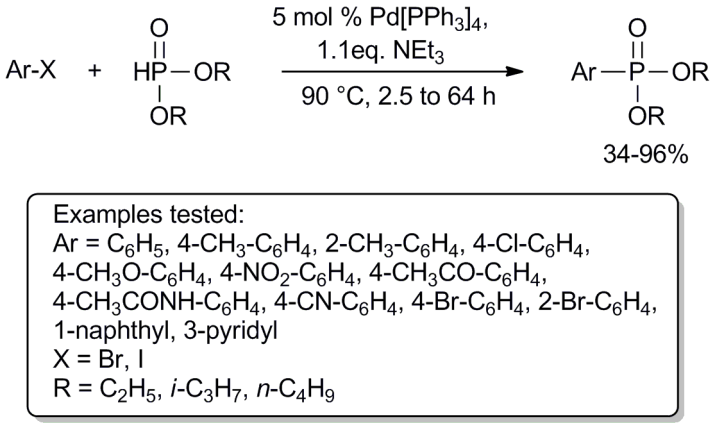
Scheme 4.17: The free radical phosphonation of aromatics.



R = Me, Et, *n*-Bu
Ar = 4-$CH_3C_6H_4$ (95 %), 4-$CH_3OC_6H_4$ (95 %), 2,6-$(CH_3)_2C_6H_3$ (87 %), 3-$CF_3C_6H_4$ (95 %), 1-naphthyl (93 %), 3-FC_6H_4 (96 %), 3-ClC_6H_4 (89 %), 3-BrC_6H_4 (87 %)
$((OR)_2PO)_2Ar$ also formed from *m*-IC_4H_4I (94 %), *p*-IC_4H_4I (87 %)

Scheme 4.18: The reaction of aryl iodides with potassium dialkyl phosphites in liquid ammonia with UV irradiation.

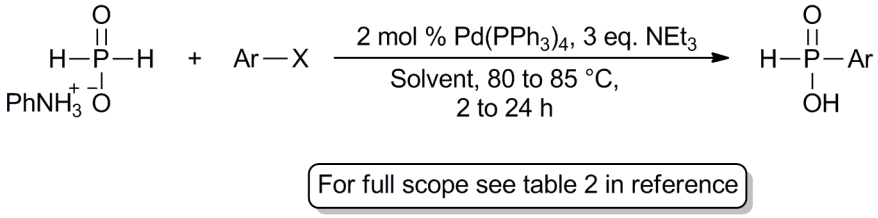
However, it was not until 1981 when a more facile method for the formation of aryl dialkylphosphonates was published. Hirao *et al*. shown that aryl iodides reacted with dialkyl phosphites, catalysed by tetrakis(triphenylphosphine)palladium(0) to give aryl dialkylphosphonates in high yields (Scheme 4.19).[109]



Scheme 4.19: The palladium catalysed synthesis of aryl dialkylphosphonates.

Since this seminal reaction a large amount of research has been published on P-C bond formation catalysed by a range of metal and ligand combinations.[110-113]

However, the first method of the formation of aryl H-phosphinic acids via palladium catalysed cross-coupling reactions was published by Montchamp *et al*. in 2001.[3] The reaction, with anilinium hypophosphite, proceeds using 2 mol % palladium catalyst, in acetonitrile or DMF at 80-85 ℃ with a range of functionalised aryl iodides, bromides, triflates, chlorides and benzylic chlorides (Scheme 4.20), giving good to excellent yields.

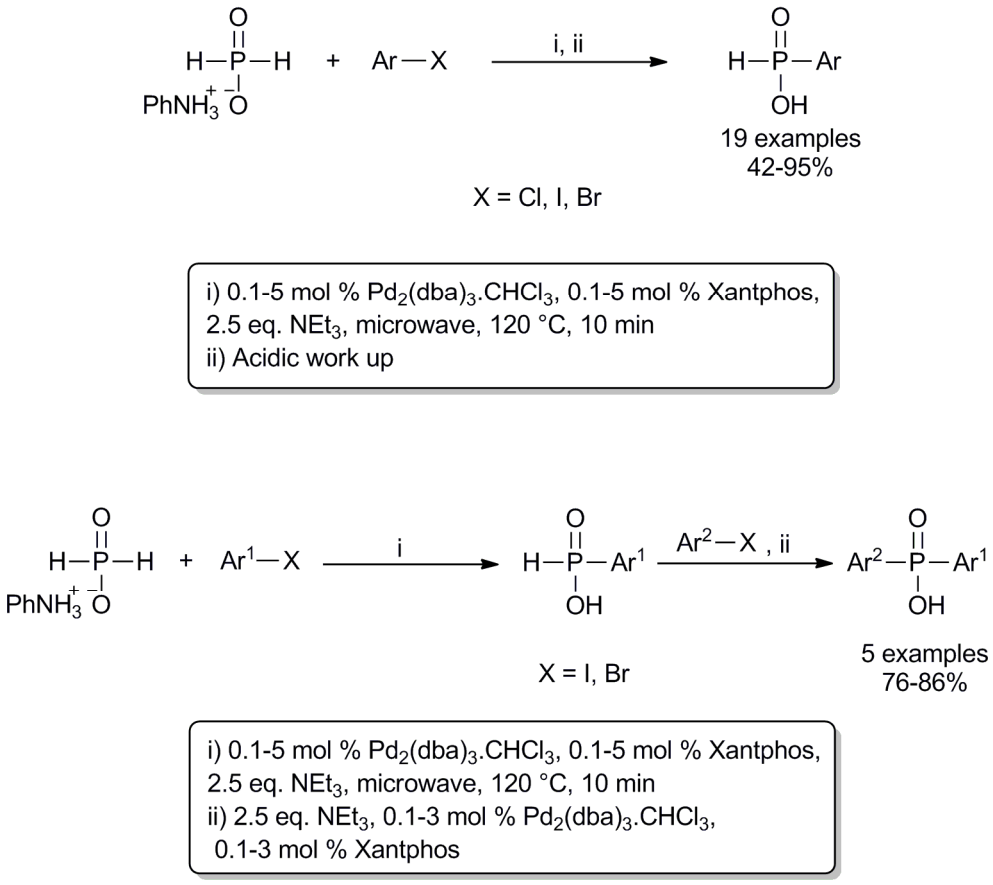


Scheme 4.20: Montchamp *et al*. seminal palladium catalysed synthesis of aryl and benzylic H-phosphinic acids.

Aqueous work-up gave the acids in a purity of >95%. This work was further extended by Montchamp *et al*. to the palladium catalysed cross-coupling of anilinium hypophosphites and alkenyl bromides and triflates.[114] With Montchamp's results a range of functionalised aryl H-phosphinic acids were easily accessible.

Since the publication of Monchamp's synthesis of aryl H-phosphinic acids, a large amount of research has been published on the synthesis of substituted H-phosphinic acids, H-phosphinates and phosphonates via cross-coupling reactions.[1, 2, 115-119]

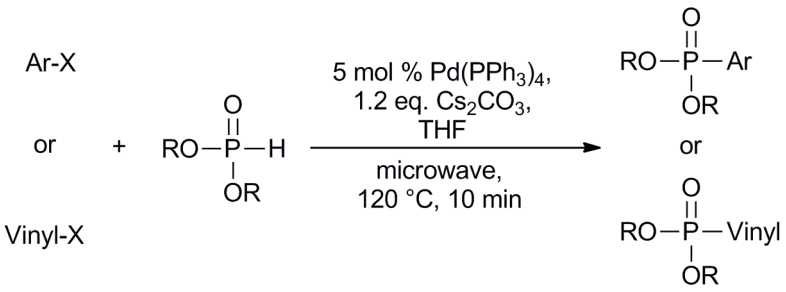
The use of microwave irradiation, in the palladium catalysed cross-coupling of hypophosphites and aryl halides, allowed for reduced catalyst loading and reduced reaction times. Kalek and Stawinski published the synthesis of aryl- and diaryl-phosphinic acids via microwave assisted palladium catalysed cross-coupling reaction of anilinum hypophosphite with aryl bromides (Scheme 4.21).[120] Symmetrical diaryl-phosphinic acids were also synthesised, in a one pot procedure using 2.5 equivalents aryl halide, 3.5 equivalents NEt_3 and 15 min irradiation time.



Scheme 4.21: The microwave assisted palladium catalysed synthesis of aryl-H-phosphinic acids and diaryl-phosphinic acids.

The reaction was advantageous over previous results as high yields were obtained with dramatically reduced catalyst loading (0.1 mol % Pd catalyst and Xantphos loading, compared to previous catalyst and ligand loading of 2 mol %) and reduced reaction time.

A series of aryl and vinyl phosphonates has also been published, using microwave synthesis, by Stawinski *et al* (Scheme 4.22).[121] This reaction proceeded with 5 mol % palladium catalyst to give aryl and vinyl phosphonates.



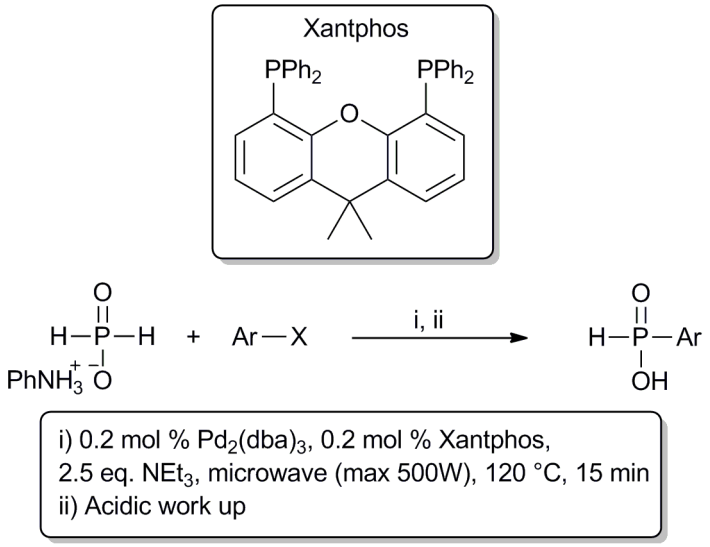
See table 3 in reference for aryl and vinyl groups used

Scheme 4.22: The microwave assisted palladium catalysed synthesis of aryl and vinyl phosphonates.

4.4. Results and Discussion

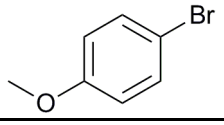
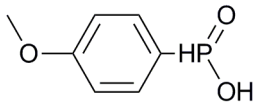
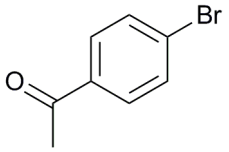
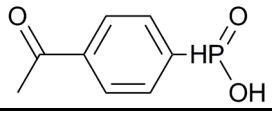
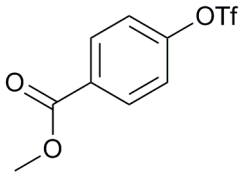
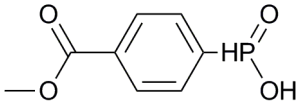
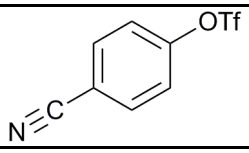
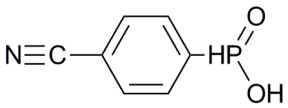
4.4.1. Synthesis of Aryl H-phosphinic acids

A series of functionalised aryl H-phosphinic acids were required, as precursors to aryl- dichlorophosphines. These were accessible by microwave assisted palladium catalysed cross-coupling of aryl bromides with anilinium hypophosphite.[120] As an extension to the literature results, it was found that aryl-triflates under go cross-coupling with anilinium hypophosphite, under microwave conditions, to give aryl H-phosphinic acids, (Scheme 4.23, where X = OTf and Br, and Table 4.1).



Scheme 4.23: The synthesis of Aryl H-phosphinic acids via a palladium catalysed coupling reaction, under microwave radiation.

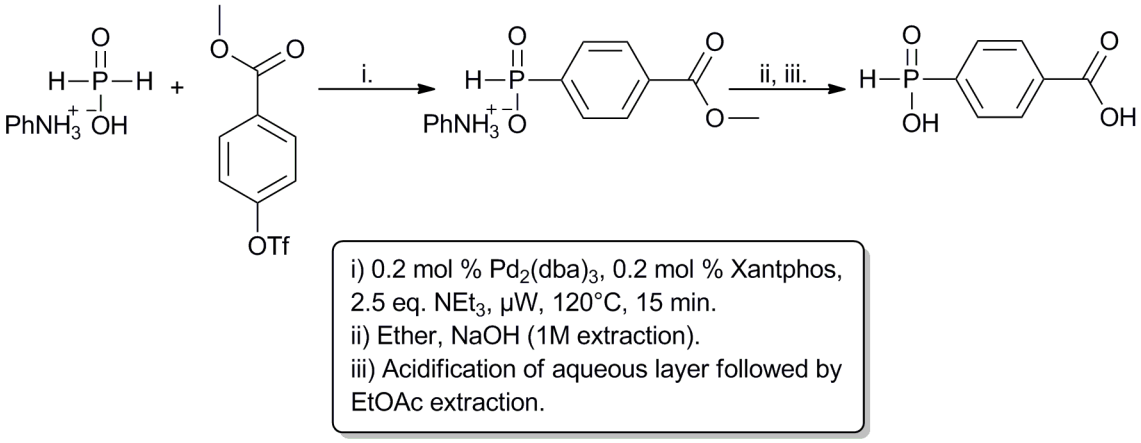
Table 4.1: Results of Aryl H-phosphinic acid synthesis

Entry[a]	Ar-X	Product	Yield[b]
1			67%
2			40%
3			50%
4			45%

Reaction conditions:
a) Anilinium hypophosphite (1 eq.), 0.2 mol % $Pd_2(dba)_3$/Xantphos, NEt_3 (2.5 eq.), THF, microwave radiation, 120 °C, 15 min, Ar-X (1 eq.). b) Isolated yield, after recrystallisation.

The material isolated after work-up was found to be of reasonable purity (approximately >85%), however recrystallisation afforded pure aryl H-phosphinic acids. The yields of the acids were moderate, compared to Kalek and Stawinski's results, which can be attributed to material lost during the recrystallisation process.

4-Methoxycarbonylphenyl H-phosphinic acid (Table 4.1, Entry 3) was worked-up in a different manner to the other acids shown. This was due to saponification of the ester functional group to the corresponding carboxylic acid under standard work-up conditions (Scheme 4.24).

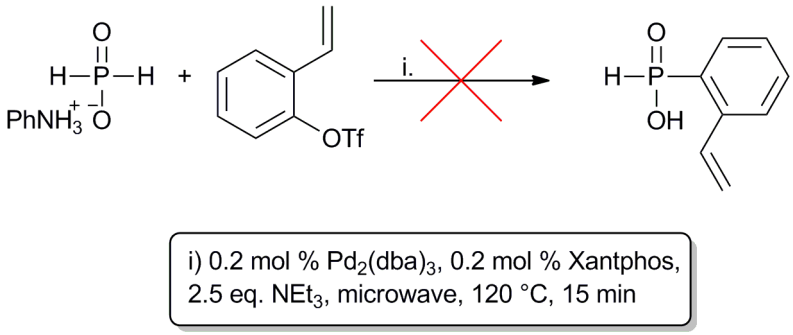


Scheme 4.24: The cleavage of the ester group during work-up of 4-methoxycarbonylphenyl H-phosphinic acid.

To overcome this problem the reaction was worked up in the absence of aq. NaOH. Instead the volatiles were removed and the residue was partitioned between ether and water. The product, in its ionic form, is aqueous soluble and the ether wash allows for removal of organic impurities. Acidification of the aqueous layer followed by extraction with ethyl acetate afforded crude 4-methoxy-carbonylphenyl H-phosphinic acid, in 50% yield. The other acids mentioned were worked up using aq. NaOH with no problems arising.

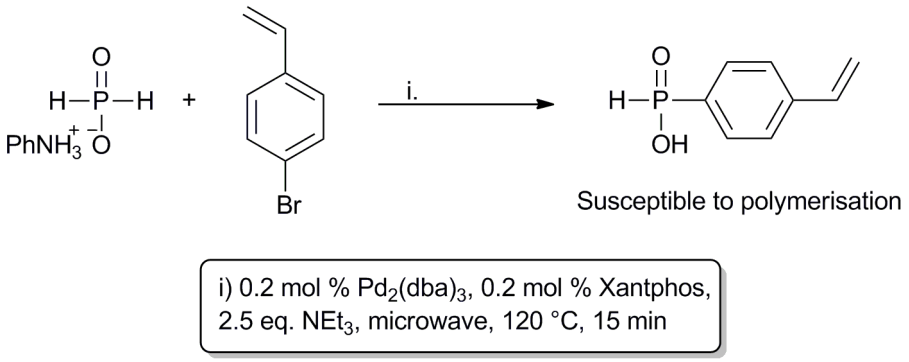
4.1.1.1. Alkene functionalities:

The synthesis of 2- and 4-vinylphenyl H-phosphinic acid was tested, in order to test the alkene functional group in the reductive chlorination reaction. However formation and isolation of such compounds proved challenging. The reaction of 1-vinylphenyl-2-triflate with ammonium hypophosphite under microwave conditions was tested, however no product was observed by NMR analysis (Scheme 4.25).



Scheme 4.25: The attempted synthesis of 2-vinylphenyl H-phosphinic acid.

The lack of product formed is likely due to the steric effects of the 1,2-aryl position.



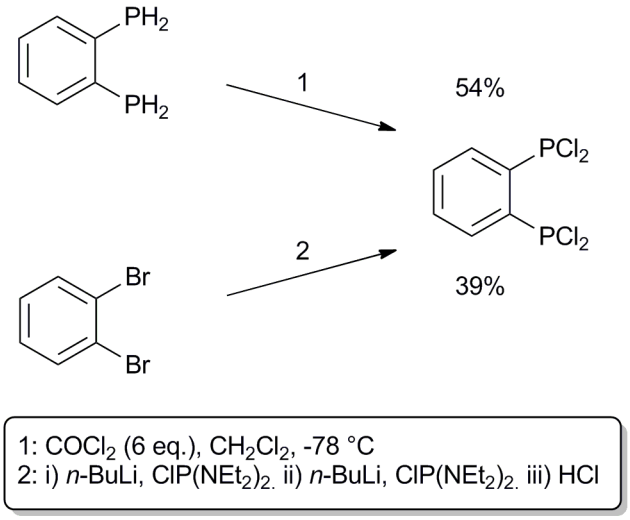
Scheme 4.26: The synthesis of 4-vinylphenyl H-phosphinic acid.

The reaction of Kalek and Stawinski was performed using 4-bromostyrene (Scheme 4.26).[120] After work-up, the reaction looked promising with ^{1}H and ^{31}P NMR data in good agreement with the literature.[120] However, a large amount of insoluble material was formed upon concentration of the EtOAc solution and

further drying *in vacuo.* It appears that, despite the initial reaction working, the product is prone to polymerisation.

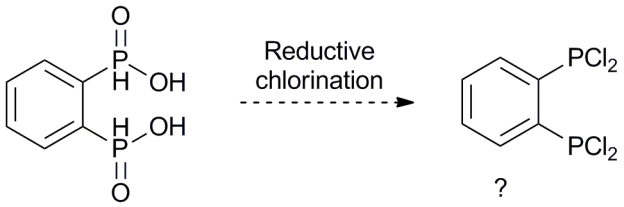
4.1.1.2. Attempted synthesis of phenyl-1,2-bis(H-phosphinic acid):

Phenyl-1,2-bis(H-phosphinic acid) was targeted as a precursor to 1,2-bis(dichlorophosphino)benzene, an important ligand and ligand precursor.[122] Typically this compound has been synthesised by chlorination of the bis(phosphine) with triphosgene (54% yield) (Scheme 4.27, route A),[123] or via the sequential double lithiation of 1,2-dibromobenzene and treatment with bis(diethylamino)-chlorophosphine (39% yield) (Scheme 4.27, route B).[124]



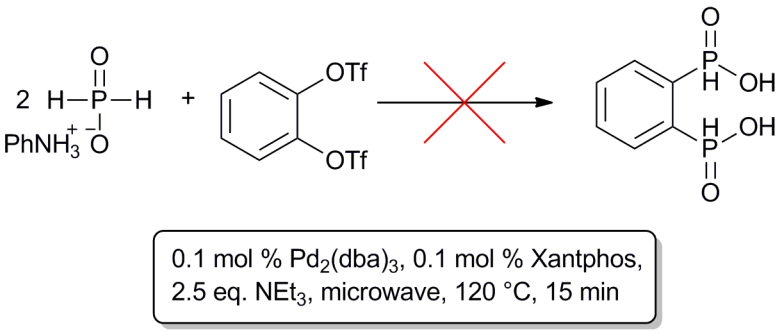
Scheme 4.27: Previous syntheses of 1,2-bis(dichlorophosphino)benzene.

In principle, reductive chlorination of phenyl-1,2-bis(H-phosphinic acid) could give 1,2-bis(dichlorophosphino)benzene (Scheme 4.28).



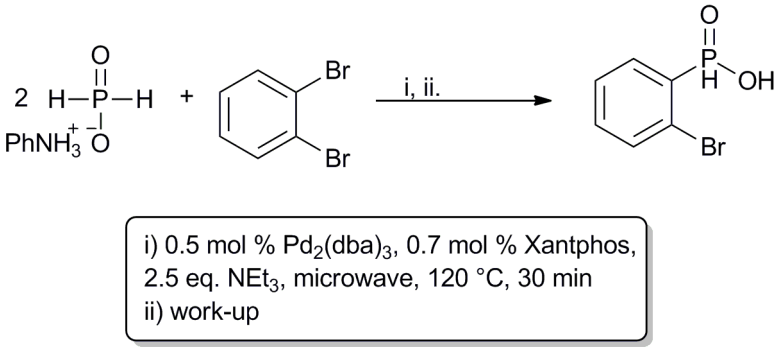
Scheme 4.28: Proposed reductive chlorination of phenyl-1,2-bis(H-phosphinic acid).

The synthesis of phenyl-1,2-bis(H-phosphinic acid) was investigated. Expanding on the use of triflates in the microwave reaction (Scheme 4.23), 1,2-bis(triflyl)benzene, from 1,2-dihydroxybenzene (catechol), was used in the coupling reaction with anilinium hypophosphite (Scheme 4.29). No coupling products were observed by ^{31}P NMR data of the reaction mixture.



Scheme 4.29: The attempted synthesis of phenyl-1,2-bis(H-phosphinic acid).

The reaction of 1,2-dibromobenzene and anilinium hypophosphite was also tested. A higher catalyst loading was used this time with 30 min irradiation time (Scheme 4.30).



Scheme 4.30: The attempted synthesis of phenyl-1,2-bis(H-phosphinic acid) from 1,2-dibromobenzene.

With the higher catalyst loading, coupling was achieved. However, multinuclear NMR data suggests that only one phosphorus group coupled to the aromatic group. The reaction was repeated with 5 mol % palladium catalyst and Xantphos. The reaction was worked up in a similar procedure to the aryl H-phosphinic acids

previously discussed. Recrystallisation of the crude product, from CH_2Cl_2, gave 2-bromophenyl H-phosphinic acid in 18% yield. The synthesis and isolation of 2-bromophenyl H-phosphinic acid has been previously published, but no experimental data was given.[3, 125]

The target compound phenyl-1,2-bis(H-phosphinic acid) could not be synthesised by the microwave assisted palladium catalysed reaction of 1,2-dibromobenzene. Even at high catalyst loadings (5 mol %) only 2-bromophenyl H-phosphinic acid was formed in the reaction. ^{1}H, ^{31}P and ^{13}C NMR and HRMS has been collected for 2-bromophenyl H-phosphinic acid.

4.4.2. Chlorination of Aryl H-phosphinic acids:

Silicon tetrachloride was chosen for preliminary testing, as it is commercially available in high purity and is priced similarly to PCl_3 ($SiCl_4$, 100 g, 99 % = £19.20 vs. PCl_3, 250 g, 99 % = £33.00. Prices from Sigma Aldrich, September 2015). Silicon tetrachloride was added to a suspension of $PhPO_2H_2$ in toluene. At room temperature no reaction occurred, between $PhPO_2H_2$ and $SiCl_4$ (^{31}P NMR monitoring), however at elevated temperatures $PhPCl_2$ was observed. A 1:1.1 equivalent reaction with $SiCl_4$ converted half of the phenyl H-phosphinic acid to $PhPCl_2$ (Table 4.2, Entry 1). A large excess was also tested (Table 4.2, entry 2), giving a much higher yield. However, it became apparent that there was a significant loss of volatile $SiCl_4$ from the system (a large amount of fuming and build-up of silica was observed on the argon bubbler) due to the elevated temperature.

Table 4.2: Reaction of $PhPO_2H_2$ with varying amounts of $SiCl_4$

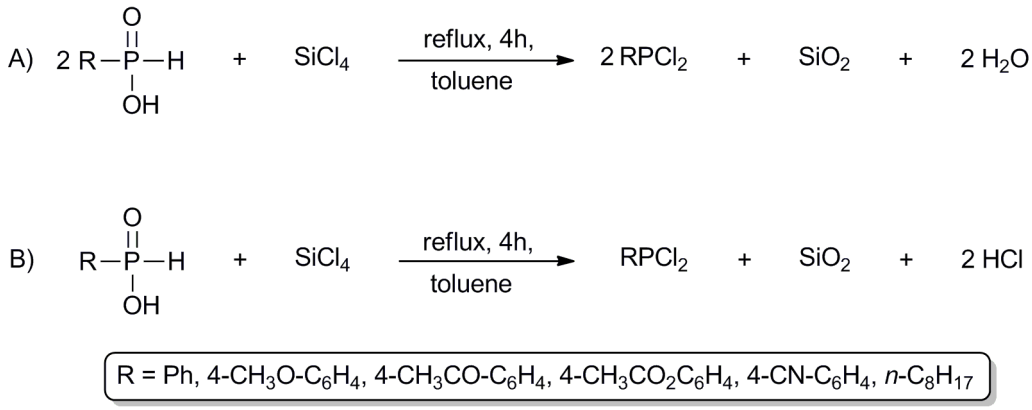
Entry[a]	Molar equivalents of $SiCl_4$	Yield of $PhPCl_2$ (%)[d]
1	1.1	48
2	5.2	83
3[b]	1.1	64
4[b,c]	3.0	81

a) PhP(O)(OH)H (6.6 g, 46.5 mmol) in toluene (100 mL) with relevant amount of $SiCl_4$ was refluxed for 24 h. Reaction was cannula filtered and subjected to vacuum distillation. b) Cold finger condenser at -60 ℃ was used (dry ice/$CHCl_3$). c) $SiCl_4$ (1.5 eq.) added and refluxed for four hours. A second aliquot of $SiCl_4$ (1.5 eq.) and refluxed for four hours. d) Isolated yield, based on $PhPO_2H_2$.

In an attempt to minimize loss of $SiCl_4$, a more efficient condenser was used. The yield increased when a cold finger condenser filled with dry ice/chloroform (-60 ℃) was used (Table 4.2, entry 3). N.B. a dry ice/acetone (-78 ℃) condenser was also

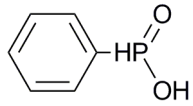
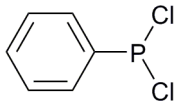
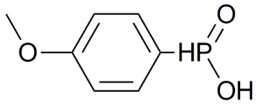
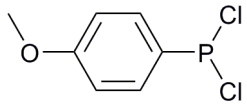
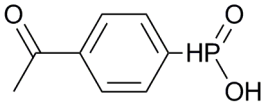
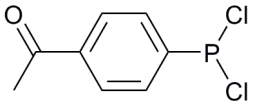
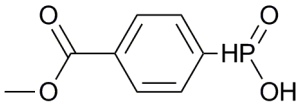
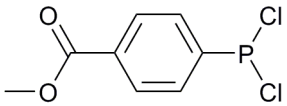
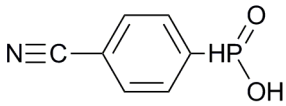
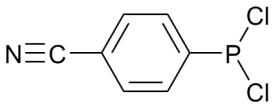
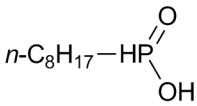
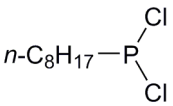
tested, however the yield was low (32%) presumable due to removal of $SiCl_4$ (m.p. -70℃) from the reaction due to freezing on the inside of the condenser. It was found that adding 3 equivalents of $SiCl_4$, in two aliquots of 1.5 equivalents with 4 hours of refluxing between additions (Table 4.2, entry 4), using a dry ice/chloroform cold finger condenser, gave a yield of 81% of $PhPCl_2$. Compared to when a large excess of $SiCl_4$ was used with a conventional condenser (Table 4.2, entry 2, 83%), the yields are similar therefore a cold finger condenser (-60℃) with a total of 3 eq. of $SiCl_4$ was used for the next series of reactions.

A series of aryl H-phosphinic acids and a linear alkyl H-phosphinic acid were tested under these optimised conditions. There are two possible reaction routes (Scheme 4.31). The first is a 2:1 with respect to RPO_2H_2 and $SiCl_4$ (Scheme 4.31, route A). In this reaction water is generated, which would react with either $SiCl_4$ to give silica and HCl or with $PhPCl_2$ to give RPO_2H_2 and HCl. The second reaction (Scheme 4.31, route B) is the stoichiometric reaction of RPO_2H_2 and $SiCl_4$. This reaction involves the generation of $RPCl_2$, silica and HCl. There is no evidence in this work to suggest which reaction is taking place. More investigation would be necessary to prove reaction route A or B.



Scheme 4.31: Possible reaction routes in the synthesis of functionalised aryl dichlorophosphines (see Table 4.3 for results).

Table 4.3: The reductive chlorination of aryl- and alkyl H-phosphinic acids with $SiCl_4$.

Entry	Starting material	Product	Yield[c] (%)
1[a]			81
2[a]			90
3[a]			28
4[b]			84
5[a]			0
6[a]			62

a) $ArP(O)(OH)H$ (46.5 mmol) in toluene (100 mL) with $SiCl_4$ (69.82 mmol, 1.5 eq) was refluxed (cold finger condenser, dry ice/$CHCl_3$) for 4 h. Another aliquot of $SiCl_4$ (69.82 mmol, 1.5 eq) was added and refluxed for 4 h. Reaction was cannula filtered and subjected to vacuum distillation. b) An additional aliquot of $SiCl_4$ (69.82 mmol, 1.5 eq) was added and heated for a further 4 hours (4.5 eq total of $SiCl_4$ with 12h reflux). c) Isolated yield, based on H-phosphinic acid based on $ArPO_2H_2$.

Both the phenyl- and methoxyphenyl- derivatives (Table 4.3, entries 1 and 2) proceeded smoothly to give high yields of the respective aryldichlorophosphines. After approximately 45 minutes of heating little to no starting material (for both phenyl- and methoxyphenyl- H-phosphinic acid) was observed. Silica was observed being deposited in the reaction flask, which served as an indication of the reaction taking place. See below for the discussion of these results.

4.4.2.1. 4-methoxyphenyldichlorophosphine

The reductive chlorination of 4-methoxyphenyl H-phosphinic acid with $SiCl_4$ was performed, on the multi-gram scale, giving 90% yield of 4-methoxyphenyldichlorophosphine after work-up. The work-up consisted of a cannula filtration (to remove silica formed during reaction), removal of solvents *in vacuo* and vacuum distillation. The multinuclear NMR spectra of 4-methoxyphenyldichlorophosphine (4-$MeOC_6H_4PCl_2$), isolated from the H-phosphinic acid and $SiCl_4$, are presented below. The data is in agreement with the literature.[126]

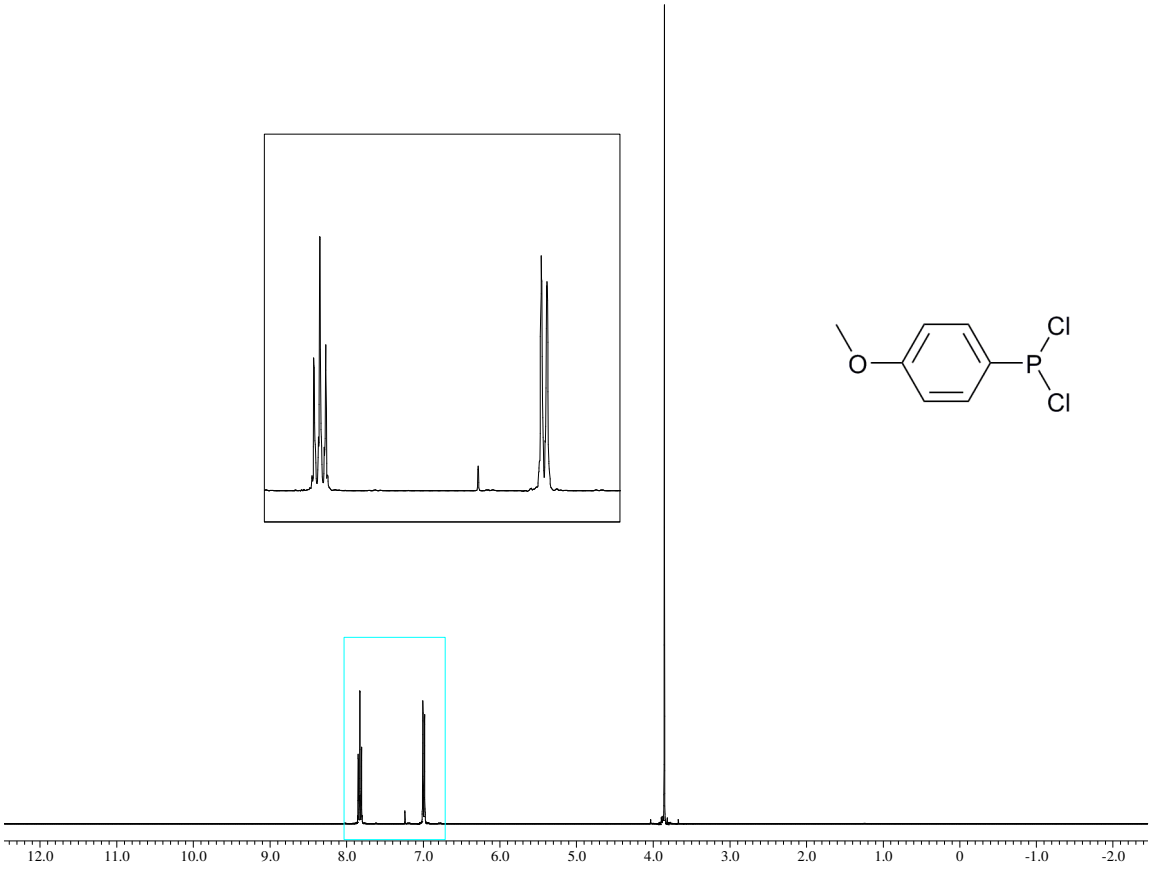


Figure 4.1: ^{1}H NMR spectrum of 4-methoxyphenyldichlorophosphine ($CDCl_3$).

Only peaks from the expected product and residual solvent peak from $CDCl_3$ were observed on the ^{1}H NMR of 4-$MeOC_6H_4PCl_2$ (Figure 4.1). The aromatic protons

are visible as a multiplet at 7.8 ppm and a doublet at 7.0 ppm. The methoxy protons are shown as a singlet at 3.86 ppm.

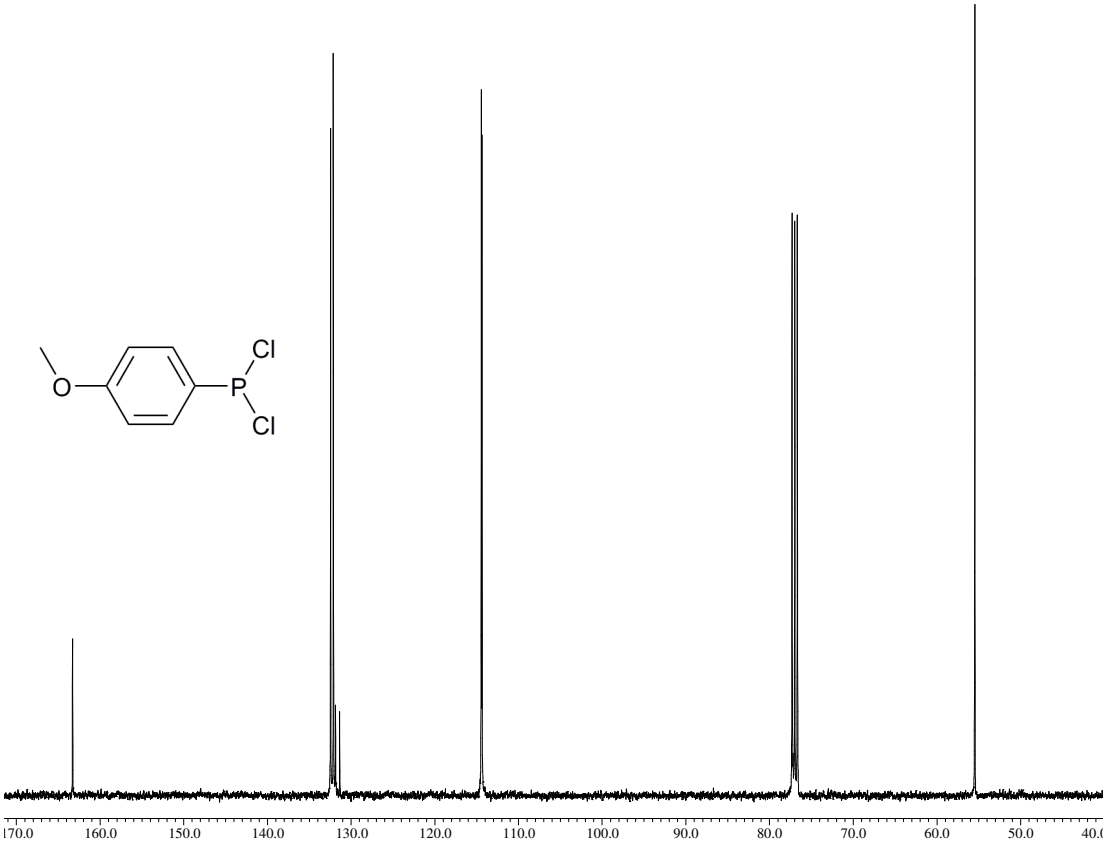


Figure 4.2: ^{13}C NMR spectrum of 4-methoxyphenyldichlorophosphine ($CDCl_3$).

In the ^{13}C NMR spectrum of 4-$MeOC_6H_4PCl_2$ (Figure 4.2), the relatively de-shielded quaternary aromatic carbon linked to the methoxy group is observed at 163.3 ppm. The quaternary carbon bonded to the phosphorus centre is visible as a doublet centred at 131.6 ppm with a coupling constant of 51 Hz. The remaining aromatic carbons are observed as doublets at 132.3 ppm ($^2J_{C-P}$ = 40 Hz) and 114.5 ppm ($^3J_{C-P}$ = 10 Hz). The methoxy group is shown upfield at 55.5 ppm.

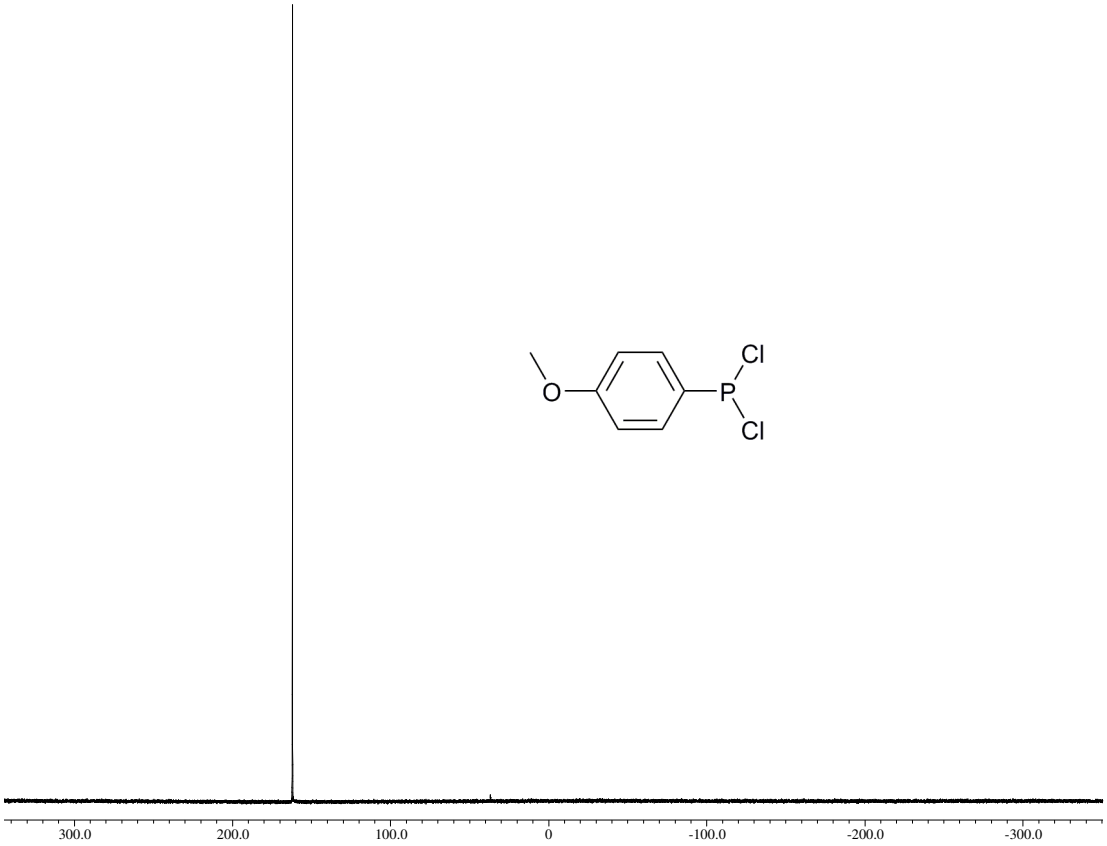


Figure 4.3: ^{31}P NMR spectrum of 4-methoxyphenyldichlorophosphine ($CDCl_3$).

Only 1 peak was observed in the ^{31}P NMR spectrum (Figure 4.3) of 4-$MeOC_6H_4PCl_2$ at a shift of 162.1 ppm.

4.4.2.2. Carbonyl containing aryldichlorophosphines

Of particular interest was the formation of 4-acetylphenyldichlorophosphine (4-$MeCOC_6H_4PCl_2$) (Table 4.3, Entry 3) and 4-methoxycarbonylphenyldichloro-phosphine (4-$MeO(CO)C_6H_4PCl_2$) (Table 4.3, Entry 4). Both of these compounds are novel and contain carbonyl functionalities, which as described in the introduction are not stable to some previous methodologies.

4.4.2.3. 4-acetylphenyldichlorophosphine

The reaction of 4-acetylphenyl H-phosphinic acid with $SiCl_4$ was performed in the same manner as 4-$MeOC_6H_4PCl_2$. After 8 hours of reflux the reaction was worked-

up. Silica was visible and a yellow residue was present. The low yield (28% of 4-$MeCOC_6H_4PCl_2$) compared to $PhPCl_2$ and 4-$MeOC_6H_4PCl_2$ can be attributed to the reaction not running to completion. This could be due to the lower solubility of 4-acetylphenyl-H-phosphinic acid in toluene compared to the other aryl-H-phosphinic acids tested. The low yield could also be due to the difference in electronics of 4-acetylphenyl-H-phosphinic acid compared to the other aryl H-phosphinic acids tested. The acetyl functionality is more electron withdrawing than the highly electron donating methoxy functionality (of 4-methoxyphenyl-H-phosphinic acid). It is possible that prolonged heating or more extreme reaction conditions (>110 ℃ sealed reaction) could give a higher yield of $MeCOC_6H_4PCl_2$.

Despite a lower yield, compared to the other acids tested, pure 4-$MeCOC_6H_4PCl_2$ was obtained and characterised. The ^{1}H NMR spectrum (Figure 4.4) shows the methyl group of the acetyl moiety as a singlet at 2.63 ppm. The aromatics are visible as two multiplets between 8.05-7.97 ppm.

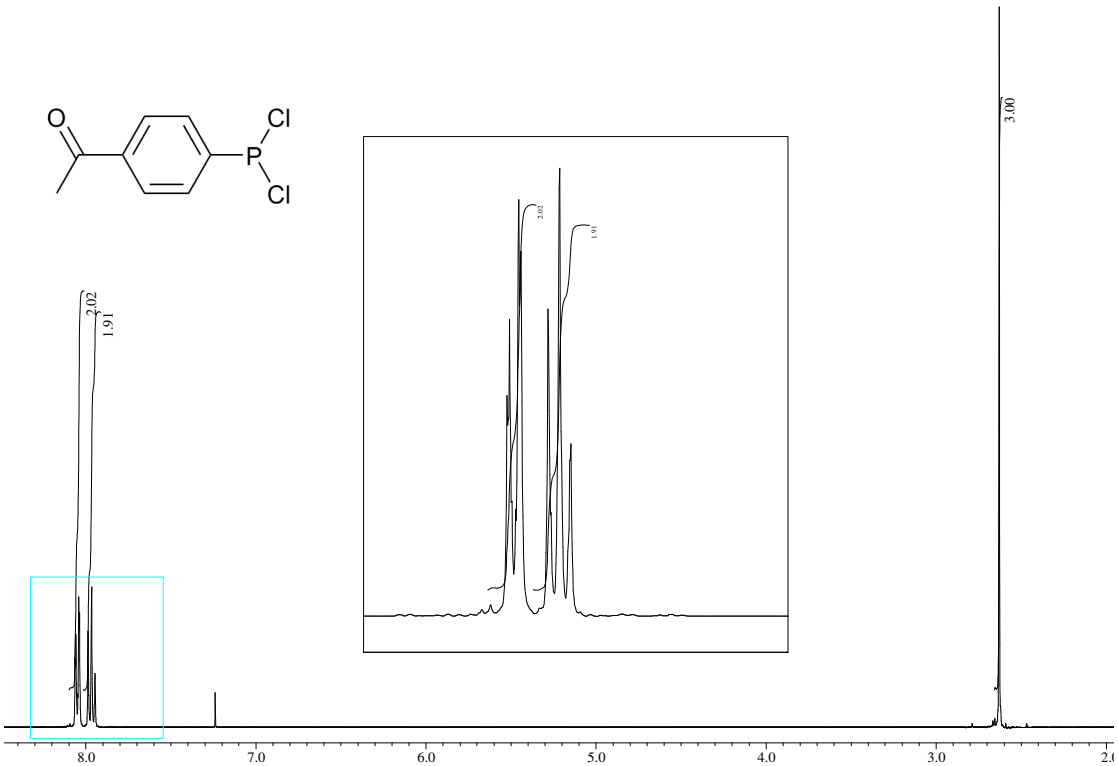


Figure 4.4: ^{1}H NMR spectrum of 4-acetylphenyldichlorophosphine ($CDCl_3$).

The ^{13}C NMR of 4-$MeCOC_6H_4PCl_2$ is shown below (Figure 4.5). Assignments were confirmed by HMQC. The more de-shielded carbonyl group is visible at 197 ppm. The quaternary carbon directly bonded to phosphorus is visible as a doublet centred at 145 ppm with a coupling constant of 54 Hz. Further downfield, the quaternary aromatic carbon linked to acetyl group is visible at 139.9 ppm. The methyl group, of the acetyl functionality, is visible at 26.8 ppm. The remaining aromatic carbons are visible as two doublets at 130.4 ppm ($^2J_{C-P}$ = 30 Hz) and 128.5 ($^3J_{C-P}$ = 10 Hz).

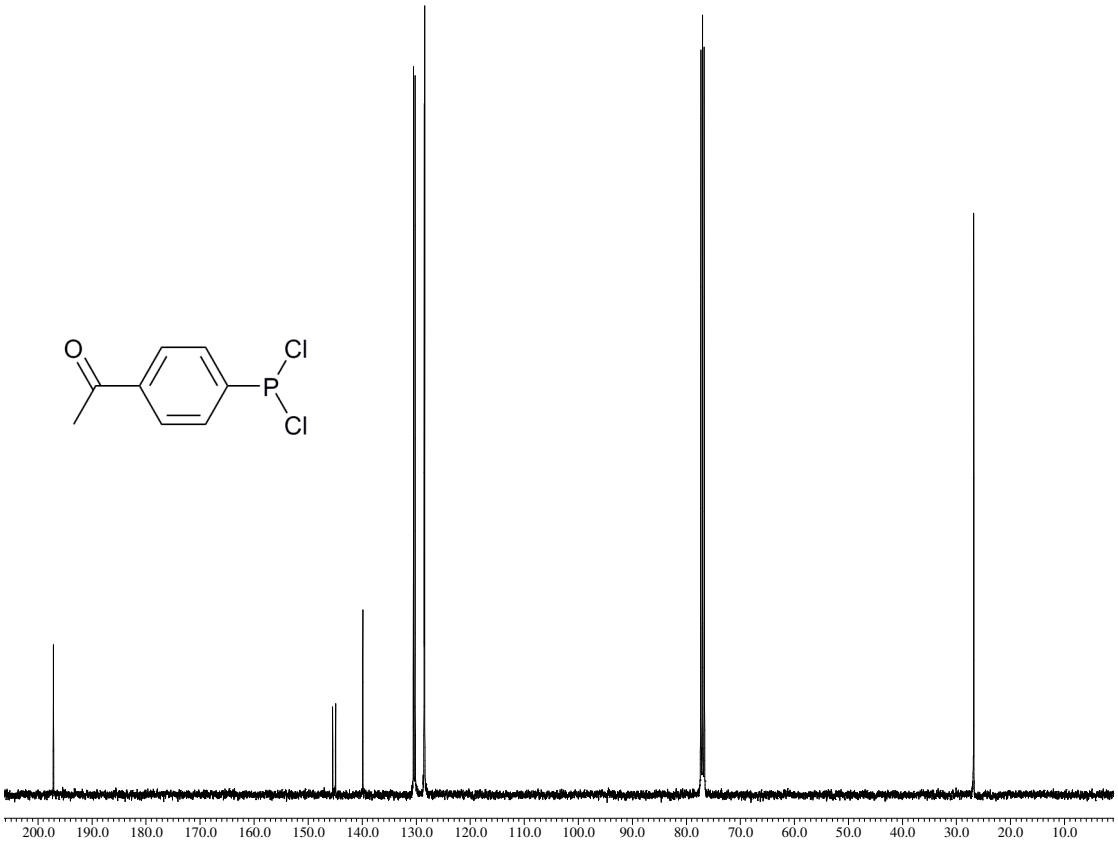


Figure 4.5: ^{13}C NMR spectrum of 4-acetylphenyldichlorophosphine ($CDCl_3$).

One peak at 158.1 ppm was observed in ^{31}P NMR of $MeCOC_6H_4PCl_2$ (Figure 4.6).

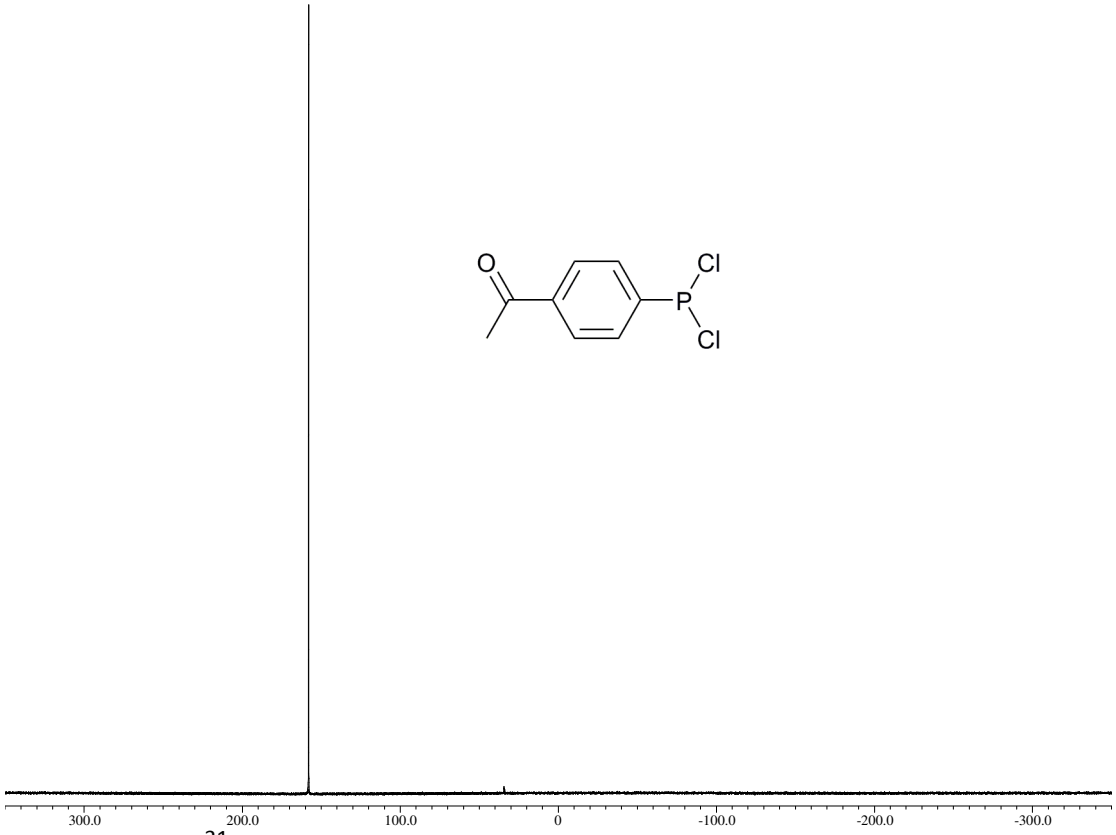


Figure 4.6: ^{31}P NMR spectrum of 4-acetylphenyldichlorophosphine ($CDCl_3$).

4.4.2.4. 4-methoxycarbonylphenyldichlorophosphine

4-methoxycarbonylphenyl H-phosphinic acid was reacted with $SiCl_4$ in toluene at 110℃ (Table 4.3, Entry 4). A significant amount of off white residue remained, which appeared to be un-reacted 4-methoxycarbonylphenyl H-phosphinic acid, after 8 hours reflux with 3 eq. of $SiCl_4$. Therefore another aliquot of $SiCl_4$ was added and the reaction was refluxed for a further 4 hours. After which, there was less residue visible and the presence of silica was observed. The reaction was subjected to cannula filtration and vacuum distillation to give pure 4-methoxycarbonylphenyldichlorophosphine (4-$MeO(CO)C_6H_4PCl_2$) in 84% yield.

The expected shift patterns and integrations of 4-$MeO(CO)C_6H_4PCl_2$ were observed in the ^{1}H NMR spectrum (Figure 4.7) of the isolated product. The

aromatic protons appear as a doublet and triplet between 8.2-7.8 ppm. The methoxy group appears as a singlet at 3.9 ppm, further downfield than the acetyl group of $MeCOC_6H_4PCl_2$ due to more de-shielding of the ester functionality.

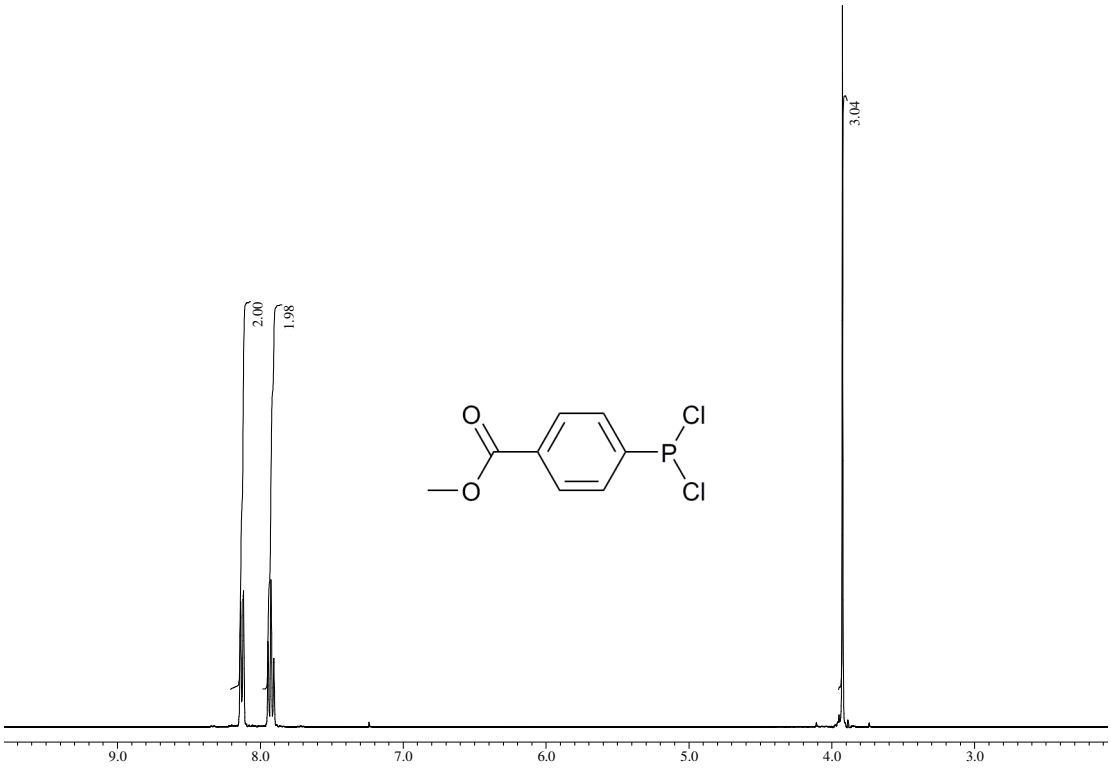


Figure 4.7: ^{1}H NMR spectrum of 4-methoxycarbonylphenyl-dichlorophosphine ($CDCl_3$).

The ^{13}C NMR spectrum of 4-$MeO(CO)C_6H_4PCl_2$ (Figure 4.8) is similar to that of 4-$MeCOC_6H_4PCl_2$. The carbonyl group of the ester, of 4-$MeO(CO)C_6H_4PCl_2$, is at a shift of 166 ppm. The ipso-aromatic carbon is visible as a doublet at 145 ppm with a coupling of 55 Hz, similar to that of 4-$MeCOC_6H_4PCl_2$ (54 Hz). The quaternary aromatic carbon of the ester group is observed at 133.6 ppm. The remaining aromatic carbons are observed as doublets at 130.1 ppm ($^{2}J_{C\text{-}P}$ = 40 Hz) and 129.8 ($^{3}J_{C\text{-}P}$ = 10 Hz). The methoxy group is observed at 52.7 ppm.

Figure 4.8: ^{13}C NMR spectrum of 4-methoxycarbonylphenyl-dichlorophosphine ($CDCl_3$).

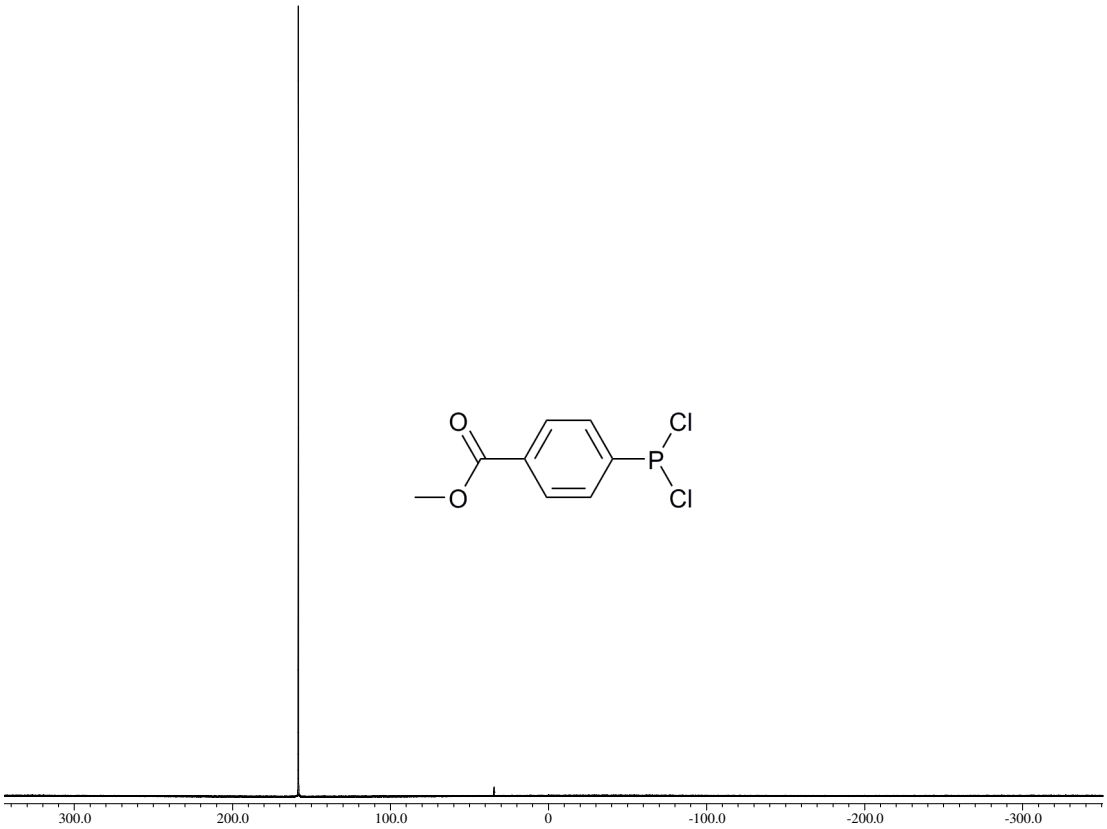


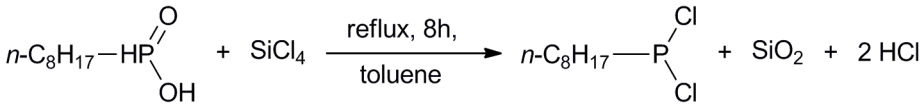
Figure 4.9: ^{31}P NMR spectrum of 4-methoxycarbonylphenyl-dichlorophosphine ($CDCl_3$).

The ^{31}P NMR spectrum of 4-MeO(CO)$C_6H_4PCl_2$ (Figure 4.9) has only one visible peak at 158.3 ppm as a broad singlet. A similar shift value to that of 4-$MeCOC_6H_4PCl_2$.

4.4.2.5. Attempted synthesis of 4-cyanophenyldichlorophosphine

The reaction of 4-cyanophenyl H-phosphinic acid did not proceed as expected (Table 4.3, Entry 5). No product was observed after 8 hours reflux with $SiCl_4$ in toluene. A small scale test reaction was performed prior to the full scale synthesis. In this reaction 4-cyanophenyl H-phosphinic acid was heated, using an oil bath at 140 ℃, with 5.7 eq. $SiCl_4$ in toluene in a sealed Schlenk flask. ^{31}P NMR data screening was performed and indicated a peak at δ 164.1 in toluene, which is similar to the literature δ 155.4 in $CDCl_3$[75] and in good agreement with the ^{31}P NMR data of aryl dichlorophosphines previous discussed.

4.4.2.6. The synthesis of *n*-octyldichlorophosphine



Scheme 4.32: The synthesis of *n*-octyldichlorophosphine.

As an extension to this work, a saturated H-phosphinic acid was also tested (Table 4.3, Entry 6). When $SiCl_4$ was added to a solution of *n*-octyl H-phosphinic acid a large amount of silica appeared to form. This suggests that the reaction may occur at ambient temperature, however to ensure reaction proceeded to completion, it was heated to reflux under the optimised conditions (Scheme 4.32). The SiO_2 formed during this reaction was more gelatinous compared to the previous aryl reactions. As such the cannula filtration became blocked several times. The reaction was therefore worked-up, with the silica remaining. This is likely the

reason for a moderate yield of 62%, as previous NMR studies, of small scale chlorination of *n*-octyl-H-phosphinic acid, indicated an almost quantitative conversion (See Figure 4.10, peak at 196 ppm).

Despite the lower than expected yield, the reaction of $SiCl_4$ with saturated H-phosphinic acids appears to be a viable route in the synthesis of saturated alkyl dichlorophosphines, however further testing is required to determine the full scope of this reaction towards alkyl derivatives.

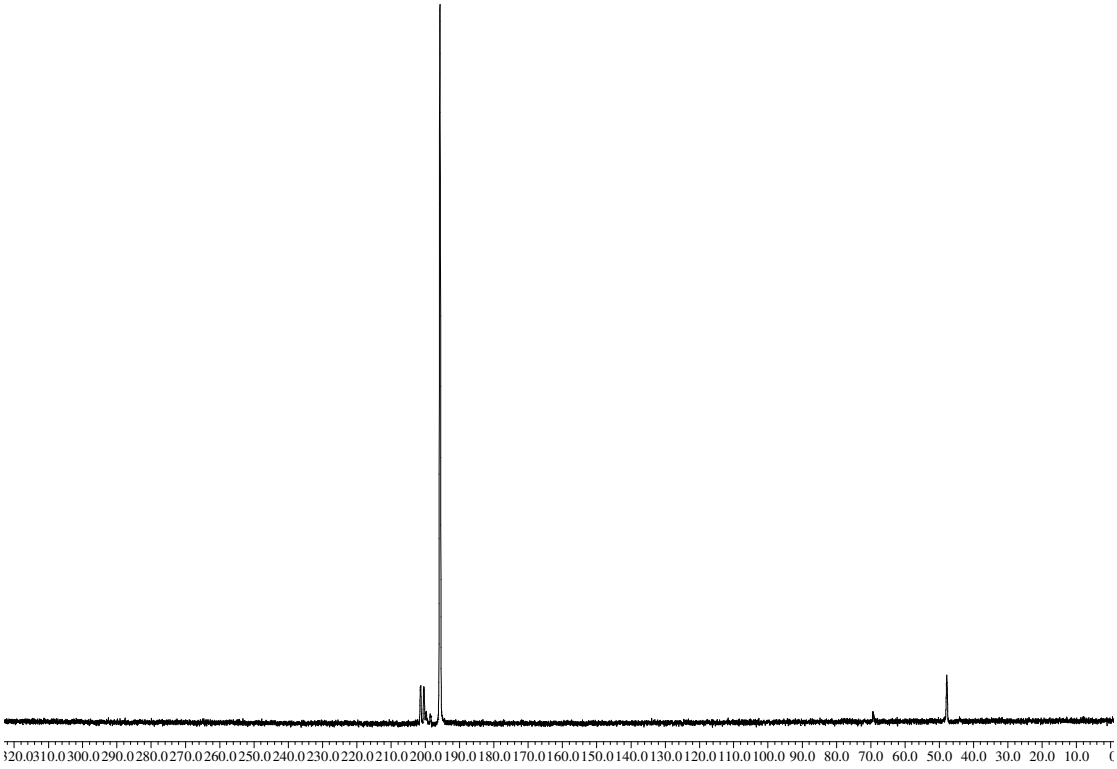


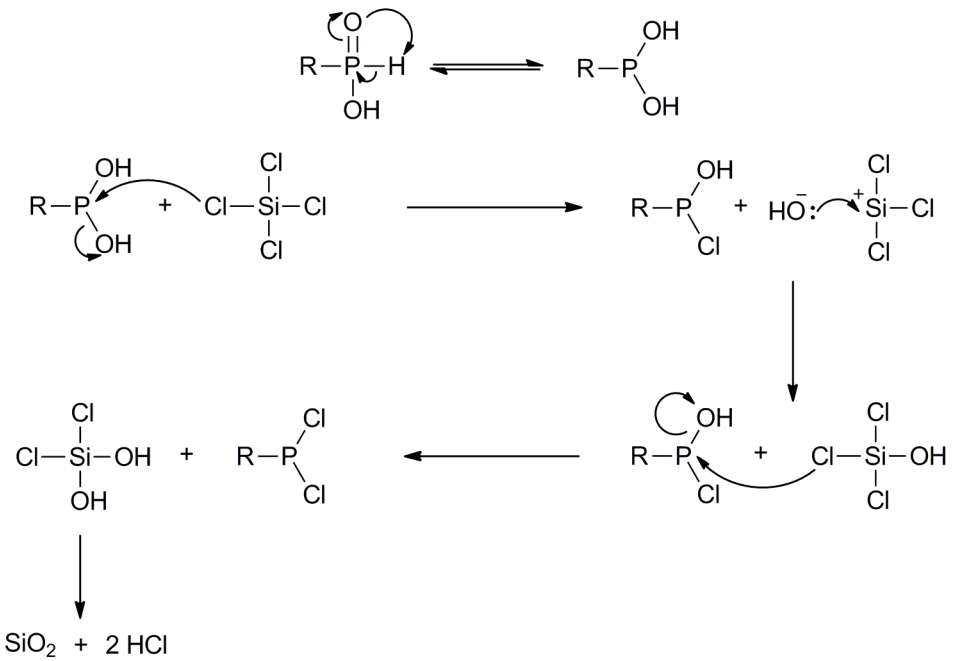
Figure 4.10: ^{31}P NMR spectrum of a test scale chlorination of *n*-octyl H-phosphinic acid (toluene).

Accurate mass data was collected on functionalised aryl dichlorophosphines and *n*-octyl dichlorophosphine. The experimental values agree with the calculated accurate mass values.

4.4.3. Mechanistic considerations

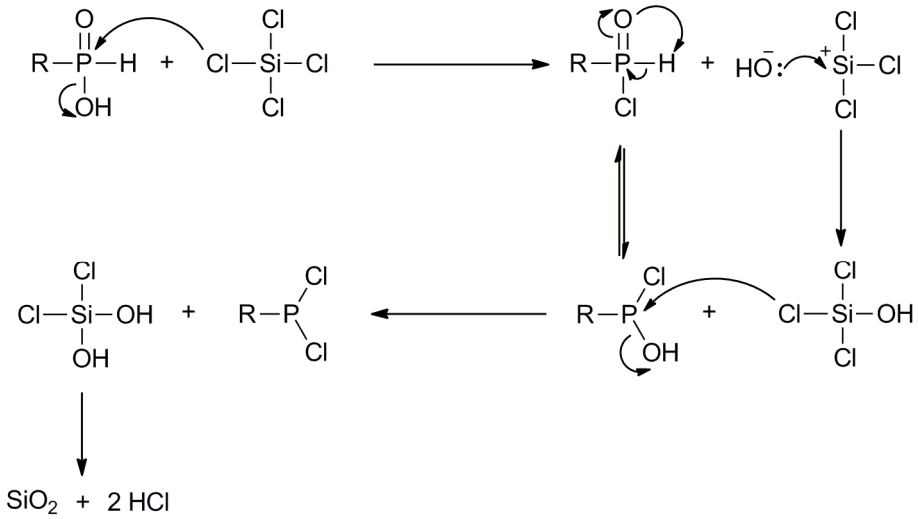
The mechanism for the chlorinations, described above, has not been determined. Despite this, there a several possible mechanisms that could account for this reaction. These types of reactions have been mentioned previously, using PCl_3 as the chlorinating agent, by Quin and Anderson.[98] The mechanisms below are based on these previous discussions.

Two possible mechanisms are based on the tautomerisation of the acid. The first mechanism involves the tautomerisation of the functionalised H-phosphinic acid followed by nucleophillic attack on to the phosphorus centre (Scheme 4.33).



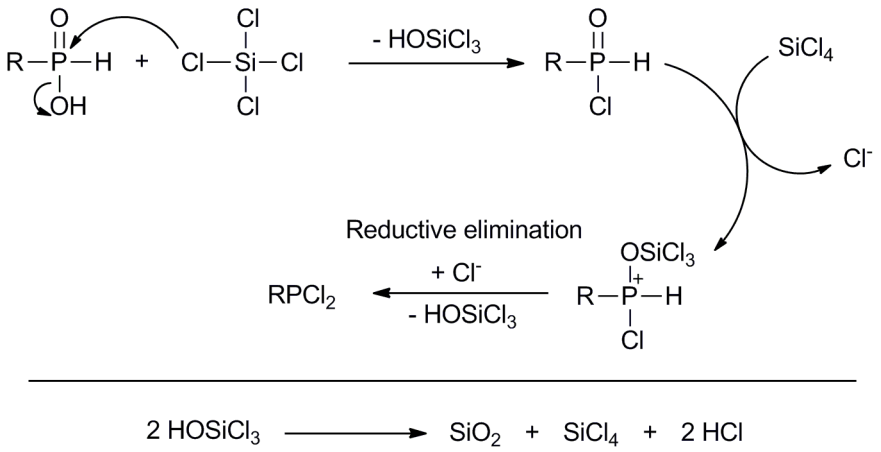
Scheme 4.33: Nucleophilic attack on H-phosphinic acid tautomer.

The second shows the initial chlorination could take place on the phosphorus centre followed by tautomerisation and further chlorination (Scheme 4.34). This is almost identical to the first mechanism however, the order of tautomerisation is changed.



Scheme 4.34: Nucleophilic attack on H-phosphinic acid followed by tautomerisation.

The third possible mechanism does not rely on tautomerisation of the acid (Scheme 4.35).



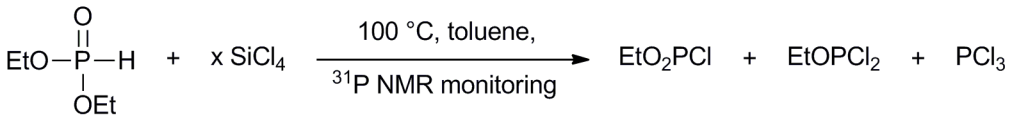
Scheme 4.35: The possible mechanism for the synthesis of $RPCl_2$ via a siloxy intermediate.

Instead direct nucleophilic attack on the phosphorus centre occurs. This reaction proceeds through a phosphinic acid chloride siloxy intermediate, however during ^{31}P NMR screening reactions no such compound was observed.

4.4.4. The reaction of $SiCl_4$ with other Phosphorus(V) compounds

4.4.4.1. Reaction of diethyl phosphite with $SiCl_4$

In an extension to the work above, the chlorination of several other phosphorus(V) compounds were tested. First of which, was the reaction of diethyl phosphite with $SiCl_4$. It was surmised that the reaction could generate diethyl chlorophosphite (EtO_2PCl) and ethyl dichlorophosphite ($EtOPCl_2$). These reactions were performed in a sealed NMR tube and a percentage of each compound was assigned from the integration of ^{31}P NMR screening. Diethyl phosphite in toluene was heated with $SiCl_4$ (5 eq) for 40 minutes. ^{31}P NMR indicated a mixture of compounds (Scheme 4.36).



Scheme 4.36: The reaction of diethyl phosphite with varying amounts of $SiCl_4$.

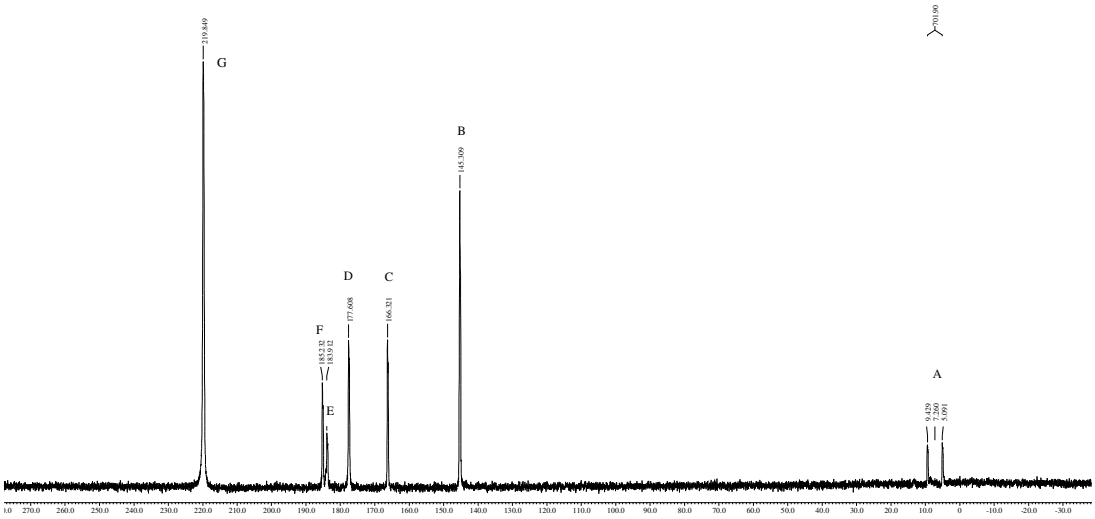


Figure 4.11: ^{31}P NMR spectrum of diethyl phosphite heated with excess $SiCl_4$ in toluene.

Despite the use of excess $SiCl_4$ starting diethyl phosphite was visible (peak A) (Figure 4.11). Based on literature values Peak C was assigned as $(EtO)_2PCl$.[127]

Peak D was assigned as $EtOPCl_2$.[127] Upon further heating (6.5 hours) the main compounds present were PCl_3 (peak G) and $EtOPCl_2$ (peak D). All other compounds were significantly lower in concentration.

Reactions were performed where the stoichiometry of $SiCl_4$ was altered and ^{31}P NMR was used to measure the percentage amounts of each phosphorus containing compound (Table 4.4).

Table 4.4: Reactions of $SiCl_4$ with triethyl phosphite

Entry[a]	Molar equivalents of $SiCl_4$	PCl_3 (%)	$EtOPCl_2$ (%)	EtO_2PCl (%)	$EtO_2P(O)H$ (%)
1[b]	0.5	1	40	18	40
2[b]	1.0	4	60	13	22
3[b]	2.0	27	37	11	9
4[c]	5.2	74	20	>1	0

a) reaction run in a sealed NMR tube in anhydrous toluene. b) reaction run at room temperature for 5 hours. c) reaction run at 100°C for 5 hours.

As can be seen in Table 4.4, the reaction proceeds well at room temperature to give up to 60% of $EtOPCl_2$. A large amount of PCl_3 was formed when a large excess of $SiCl_4$ was used.

In conclusion the reaction is not selective, under these conditions, to mono- di- or tri- chlorination as a substantial amount of each chlorinated product is present. However, further optimisation of this reaction could allow for moderate yields of EtO_2PCl and $EtOPCl_2$.

4.4.4.2. Reaction of triethyl phosphite with $SiCl_4$

The reaction of triethylphosphite and $SiCl_4$ was also investigated. A series of reactions with varying amounts of $SiCl_4$ were performed in toluene, under argon in

a sealed NMR tube (Table 4.5). The reactions were left at room temperature for 4.5 hours and ^{31}P NMR data collected.

Table 4.5: Reactions of $SiCl_4$ with triethyl phosphite

Entry[a]	Molar equivalents of $SiCl_4$	$(EtO)_2PCl$ (%)	$P(OEt)_3$	Unknown peak δ146 (%)
1	0.6	37	48	9
2	1.0	60	2	16
3	1.9	62	4	25

a) reactions run in a sealed NMR tube in anhydrous

Unlike the reaction of diethyl phosphite with $SiCl_4$ (Scheme 9), no PCl_3 or $EtOPCl_2$ was observed. However, moderate yields of $(EtO)_2PCl$ were formed during this reaction.

4.5. Conclusion

The reaction of silicon tetrachloride with aryl H-phosphinic acids shows excellent promise of being a viable alternative route in the synthesis of aryl- dichloro-phosphines, however further investigation is required to determine the full scope and functional group tolerance of the reductive chlorination of aryl- and alkyl- H-phosphinic acids.

Aryl H-phosphinic acids are readily accessible by palladium catalysed microwave synthesis from aryl triflates. The “one-pot” chlorination of aryl H-phosphinic acids with silicon tetrachloride is simple to perform and the products are easily separated, as the main side product formed is silica which is filtered from the reaction mixture. A small series of functionalised aryl H-phosphinic acids were reacted with silicon tetrachloride on the multi-gram scale. Methoxy, acetyl and ester functionalities were tolerated, giving the relevant aryl dichlorophosphines. Two previously unknown carbonyl containing aryl dichlorophosphines, 4-acetylphenyldichlorophosphine (4-$MeCOC_6H_4PCl_2$) and 4-methoxycarbonylphenyl-dichlorophosphine (4-$MeO(CO)C_6H_4PCl_2$) were formed and isolated. Unfortunately, 4-cyanophenyl H-phosphinic acid, did not react under standard conditions, however trace amounts of the product, 4-cyanophenyldichloro-phosphine (4-$CN\text{-}C_6H_4PCl_2$), was observed by ^{31}P NMR under more forcing conditions.

The reaction of a saturated H-phosphinic acid was also tested giving *n*-octyldichlorophosphine in good yield, extending the reaction to the formation of non-aromatic dichlorophosphines. A brief study of the reactivity of di- and triethylphosphites with silicon tetrachloride is also presented, showing the formation of ethoxychlorophosphines.

Chapter 5

Experimental

5.1. General Experimental:

Unless otherwise stated, all reactions were performed under argon or nitrogen, using standard Schlenk techniques. Anhydrous THF, CH_2Cl_2, ether and toluene were obtained from a Grubb's solvent drying system. Acetone and *n*-hexane were dried over 3 Å molecular sieves. Ammonium hypophosphite, HMDS, BINOL, triflic anhydride, Ni(dppp)Cl_2, *N*-bromosuccinimide, Dess-Martin periodinane, methyl 4-hydroxybenzoate and $SiCl_4$ were purchased from Sigma Aldrich and used as received. Perfluoroalkyl iodides were purchased from Apollo Scientific and were stored over copper wire. NaHMDS and NFSI were purchased from Apollo Scientific and were used as received. 4-hydroxybenzonitrile, 4-acetylphenyl bromide, 4-bromoanisole and 1-octene were purchased from Alfa Aesar and were used as received. Anilinium hypophosphite was synthesised by the literature procedure.[3] Thin layer chromatography was performed using Alfa Aesar silica gel 60 F254 plates. Column Chromatography was performed using Sigma Aldrich silica gel pore size 60 Å, 230-400 mesh.

NMR spectra were recorded on a JEOL ECS 400 MHz FT NMR spectrometer with external references of 85% H_3PO_4 for ^{31}P, CCl_3F for ^{19}F and Me_4Si for ^{13}C and ^{1}H NMR. High resolution mass spectrometry (HRMS), ESI unless stated otherwise, spectra were recorded on an Agilent 6540 Q-TOF mass spectrometer. Accurate mass analysis of aryl dichloro-phosphines was performed by EPSRC UK National Mass Spectrometry Facility at Swansea University. Single crystal X-ray diffractions were collected by the EPSRC UK National Crystallography Service at the University of Southampton.[128] See experimental section 5.6 (page 163) for X-ray crystallographic data.

5.2. The reactions of BTSP with perfluoroalkyl iodides

5.2.1. Synthesis of [*p*-$MeC_6H_4NH_3$][*n*-$C_4F_9P(O)_2H$]

$[NH_4][H_2PO_2]$ (1.25 g, 15.1 mmol) was heated, to 110 °C, with $(Me_3Si)_2NH$ (3.2 mL, 15.4 mmol) for 2 h. The reaction was cooled to 0 °C and CH_2Cl_2 (15 mL) was added followed by C_4F_9I (2.6 mL, 15.1 mmol). The reaction was allowed to warm up to room temperature and was stirred overnight. The reaction was filtered and the residue portioned between Et_2O (80 mL) and 2M HCl (30 mL). This was shaken and the layers separated. The organics were then washed with 2M HCl and water (30 mL each). The organics were dried over $MgSO_4$, filtered and solvent removed, *in vacuo*, to give crude *n*-$C_4F_9PO(OH)H$ as a pale yellow oil (0.93 g, 22%, 3.30 mmol). A solution of *p*-toluidine (0.43 g, 3.96 mmol, 1.2 eq.) in Et_2O (20 mL) was added slowly to a solution of the crude *n*-$C_4F_9PO(OH)H$ in Et_2O (20 mL). The resulting white precipitate was filtered. The solvent was removed from the filtrate *in vacuo* and the resulting solid was washed with *n*-pentane to afford pure [*p*-$MeC_6H_4NH_3$][*n*-$C_4F_9P(O)_2H$] as a white solid (0.73 g, 12.4%). **^{1}H NMR (DMSO-d_6):** δ 9.64 (br s, 3H, $ArNH_3^+$), 7.26 (d, J = 8.2 Hz, 2H, Ar), 7.12 (d, J = 7.8 Hz, 2H, Ar), 6.97 (d, $^1J_{P\text{-}H}$ = 535 Hz, 1H, P-H), 2.22 (s, 3H, CH_3). **^{19}F NMR (DMSO-d_6):** δ -80.3 (s, 3F, CF_3), -122.5 (s, 2F, CF_2), -125.6 (s, 2F, CF_2), -128.4 (d, $^2J_{P\text{-}F}$ = 70 Hz, 2F, CF_2-P). **^{31}P NMR (DMSO-d_6):** δ -0.3 (d t, $^1J_{P\text{-}H}$ = 536 Hz, $^2J_{P\text{-}F}$ = 70 Hz).

5.2.2. Attempted synthesis of [*p*-$MeC_6H_4NH_3$][*n*-$C_6F_{13}P(O)_2H$]

$[NH_4][H_2PO_2]$ (0.59 g, 7.14 mmol), $(Me_3Si)_2NH$ (1.56 mL, 1.21 g, 7.5 mmol), CH_2Cl_2 (7.5 mL) and *n*-$C_6F_{13}I$ (1.51 mL, 3.12 g, 7 mmol) were used in an analogous method to experiment 5.2.1. To a solution of crude *n*-$C_6F_{13}PO(OH)H$ in Et_2O (40 mL) was added to a solution of *p*-toluidine (0.80 g, 7.47 mmol) in Et_2O

(20ml). The solvent was removed under reduced pressure and the residue was washed with hot $CHCl_3$. The residue was recrystallised from $CHCl_3$/acetone (9:1) to give crude [*p*-$MeC_6H_4NH_3$][$C_6F_{13}P(O)_2H$] a white solid (0.78 g, 23%). **^{19}F NMR (DMSO-d$_6$):** δ -80.2 (s), -120.2 (s), -121.6 (s), -122.1 (s), -122.2 (s), -122.7 (s), -125.8 (s), -128.2 (d, $^2J_{P-F}$ = 70 Hz). **^{31}P NMR (DMSO-d$_6$):** δ 0 (s), -1.9 (d t, $^1J_{P-H}$ = 532 Hz, $^2J_{P-F}$= 70 Hz), -3.9 (t, $^2J_{P-F}$ = 74 Hz). Product not isolated.

5.2.3. Synthesis of [*p*-$MeC_6H_4NH_3$][*n*-$C_8F_{17}P(O)_2H$]

$[NH_4][H_2PO_2]$ (1.25 g, 15.1 mmol), $(Me_3Si)_2NH$ (3.2 mL, 2.48 g, 15.4 mmol), CH_2Cl_2 (15 mL) and *n*-$C_8F_{17}I$ (4.0 mL, 8.27 g, 15.1 mmol) were used in an analogous method to experiment 5.2.1. To a solution of crude *n*-$C_8F_{17}PO(OH)H$ (4.12 g, 8.51 mmol) in Et_2O (40 mL) was added to a solution of *p*-toluidine (1.09 g, 10.22 mmol, 1.2 eq.) in Et_2O (20 mL). The solvent was reduced *in vacuo* to initiate crystallisation of the product. The precipitate was filtered and washed with *n*-pentane to afford pure [*p*-$MeC_6H_4NH_3$][*n*-$C_8F_{17}P(O)_2H$] as a white solid (2.95 g, 33%). **^{1}H NMR (DMSO-d$_6$):** δ 9.40 (br s, 3H, $ArNH_3^+$), 7.19 (d, J = 7.8 Hz, 2H, Ar), 7.10 (d, J = 8.2 Hz, 2H, Ar), 6.97 (d, $^1J_{P-H}$ = 540 Hz, 1H, P-H), 2.11 (s, 3H, CH_3). **^{19}F NMR (DMSO-d$_6$):** δ -80.3 (s, 3F, CF_3), -121.8 (s, 8F, CF_2), -122.8 (s, 2F, CF_2), -126.1 (s, 2F, CF_2), -128.4 (d, $^2J_{P-F}$ = 70 Hz, 2F, CF_2-P). **^{31}P NMR (DMSO-d$_6$):** δ 0.0 (dt, $^1J_{P-H}$ = 540 Hz, $^2J_{P-F}$ = 70 Hz). **HRMS:** calcd for $C_8HF_{17}O_2P^-$ $(M)^-$: 482.9448. Found: 482.9438. NMR data agrees with the literature.[19]

5.2.4. Synthesis of [*p*-$MeC_6H_4NH_3$]$_2$[*n*-$C_4F_9P(O)_3$]

$[NH_4][H_2PO_2]$ (1.25 g, 15.1 mmol) was heated with $(Me_3Si)_2NH$ (3.2 mL, 2.48 g, 15.2 mmol) for 2 h. The reaction was cooled to 0 °C and CH_2Cl_2 (15 mL) was added followed by *n*-C_4F_9I (2.6 mL, 5.23 g, 15.1mmol). The reaction was allowed

to warm up to room temperature and stirred overnight. The reaction was quenched with MeOH (5 mL), filtered and solvent removed *in vacuo*. The resulting oil was dissolved in Et_2O (40 mL) and cooled to 0 ℃. 35% H_2O_2 (15 mL) was slowly added. This was vigorously stirred for 30 minutes. The mixture was boiled for 1 hour (to destroy H_2O_2) and cooled to room temperature. The aqueous layer was extracted with Et_2O (5 × 50 mL). The Et_2O fractions were combined, dried over $MgSO_4$ and solvent removed under reduced pressure to give crude *n*-$C_4F_9P(O)(OH)_2$ (4.32 g, 95%). This was converted to the bis(toluidinium) salt. To a solution of crude *n*-$C_4F_9P(O)(OH)_2$ (4.32 g, 14.4 mmol) in methanol (20 mL) was added *p*-toluidine (3.70 g, 35 mmol) in methanol (20 mL). Concentration and cooling of the solution gave, after 24 h, [*p*-$MeC_6H_4NH_3]_2[C_4F_9P(O)_3]$ as fine white crystals (0.57 g, 7.3 %). **^{1}H NMR (DMSO-d_6):**δ 8.43 (br s, 3H, $ArNH_3^+$), 7.02 (d, J = 8 Hz, 2H, Ar), 6.85 (d, J = 8 Hz, 2H, Ar), 2.14 (s, 3H, CH_3). **^{19}F NMR (DMSO-d_6):** δ -80.6 (s, 3F, CF_3), -121.1 (s, 2F, CF_2), -122.3 (d, $^2J_{P\text{-}F}$ = 70 Hz, 2F, CF_2), -125.6 (s, 2f, CF_2). **^{31}P NMR (DMSO-d_6):** δ -4.4 (t, $^2J_{P\text{-}F$ = 70 Hz). **HRMS:** calcd for $C_4HF_9O_3P^-$ $(M)^-$: 298.9525. Found: 298.9520. NMR data agrees with the literature.[19]

5.2.5. Synthesis of [*p*-$MeC_6H_4NH_3$][*n*-$C_6F_{13}P(O)_2OH$]

$[NH_4][H_2PO_2]$ (1.25 g, 15.1 mmol) and $(Me_3Si)_2NH$ (3.1 mL, 2.40 g, 14.9 mmol) were heated to 110 ℃ for 2 h. The reaction was cooled to 0 ℃ and CH_2Cl_2 (10 mL) was added followed by *n*-$C_6F_{13}I$ (3.2 mL, 6.60 g, 14.9 mmol). This was stirred for 30 mins and allowed to warm up to room temp and stirred overnight. The reaction was filtered and quenched with 2M HCl (20 mL). The crude product, as an oil separated from the chlorinated and aqueous layer. The oil was taken up in Et_2O. The Et_2O was removed to give crude *n*-$C_6F_{13}PO(OH)H$ a clear oil. The oil

was dissolved in Et_2O (30 mL) and vigorously stirred with 35% H_2O_2 (14 mL) for 30 mins. The Et_2O layer was separated and washed with water (50 mL). The Et_2O layer was pumped down and the resulting oil was washed with 5 lots of hexane (5 mL each). The crude oil (2.38 g, 40%, 5.95 mmol) was dissolved in Et_2O (10 mL) and added to a solution of *p*-toluidine (0.67 g, 6.3 mmol) in Et_2O (10 mL). The white precipitate was collected and washed with Et_2O (10 mL) and CH_2Cl_2 (10 mL) and recrystallised from methanol to give white fine crystals of [*p*-$MeC_6H_4NH_3$][*n*-$C_6F_{13}P(O)_2OH$] (1.17 g, 16%). **^{1}H NMR (DMSO-d_6):** δ 8.88 (br s, 3H, $ArNH_3^+$), 7.09 (d, J = 8.2 Hz, 2H, Ar), 6.94 (d, J = 8.2 Hz, 2H, Ar), 2.23 (s, 3H, CH_3). **^{19}F NMR (DMSO-d_6):** δ -76.6 (s, 3F, CF_3), -119.5 (s, 2F, CF_2), -121.0 (s, 2F, CF_2), -121.3 (d, 2F, CF_2-P, $^2J_{P-F}$ = 75 Hz), -122.0 (s, 2F, CF_2), -125.2 (s, 2F, CF_2). **^{31}P NMR (DMSO-d_6):** δ -3.6 (t, $^2J_{P-F}$ = 70 Hz). NMR data agrees with the literature.[19]

5.2.6. Synthesis of [*p*-$MeC_6H_4NH_3$][*n*-$C_8F_{17}P(O)_2OH$]

$[NH_4][H_2PO_2]$ (0.59 g, 7.14 mmol), $(Me_3Si)_2NH$ (1.56 mL, 1.21g, 7.5 mmol), $C_8F_{17}I$ (1.85 mL, 3.82 g, 7 mmol) and CH_2Cl_2 (7.5 mL) were used in an analogous procedure to experiment 5.2.5. The solvent, from the reaction, was removed in vacuo and the residue was taken in Et_2O (40 mL). The Et_2O was washed with 2M HCl (2 × 15 mL) and water (15 mL). The organic layer was separated, dried over $MgSO_4$, filtered and solvent removed, *in vacuo*, to give a sticky white solid (1.78 g). The white solid was redissolved in Et_2O (40 mL) and was vigorously shaken with 35% H_2O_2 (50 mL) and ethereal layer separated. The organics were washed free of peroxide with 50 ml aliquots of water (typically 5 washings, using litmus paper to test for peroxide). The organics were then added drop wise to a solution of *p*-toluidine in Et_2O (30 mL). This was left for several hours and the precipitate was filtered and washed with Et_2O to give a white crystalline [*p*-$MeC_6H_4NH_3$]-

$[C_8F_{17}P(O)_3]$ (0.1038 g, 2.4%). **^{1}H NMR (DMSO-d_6):** δ 8.63 (br s, 3H, $ArNH_3^+$), 7.06 (d, J = 8 Hz, 2H, Ar), 6.89 (d, J = 8 Hz, 2H, ArH), 2.21 (s, 3H, CH_3) **^{19}F NMR (DMSO-d_6):** δ -80.1 (s, 3F, $-CF_3$), -120.1 (s, 2F, $-CF_2-$), -121.3 (s, 2F, $-CF_2-$), -121.7 (s, 6F, $-CF_2-$), -122.5 (s, 2F, $-CF_2-$), -125.7 (s, 2F, $-CF_2-$). **^{31}P NMR (DMSO-d_6):** δ -4.2 (t, $^2J_{P-F}$ = 70 Hz). **HRMS:** calcd for $C_8HF_{17}O_3P^-$ $(M)^-$: 498.9397. Found: 498.9417. NMR data agrees with the literature.[19]

5.2.7. Attempted synthesis of [*p*-$MeC_6H_4NH_3]_2[CF_3P(O)_3]$

$[NH_4][H_2PO_2]$ (1.27 g, 15.3 mmol) was heated neat with $(Me_3Si)_2NH$ (3.2 mL, 15 mmol) to 110 ℃ for 2 h. The reaction was cooled to 0 ℃ and CH_2Cl_2 (10 mL) was added. CF_3I (8 g, large excess) was then added and condensed using a cold finger condenser. The reaction was stirred for 30 mins and allowed to warm up to room temperature. This was stirred overnight. The reaction was filtered and solvent removed under reduced pressure. The resulting oil was dissolved in water (10 mL) and cooled to 0 ℃. H_2O_2 (10 mL, 35% w/w) was added and stirred for 15 mins. The mixture was allowed to warm up to room temperature and stirred for 25 mins, then boiled for 1 h and dried under reduced pressure. The resulting oil was dissolved in Et_2O (20 mL) and a solution of *p*-toluidine (3.2 g, 30 mmol) in Et_2O (20 mL) was added and left overnight and filtered. Attempted recrystallised from methanol to give a white solid, which was not product. The mother liquor was pumped down to give crude [*p*-$MeC_6H_4NH_3]_2[CF_3P(O)_3]$. **^{19}F NMR (DMSO-$d_6$):** δ -71.7 (d, $^2J_{P-F}$ = 93 Hz). **^{31}P NMR (DMSO-d_6):** δ 2.7 (d, $^1J_{P-H}$ = 636 Hz), 0.6 (s), -5.8 (q, $^2J_{P-F}$ = 95 Hz). Product not isolated.

5.2.8. Attempted synthesis of (*n*-$C_4F_9)_2PO(OH)$

$[NH_4][H_2PO_2]$ (1.25 g, 15.1 mmol) was heated to 110 ℃ with $(Me_3Si)_2NH$ (3.1 mL, 2.40 g, 14.9 mmol) for 2 h. The reaction was cooled to 0 ℃ and CH_2Cl_2 (10 mL)

was added followed by *n*-C_4F_9I (2.6 mL, 5.23 g, 15.1 mmol) and stirred for 1 h. The reaction was then allowed to warm up to room temperature and stirred overnight. The volatiles were removed from the reaction under reduced pressure. $(Me_3Si)_2NH$ (3.1 mL, 2.40 g, 14.9 mmol) was then added to the residue and stirred for 30 minutes at room temperature then for 2 h at 110 °C. The reaction was then cooled to 0 °C and CH_2Cl_2 (10 mL) followed by *n*-C_4F_9I (2.6 mL, 5.23 g, 15.1 mmol) was added and stirred for 30 mins. The reaction was allowed to warm up to room temperature and stirred overnight. The solvent removed *in vacuo* to give an oily cream coloured solid (3.03 g). **^{31}P NMR (D_2O):** δ 13.2 (d sextet, J = 709 Hz, J = 12 Hz), 11.6 (s), 8.7 (s), 4.7 (dt, $^1J_{P\text{-}H}$ = 575 Hz, $^2J_{P\text{-}F}$ = 79 Hz), 3.1 (s), 2.4 (s), 1.5 (s), 1.1 (s), -1.7 (t, $^2J_{P\text{-}F}$ = 79 Hz), -6.3 (s). No product observed.

5.2.9. Attempted synthesis of HP(O)(OH)-C_2F_4-P(O)(OH)H

$[NH_4][H_2PO_2]$ (0.71 g, 8.6 mmol) was heated to 110 °C with $(Me_3Si)_2NH$ (1.8 mL, 1.39 g, 8.6 mmol) for 2 h. The reaction was cooled to 0 °C and CH_2Cl_2 (10 mL) was added. ICF_2CF_2I (0.62 mL, 1.63 g, 4.6 mmol) was then added slowly and the reaction was allowed to warm up to room temperature and stirred for 24 h. The solvent was removed *in vacuo* and the residue was stirred with MeOH/THF (1:3, 20 mL) for 15 mins and solvent removed to give an orange solid (1.5g). **^{31}P NMR (DMSO-d_6):** δ 7.0, 6.9, 5.3, 2.1, 0.38, -0.43. No product observed.

5.2.10 Attempted *in situ* formation of bis(triethoxysilyl)phosphonite and reaction with perfluorobutyl iodide

i-Pr_2NEt (2.6 mL, 1.90 g, 14.9 mmol) and $Si(OEt)_3Cl$ (2.9 mL, 2.90 g, 14.8 mmol) were added to $[NH_4][H_2PO_2]$ (0.6 g, 7.1 mmol) in dichloromethane (15 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. *n*-C_4F_9I (1.2 mL, 2.42 g, 7mmol) was added at 0 °C and stirred for 24 h at room temperature. The solvent

was removed and the resulting oil was diluted to approx. 20 mL of dichloromethane and methanol (1 mL) was added and stirred for 5 minutes. The solvent was removed to give an oily solid residue. **^{1}H (DMSO-d$_6$):** δ 7.0 (d, J = 472 Hz). **^{19}F NMR (DMSO-d$_6$):** No peaks observed. **^{31}P NMR (DMSO-d$_6$):** δ -4.2 (t, J = 475 Hz), -0.6. No product observed.

5.3. Formation of perfluoroalkyl(phenyl)phosphinic acids

5.3.1. Experimental using HMDS [$(Me_3Si)_2NH$]

5.3.1.1. Synthesis of [*p*-$MeC_6H_4NH_3$] [(*n*-C_4F_9)$PhPO_2$]

PhPO(OH)H (1.00 g, 7.05 mmol) was heated to 90 ˚C with $(Me_3Si)_2NH$ (1.50 mL, 1.16 g, 7.19 mmol) for 2 h. CH_2Cl_2 (15 mL) and *n*-C_4F_9I (1.21 mL, 2.43 g, 7.00 mmol) were added at 0 ˚C. The reaction was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was diluted in Et_2O (40 mL) and washed with 2M aq HCl (2 × 15 mL) and water (15 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The resulting oil was washed with hexane (3 × 10 mL) and dried under reduced pressure to give crude (*n*-C_4F_9)PhP(O)OH as a pale yellow oil (1.57 g, 62%, 4.35 mmol). The oil was dissolved in Et_2O (10 mL) and mixed with a solution of *p*-toluidine (0.54 g, 5.00 mmol, 1.2 eq.) in Et_2O (10 mL) and left overnight. The solvent was removed *in vacuo* and the residue was recrystallised from acetone/chloroform (1:9). The resulting white material was washed with ice cold Et_2O, toluene and hexane to give white crystalline [*p*-$MeC_6H_4NH_3$][(*n*-C_4F_9)$PhPO_2$] (1.28 g, 40%) **m.p.** 216-218 ℃. **^{1}H NMR (DMSO-d_6):** δ 9.65 (br s, 3H, $ArNH_3^+$), 7.70 (m, 2H, Ar), 7.46 (m, 1H, Ar), 7.39 (m, 2H, Ar), 7.24 (d, J = 8 Hz, 2H, Ar), 7.16 (d, J = 8 Hz, 2H, Ar), 2.28 (s, 3H). **^{13}C NMR (DMSO-d_6):** δ 20.5, 122.0, 127.5, 127.6, 130.1, 130.9, 133.1, 133.2, 134.6, 136.3. **^{19}F NMR (DMSO-d_6):** δ -80.4 (s, 3F), -120.6 (s, 2F), -122.0 (dt, $^2J_{P\text{-}F}$ = 64 Hz, J = 14 Hz, 2F), -125.5 (t, J = 14 Hz, 2F). **^{31}P NMR (DMSO-d_6):** δ 9.1 (tt, $^2J_{P\text{-}F}$ = 63 Hz, $^3J_{P\text{-}H}$ = 13 Hz). **HRMS** calcd for $C_{10}H_5F_9O_2P^-$ $(M)^-$: 358.9889, found: 358.9888. NMR data agrees with the literature.[20]

5.3.1.2. Synthesis of [*p*-$MeC_6H_4NH_3$][(*n*-C_6F_{13})$PhPO_2$]

PhPO(OH)H (1.01 g, 7.07 mmol), $(Me_3Si)_2NH$ (1.50 mL, 1.16 g, 7.19 mmol) and *n*-$C_6F_{13}I$ (1.51 mL, 3.12 g, 7.00 mmol) were used in an analogous procedure to experiment 5.3.1.1. to give crude (*n*-C_6F_{13})PhP(O)OH as a white solid (1.91 g, 59%, 4.15 mmol). The crude product was dissolved in Et_2O (10 mL) and mixed with a solution of *p*-toluidine (0.52 g, 4.81 mmol, 1.2 eq.) in Et_2O (10 mL). The resulting white solid was filtered, washed with ice cold Et_2O, toluene and hexane and air dried. The solid was recrystallised from acetone/chloroform (1:3), washed with ice cold Et_2O, toluene, hexane and dried to give white crystalline [*p*-$MeC_6H_4NH_3$][(*n*-C_6F_{13})$PhPO_2$] (1.40 g, 35%) **m.p.** 194-196 °C. **^{1}H NMR (DMSO-d_6):** δ 9.64 (br s, 3H, $ArNH_3^+$), 7.71 (m, 2H, Ar), 7.46 (m, 1H, Ar), 7.39 (m, 2H, Ar), 7.24 (d, J = 8 Hz, 2H, Ar), 7.16 (d, J = 8 Hz, 2H, Ar), 2.29 (s, 3H, CH_3). **^{13}C NMR (DMSO-d_6):** δ 20.4, 122.1, 127.5, 127.6, 130.1, 130.9, 133.1, 133.2, 134.5, 135.9, 136.3. **^{19}F NMR (DMSO-d_6):** δ -80.2 (t, J = 12 Hz, 3F), -119.7 (s, 2F), -121.6 (s, 2F), -121.8 (br d, not resolved, 2F), -122.6 (s, 2F), -125.8 (s, 2F). **^{31}P NMR (DMSO-d_6):** δ 9.3 (t, $^2J_{P\text{-}F}$ = 61 Hz). **HRMS** calcd for $C_{12}H_5F_{13}O_2P^-$ $(M)^-$: 458.9825, found: 458.9813. NMR data agrees with the literature.[20]

5.3.1.3. Synthesis of [*p*-$MeC_6H_4NH_3$][(*n*-C_8F_{17})$PhPO_2$]

PhPO(OH)H (1.00 g, 7.06 mmol), $(Me_3Si)_2NH$ (1.50 mL, 1.16 g, 7.19 mmol) and *n*-$C_8F_{17}I$ (1.85 mL, 3.82 g, 7.00 mmol) were used in an analogous procedure to to experiment 5.3.1.1. to give crude (*n*-C_8F_{17})PhP(O)OH as a white solid (2.42 g, 62%, 4.32 mmol). The crude product was dissolved in Et_2O (20 mL) and mixed with a solution of *p*-toluidine (0.54 g, 5.0 mmol, 1.6 eq.) in Et_2O (10 mL). The resulting white solid was filtered and washed with ice cold Et_2O, toluene and hexane. The solid was recrystallised from acetone/Et_2O (3:7), washed with ice cold

Et_2O, toluene and hexane, and dried to give white crystalline [*p*-$MeC_6H_4NH_3$][(*n*-C_8F_{17})$PhPO_2$] (2.02 g, 43%) **m.p.** 200-203 ℃. **^{1}H NMR (DMSO-d_6):** δ 9.76 (br s, 3H, $ArNH_3^+$), 7.71 (m, 2H, Ar), 7.46 (m, 1H, Ar), 7.39 (m, 2H, Ar), 7.23 (d, J = 8 Hz, Ar), 7.16 (d, J = 8 Hz, 2H, Ar), 2.28 (s, 3H, CH_3). **^{13}C NMR (DMSO-d_6):** δ 20.4, 122.1, 127.5, 127.6, 130.0, 130.7, 131.0, 133.1, 133.2, 134.3, 135.7, 136.4. **^{19}F NMR (DMSO-d_6):** δ -80.2 (s, 3F), -119.6 (s, 2F), -121.4 (s, 2F), -121.7 (s, 6F), -122.5 (s, 2F), -125.8 (s, 2F) (N.B. $^2J_{P-F}$ coupling not resolved). **^{31}P NMR (DMSO-d_6):** δ 9.3 (t, $^2J_{P-F}$ = 65 Hz). **HRMS** calcd for $C_{14}H_5F_{17}O_2P^-$ $(M)^-$: 558.9761, found: 558.9757. NMR data agrees with the literature.[20]

5.3.1.4. Attempted synthesis of [*p*-$MeC_6H_4NH_3$] [$PhP(O)_2CF_3$]

PhPO(OH)H (1.01 g, 7.12 mmol) was heated to 90 ˚C with $(Me_3Si)_2NH$ (1.5 mL, 1.16 g, 7.2 mmol) for 2 h. The reaction was cooled to 0 ˚C and CH_2Cl_2 (15 mL) was injected. CF_3I (3 g, excess) was condensed using a chloroform/dry ice cold finger condenser. The reaction was allowed to warm up to room temperature and stirred for 24 h. The solvent was removed from the reaction mixture under reduced pressure. The resulting residue was stirred with THF/MeOH (3:1) for 30 mins. The solvent was removed *in vacuo* to give a white solid (2.25 g). This was dissolved in MeOH (20 mL) and a solution of *p*-toluidine (0.77 g ,7.2 mmol) in MeOH (minimum volume) was added and stirred overnight and solvent was removed under reduced pressure. The residue was recrystallised from hot acetone to give crude [*p*-$MeC_6H_4NH_3$] [$PhP(O)_2CF_3$] as a pale yellow solid (0.4071 g, 18%). **^{19}F NMR (DMSO-d_6):** δ -73.3 (d, $^2J_{P-F}$ = 75.1 Hz, -CF_3). **^{31}P NMR (DMSO-d_6):** δ 4.5 (qt, $^2J_{P-F}$ = 78.5 Hz, $^3J_{P-H}$ =11 Hz), δ 13.1 (t, $^3J_{P-H}$ = 13.1 Hz), 16.5 (dt, $^1J_{P-H}$ = 540 Hz, $^3J_{P-H}$ =13 Hz). Product not successfully isolated.

5.3.1.5. Attempted synthesis of PhP(O)(OH)-C_2F_4-PhP(O)(OH)

PhPO(OH)H (1.04 g, 7.3 mmol) and $(Me_3Si)_2NH$ (1.50 mL, 1.16 g, 7.19 mmol) were stirred at 90 ℃ for 2 h. The reaction was cooled to 0 ℃ and CH_2Cl_2 (15 mL) was added followed by ICF_2CF_2I (0.47 mL, 1.24 g, 3.5 mmol). The reaction was stirred overnight at room temperature. The solvent was removed to give a yellow/brown residue (4.05 g). **^{19}F NMR (DMSO-d_6):** δ -60.0. **^{31}P NMR (DMSO-d_6):** δ 6.1 (s), 7.2 (s), 12.0 (s), 13.3 (t, $^3J_{P-H}$ = 13 Hz), 18.8 (s), 23.8 (s). No product observed.

5.3.1.6. Attempted synthesis of PhP(O)(OH)C_2F_4I

PhPO(OH)H (1.03 g, 7.3 mmol) and $(Me_3Si)_2NH$ (1.50 mL, 1.16 g, 7.19mmol) and ICF_2CF_2I (0.99 mL, 2.58 g, 7.3 mmol) were used in an analogous procedure to experiment 5.3.1.5. **^{19}F NMR (DMSO-d_6):** δ-60.0, -65.6. **^{31}P NMR (DMSO-d_6):** δ 6.1, 7.2, 12.2, 12.8, 13.3 (t, $^3J_{P-H}$:= 13 Hz), 18.8. No product observed.

5.3.2. "Hunig's base/TMSCl" method

5.3.2.1. Attempted synthesis of [*p*-$MeC_6H_4NH_3$][(*n*-C_4F_9)$PhPO_2$]

i-Pr_2NEt (2.5 mL, 1.85 g, 14.4 mmol) and Me_3SiCl (1.8 mL, 1.54 g, 14.2 mmol) was added to a PhPO(OH)H (1.00 g, 7 mmol) in CH_2Cl_2 (15 mL) at 0 ℃ and stirred for 30 min at 0 ℃ and then at room temperature for 2 h. The reaction was cooled to 0 ℃ and *n*-C_4F_9I (1.2 mL, 2.41 g, 7 mmol) was added and stirred for 30 mins at 0 ℃ then overnight at room temperature. The reaction was washed with 2M aq HCl (2 × 20 mL) and water (20 mL). The organic fraction were dried over $MgSO_4$, filtered and solvent removed and the resulting residue washed with hexane to give crude (*n*-C_4F_9)PhP(O)OH (1.58 g, 63%). Crude (*n*-C_4F_9)PhP(O)OH (0.77 g, 2.14 mmol) was dissolved in Et_2O (10 mL) and added to a solution of *p*-toluidine (0.28 g, 2.56

mmol) in Et_2O (10 mL). The resulting solid was filtered and washed with cold Et_2O to give a white solid (0.55 g, 55% conversion). **^{1}H NMR (DMSO-d_6):**δ 9.28 (br s), 8.47 (br s), 7.71 (m, 2H), 7.44 (m, 1H), 7.37 (m, 2H), 7.20 (d, J = 8 Hz, 2H), 7.09 (d, J = 8 Hz, 2 H), 3.60 (m, 1H), 3.12 (m, 1H), 2.27 (s, 3H),1.25 (t, J = 7 Hz, 12H). N.B. Residual water peak appears to be obscuring a multiplet. **^{19}F NMR (DMSO-d_6):** δ -80.4 (s, 3F), -120.5 (s, 2F), -121.9 (d, $^2J_{P\text{-}F}$ = 64 Hz, 2F), -125.5 (t, J = 12 Hz, 2F). **^{31}P NMR (DMSO-d_6):** δ 8.8 (t, $^2J_{P\text{-}F}$ = 61 Hz). **HRMS** calcd for $C_{10}H_5F_9O_2P^-$ $(M)^-$: 358.9889, found: 358.9893. Mass Spec ESI $(M)^+$ calcd: 108.1, Found: 108.1, 130.2. Anion is pure, however a mixture of cations are present.

5.3.2.2. Attempted synthesis of PhP(O)(OH)*i*-C_3F_7

i-Pr_2NEt (5.3 mL, 3.93 g, 30.4 mmol), Me_3SiCl (3.8 mL, 3.25 g, 30.0 mmol), PhPO(OH)H (2.1 g, 15.0 mmol) and *i*-C_3F_7 (2.2 mL, 4.51 g, 15.2 mmol) were used in an analogous procedure to experiment 5.3.2.1. to give an oil. **^{19}F NMR (DMSO-d_6):**δ -55.5, -63.6, -66.8 (d, J = 12 Hz), -69.7, -70.6, -73.1, -73.3, -73.6, -74.8, -74.9, -82.4, -82.5. **^{31}P NMR (DMSO-d_6):** δ 13.2 (t, $^3J_{P\text{-}H}$ = 13 Hz), 16.9 (q, J = 13 Hz). Product not observed.

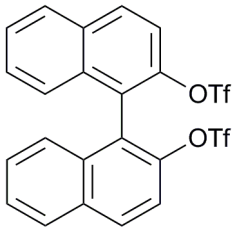
5.3.2.3. Attempted synthesis of PhPO(OH)C_4F_9 (triethoxychlorosilane method)

i-Pr_2NEt (2.6 mL, 1.90 g, 14.9 mmol) and $Si(OEt)_3Cl$ (2.9 mL, 2.90 g, 14.8 mmol) were added to PhPO(OH)H (1.01 g, 7.1 mmol) in CH_2Cl_2 (15 mL) at 0 ℃. This was stirred at room temperature for 3 h then cooled to 0 ℃ and *n*-C_4F_9I (1.2 mL, 2.41 g, 7 mmol) was added. This was stirred at room temperature overnight. The reaction mixture was washed with 2M aq HCl (10 mL) and water (10 mL). The organic layer were dried over $MgSO_4$, filtered and solvent removed to give an oil.

^{19}F NMR ($CDCl_3$): No visible peaks.**^{31}P NMR ($CDCl_3$):** δ 18.6, 21.0, 25.4 (d, J = 571 Hz). No product observed.

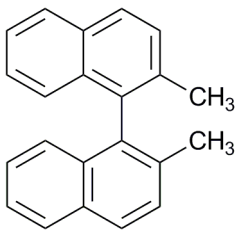
5.4. The stepwise synthesis of 2,2'-bis(difluoro-methylene)-1,1'-binaphthyl phosphinic acid 1:

5.4.1. (*rac*)-2,2'-bistriflate-1,1'-binaphthyl



To a solution of (*rac*)-1,1'-binaphthol (2.36 g, 8.24 mmol) in CH_2Cl_2 (40 mL) and pyridine (2.5 mL, 2.45 g, 31.0 mmol) was added drop wise triflic anhydride (3 mL, 5.00 g, 17.7 mmol) at 0 ℃. The reaction was then stirred overnight at room temperature. Solvent was then removed *in vacuo.* The resulting residue was diluted in EtOAc (100 mL) and washed with 5% aq. HCl (20 mL), saturated aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic fraction was then dried over $MgSO_4$ and solvent removed under reduced pressure to give crude product. The crude product was passed through a short pad of silica gel eluting with CH_2Cl_2. Evaporation of the solvent under reduced pressure gave (*rac*)-2,2'-bistriflate-1,1'-binaphthyl as a white solid (3.54 g, 78%). **^{1}H NMR ($CDCl_3$):** δ 8.12 (d, J = 9 Hz, 2H, Ar), 7.99 (d, J = 8 Hz, 2H, Ar), 7.59 (m, 4H, Ar), 7.39 (m, 2H, Ar), 7.23 (d, J = 8 Hz, Ar). **^{13}C NMR ($CDCl_3$):** δ 145.3, 133.1, 132.3, 132.0, 128.3, 128.0, 127.3, 126.7, 123.4, 119.3, 118.1 (q, $^1J_{C-F}$ = 320 Hz, -CF_3). NMR data agrees with the literature.[129]

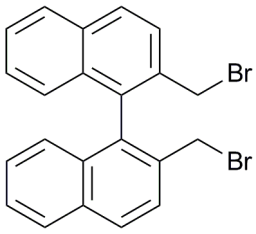
5.4.2. (*rac*)-2,2'-dimethyl-1,1'-binaphthyl



To a solution of (*rac*)-2,2'-bistriflate-1,1'-binaphthyl (4.12 g, 7.50 mmol) and Ni(dppp)Cl_2 (0.21 g, 0.39 mmol) in Et_2O (30 mL) was added dropwise an ethereal solution of MeMgI (1.55 M, 30 mL, 46.5 mmol) at 0 ℃. The reaction was refluxed for 7.5 h. The reaction was quenched by carefully pouring over ice and Et_2O (200 mL) was

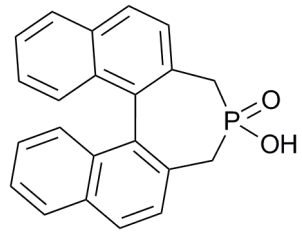
added. The mixture was then shaken with 5% aq. HCl (40 mL) and separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic fractions were combined and washed with saturated $NaHCO_3$ (100 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a crude residue. The residue was passed through a short pad of silica gel eluting with *n*-hexane/CH_2Cl_2 (9:1). Removal of solvent under reduced pressure gave pure (*rac*)-2,2'-dimethyl-1,1'-binaphthyl as a pale white solid (1.74 g, 82%). **^{1}H NMR ($CDCl_3$):** δ 7.87 (m, 4H, Ar), 7.49 (d, J = 9 Hz, 2H, Ar), 7.37 (m, 2H, Ar), 7.19 (m, 2H, Ar), 7.02 (d, J = 8 Hz, 2H, Ar), 2.01 (s, 6H, -CH_3). **^{13}C NMR ($CDCl_3$):** δ 135.1, 134.3, 132.7, 132.2, 128.7, 127.9, 127.4, 126.1, 125.6, 124.9, 20.0. NMR data agrees with the literature.[130]

5.4.3. (*rac*)-2,2'-di(bromomethyl)-1,1'-binaphthyl



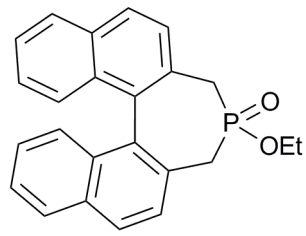
A mixture of (*rac*)-2,2'-dimethyl-1,1'-binaphthyl (7.06 g, 25 mmol), *N*-bromosuccinimide (8.91 g, 50 mmol) and azobis-isobutyronitrile (AIBN) (84 mg, 0.51 mmol) in tetrachloro-ethylene (100 mL) was stirred and irradiated with a sun lamp for 5 h. Solvent was the removed *in vacuo* and the residue was passed through a short pad of silica gel eluting with pet. ether (60-80)/ CH_2Cl_2 (1:1). The solvent was removed under reduced pressure and the resulting residue was recrystallised from *n*-hexane to afford pure (*rac*)-2,2'-di(bromomethyl)-1,1'-binaphthyl as pale yellow crystals (5.16 g, 47%). **^{1}H NMR ($CDCl_3$):** δ 8.01 (d, J = 9 Hz, 2H, Ar), 7.91 (d, J = 8 Hz, 2H, Ar), 7.73 (d, J = 8 Hz, 2H, Ar), 7.48 (m, 2H, Ar), 7.26 (m, 2H, Ar), 7.06 (d, J = 8 Hz, 2H, Ar), 4.24 (s, 4H, -CH_2Br). NMR data agrees with the literature.[131]

5.4.4. (*rac*)-2,2'-bis(methylene)-1,1'-binaphthyl phosphinic acid (4)



To a suspension of $[NH_4][H_2PO_2]$ (1.15 g, 13.8 mmol) in CH_2Cl_2 (80 mL) was added *i*-Pr_2NEt (8.74 mL, 6.49 g, 50.2 mmol) at 0 ℃ and stirred for 20 mins. Me_3SiCl (6.40 mL, 5.48 g, 50.4 mmol) was then added and stirred for 2 h at room temperature. The reaction was cooled to 0 ℃ and a solution of (*rac*)-2,2'-di(bromomethyl)-1,1'-binaphthyl (4.02 g, 9.1 mmol) in CH_2Cl_2 (20 mL) was added and stirred for 48 h at room temperature. The reaction was carefully quenched at 0 ℃ with water (20 mL). The organics were washed with 2M aq. HCl (2 × 20 mL) and water (20 mL). The organics were then dried over $MgSO_4$ and solvent removed *in vacuo*. The resulting residue was purified by silica gel chromatography eluting first with $CHCl_3$ then with $CHCl_3$/MeOH (85:15) to give (*rac*)-2,2'-bis(methylene)-1,1'-binaphthyl phosphinic acid as a pale brown solid (1.51 g, 32%). **^{1}H NMR ($CDCl_3$):** δ 7.83 (m, 4H, Ar), 7.44 (d, J = 8 Hz, 2H, Ar), 7.39 (t, J = 7 Hz, 2H, Ar),7.18 (m, 4H, Ar), 3.01 (m, 4H,-CH_2-). **^{13}C NMR ($CDCl_3$):** δ 133.6, 132.6, 132.1, 130.4, 129.0, 128.2, 128.1, 126.9, 126.2, 125.5, 35.3 (d, $^1J_{C\text{-}P}$ = 90 Hz). **^{31}P NMR ($CDCl_3$):** δ 66.7. **HRMS** calcd for $C_{22}H_{18}O_2P^+$ $(M+H)^+$: 345.1044 found: 345.1038. NMR data agrees with the literature.[7]

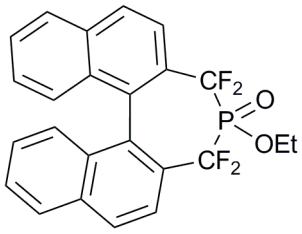
5.4.5. (*rac*)-ethyl-2,2'-bis(methylene)-1,1'-binaphthyl phosphinate (5)



(*Rac*)-2,2'-bis(methylene)-1,1'-binaphthyl phosphinic acid (**4**) (11.07 g, 32.2 mmol) was refluxed in $SOCl_2$ (40 mL, excess) for 2.5 h. The reaction was allowed to cool to room temperature and volatiles were removed *in vacuo*. The resulting residue was cooled to 0 ˚C and diluted in CH_2Cl_2 (30 mL). Pyridine (5 mL, 4.89 g, 61.8mmol) followed by absolute EtOH (5 mL, 85.6 mmol) were slowly

added. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction was then quenched with 2M aq. HCl (60 mL) and diluted with CH_2Cl_2 (120 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 120 mL). The organic fractions were combined, washed with water (120 mL) and 2M aq. HCl (120 mL), dried over $MgSO_4$ and solvent removed *in vacuo.* The crude product was purified by flash chromatography eluting with EtOAc to give (*rac*)-ethyl-2,2'-bis(methylene)-1,1'-binaphthyl-phosphinate as a crystalline white powder (6.55 g, 55%). **m.p:** 99-105 ℃. **Rf:** 0.41 (EtOAc). **IR** (KBr pellet, cm^{-1}): 3052 (CH aromatic), 2979 (CH aliphatic), 1593 and 1508 (CC aromatic), 1407 (CH methylene), 1250 and 1234 (P=O), 1033 and 955 (POC), 833 (PC aliphatic), 755 (CH aromatic). **^{1}H NMR (CD_2Cl_2):** δ 7.97 (m, 4H, Ar), 7.61 (d, J = 9 Hz, 1H, Ar), 7.50 (d, J = 8 Hz, 1H, Ar), 7.46 (t, J = 7 Hz, 2H, Ar), 7.24 (m, 2H, Ar), 7.16 (d, J = 9 Hz, 2H, Ar), 4.13 (m, 2H, PO-CH_2-), 3.20 (m, 4H, -CH_2-P), 1.31 (t, J = 7 Hz, 3H, -CH_3). **^{13}C NMR (CD_2Cl_2):** δ 134.0 (dd, J = 28 Hz, J = 5 Hz), 133.1 (d, J = 16 Hz), 132.6, 131.2 (d, J = 10 Hz), 130.1 (d, J = 9 Hz), 129.4 (d, J = 18 Hz), 128.6 (d, J = 9 Hz), 128.3 (dd, J = 28 Hz, J = 5 Hz), 127.1 (d, J = 8 Hz), 126.6, 125.9, 61.1 (d, J = 7 Hz), 34.8 (dd, $^1J_{C\text{-}P}$ = 88 Hz, J = 67 Hz), 16.9 (d, 5 Hz). **^{31}P NMR (CD_2Cl_2):** δ 64.5. **HRMS** calcd for $C_{24}H_{21}NaO_2P^+$ $(M+Na)^+$: 395.1171 found: 395.1189. See appendices 9-11 for NMR spectra.

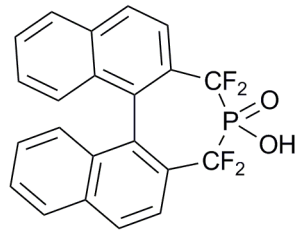
5.4.6. (*rac*)-ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (6)



A solution of (*rac*)-ethyl-2,2'-bis(methylene)-1,1'-binaphthylphosphinate (**5**) (2.68 g, 7.2 mmol) in THF (100 mL) was added, over a period of 3 mins, to a solution of NaHMDS (7.27 g, 39.7 mmol) in THF (100 mL) at -78 ℃. The resulting orange/red solution was stirred for 1 h at -78 ℃ and a solution of

NFSI (16.59 g, 52.6 mmol) in THF (100 mL) was added over a period of 3 mins. The reaction was stirred at -78 ℃ for a further 2 h. The reaction was allowed to warm up, over a period of 5 mins and quenched with 0.01N aq. HCl (100 mL). The reaction was reduced *in vacuo*. The mixture was extracted with EtOAc (3 × 100 mL). The organic fractions were combined and dried over $MgSO_4$ and solvent removed *in vacuo*. The resulting residue was purified by flash chromatography over silica gel first eluting with $CHCl_3$ then with $CHCl_3$/EtOAc (98:2) to give pure (*rac*)-ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate as a cream coloured crystalline material (1.93 g, 60%). **m.p:** 90-93℃. **Rf:** 0.32 ($CHCl_3$). **IR** (KBr pellet, cm^{-1}): 3066 (CH aromatic), 2986 (CH aliphatic), 1596 and 1508 (CC aromatic), 1273 (P=O), 1100 and 1066 (CF), 1015 and 949 (POC), 857 and 816 (PC aliphatic), 747 (CH aromatic). **^{1}H NMR (CD_2Cl_2):** δ 8.18 (t, J = 9 Hz, 2H, Ar), 8.03 (d, J = 8 Hz, 2H, Ar), 7.85 (dd, J = 21 Hz, J = 9 Hz, 2H, Ar), 7.60 (t, J = 7 Hz, 2H, Ar), 7.32 (t, J = 8 Hz, 2H, Ar), 7.14 (d, J = 9 Hz, 2H, Ar), 4.43 (m, 2H, P-O-CH_2-), 1.38 (t, J = 7 Hz, 3H, -CH_3). **^{13}C NMR (CD_2Cl_2):** δ 134.9, 132.9, 130.5, 130.4, 128.8, 128.3, 127.7, 127.4, 126.9 (br s), 121.8 (dd, J = 27 Hz, J = 14 Hz), 118.3 (dt, $^1J_{C-P}$ = 138 Hz, $^1J_{C-F}$ = 271 Hz, -CF_2-P). **^{19}F NMR (CD_2Cl_2):** δ -91.5 (dd, $^2J_{F-F}$ = 277 Hz, $^2J_{F-P}$ = 87 Hz, 1F), -93.5 (dd, $^2J_{F-F}$ = 295 Hz, $^2J_{F-P}$ = 110 Hz, 1F), -121.7 (ddd, $^2J_{F-F}$ = 283 Hz, $^2J_{F-P}$ = 98 Hz, $^4J_{F-F}$ = 12 Hz, 1F), -123.8 (ddd, $^2J_{F-F}$ = 294.8 Hz, $^2J_{F-P}$ = 93 Hz, $^4J_{F-F}$ = 12 Hz, 1F). **^{31}P NMR (CD_2Cl_2):** δ 25.6 (pseudo-pent, $^2J_{P-F}$ = 105 Hz, $^2J_{P-F}$ = 92 Hz). **HRMS** calcd for $C_{24}H_{17}F_4NaO_2P^+$ $(M+Na)^+$: 4467.0795 found: 467.0793. See appendices 5-8 for NMR spectra.

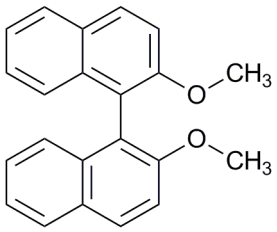
5.4.7. (*rac*)-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (1)



TMSBr (0.92 mL, 1.07 g, 6.99 mmol) was added to a solution of (*rac*)-ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**) (1.50 g, 3.38 mmol) in CH_2Cl_2 (50 mL) at room temperature. This was heated to reflux for 96 h (with T.L.C. monitoring). A second aliquot of TMSBr (0.45 mL, 0.52 g, 3.41 mmol) was added and refluxed until complete silylation is achieved (≈ 8 h). Solvent and un-reacted TMSBr were removed *in vacuo*. The resulting pale brown residue was then dissolved in MeOH (60 mL) and stirred at room temperature for 24 h. Solvent was removed under reduced pressure to give bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid as a pale brown powder (1.39 g, 99%). **^{1}H NMR (DMSO-d_6):** δ 11.04 (br s, 1H, P-OH), 8.18 (d, J = 9 Hz, 2H, Ar), 8.08 (d, J = 8 Hz, 2H, Ar), 7.75 (d, J = 9 Hz, 2H, Ar), 7.56 (t, J = 8 Hz, 2H, Ar), 7.32 (d, J = 7 Hz, 2H, Ar), 6.99 (d, J = 9 Hz, 2H, Ar). **^{13}C NMR (DMSO-d_6):** δ 133.7, 133.6, 132.2, 129.6, 129.2 (br s), 128.6, 127.5, 127.4, 126.7, 122.0, 119.2 (dt, $^{1}J_{C-P}$ = 137 Hz, $^{1}J_{C-F}$ = 269 Hz, -CF_2-P). **^{19}F NMR (DMSO-d_6):** δ -90.6 (dd, $^{2}J_{F-F}$ = 280 Hz, $^{2}J_{F-P}$ = 87 Hz, 2F), -124.1 (dd, $^{2}J_{F-F}$ = 283 Hz, $^{2}J_{F-P}$ = 87 Hz, 2F). **^{31}P NMR (DMSO-d_6):** δ 18.1 (pent, $^{2}J_{P-F}$ = 87 Hz). **HRMS** (ESI) calcd for $C_{22}H_{12}F_4O_2P^-$ (M^-): 415.0511. Found: 415.0522. See appendices 1-4 for NMR spectra.

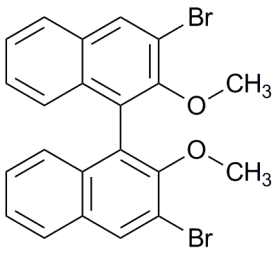
5.5. The Stepwise synthesis of 3,3-diphenyl-BINOL-phosphoric acid (Control for catalytic testing)

5.5.1. (*rac*)-2,2'-dimethoxy-1,1'-binaphthyl



(*rac*)-2,2'-dimethoxy-1,1'-binaphthyl was prepared according to the literature.[69] To a homogenous solution of (*rac*)-BINOL (18.7 g, 65.2 mmol) in acetone (600 mL) was added K_2CO_3 (30.0 g, 217 mmol) followed by CH_3I (20 mL, 45.6 g, 321 mmol). The mixture was refluxed for 24 h after which a second portion of CH_3I (10 mL, 22.8 g, 161 mmol) was added. The reaction was refluxed for a further 12 h. The solvent was removed *in vacuo* to give a white solid. Water (650 mL) was added to the solid and the mixture was stirred for 12 h. The mixture was filtered and the resulting solid was washed with water and then dried under reduced pressure to give (*rac*)-2,2'-dimethoxy-1,1'-dinaphthyl as a fine white powder (18.44 g, 90%). **^{1}H NMR ($CDCl_3$):** δ 7.96 (d, J = 9 Hz, 2H, Ar), 7.85 (d, J = 8 Hz, 2H, Ar), 7.44 (d, J = 9 Hz, 2H, Ar), 7.30 (m, 2H, Ar), 7.19 (m, 2H, Ar), 7.09 (d, J = 8 Hz, 2H, Ar), 3.75 (s, 6H, $-OCH_3$). NMR data agrees with the literature.[69]

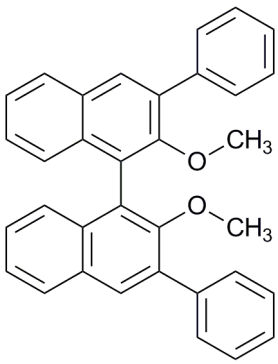
5.5.2. *(rac)*-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl



This was synthesised in a similar method to the literature.[69, 132] *n*-BuLi (1.15 M in hexanes, 63 mL, 72.5 mmol) was added cautiously to a stirring mixture of TMEDA [$(CH_3)_2NCH_2CH_2N(CH_3)_2$] (10 mL, 7.75 g, 66.7 mmol) in Et_2O (500 mL) at room temperature. This was stirred for 15 mins and (*rac*)-2,2'-dimethoxy-1,1'-dinaphthyl (10 g, 31.8 mmol) was added. The mixture was then stirred for 3 h and cooled to -78 °C. Bromine (15 mL, 46.8 g, 292 mmol) in hexane

(50 mL) was added over a period of 15 mins. The reaction was allowed to warm up to room temperature and stirred for a further 4 h. The reaction was then quenched with a saturated aqueous solution of Na_2SO_3 (300 mL). The mixture was stirred for 4 h and diluted with $CHCl_3$ (1L) and water (1L). The mixture was shaken and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The resulting residue was purified by column chromatography eluenting with cyclohexane/toluene (4:1, 3:2) to give the product contaminated with monobrominated side-product. The residue was recrystallised from CH_2Cl_2/*n*-hexane to afford (*rac*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-dinaphthyl as pale yellow crystals (6.44 g, 43%). **^{1}H NMR ($CDCl_3$):** δ 8.25 (s, 2H, Ar), 7.80 (d, J = 8 Hz, 2H, Ar), 7.41 (m, 2H, ArH), 7.25 (m, 2H, Ar), 7.06 (d, J = 8 Hz, 2H, Ar), 3.49 (s, 6H, OCH_3). **^{13}C NMR ($CDCl_3$):** δ 152.5, 133.0, 132.9, 131.4, 127.1, 126.8, 126.5, 125.9, 125.7, 117.5, 61.1. NMR data agrees with the literature.[69]

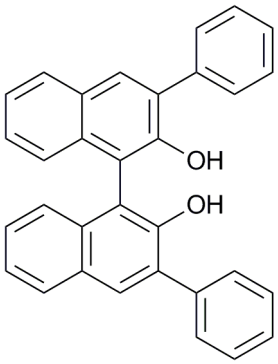
5.5.3. (*rac*)-3,3'-diphenyl-2,2'-dimethoxy-1,1'-binaphthyl



(*rac*)-3,3'-diphenyl-2,2'-dimethoxy-1,1'-binaphthyl was prepared in a similar method to the literature.[69] To a suspension of $Ni(PPh_3)_2Cl_2$ (500 mg, 0.76 mmol) and (*rac*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl (6.35 g, 13.43 mmol) in Et_2O (85 mL) was added PhMgBr (0.67 M in Et_2O, 56 mL, 37.52 mmol) over a period of 20 mins. After 20 h reflux, the reaction was cooled to room temperature and carefully quenched with 1M HCl (600 mL) and shaken with $CHCl_3$ (600 mL). The organic layer was separated, dried over $MgSO_4$, filtered and solvent removed *in vacuo* to give a dark green residue. The residue was purified by column chromatography eluting with toluene/cyclohexane (6:4) to give (*rac*)-3,3'-diphenyl-2,2'-dimethoxy-1,1'-binaphthyl as a white crystalline solid

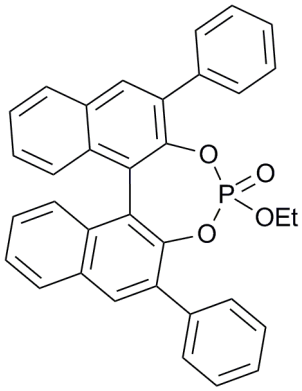
(4.90 g, 78%). **^{1}H NMR ($CDCl_3$):** δ 8.00 (s, 2H, Ar), 7.92 (d, J = 8, 2H, Ar), 7.74 (d, J = 8 Hz, 4H, Ar), 7.49 (t, J = 8 Hz, 4H, Ar), 7.39 (m, 4H, Ar), 7.19 (m, 4H, Ar), 3.14 (s, 6H, -OCH_3). NMR data agrees with the literature.[70]

5.5.4. (*rac*)-3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl



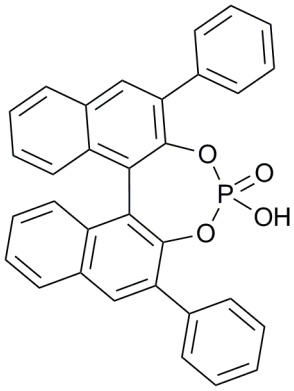
(*rac*)-3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl was prepared according to the literature.[70] BBr_3 (1.5 mL, 3.90 g, 15.60 mmol) was added drop wise to a solution of (*rac*)-3,3'-diphenyl-2,2'-dimethoxy-1,1'-binaphthyl (1.00 g, 2.14 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred for 24 h. The reaction was then cooled to 0 °C and excess BBr_3 was destroyed by drop wise addition of water (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 100mL). The organic fractions were combined and washed with brine (50 mL), dried over $MgSO_4$ and solvent removed under reduced pressure to give a crude residue. The residue was purified by flash chromatography over silica gel eluting with *n*-hexane/EtOAc (9:1) to give (*rac*)-3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl as a white solid (0.83 g, 88%). **^{1}H NMR (CD_2Cl_2):** δ 8.04 (s, 2H, Ar), 7.95 (d, J = 8.2 Hz, 2H, Ar), 7.74 (m, 4H, Ar), 7.50 (t, J = 8 Hz, 4H, Ar), 7.41 (m, 4H, Ar), 7.33 (m, 2H, Ar), 7.20 (d, J = 8 Hz, 2H, Ar), 5.44 (s, 2H, -OH). **^{13}C NMR (CD_2Cl_2):** δ 150.6, 138.0, 133.4, 131.7, 131.1, 130.0, 129.9, 128.8, 128.1, 127.6, 124.6, 124.5, 112.8. NMR data agrees with the literature.[70, 133]

5.5.5. (*rac*)-3,3'-diphenyl-1,1'-binaphthyl-2,2'-diyl ethyl phosphate (7)



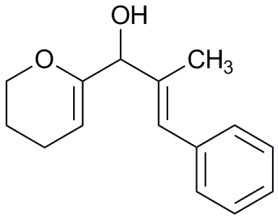
Phosphoryl chloride (0.73 mL, 1.20 g, 7.77 mmol) was carefully added to a solution of (*rac*)-3,3'-diphenyl-2,2'-dihydroxy-1,1'-binaphthyl (0.74 g, 1.69mmol) in pyridine (40 mL) at room temperature. The reaction was then heated to 95 ℃ for 12 h and cooled to 0 ℃. Absolute EtOH (3 mL, 2.37 g, 51.4 mmol) was then cautiously added. The reaction was allowed to warm up to room temperature and was stirred for 24 h. Solvent was then removed *in vacuo* and the resulting white residue was partitioned between CH_2Cl_2 (100 mL) and 2M aq. HCl (100 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were combined, dried over Na_2SO_4 and purified by flash chromatography, eluting with *n*-hexane/EtOAc (8:2), gave (*rac*)-3,3'-diphenyl-1,1'-binaphthyl-2,2'-diyl ethyl phosphate as a white crystalline solid (0.40 g, 45%). **Rf:** 0.3 *n*-hexane/EtOAc (8:2). **^{1}H NMR (CD_2Cl_2):** δ 8.14 (d, J = 15 Hz, 2H, Ar), 8.04 (d, J = 8 Hz, 2H, Ar), 7.80 (m, 4H, Ar), 7.55 (m, 6H, Ar), 7.45 (m, 3H, Ar), 7.35 (m, 3H, Ar), 3.47 (dm, J = 247 Hz, 2H, -OCH_2-), 0.91 (td, J = 9 Hz, J = 1 Hz, 3H, -CH_3). **^{13}C NMR (CD_2Cl_2):** δ 145.3 (d, J = 12 Hz), 144.1 (d, J = 8 Hz), 137.3 (d, J = 14 Hz), 134.0 (d, $^1J_{C\text{-}P}$ = 50 Hz), 132.3, 132.0, 131.6, 130.3, 128.8, 128.6, 128.2 (d, J = 24 Hz), 127.1 (d, J = 13 Hz), 126.5 (d, J = 8 Hz), 123.0 (d, J = 23 Hz), 65.7, 15.8. **^{31}P NMR (CD_2Cl_2):** δ 1.75. **HRMS** calcd for $C_{34}H_{25}O_4P^+$ $(M+H)^+$: 529.1563. Found: 529.1566. See appendices 12-14 for NMR spectra.

5.5.6. (*rac*)-3,3'-diphenyl-1,1'-binaphthyl phosphoric acid



Me_3SiBr (0.19 mL, 0.22 g, 1.44 mmol) was added to a solution of (*rac*)-3,3'-diphenyl-1,1'-binaphthyl-2,2'-diyl ethyl phosphate (**7**) (0.35 g, 0.66 mmol) in CH_2Cl_2 (20 mL) at room temperature. The reaction was refluxed for 12 hours and cooled to room temperature. Another portion of Me_3SiBr (0.11 mL, 0.13 g, 0.83 mmol) was added and the reaction was refluxed for a further 12 h until completion (by T.L.C. monitoring). Volatiles were removed *in vacuo* with gentle heating (35-40 °C) to give a white crystalline material. The material was dissolved in CH_2Cl_2 (40 mL) and methanol (20 mL) was added. The reaction was stirred at room temperature for 24 h to ensure complete desilylation. Removal of volatiles under reduced pressure gave (*rac*)-3,3'-diphenyl-1,1'-binaphyl phosphoric acid as a white powder (0.31 g, 95%). **^{1}H NMR (CD_2Cl_2):** δ 8.68 (br s, 1H, P-OH), 8.06 (s, 2H, Ar), 8.00 (d, J = 8 Hz, 2H, Ar), 7.61 (d, J = 6 Hz, 4H, Ar), 7.54 (m, 2H, Ar), 7.37-7.23 (m, 10H, Ar). **^{13}C NMR (CD_2Cl_2):** δ 144.6 (d, J = 10 Hz), 137.0, 134.11, 134.08 132.2, 132.0, 131.9, 130.0, 128.9, 128.6, 128.1, 127.2, 127.0, 126.5, 122.71, 122.69. **^{31}P NMR (CD_2Cl_2):** δ 3.93. **HRMS** calcd for $C_{32}H_{21}O_4P^+$ $(M+H)^+$: 501.1250. Found: 501.1232. NMR data agrees with the literature.[70]

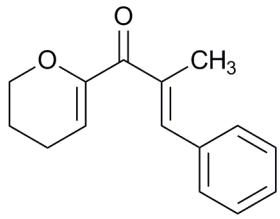
5.5.7. 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-prop-2-en-1-ol



n-BuLi in hexanes (1.1 M, 26.5 mL, 30.5 mmol) was added drop wise to a stirring solution of 3,4-dihydro-2H-pyran (2.3 mL, 2.12 g, 25.2 mmol) and TMEDA (1.3 mL, 1.00 g, 8.6 mmol) at room temperature. The mixture was heated to 45 °C for 2.5 h.[71] The reaction was cooled to room temperature then -78 °C. The lithiated pyran was

diluted in THF (80 mL) at -78 ℃ and a solution of α-methyl-trans-cinnamaldehyde (3.9 mL, 4.08 g, 27.9 mmol) in THF (10 mL) was then added drop wise and stirred for 1 hour at -78 ℃. The reaction was allowed to warm up for 5 mins and was carefully quenched with water (50 mL). The mixture was reduced *in vacuo* and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic fractions were combined, washed with brine (80 mL), dried over $MgSO_4$ and solvent removed *in vacuo.* The resulting yellow oil was purified by column chromatography eluting with pet. ether (60-80)/EtOAc (6:1) to give 1-(5,6-Dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-prop-2-en-1-ol as a pale yellow oil (3.77 g, 65%). **^{1}H NMR (CD_2Cl_2):** δ 7.32 (m, 4H, Ar), 7.21 (m, 1H, Ar), 6.59 (s, 1H), 4.87 (t, J = 4 Hz, 1H), 4.45 (d, J = 5 Hz, 1H), 4.01 (m, 2H), 2.21 (d, J = 4 Hz, 1H), 2.07 (m, 2H), 1.82 (m, 5H). **^{13}C NMR (CD_2Cl_2):** δ 153.6, 138.2, 129.3, 128.4, 126.7, 126.1, 98.1, 77.8, 66.8, 22.8, 20.3, 14.6. NMR data agrees with the literature.[68]

5.5.8. 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone



1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone was prepared according to the literature.[68] Dess-Martin periodinane (3.16 g, 7.45 mmol) was added to a stirring solution of 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-prop-2-en-1-ol (1.28 g, 5.56 mmol) with pyridine (5 mL) in CH_2Cl_2 (120 mL) at room temperature. This was stirred for 20 mins and quenched with 3M aq. NaOH (100 mL). The mixture was vigorously stirred for a further 10 mins then diluted with CH_2Cl_2 (80 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The organic fractions were combined and dried over anhydrous $MgSO_4$, filtered and solvent removed *in vacuo* to give crude residue. The residue was

purified by column chromatography eluting with cyclohexane/EtOAc (9:1) to give 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone as a pale yellow oil (0.46 g, 36%). **^{1}H NMR (CD_2Cl_2):** δ 7.42 (m, 4H), 7.33 (m, 1H), 7.26 (d, J = 1 Hz, 1H), 5.78 (t, J = 4 Hz, 1H), 4.13 (t, J = 5 Hz, 2H), 2.24 (m, 2H), 2.09 (d, J = 1 Hz, 3H), 1.90 (m, 2H). **^{13}C NMR (CD_2Cl_2):** δ 193.7, 151.6, 139.1, 136.3, 136.2, 129.9, 128.7, 128.6, 113.2, 66.7, 22.0, 21.1, 14.7. NMR data agrees with the literature.[68]

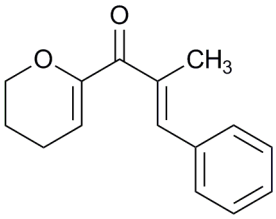
5.6. Crystallographic data for 2,2'-bis(difluoromethylene-)-1,1'-binaphthyl phosphinic acid 1 and ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (6)

Crystals of **1** were formed by slow diffusion of CH_2Cl_2 into a solution of **1** in absolute ethanol. Crystals of **6** were formed by slow diffusion of *n*-hexane into a solution of **6** in Et_2O. Selected crystallographic data is shown in Table 5.1. The crystal structures were solved by X-Seed[134] and refined in SHELXL-97[135] by full matrix least squares using anisotropic thermal displacement parameters for all non-carbon and non-hydrogen atoms. Figures were made with ORTEP-III (1.0.3).[136]

Table 5.1: Selected crystallographic data of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) and ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)

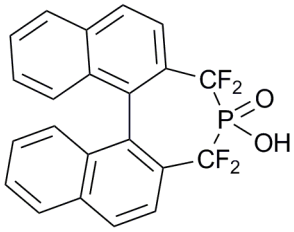
	Phosphinate 6	**Acid 1**
Empirical formula	$C_{24}H_{17}F_4O_2P$	$C_{22}H_{13}F_4O_2P$
Formula weight	444.34	416.29
Temperature/K	373(2)	173(2)
Crystal habit	colourless block	colourless plate
Crystal size/mm	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.1
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
***a*/Å**	15.186(3)	10.999(2)
***b*/Å**	18.106(3)	12.705(3)
***c*/Å**	14.814(2)	25.642(5)
***β*/deg**	94.653(3)	95.21(3)
***V*/Å**	4060.0(11)	3568.6(12)
Z	8	8
D_{calc} / g cm^{-3}	1.454	1.550
***μ*/cm^{-1}**	0.191	0.211
***Λ*(Mo K\α)/Å**	0.71073	0.71073
***F*(000)**	1824	1696
Maximum θ/deg	26.372	27.472
Reflections measured	8228	24019
Unique data	8228	8117
R_{int}		0.0329
Reflections used	6430	6300
RefIn/param ratio	14.6	15.3
Goodness of fit	1.048	1.053
R_1 **(all data)**	0.0579 (0.0731)	0.0451 (0.0605)
$w R_2$ **(all data)**	0.1506 (0.1616)	0.1144 (0.1237)

5.7. Sample preparation for the kinetic testing of the Brønsted acid catalysed Nazarov cyclisation of 1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone.



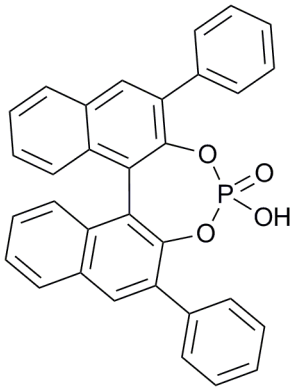
1-(5,6-dihydro-4H-pyran-2-yl)-2-methyl-3-phenyl-propenone (0.1018 g 0.446 mmol) was added to a 5 mL volumetric flask and made up to mark with $CDCl_3$.

Stock = 0.0892 M. 0.5 mL = 0.0446 mmol



1 (3.60 mg 0.0087 mmol) was added to a 2 mL volumetric flask and made up to mark with $CDCl_3$.

Stock = 0.0043 M. 0.2 mL = 0.00087 mmol



3,3'-diphenyl-BINOL-phosphoric acid (8.81 mg 0.0176 mmol) was added to a 1 mL volumetric flask and made up to mark with $CDCl_3$. 0.2 mL of this solution was added to a 2 mL volumetric flask and made up to mark with $CDCl_3$.

Stock = 0.00176 M. 0.5 mL = 0.00088 mmol

The control samples were made up by adding 0.5 ml (0.0446 mmol) of the ketone stock solution and 0.5 mL (0.00088 mmol) of 3,3'-diphenylBINOL phosphoric acid stock solution into an NMR tube. Time was measured when solutions were added together. Solutions were mixed well and monitored by ^1H NMR spectroscopy.

The bis(difluoromethylene)-1,1'binaphthyl phosphinic acid (**1**), samples were made up by adding 0.5 mL (0.0446 mmol) of the ketone stock solution with 0.3 mL of $CDCl_3$ and 0.2 mL (0.00087mmol) of bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**) stock solution.

Table 5.2: Control testing of the Nazarov cyclisation catalysed by 3,3'-diphenyl-BINOL-phosphoric acid

Control 1		**Control 2**		**Control 3**	
Time (seconds)	**Conversion (%)**	**Time (seconds)**	**Conversion (%)**	**Time (seconds)**	**Conversion (%)**
14525	1.37	14667	1.44	14784	1.76
19926	2.37	20060	2.35	20179	2.93
34317	5.40	34458	6.24	34581	7.07
48720	8.91	48855	10.28	48975	12.12
63104	12.88	63258	14.48	63394	17.63
91914	21.85	156608	47.44	92181	30.28
-log(K_i) = 5.52		**-log(K_i) = 5.34**		**-log(K_i) = 5.36**	
Average -log(K_i) = 5.41					

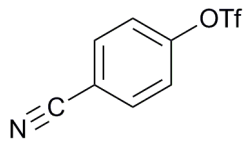
Table 5.3: Results of the Nazarov cyclisation catalysed by **1**

Sample 1		Sample 2		Sample 3	
Time (seconds)	**Conversion (%)**	**Time (seconds)**	**Conversion (%)**	**Time (seconds)**	**Conversion (%)**
367	3.28	365	2.93	388	3.28
553	6.93	539	5.66	572	6.93
739	11.10	711	8.85	758	11.10
967	16.07	883	12.65	944	16.07
1344	32.27	1216	20.53	1550	32.27
1640	47.08	2019	38.32	2146	47.08
2237	58.63	2621	50.57	2753	58.63
2845	68.16	3224	60.55	3341	68.16
3442	76.90	3827	67.97	3941	76.90
-log(K_i) = 3.52		**-log(K_i) = 3.48**		**-log(K_i) = 3.40**	
Average -log(K_i) = 3.47					

5.8. Synthesis of $ArPCl_2$ precursors

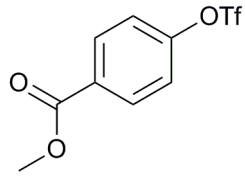
5.8.1. Synthesis of Aryl Triflates

5.8.1.1. 4-cyanophenyltriflate



4-cyanophenyltriflate was prepared according to the literature.[137] Triflic anhydride (10 mL, 16.77 g, 60 mmol) was added drop wise to a solution of 4-hydroxybenzonitrile (6.44 g, 54 mmol) and pyridine (13.2 mL, 12.82 g, 162 mmol) in CH_2Cl_2 (150 mL) at room temperature. The reaction was stirred for 1 h and quenched with water (150 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 150 mL). The CH_2Cl_2 layers were combined and washed with aq. 2M HCl, water and brine (250 mL each). The organics were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography on silica gel (pet ether 60-80/EtOAc, 3:1) to give 4-cyanophenyltriflate as a clear oil (12.70 g, 94%). **^{1}H NMR ($CDCl_3$):** δ 7.78 (d, J = 9 Hz, 2H, Ar), 7.40 (d, J = 9 Hz, 2H, Ar). **^{13}C NMR ($CDCl_3$):** δ 151.9, 134.5, 122.6, 118.6 (q, $^1J_{C\text{-}F}$ = 320 Hz, -CF_3), 117.0, 112.8. **^{19}F NMR ($CDCl_3$):** δ -72.6 (s, -CF_3). NMR data agrees with the literature.[137]

5.8.1.2. 4-methoxycarbonylphenyltriflate



4-methoxycarbonylphenyltriflate was prepared according to the literature.[137] Triflic anhydride (11 ml, 18.45 g, 65.38 mmol), methyl 4-hydroxybenzoate (9.13g, 60mmol), pyridine (15 mL, 14.6 g 180 mmol) and CH_2Cl_2 (200 mL) was used in an analogous procedure to experiment 5.8.1.1. Crude product was purified by flash chromatography (*n*-hexane/EtOAc, 5:1) to give 4-methoxycarbonylphenyltriflate as a clear oil (16.00 g, 94%). **^{1}H NMR ($CDCl_3$):** δ 8.12 (d, J = 9 Hz, 2H, Ar), 7.33 (d, J = 9 Hz, 2H, Ar),

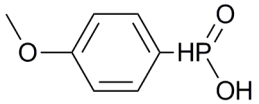
3.92 (s, 3H, -CO_2CH_3). **^{13}C NMR ($CDCl_3$):** δ 165.4, 152.5, 131.9, 130.3, 121.4, 118.7 (q, $^1J_{C-F}$ = 321 Hz, -CF_3), 52.5. **^{19}F NMR ($CDCl_3$):** δ -72.7 (s, -CF_3). NMR data agrees with the literature.[137]

5.9. Synthesis of Aryl- H-phosphinic acids

5.9.1. General procedure for microwave reactions

A thick-walled 30 mL (G30) Anton-Parr microwave vial, capped with a rubber septum, was charged with anilinum hypophosphite (1.59 g, 10 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0183 g, 0.02 mmol, 0.2 mol %), Xantphos (0.0116 g, 0.02 mmol, 0.2 mol %) and solid aryl halide (10 mmol). The vial was placed under argon by three cycles of vacuum and argon back-fill. THF (12 mL) followed by liquid aryl halide (10 mmol) and triethylamine (3.5 mL, 2.54 g, 25.1 mmol) was then added. The rubber septum was replaced with a microwave suitable septum. The reaction was heated to 120 ℃ as quickly as possible, using a maximum power of 500 W, and held for 15 mins at 120 ℃. The reaction was repeated three further times. All four lots of these reactions were combined and worked-up as one in the following manner; solvent was removed *in vacuo* and the resulting residue was portioned between Et_2O (220 mL) and aq 1M NaOH (220 mL). The organic layer was then extracted with aq 1M NaOH (2 × 160 mL). The aqueous layers were then combined and carefully acidified with conc. HCl (130 mL) and saturated with NaCl. The aqueous fraction was then extracted with EtOAc (5 × 220 mL). EtOAc fractions were then combined, dried over $MgSO_4$ or Na_2SO_4 and solvent was removed *in vacuo* to give crude product. Recrystallisation afforded pure aryl H-phosphinic acids.

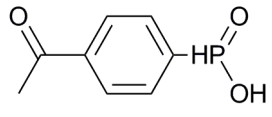
5.9.1.1. 4-methoxyphenylphosphinic acid



Pale yellow crystals (4.62 g, 67%), from CH_2Cl_2/*n*-hexane. **^{1}H NMR (DMSO-d_6):** δ 11.64 (br s, 1H, P-OH), 7.62 (dd, J = 13 Hz, J = 9 Hz, 2H, Ar), 7.43 (d, $^1J_{P\text{-}H}$ = 545 Hz, 1H, P-H), 7.07 (dd, J = 9 Hz, J = 3

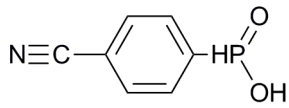
Hz, 2H, Ar), 3.80 (s, 3H, -OCH_3). **^{13}C NMR (DMSO-d_6):** δ 162.2, 132.3 (d, J = 13 Hz), 125.1 (d, $^1J_{C-P}$ = 135 Hz), 114.1 (d, J = 14 Hz), 55.4. **^{31}P NMR (DMSO-d_6):** δ 16.7 (dt, $^1J_{P-H}$ = 545 Hz, $^3J_{P-H}$ = 13 Hz). **HRMS** calcd for $C_7H_8O_3P^-$ $(M)^-$: 171.0211. Found: 171.0216. NMR data agrees with the literature.[3]

5.9.1.2. 4-acetylphenylphosphinic acid



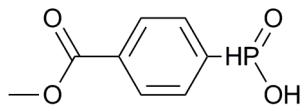
Yellow crystals (2.94 g, 40%), from CH_2Cl_2/*n*-hexane. **^{1}H NMR (DMSO-d_6):**δ 12.02 (br s, 1H, P-OH), 8.07 (dd, J = 8 Hz, J = 2 Hz, 2H, Ar), 7.83 (dd, J = 13 Hz, J = 8 Hz, 2H, Ar), 7.52 (d, $^1J_{P-H}$ = 554 Hz, 1H, P-H), 2.62 (s, 3H, CH_3CO). **^{13}C NMR (DMSO-d_6):** 197.9, 139.3, 138.4 (d, $^1J_{C-P}$ = 125 Hz), 130.5 (d, J = 13 Hz), 128.2 (d, J = 13 Hz), 27.0. **^{31}P NMR (DMSO-d_6):** δ 15.9 (dt, $^1J_{P-H}$ = 554 Hz, $^3J_{P-H}$ = 13 Hz). **HRMS** calcd for $C_8H_8O_3P^-$ $(M)^-$: 183.0211. Found: 183.0214. NMR data agrees with the literature.[120]

5.9.1.3. 4-cyanophenylphosphinic acid



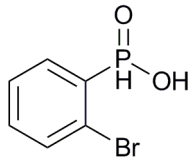
Yellow crystals (2.98 g, 45%), from EtOAc. **^{1}H NMR (DMSO-d_6):** δ 10.50 (br s, 1H, P-OH), 8.00 (dd, J = 8 Hz, J = 2 Hz, 2H, Ar), 7.86 (dd, J = 13 Hz, J = 8 Hz, 2H, Ar), 7.52 (d, $^1J_{P-H}$ = 561 Hz, 1H, P-H). **^{13}C NMR (DMSO-d_6):** δ 139.0 (d, $^1J_{C-P}$ = 124 Hz), 132.5 (d, J = 12 Hz), 130.9 (d, J = 12 Hz), 118.2, 114.6. **^{31}P NMR (DMSO-d_6):** δ 15.0 (dt, $^1J_{P-H}$ = 562 Hz, $^3J_{P-H}$ = 13 Hz). **HRMS** calcd for $C_7H_5NO_2P^-$ $(M)^-$: 166.0058. Found: 166.0060. This is a known compound, however no NMR or mass spec. data was presented.[3, 138]

5.9.1.4. 4-methoxycarbonylphenylphosphinic acid



4-methoxycarbonylphenylphosphinic acid was synthesised by the procedure of 5.9.1. The reaction was run four times and the product mixtures combined. The solvent was removed *in vacuo* and the residue was partitioned between Et_2O (220 mL) and water (220 mL). The aqueous layer was separated and carefully acidified with conc. HCl (minimum amount) and saturated with NaCl. The aqueous layer was then extracted with EtOAc (5 × 220 mL). The EtOAc fractions were combined, dried over $MgSO_4$ and solvent removed *in vacuo* to give crude product. Recrystallisation from MeOH/Et_2O afforded pure 4-methoxycarbonylphenylphosphinic acid as pale yellow crystals (3.97 g, 50%). **^{1}H NMR (DMSO-d_6):** δ 11.58 (br s, 1H, P-OH), 8.08 (dd, J = 8 Hz, J = 3 Hz, 2H, Ar), 7.84 (dd, J = 13 Hz, J = 8 Hz, 2H, Ar), 7.52 (d, $^1J_{P\text{-}H}$ = 555 Hz, 1H, P-H), 3.87 (s, 3H, -OCH_3). **^{13}C NMR (DMSO-d_6):** δ 167.7, 138.7 (d, $^1J_{C\text{-}P}$ = 125 Hz), 132.6, 130.6 (d, J = 12 Hz), 129.2 (d, J = 13 Hz), 52.5. **^{31}P NMR (DMSO-d_6):** δ 15.7 (dt, $^1J_{P\text{-}H}$ = 554 Hz, $^3J_{P\text{-}H}$ = 13 Hz). **HRMS** calcd for $C_8H_8O_4P^-$ $(M)^-$: 199.0160. Found: 199.0166. This is a known compound, however no NMR or mass spec. data was presented.[3]

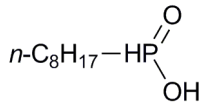
5.9.1.5. 2-bromophenyl H-phosphinic acid



To a 30 mL microwave vial charged with anilinium hypophosphite (0.60 g, 3.75 mmol), $Pd_2(dba)_3$ (0.18 g, 0.2 mmol 5 mol %) and Xantphos (0.12 g, 0.2 mmol, 5 mol %) was added THF (18 mL) followed by 1,2-dibromobenzene (0.22 mL, 0.43 g, 1.82 mmol, 0.5 eq.) and NEt_3 (1.3 mL, 0.96 g, 9.47 mmol, 2.5 eq.) The reaction was heated, in the microwave reactor, to 120 ℃ for 30 mins. The solvent was removed *in vacuo* and the resulting brown residue was partitioned between Et_2O (60 mL) and 1M aq. NaOH

(60 mL). The layers were separated and the organic layer was extracted with 1M aq. NaOH (2 × 60 mL). The aqueous fractions were combined and acidified with conc. HCl (36 mL) and saturated with NaCl. The aqueous layer was then extracted with EtOAc (5 × 60 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to give crude 2-bromophenyl H-phosphinic acid as a deep yellow/brown solid (0.29 g, 72%). The crude product was recrystallised from CH_2Cl_2 to give 2-bromophenyl H-phosphinic acid as yellow crystals (71 mg, 18%). **^{1}H NMR (DMSO-d_6):** δ 11.9 (br s, 1H, P-OH), 7.81-7.70 (m, 2H, Ar), 7.53 (m, 2H, Ar), 7.49 (d, $^1J_{P-H}$ = 571 Hz, 1H, P-H). **^{13}C NMR (DMSO-d_6):** δ 134.0, 133.6 (d, $^1J_{C-P}$ = 130 Hz), 133.4 (d, J = 8 Hz), 133.2 (d, J = 8 Hz), 127.7 (d, J = 11 Hz), 124.0 (d, J = 8 Hz). **^{31}P NMR (DMSO-d_6):** δ 15.7 (dt, $^1J_{P-H}$ = 571 Hz, $^3J_{P-H}$ = 13 Hz). **HRMS** calcd for $C_6H_5BrO_2P^-$ (M^-): 218.9216. Found: 218.9219. This is a known compound, however no NMR or mass spec. data was presented.[3, 125]

5.9.1.6. *n*-octyl H-phosphinic acid



n-octyl H-phosphinic acid was synthesised by a modified procedure.[139] To a suspension of ammonium hypophosphite (15.66 g, 189 mmol) in ethanol (I.M.S grade, 200 mL) was added 2,2′-azobis(2-methylpropionitrile) (AIBN) (1.0 g, 6.3 mmol), 1-octene (10 mL, 7.2 g, 64 mmol) and conc. H_2SO_4 (5 mL, 9.2 g, 94 mmol). The mixture was heated to reflux, under standard atmosphere, for 4 h and allowed to cool to room temperature. Another portion of AIBN (0.66 g, 4.00 mmol) was added and the reaction was heated to reflux for a further 20 h. The reaction was allowed to cool to room temperature and filtered. The solvent was removed under reduced pressure and the residue diluted with water (100 mL) and made basic with 50% w/v aq. NaOH. This was then washed with Et_2O (2 × 100 mL) and the aqueous fraction was made acidic with

conc. H_2SO_4. The aqueous fraction was then extracted with EtOAc (3 × 100 mL). The EtOAc fractions were combined, washed with brine (100 mL), dried over $MgSO_4$ and solvent removed *in vacuo* to give crude *n*-octyl H-phosphinic acid (8.4 g, 46 mmol, 74%).

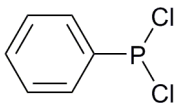
The crude product was purified by conversion to the 1-adamantanamine salt. To a solution of crude *n*-octyl H-phosphinic acid (8.4 g, 46 mmol) in Et_2O (50 mL) was added slowly a solution of 1-adamantanamine (7.3 g, 48 mmol) in Et_2O (75 mL). The resulting white precipitate was filtered, washed with Et_2O and dried under reduced pressure to give *n*-octyl H-phosphinic 1-adamantanamine salt (13 g, 40 mmol, 62%). The free acid was generated by partitioning the *n*-octyl H-phosphinic 1-adamantanamine salt between EtOAc (300 mL) and 2M HCl (300 mL). The layers were separated and EtOAc was washed with 2M HCl and brine (300 mL each). The EtOAc fraction was then dried over $MgSO_4$ and solvent removed *in vacuo* to give pure *n*-octyl H-phosphinic acid as a colourless oil (6.2g, 55% yield from 1-octene). **^{1}H NMR (CD_2Cl_2):** δ 9.21 (br s, 1H, P-OH), 7.04 (d, $^1J_{P-H}$ = 541 Hz, 1H, P-H), 1.73 (m, 2H, alkyl-H), 1.56 (m, 2H, alkyl-H), 1.39-1.28 (m, 10H, alkyl-H), 0.87 (t, J = 7.3 Hz, 3H, alkyl-H). **^{13}C NMR (CD_2Cl_2):** δ 32.2, 30.8, 30.7, 29.6 (d, $^1J_{C-P}$ = 94 Hz), 29.4 (d, J = 5 Hz), 23.0, 20.9, 14.2. **^{31}P NMR (CD_2Cl_2):** δ 39.2 (dp, $^1J_{P-H}$ = 541 Hz, $^2J_{P-H}$ = 13 Hz). **HRMS** calcd for $C_8H_{18}O_2P^-$ (M^-): 177.1044. Found: 177.1050. NMR data agrees with the literature.[140]

5.10.The synthesis of Aryl- dichlorophosphines

5.10.1. General reactions of $ArPO_2H_2$ with $SiCl_4$

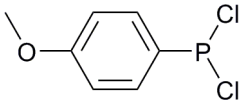
To a 250 mL two-neck round bottom flask fitted, with a cold finger condenser, was added aryl H-phosphinic acid (46.48 mmol, 1 eq.). Toluene (100 mL) followed by silicon tetrachloride (8.00 mL, 11.82 g, 69.82mmol, 1.5 eq) were added at room temperature. The mixture was then heated to reflux for 4 h using a dry ice/chloroform slurry in the cold finger condenser. The reaction was then allowed to cool to room temperature and another aliquot of silicon tetrachloride (8.00 mL, 11.82 g, 69.82mmol, 1.5 eq) was added. The reaction was heated to reflux for a further 4 h. The reaction was then allowed to cool to room temperature and was filtered by cannulation, with the residue washed with toluene (3 × 20 mL). The reaction was reduced *in vacuo* and then subjected to vacuum distillation to give pure aryl- dichlorophosphines.

5.10.1.1. Phenyldichlorophosphine



Colourless liquid (6.71 g, 81%). B.p. 40-43 °C (8.2 mbar). **^{1}H NMR ($CDCl_3$):** δ 7.89 (m, 2H, Ar), 7.52 (m, 3H, Ar). **^{13}C NMR ($CDCl_3$):** δ 140.4 (d, $^1J_{C-P}$ = 52 Hz), 132.7, 130.1 (d, $^2J_{C-P}$ = 40 Hz), 128.9 (d, $^3J_{C-P}$ = 10 Hz). **^{31}P NMR ($CDCl_3$):** δ 161.4. NMR data agrees with a genuine sample of $PhPCl_2$.

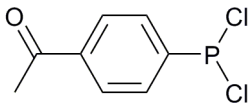
5.10.1.2. 4-methoxyphenyldichlorophosphine



Colourless liquid (8.75 g, 90%). B.p. 85-88 °C (7.7 mbar). **^{1}H NMR ($CDCl_3$):** δ 7.83 (m, 2H, Ar), 6.99 (m, 2H, Ar), 3.86 (s, 3H, $-OCH_3$). **^{13}C NMR ($CDCl_3$):** δ 163.3, 132.3 (d, $^2J_{C-P}$ = 40 Hz), 131.6 (d, $^1J_{C-P}$ = 51 Hz), 114.5 (d, $^3J_{C-P}$ = 10 Hz), 55.5. **^{31}P NMR ($CDCl_3$):** δ 162.1. **HRMS** (EI) calcd

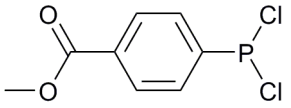
for $C_7H_7Cl_2OP$ (M): 207.9606. Found: 207.9604. NMR data agrees with the literature.[141]

5.10.1.3. 4-acetylphenyldichlorophosphine



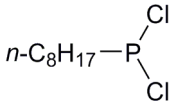
White crystalline solid (2.84 g, 28%). B.p. 120-124 ℃ (9.2 mbar). **^{1}H NMR ($CDCl_3$):** δ 8.05 (m, 2H, Ar), 7.97 (m, 2H, Ar), 2.63 (s, 3H, -CH_3). **^{13}C NMR ($CDCl_3$):** δ 197.1, 145.2 (d, $^1J_{C-P}$ = 54 Hz), 139.9, 130.4 (d, $^2J_{C-P}$ = 30 Hz), 128.5 (d, $^3J_{C-P}$ = 10 Hz), 26.8. **^{31}P NMR ($CDCl_3$):** δ 158.1. **HRMS** (EI) calcd for $C_8H_7Cl_2OP$ (M): 219.9606. Found: 219.9604. See appendices 15-17 for NMR spectra.

5.10.1.4. 4-methoxycarbonylphenyldichlorophosphine



This was prepared in similar procedure to the aromatic dichlorophosphines above, however after 8 h reflux, an extra aliquot of $SiCl_4$ (8.00 mL, 11.82 g, 69.82mmol, 1.5 eq) was added and heated for a further 4 h. The reaction was worked-up in the same manner as stated above to give 4-methoxycarbonyldichlorophosphine as a clear liquid (9.21 g, 84%). B.p. 109-111 ℃ (9.0 mbar). **^{1}H NMR ($CDCl_3$):** δ 8.13 (d, J = 7 Hz, 2H, Ar), 7.93 (t, J = 8 Hz, 2H, Ar), 3.93 (s, 3H, -OCH_3). **^{13}C NMR ($CDCl_3$):** δ 166.1, 145.1 (d, $^1J_{C-P}$ = 55 Hz), 133.6, 130.1 (d, $^2J_{C-P}$ = 40 Hz), 129.8 (d, $^3J_{C-P}$ = 10 Hz), 52.7. **^{31}P NMR ($CDCl_3$):** δ 158.3. **HRMS** (EI) calcd for $C_8H_7Cl_2O_2P$ (M): 235.9555. Found:235.9551. See appendices 17-20 for NMR spectra.

5.10.1.5. *n*-octyl dichlorophosphine



n-octyl dichlorophospine was synthesised in a similar manner to previous, however during work-up the silica generated in this reaction was too fine to efficiently filter by cannulation. Therefore after solvent was

removed from the reaction mixture, under reduced pressure, the resulting residue was subjected to vacuum distillation to give pure *n*-octyl dichlorophosphine as a clear liquid (6.19 g, 62%). B.p. 85-88 °C (9.2 mbar). **^{1}H NMR ($CDCl_3$):** δ 2.30 (m, 2H, -CH_2-P), 1.67 (m, 2H, CH_2 alkyl), 1.42 (m, 2H, CH_2 alkyl), 1.27 (m, 8H, CH alkyl), 0.87 (t, J = 7.6 Hz, 3H, -CH_3). **^{13}C NMR ($CDCl_3$):** δ 43.3 (d, $^{1}J_{C\text{-}P}$ = 44 Hz, -CH_2-P), 31.8, 30.2 (d, $^{3}J_{C\text{-}P}$ = 10 Hz), 29.1 (d, $^{2}J_{C\text{-}P}$ = 13 Hz), 23.2, 23.0, 22.6, 14.1. **^{31}P NMR ($CDCl_3$):** δ 196.3. **HRMS** (EI) calcd for $C_8H_{17}Cl_2P$ (M): 214.0439. Found: 214.0436

References

1. J-L. Montchamp, *J. Organomet. Chem.*, 2005, **690**, 2388-2406.
2. H. C. Fisher, L. Prost and J-L. Montchamp, *Eur. J. Org. Chem.*, 2013, 7973-7978.
3. J-L. Montchamp and Y. R. Dumond, *J. Am. Chem. Soc.*, 2001, **123**, 510-511.
4. J. K. Thottathil, C. A. Przybyla and J. L. Moniot, *Tetrahedron Lett.*, 1984, **25**, 4737-4740.
5. J. K. Thottathil, D. E. Ryono, C. A. Przybyla, J. L. Moniot and R. Neubeck, *Tetrahedron Lett.*, 1984, **25**, 4741-4744.
6. E. A. Boyd, M. Corless, K. James and A. C. Regan, *Tetrahedron Lett.*, 1990, **31**, 2933-2936.
7. J-L. Vasse, R. Stranne, R. Zalubovskis, C. Gayet and C. Moberg, *J. Org. Chem.,* 2003, **68**, 3258-3270.
8. C. Heid, D. Hoffman and J. Polster, *Ger. Offen*, 2,233,941, 1974.
9. Y. Mohajer, A. Panackal, J. Sharma, Y. L. Hsiao, R. Mininni, B. Thomas and J. Zhu, *PCT Int. Appl. 018592,* 2003.
10. M. B. Herath, S. E. Creager, A. Kitaygorodskiy and D. D. DesMarteau, *Chemphyschem*, 2010, **11**, 2871-2878.
11. M. B. Herath, T. Hickman, S. E. Creager and D. D. DesMarteau, *J. Fluorine Chem.*, 2011, **132**, 52-56.
12. F. W. Bennett, H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*, 1953, 1565-1571.
13. F. W. Bennett, H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*,1954, 3598-3603.
14. H. J. Emeleus, R. N. Haszeldine and R. C. Paul, *J. Chem. Soc.*, 1955, 563-574.
15. T. Mahmood and J. M. Shreeve, *Inorg. Chem.*, 1986, **25**, 3128-3131.
16. R. P. Singh and J. M. Shreeve, *Inorg. Chem.*, 2000, **39**, 1787-1789.
17. W. Cen and Y. Shen, *J. Fluorine Chem.*, 1991, **52**, 369-375.
18. M. B. Herath, S. E. Creager, A. Kitaygorodskiy and D. D. DesMarteau, *J. Phys. Chem. B*, 2010, **114**, 14972-14976.
19. A. I. Hosein, X. F. Le Goff, L. Ricard and A. J. M. Caffyn, *Inorg. Chem.*, 2011, **50**, 1484-1490.
20. A. I. Hosein and A. J. M. Caffyn, *Dalton Trans.*, 2012, **41**, 13504-13508.
21. L. M. Yagupol'skii, V. Y. Semenii, V. N. Zavatskii, K. N. Bil'dinov and A. V. Kirsanov, *J. Gen. Chem. USSR*, 1984, **54**, 692-695.
22. R. C. Paul, J. D. Bu'Lock, E. E. Aynsley, R. H. Watson, P. M. Pope, D. Woodcock, J. R. Holker, D. R. Tristram, C. S. G. Phillips, F. T. Farmer, T. Rigg, J. Weiss, P. A. J. Gorin, L. Hough, J. K. N. Jones and P. Andrews, *J. Chem. Soc.*, 1955, 574-584.
23. N. Ignatyev, M. Weiden, U. Welz-Biermann, U. Heider, P. Satori, A. Kutchaeryna,*Germany Pat., PCT 002744*, 2003.
24. N. Ignatyev, M. Weiden, U. Welz-Biermann, U. Heider, P. Satori, A. Kutchaeryna,*Germany Pat., US7,145,004,* 2003.
25. N. Ignat'ev and P. Sartori, *J. Fluorine Chem.*, 2000, **103**, 57-61.
26. F. W. Bennett, H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*, 1954, 3896-3904.
27. M. B. Murphy-Jolly, L. C. Lewis and A. J. M. Caffyn, *Chem. Commun.*, 2005, 4479-4480.
28. A. K. Brisdon and C. J. Herbert, *Coord. Chem. Rev.,* 2013, **257**, 880-901.
29. L. M. Yagupol'skii, N. V. Pavlenko, N. V. Ignat'ev, G. I. Matyushecheva and V. Y. Semenii, *J. Gen. Chem. USSR*, 1984, **54**, 297-302.

30. H. J. Emeleus and J. D. Smith, *J. Chem. Soc.*, 1959, 375-381.
31. N. V. Pavlenko, G. I. Matyushecheva, V. Y. Semenii and L. M. Yagupol'skii, *J. Gen. Chem. USSR*, 1987, **57**, 99-102.
32. S. N. Tverdomed, J. Kolanowski, E. Lork and G.-V. Roschenthaler, *Tetrahedron*, 2011, **67**, 3887-3903.
33. E. A. Boyd, A. C. Regan and K. James, *Tetrahedron Lett.,* 1992, **33**, 813-816.
34. E. A. Boyd, A. C. Regan and K. James, *Tetrahedron Lett.,* 1994, **35**, 4223-4226.
35. E. A. Boyd, M. E. K. Boyd and V. M. Loh Jr, *Tetrahedron Lett.,* 1996, **37**, 1651-1654.
36. M. S. Markoulides and A. C. Regan, *Tetrahedron Lett.,* 2011, **52**, 2954-2956.
37. A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova and V. S. Petrosyan, *Heteroat. Chem.*, 2012, **23**, 138-145.
38. M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8-27.
39. J. G. Hernandez and E. Juaristi, *Chem. Commun.*, 2012, **48**, 5396-5409.
40. U. Scheffler and R. Mahrwald, *Chem. Eur. J.*, 2013, **19**, 14346-14396.
41. J. Aleman and S. Cabrera, *Chem. Soc. Rev.*, 2013, **42**, 774-793.
42. C. Marschalk, *Bull. Soc. Chim.*, 1928, **43**, 1388.
43. T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem. Int. Ed.*, 2004, **43**, 1566-1568.
44. D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356-5357.
45. T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999-1010.
46. A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713-5743.
47. M. Terada, *Chem. Commun.*, 2008, 4097-4112.
48. D. Nakashima and H. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 9626-9627.
49. M. Rueping, W. Ieawsuwan, A. P. Antonchick and B. J. Nachtsheim, *Angew. Chem. Int. Ed.*, 2007, **46**, 2097-2100.
50. C. H. Cheon and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 9246-9247.
51. M. Treskow, J. Neudörfl and R. Giernoth, *Eur. J. Org. Chem.*, 2009, 3693-3697.
52. P. García-García, F. Lay, C. Rabalakos and B. List, *Angew. Chem.*, 2009, **121**, 4427-4430.
53. M. S. Smyth, H. Ford Jr and T. R. Burke Jr, *Tetrahedron Lett.,* 1992, **33**, 4137-4140.
54. S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron*, 1999, **55**, 12431-12477.
55. T. Yokomatsu, T. Murano, K. Suemune and S. Shibuya, *Tetrahedron*, 1997, **53**, 815-822.
56. W. Qui and D. J. Burton, *Tetrahedron Lett.,* 1996, **37**, 2745-2748.
57. E. Differding, R. O. Duthaler, A. Kreiger, G. M. Ruegg and C. Schmit, *Synlett*, 1991, 395-396.
58. S. D. Taylor, A. N. Dinaut, A. N. Thadani and Z. Huang, *Tetrahedron Lett.,* 1996, **37**, 8089-8092.
59. D. Xiao, Z. Zhang and X. Zhang, *Org. Lett.*, 1999, **1**, 1679-1681.
60. S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle and V. Snieckus, *J. Org. Chem.,* 1992, **57**, 4066-4068.

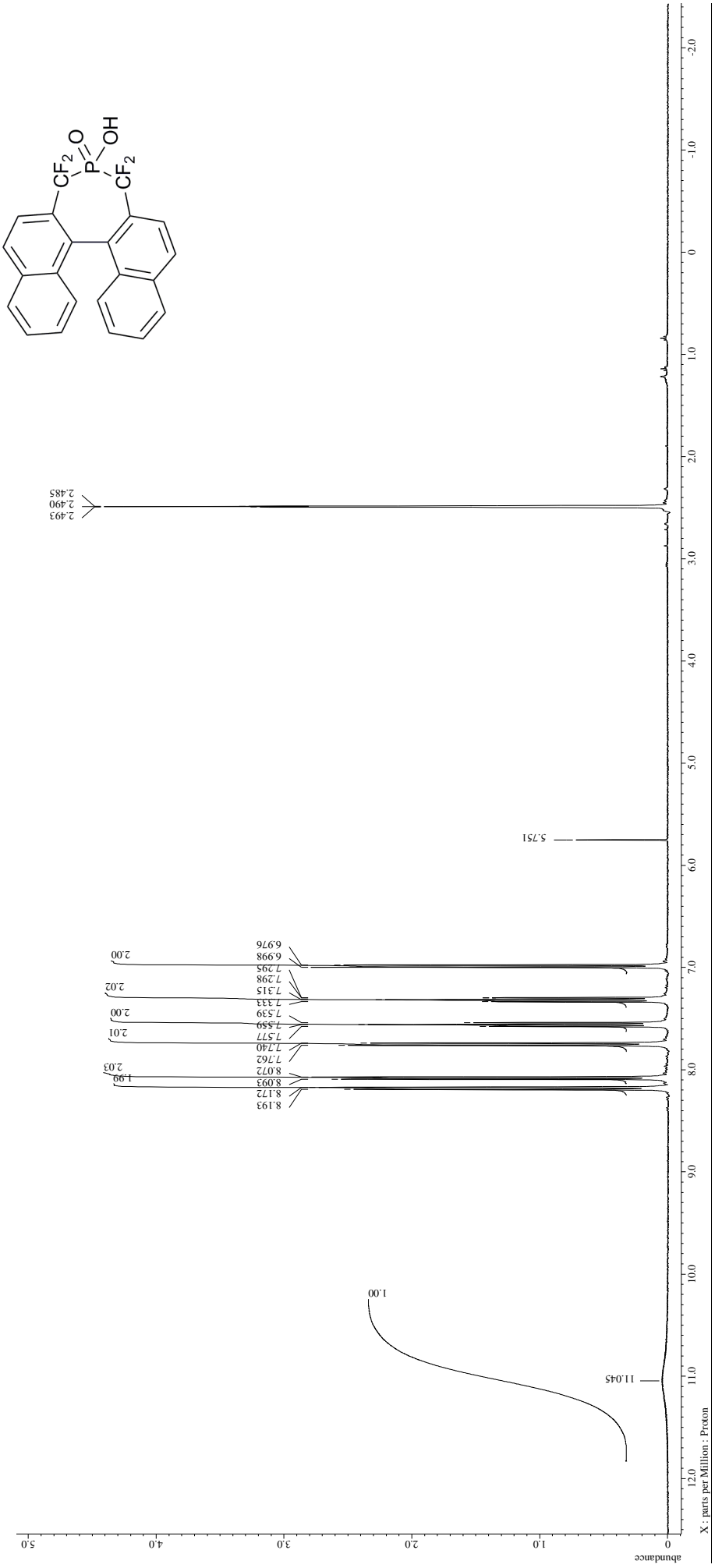
61. D. S. Clyne, J. Jin, E. Genest, J. C. Gallucci and T. V. Rajanbabu, *Org. Lett.*, 2000, **2**, 1125-1128.
62. E. A. Boyd, M. E. K. Boyd and F. Kerrigan, *Tetrahedron Lett.,* 1996, **37**, 5425-5426.
63. Y. Segall, G. B. Quistad and J. E. Casida, *Synth. Commun.*, 2003, **33**, 2151-2159.
64. C. E. McKenna, M. T. Higa, N. H. Cheung and M.-C. McKenna, *Tetrahedron Lett.,* 1977, **18**, 155-158.
65. C. E. McKenna and J. Schmidhuser, *J. Chem. Soc. Chem. Commun.*, 1979, 739-739.
66. I. Fujii and N. Hirayama, *Helv. Chim. Acta*, 2002, **85**, 2946-2960.
67. P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudorfl, A. Berkessel and A. C. O'Donoghue, *Chem. Eur. J.*, 2011, 8524-8528.
68. K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping and I. Leito, *Angew. Chem. Int. Ed.*, 2013, **52**, 11569-11572.
69. D. S. Lingenfelter, R. C. Helgeson and D. J. Cram, *J. Org. Chem.*, 1981, **46**, 393-406.
70. F. Romanov-Michailidis, L. Guénée and A. Alexakis, *Angew. Chem. Int. Ed.*, 2013, **52**, 9266-9270.
71. F. T. Oakes and J. F. Sebastian, *J. Org. Chem.,* 1980, **45**, 4959-4961.
72. L. D. Quin, in *A Guide to Organophosphorus Chemistry*, Wiley-Interscience, New York, vol. 2000, chapter 3, p. 44.
73. L. M. S. Fild, R., in *Organic phosphorus compounds*, ed. G. M. M. Kosolapoff, L., Wiley-interscience, New York, vol. 4, 1972, pp. 76-153.
74. S. A. Solomon, L. K. Allen, S. B. J. Dane and D. S. Wright, *Eur. J. Inorg. Chem.*, 2014, **2014**, 1615-1619.
75. J. Cui, F. Marankan, W. Fu, D. Crich, A. Mesecar and M. E. Johnson, *Bioorg. Med. Chem.*, 2002, **10**, 41-46.
76. A. Michaelis, *Chem. Ber.*, 1875, 1306.
77. A. Michaelis and F. Graeff, *Chem. Ber.*, 1875, 922-924.
78. A. Michaelis, *Ber. Dtsch. Chem. Ges.*, 1879, **12**, 1009-1009.
79. A. Michaelis, *Justus Liebigs Ann. Chem.*, 1896, **293**, 261-325.
80. B. Buchner and L. B. Lockhart, *J. Am. Chem. Soc.*, 1951, **73**, 755-756.
81. W. T. Dye, *J. Am. Chem. Soc.*, 1948, **70**, 2595-2596.
82. M. J. P. Harger and S. Westlake, *Tetrahedron*, 1982, **38**, 1511-1515.
83. W. Walkowiak, G. Ndip and R. A. Bartsch, *Anal. Chem.*, 1999, **71**, 1021-1026.
84. W. E. McEwen, A. B. Janes, J. W. Knapczyk, V. L. Kyllingstad, W.-I. Shiau, S. Shore and J. H. Smith, *J. Am. Chem. Soc.*, 1978, **100**, 7304-7311.
85. N. D. Contrella, J. R. Sampson and R. F. Jordan, *Organometallics*, 2014, **33**, 3546-3555.
86. C. E. Tucker, T. N. Majid and P. Knochel, *J. Am. Chem. Soc.*, 1992, **114**, 3983-3985.
87. R. B. Fox, *J. Am. Chem. Soc.*, 1950, **72**, 4147-4149.
88. M. S. Kharasch, E. V. Jensen and S. Weinhouse, *J. Org. Chem.,* 1949, **14**, 429-432.
89. F. Guichard, *Chem. Ber.*, 1899, 1572-1581.
90. V. Auger and B. Billy, *C. R.*, 1904, **139**, 597-599.
91. H. Hibbert, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 160-162.
92. D. D. Magnelli, G. Tesi, J. U. Lowe and W. E. McQuistion, *Inorg. Chem.*, 1966, **5**, 457-461.
93. J. M. Duff and B. L. Shaw, *J. Chem. Soc. Dalton Trans.*, 1972, 2219-2225.

94. F. Langer and P. Knochel, *Tetrahedron Lett.,* 1995, **36**, 4591-4594.
95. H. H. Hatt, *J. Chem. Soc.*, 1933, 776-786.
96. A. W. Frank, *J. Org. Chem.,* 1961, **26**, 850-853.
97. R. E. Montgomery and L. D. Quin, *J. Org. Chem.,* 1965, **30**, 2393-2395.
98. L. D. Quin and H. G. Anderson, *J. Org. Chem.,* 1966, **31**, 1206-1209.
99. E. E. Nifant'ev and M. P. Koroteev, *J. Gen. Chem. USSR*, 1967, **37**, 1366-1371.
100. T. Wada, H. Hotoda, M. Sekine and T. Hata, *Tetrahedron Lett.,* 1988, **29**, 4143-4146.
101. T. Wada, R. Kato and T. Hata, *J. Org. Chem.,* 1991, **56**, 1243-1250.
102. M. d. F. Fernandez, C. P. Vlaar, H. Fan, Y.-H. Liu, F. R. Fronczek and R. P. Hammer, *J. Org. Chem.,* 1995, **60**, 7390-7391.
103. H. Byrd, P. C. Bharara, T. A. Sullens, J. D. Harden and G. M. Gray, *Inorg. Chim. Acta*, 2002, **338**, 240-244.
104. L. D. Freedman and G. O. Doak, *Chem. Rev.*, 1957, **57**, 479-523.
105. E. F. Jason and E. K. Fields, *J. Org. Chem.,* 1962, **27**, 1402-1405.
106. J. F. Bunnett and X. Creary, *J. Org. Chem.,* 1974, **39**, 3612-3614.
107. J. B. Plumb, R. Obrycki and C. E. Griffin, *J. Org. Chem.,* 1966, **31**, 2455-2458.
108. R. Obrycki and C. E. Griffin, *J. Org. Chem.,* 1968, **33**, 632-636.
109. T. Hirao, T. Masunaga, Y. Ohshiro and T. Agawa, *Synthesis*, 1981, 56-57.
110. T. Hirao, T. Masunaga, N. Yamada, Y. Ohshiro and T. Agawa, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 909-913.
111. D. Prim, J-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041-2075.
112. I. P. Beletskaya and M. A. Kazankova, *Russ. J. Org. Chem.*, 2002, **38**, 1391-1430.
113. J. Yang, T. Chen and L-B. Han, *J. Am. Chem. Soc.*, 2015, **137**, 1782-1785.
114. Y. R. Dumond and J-L. Montchamp, *J. Organomet. Chem.*, 2002, **653**, 252-260.
115. K. Bravo-Altamirano, Z. Huang and J-L. Montchamp, *Tetrahedron*, 2005, **61**, 6315-6329.
116. L. J. Gooßen and M. K. Dezfuli, *Synlett*, 2005, 445-448.
117. W. Xu, G. Hu, P. Xu, Y. Gao, Y. Yin and Y. Zhao, *Ad. Synth. Catal.*, 2014, **356**, 2948-2954.
118. M. Sobkowski, A. Kraszewski and J. Stawinski, in *Phosphorus Chemistry II*, ed. J-L. Montchamp, Springer International Publishing, 2015, vol. 361, ch. 562, pp. 137-177.
119. M. Sobkowski, A. Kraszewski and J. Stawinski, in *Phosphorus Chemistry II*, ed. J-L. Montchamp, Springer International Publishing, 2015, vol. 361, ch. 563, pp. 179-216.
120. M. Kalek and J. Stawinski, *Tetrahedron*, 2009, **65**, 10406-10412.
121. M. Kalek, A. Ziadi and J. Stawinski, *Org. Lett.*, 2008, **10**, 4637-4640.
122. B. Zhao, X. Peng, Z. Wang, C. Xia and K. Ding, *Chem. Eur. J.*, 2008, **14**, 7847-7857.
123. E. P. Kyba, M. C. Kerby and S. P. Rines, *Organometallics*, 1986, **5**, 1189-1194.
124. M. T. Reetz, D. Moulin and A. Gosberg, *Org. Lett.*, 2001, **3**, 4083-4085.
125. C. Queffelec and J-L. Montchamp, *Org. Biomol. Chem.*, 2010, **8**, 267-273.
126. J. A. Miles, M. T. Beeny and K. W. Ratts, *J. Org. Chem.,* 1975, **40**, 343-347.
127. H. Qian, P. P. Gaspar and N. P. Rath, *J. Organomet. Chem.*, 1999, **585**, 167-173.

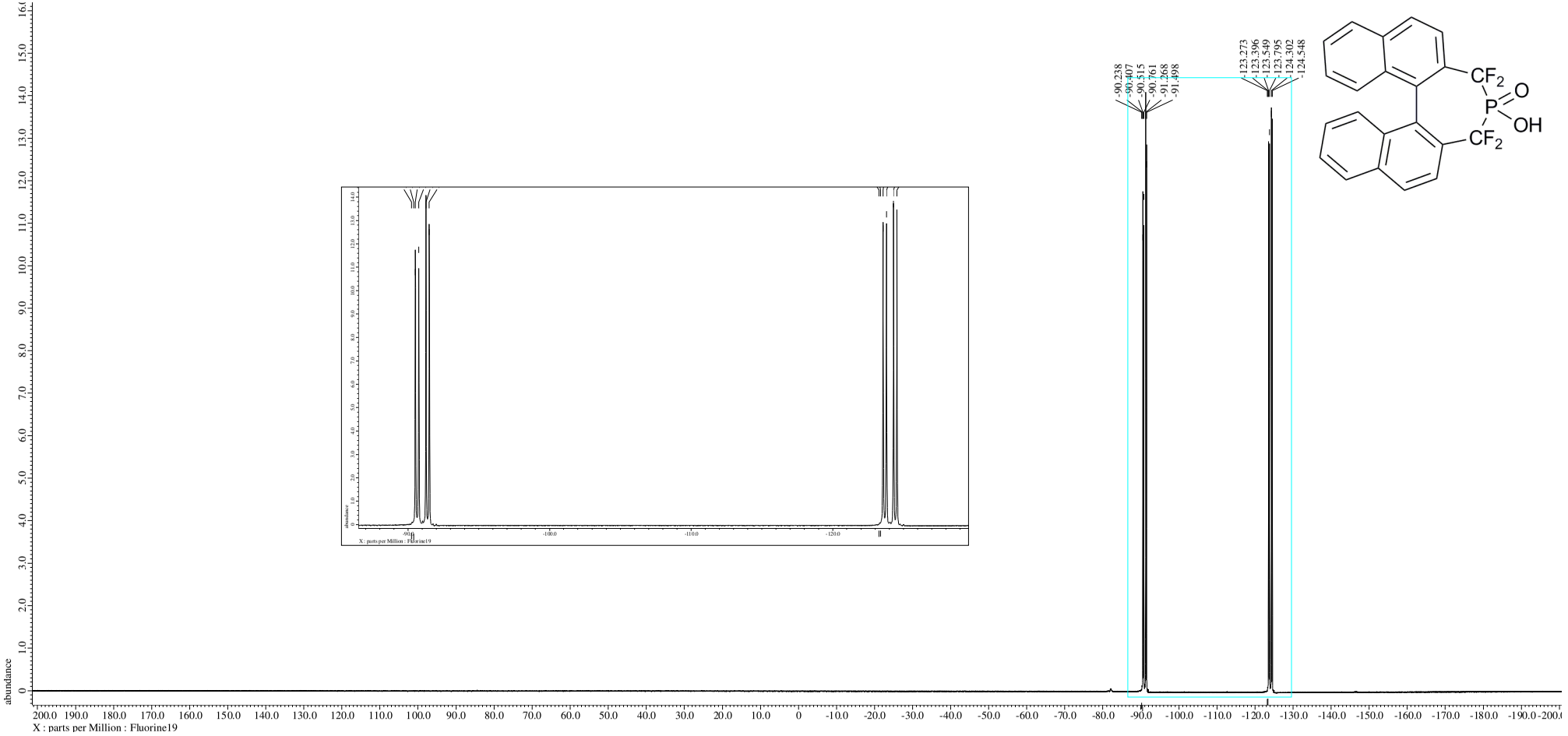
128. S. J. Coles and P. A. Gale, *Chem. Sci.*, 2012, **3**, 683-689.
129. T. H. Wöste and M. Oestreich, *Chem. Eur. J.*, 2011, **17**, 11914-11918.
130. M. Genov, A. Almorín and P. Espinet, *Chem. Eur. J.*, 2006, **12**, 9346-9352.
131. T. Mecca, S. Superchi, E. Giorgio and C. Rosini, *Tetrahedron-Asymmetry*, 2001, **12**, 1225-1233.
132. M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard and B. List, *Synlett*, 2010, 2189-2192.
133. I. Ahmed and D. A. Clark, *Org. Lett.*, 2014, **16**, 4332-4335.
134. L. J. Barbour, *J. Supramol. Chem.*, 2001, **1**, 189-191.
135. G. M. Sheldrick, *SHELXL-97; Universität Göttingen: Göttingen, Germany*, 1997.
136. L. J. Farrugia, *J. Appl. Cryst.*, 2012, **45**, 849-854.
137. F. Y. Kwong, C. W. Lai, M. Yu, Y. Tian and K. S. Chan, *Tetrahedron*, 2003, **59**, 10295-10305.
138. L. D. Quin and M. R. Dysart, *J. Org. Chem.,* 1962, **27**, 1012-1014.
139. D. S. Karanewsky, M. C. Badia, D. W. Cushman, J. M. DeForrest, T. Dejneka, M. J. Loots, M. G. Perri, E. W. Petrillo and J. R. Powell, *J. Med. Chem.*, 1988, **31**, 204-212.
140. S. Ortial, H. C. Fisher and J-L. Montchamp, *J. Org. Chem.,* 2013, **78**, 6599-6608.
141. C. D. Hall, B. R. Tweedy and N. Lowther, *Phosphorus, Sulfur, Silicon Relat. Elem.,* 1997, **123**, 341-358.

Appendices

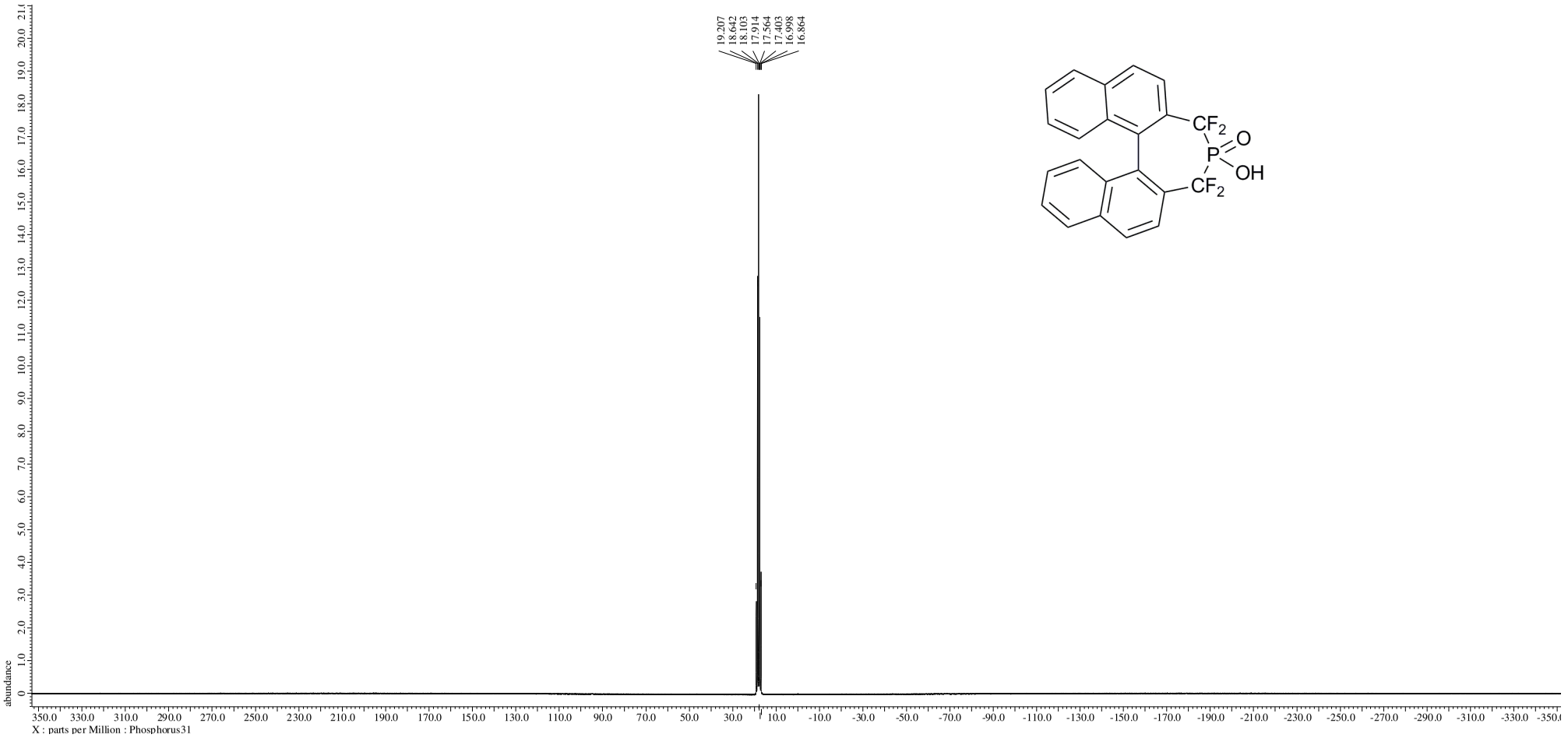
Appendix 1: ^{1}H NMR spectrum of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**)



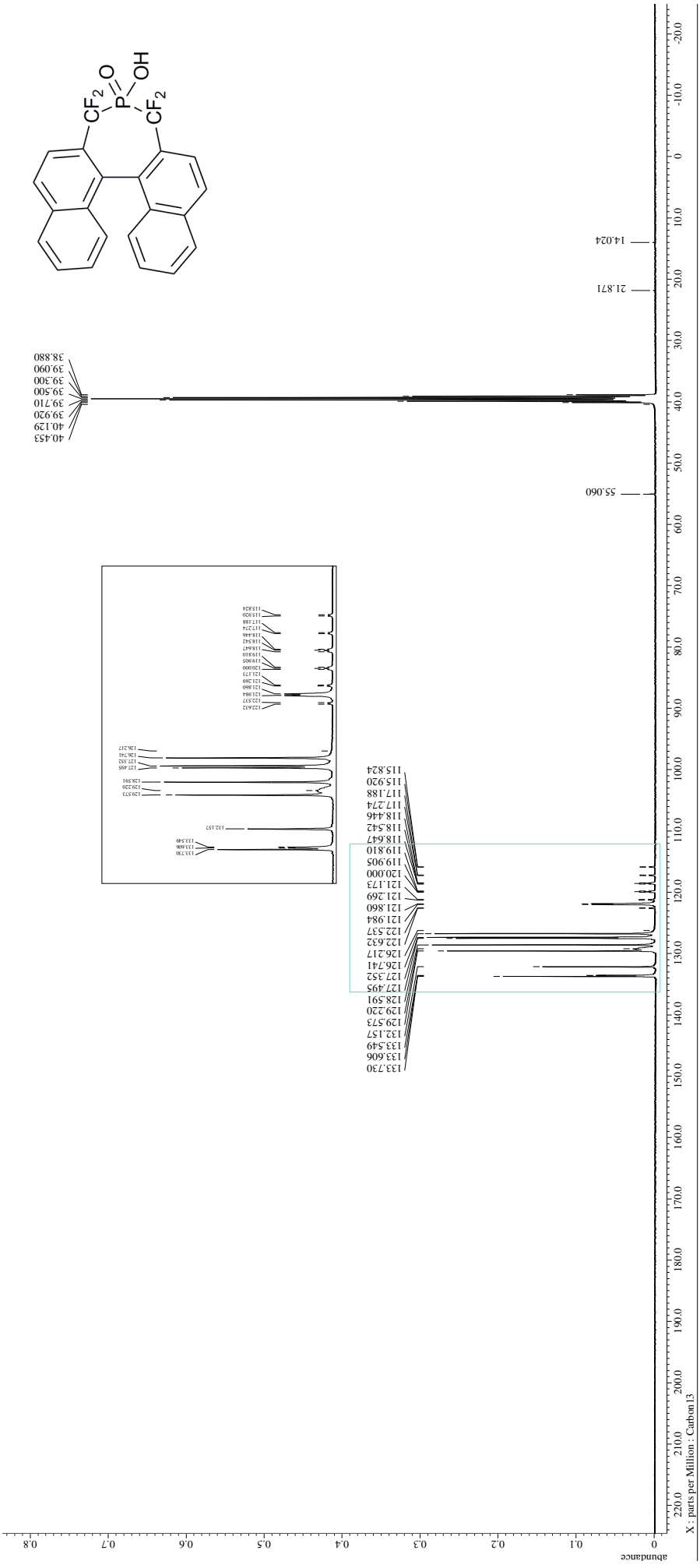
Appendix 2: ^{19}F NMR spectrum of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**)



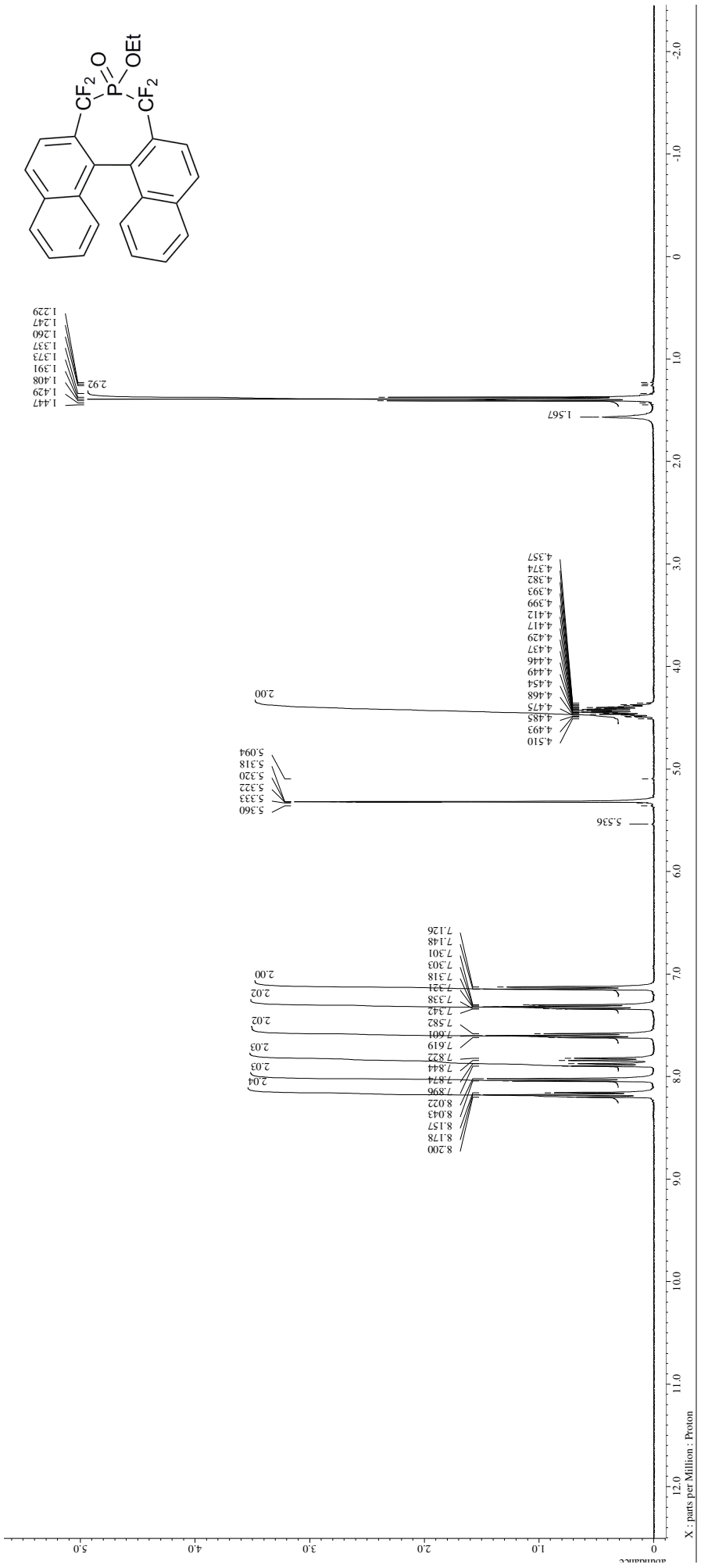
Appendix 3: ^{31}P NMR spectrum of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**)



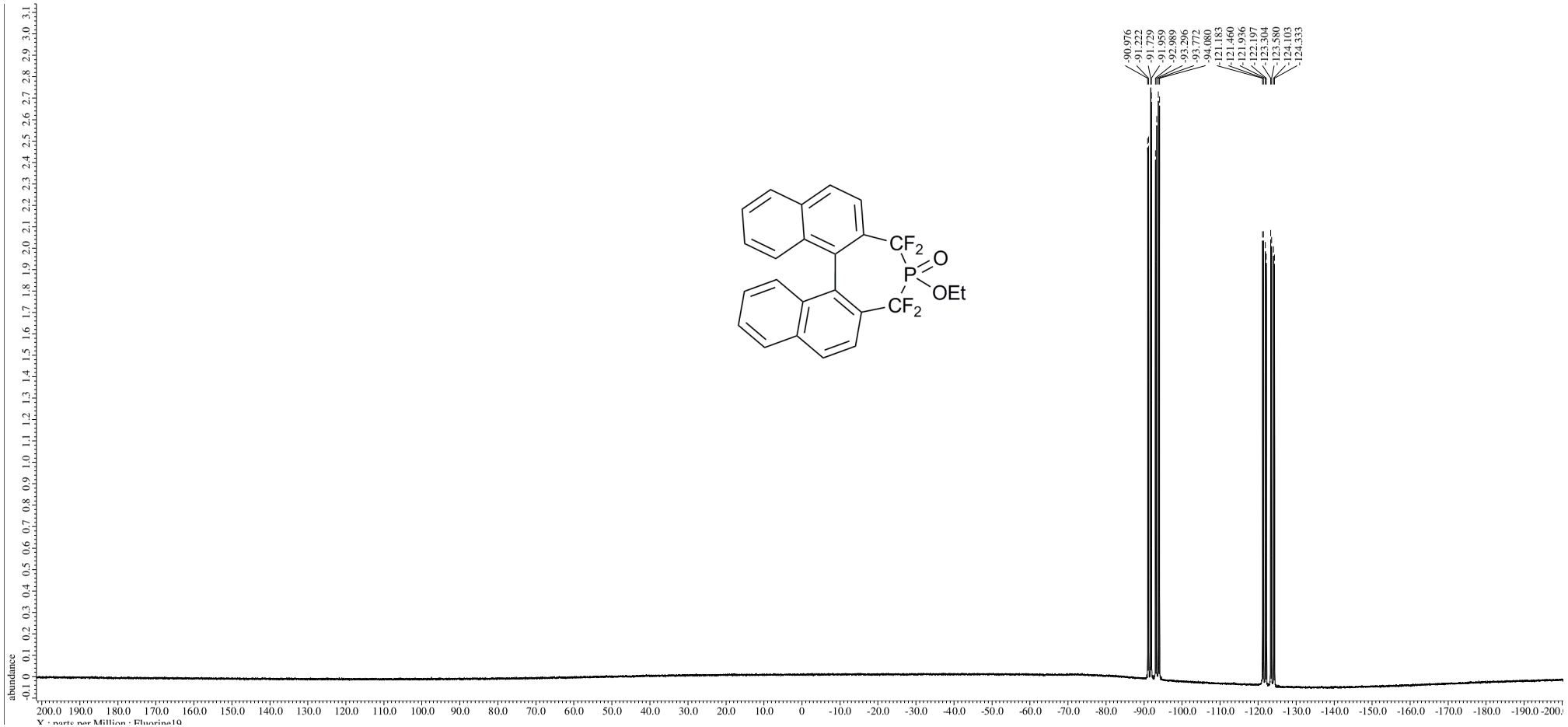
Appendix 4: ^{13}C NMR spectrum of 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinic acid (**1**)



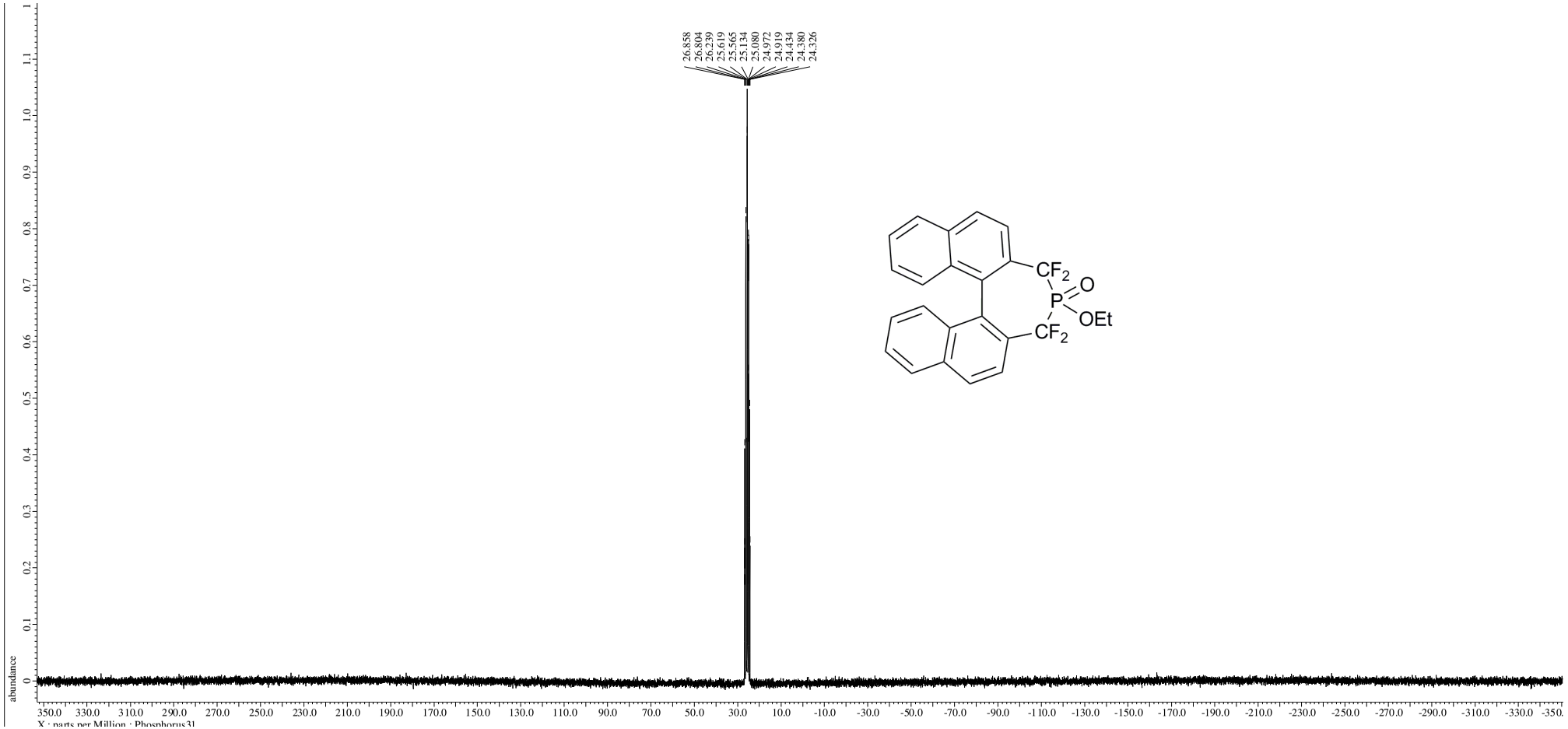
Appendix 5: ^{1}H NMR spectrum of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)



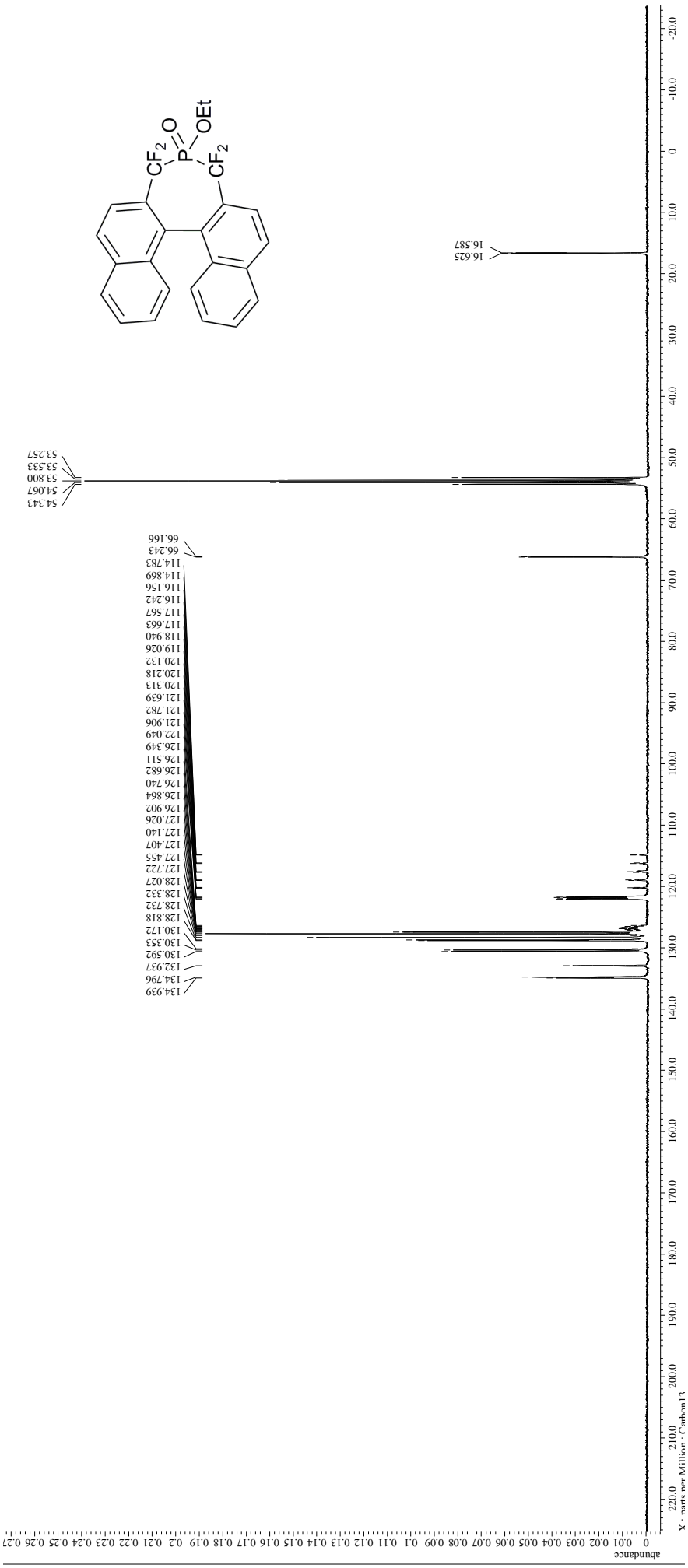
Appendix 6: ^{19}F NMR spectrum of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)



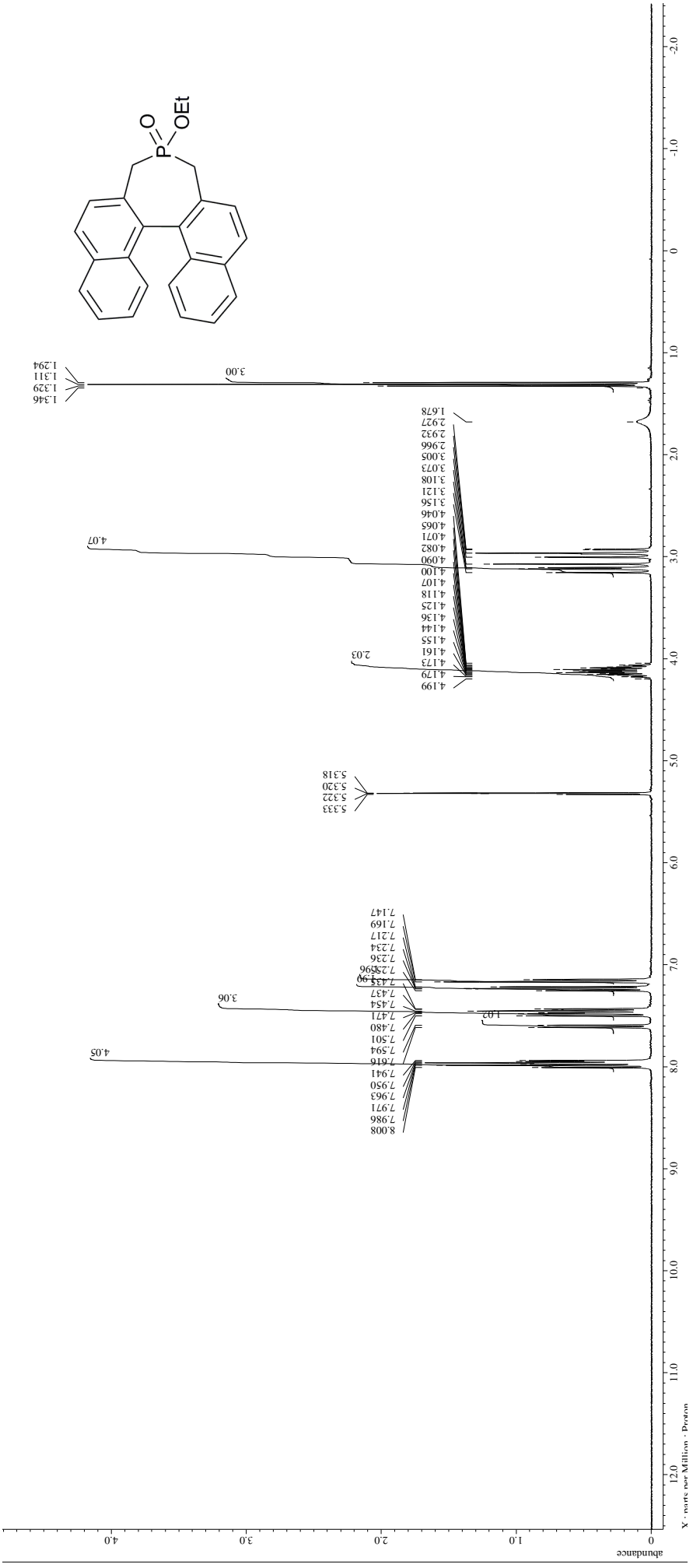
Appendix 7: ^{31}P NMR spectrum of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)



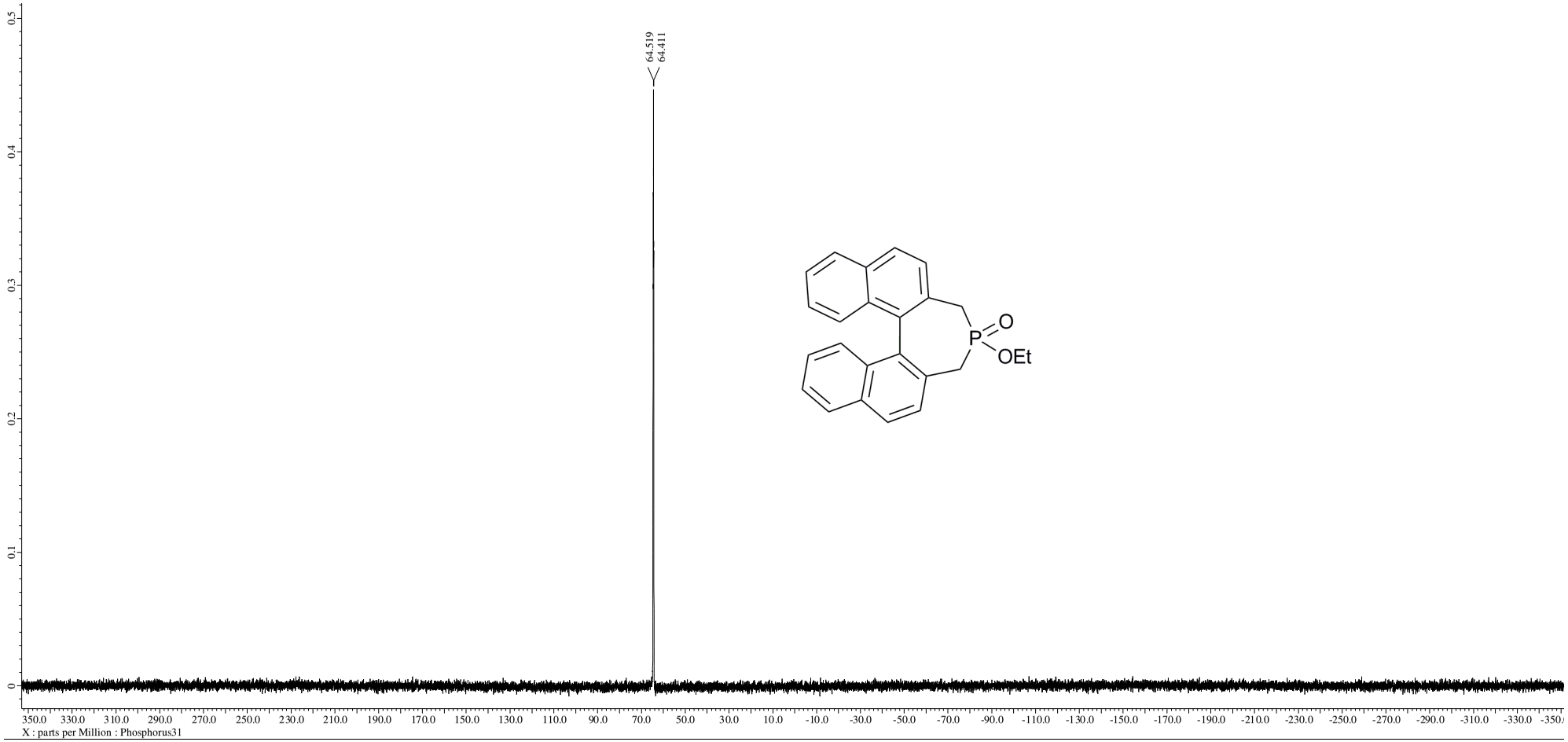
Appendix 8: ^{13}C NMR spectrum of ethyl 2,2'-bis(difluoromethylene)-1,1'-binaphthyl phosphinate (**6**)



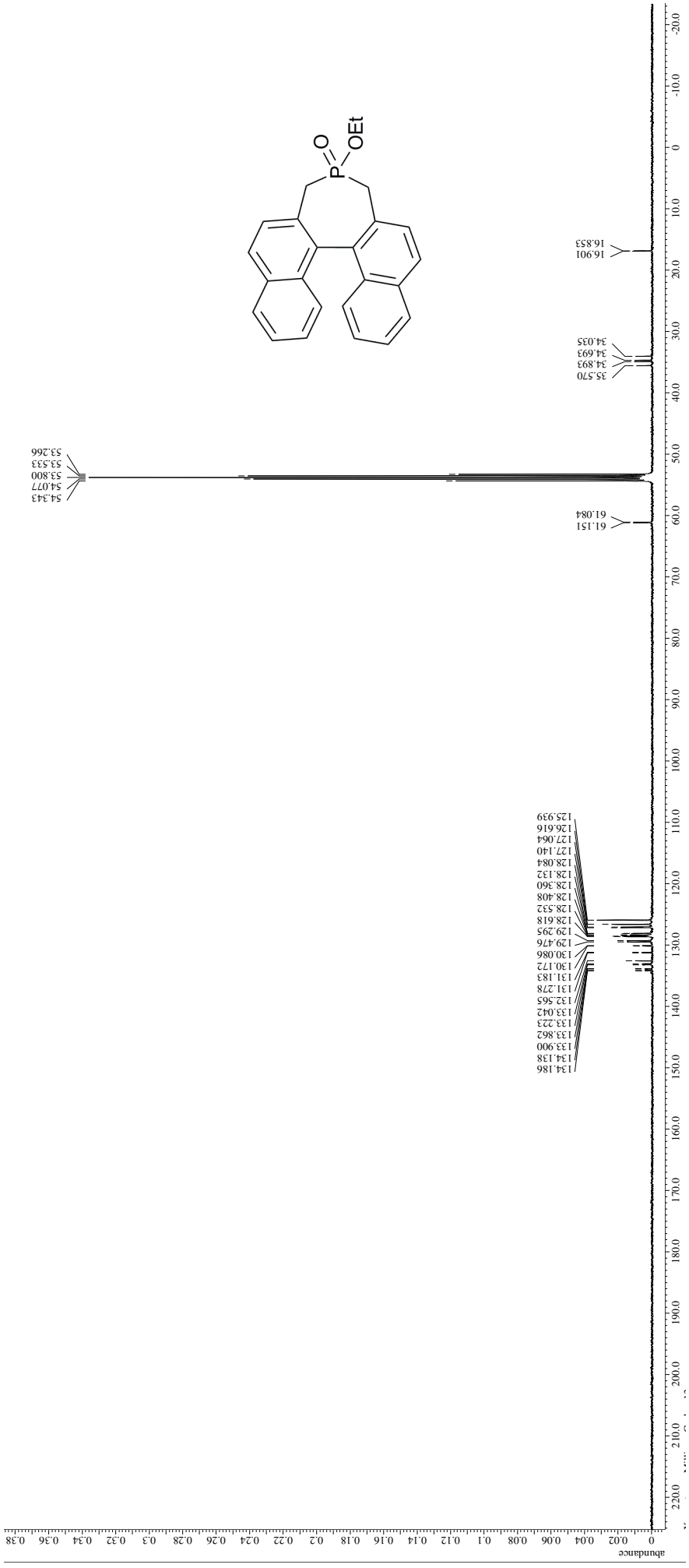
Appendix 9: ^{1}H NMR spectrum of ethyl 2,2'-bis(methylene)-1,1'-binaphthyl phosphinate (**5**)



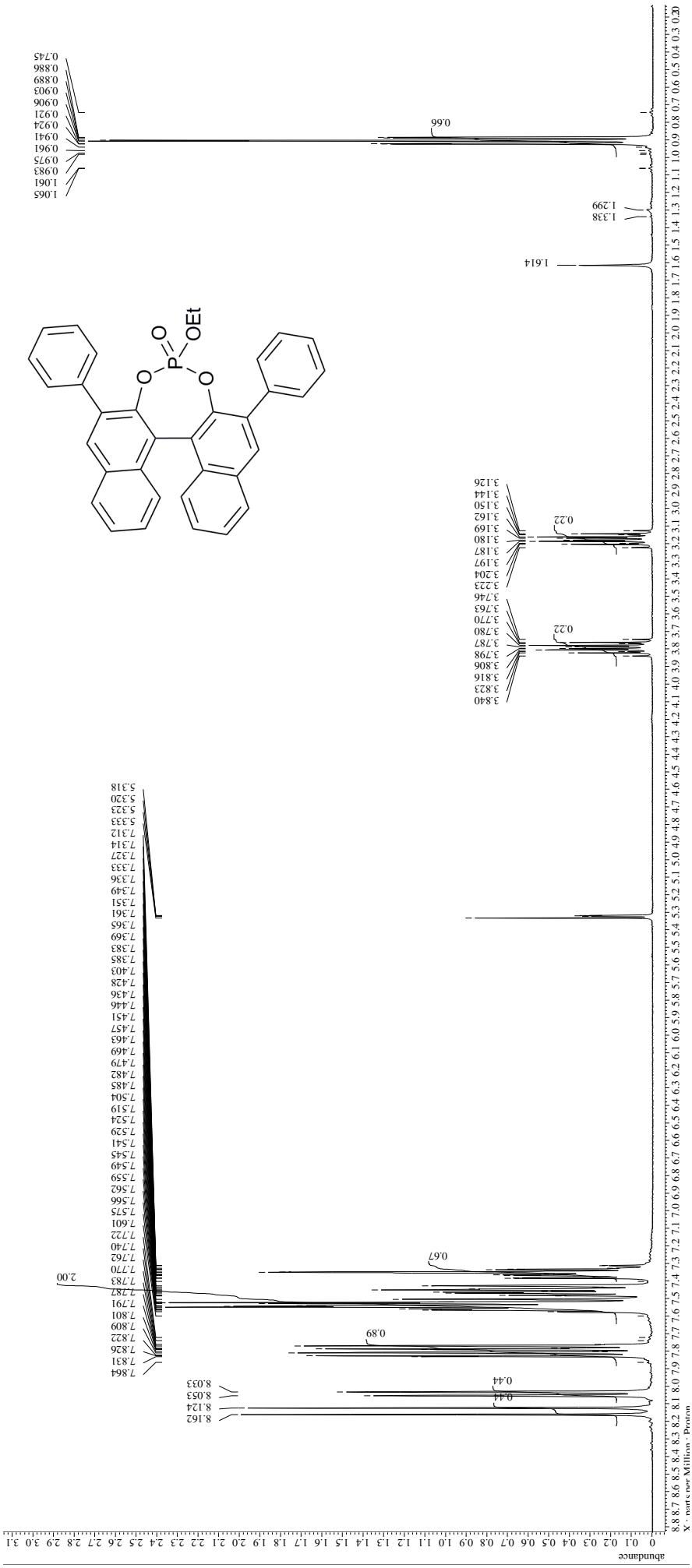
Appendix 10: ^{31}P NMR spectrum of ethyl 2,2'-bis(methylene)-1,1'-binaphthyl phosphinate (**5**)



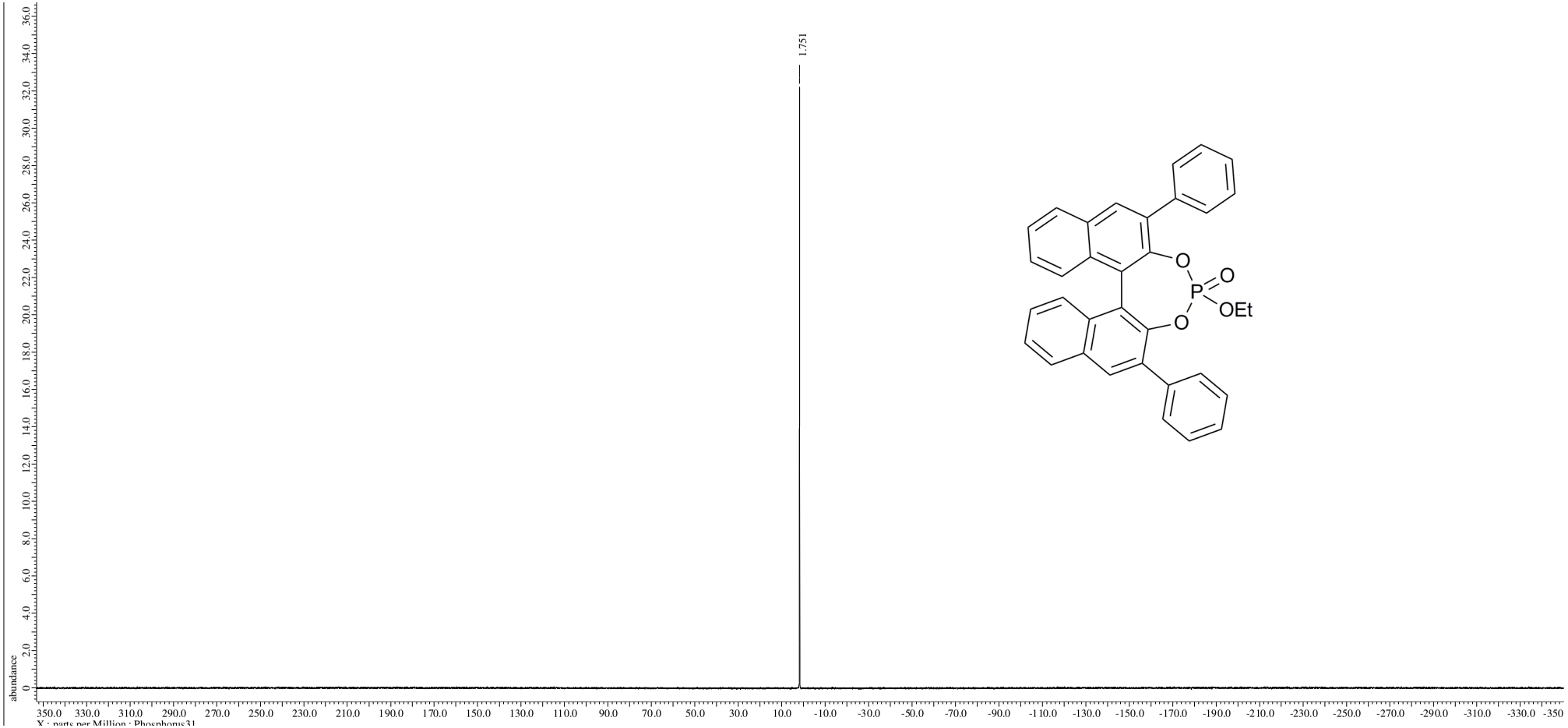
Appendix 11: ^{13}C NMR spectrum of ethyl 2,2'-bis(methylene)-1,1'-binaphthyl phosphinate (**5**)



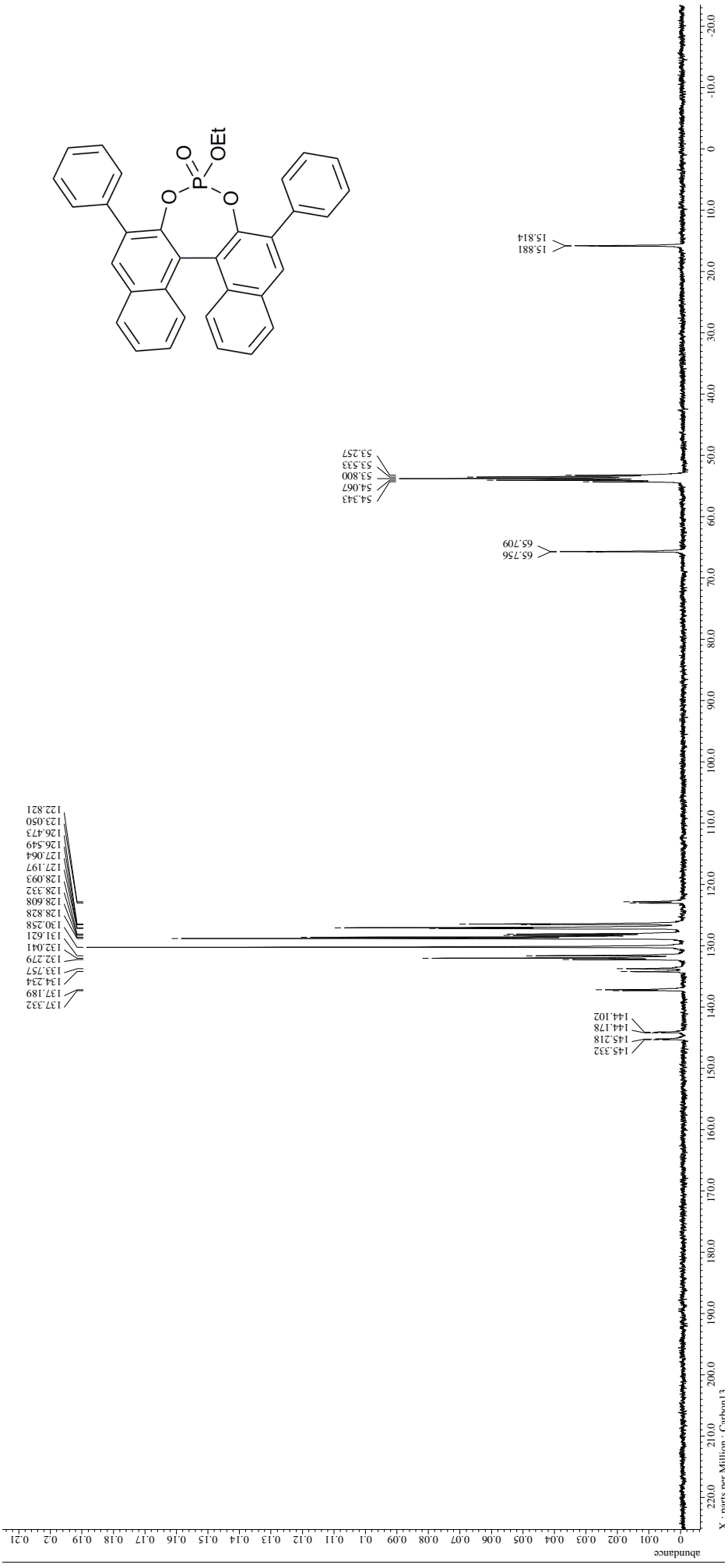
Appendix 12: ^{1}H NMR spectrum of 3,3'-diphenyl-1,1'-binaphthyl-2,2'-diyl ethyl phosphate (**7**)



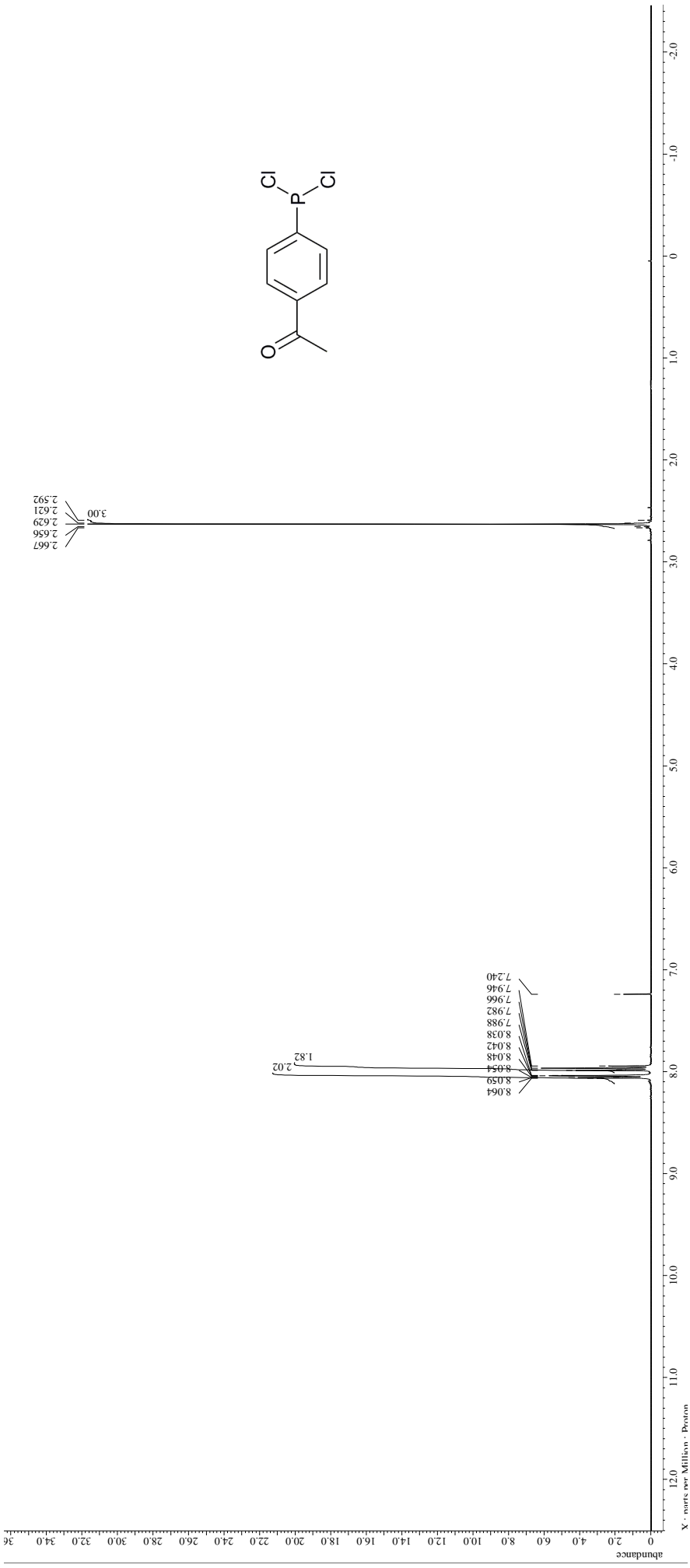
Appendix 13: ^{31}P NMR spectrum of 3,3'-diphenyl-1,1'-binaphthyl-2,2'-diyl ethyl phosphate (**7**)



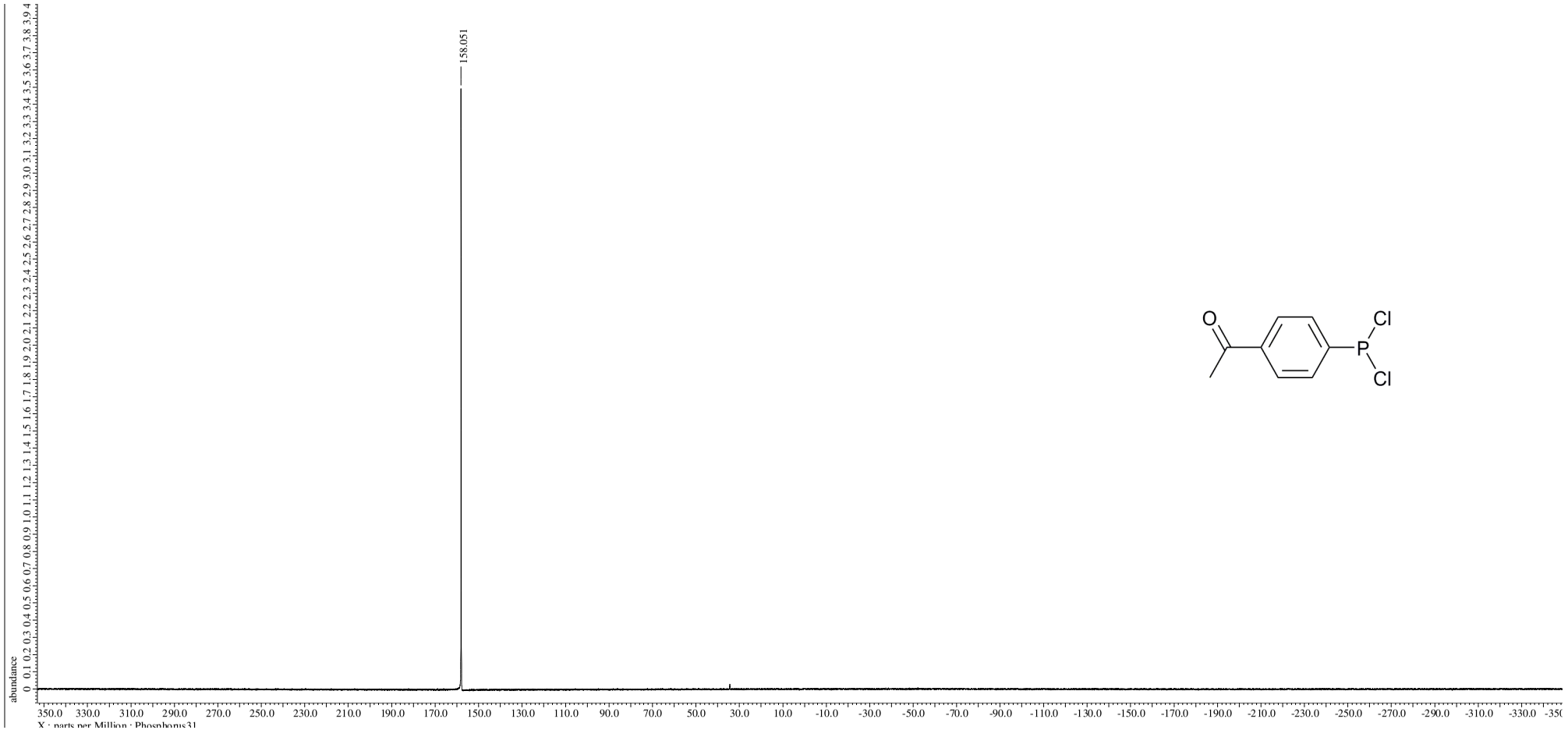
Appendix 14: ^{13}C NMR spectrum of 3,3'-diphenyl-1,1'-binaphthyl-2,2'-diyl ethyl phosphate (**7**)



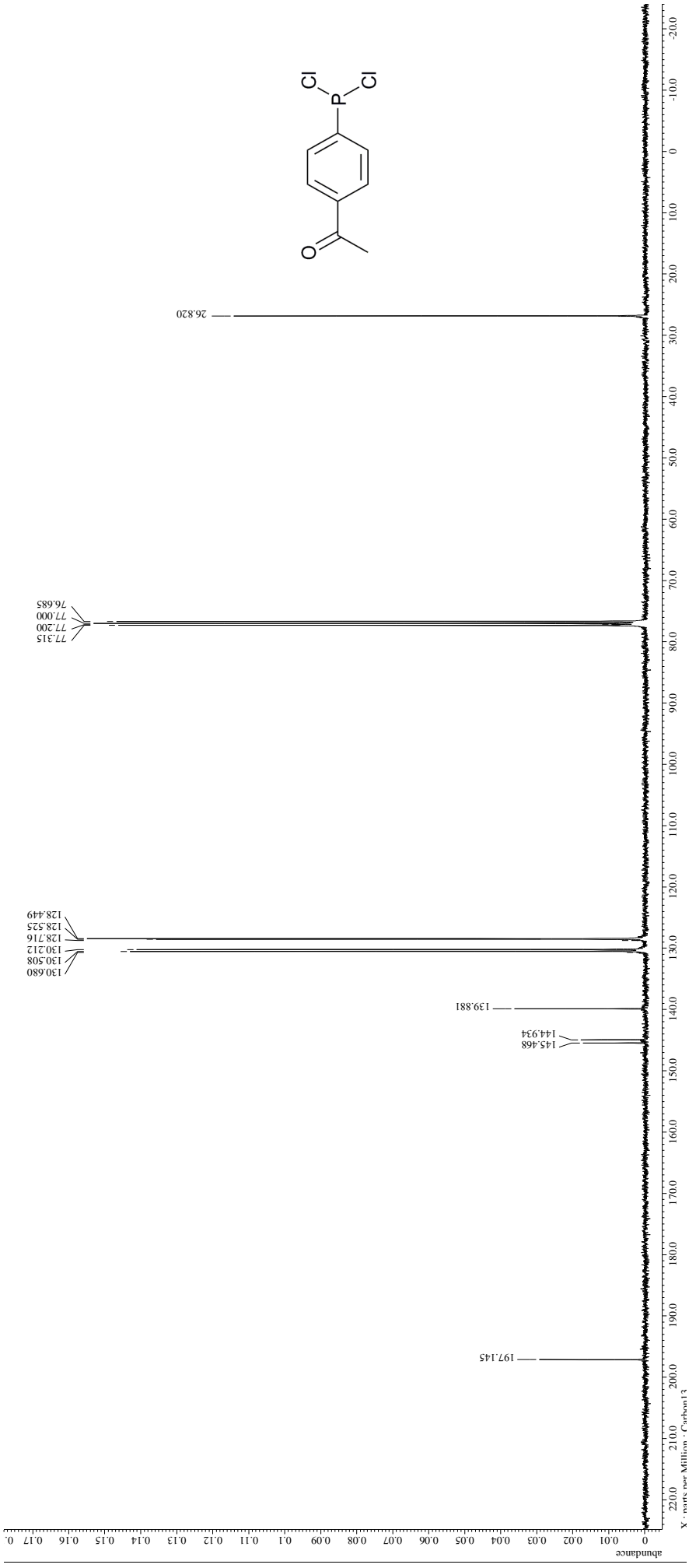
Appendix 15: ^{1}H NMR spectrum of 4-$MeCOC_6H_4PCl_2$



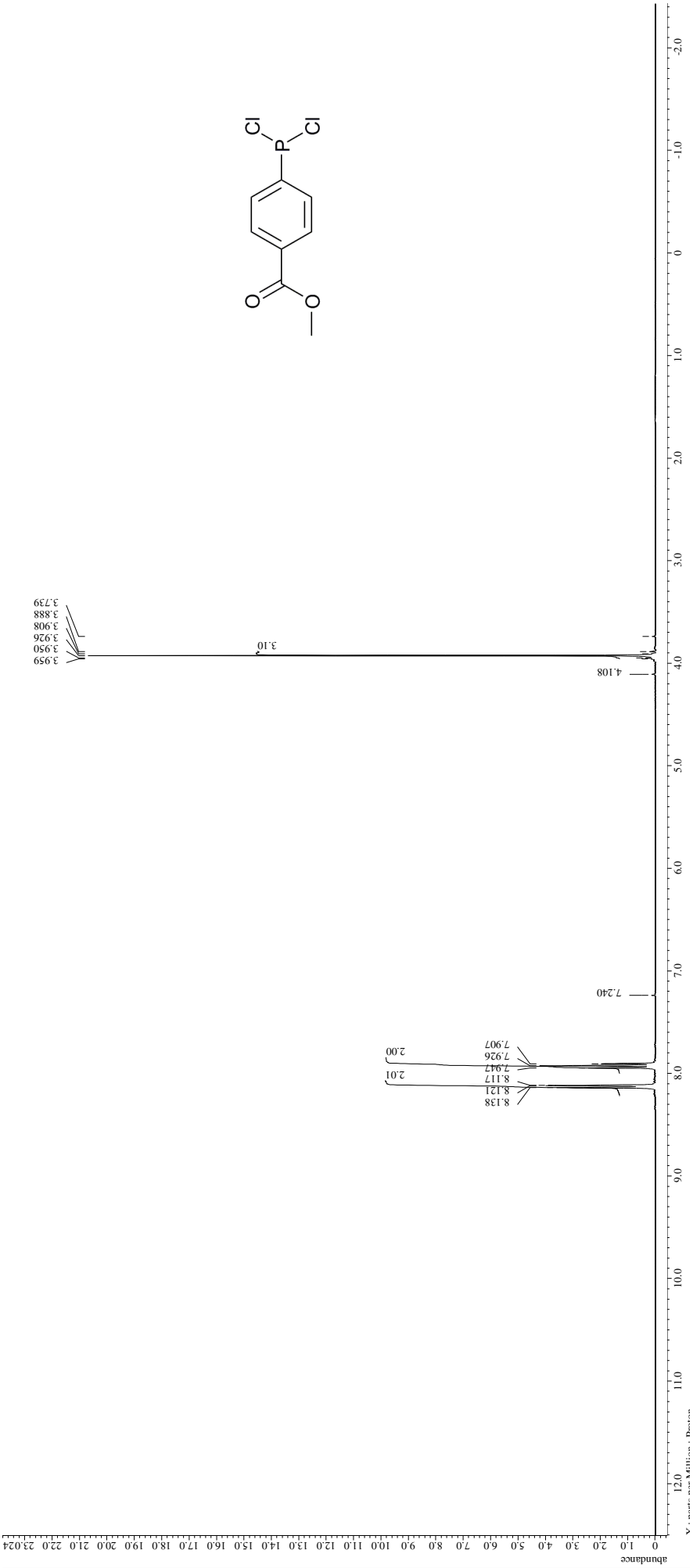
Appendix 16: ^{31}P NMR spectrum of 4-$MeCOC_6H_4PCl_2$



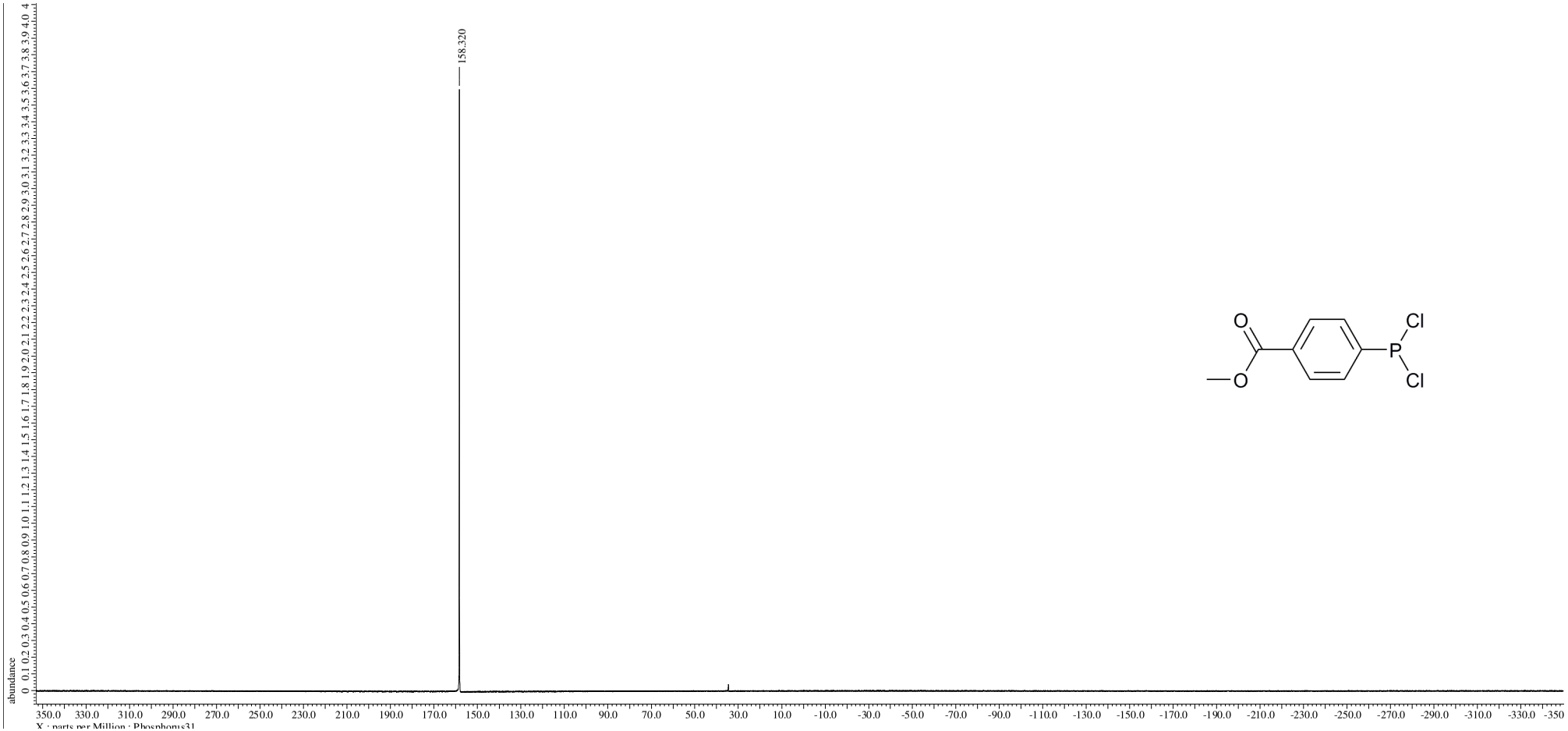
Appendix 17: ^{13}C NMR spectrum of 4-$MeCOC_6H_4PCl_2$



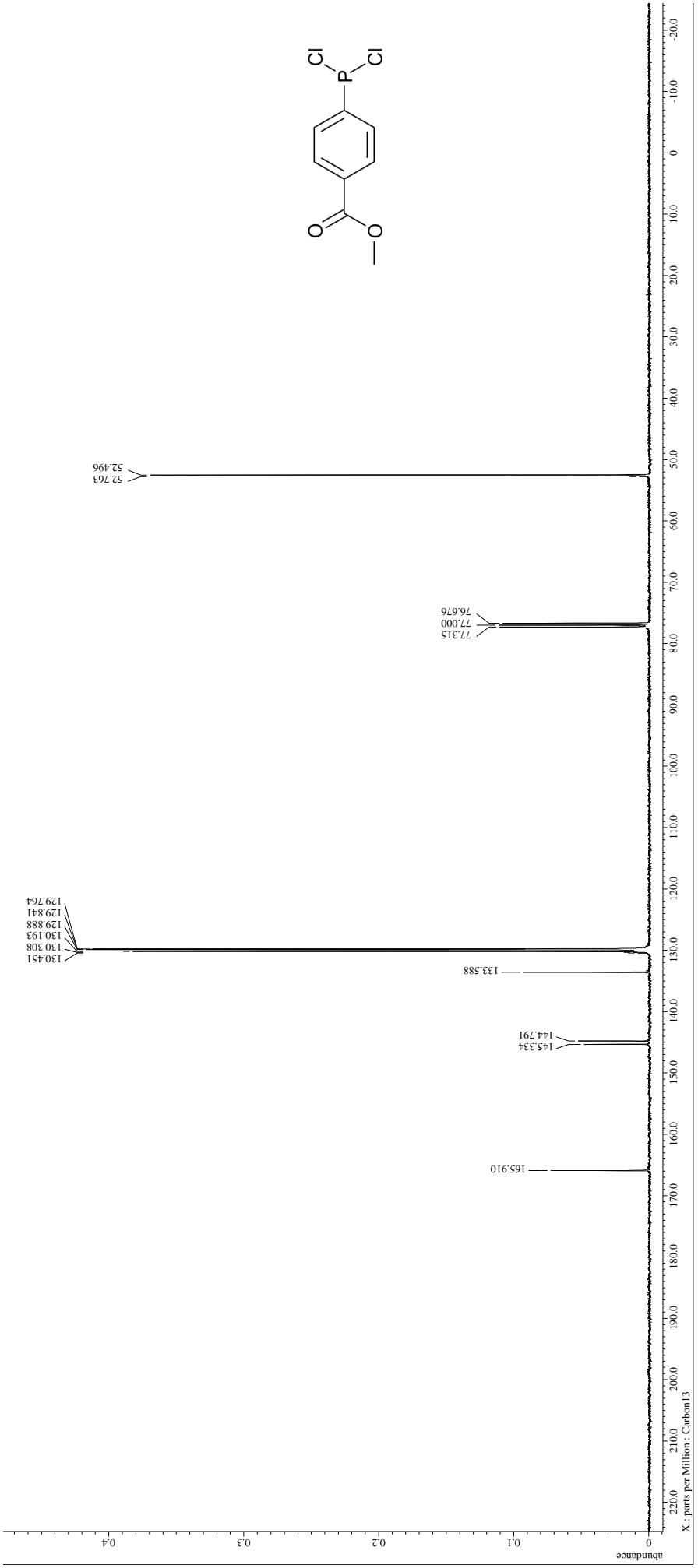
Appendix 18: ^{1}H NMR spectrum of 4-MeO(CO)$C_6H_4PCl_2$



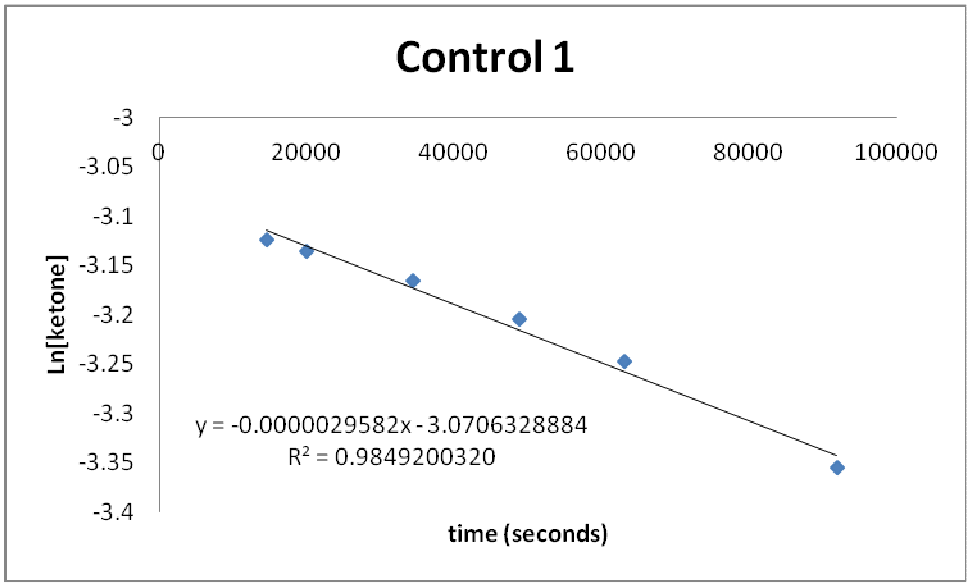
Appendix 19: ^{31}P NMR spectrum of 4-MeO(CO)$C_6H_4PCl_2$

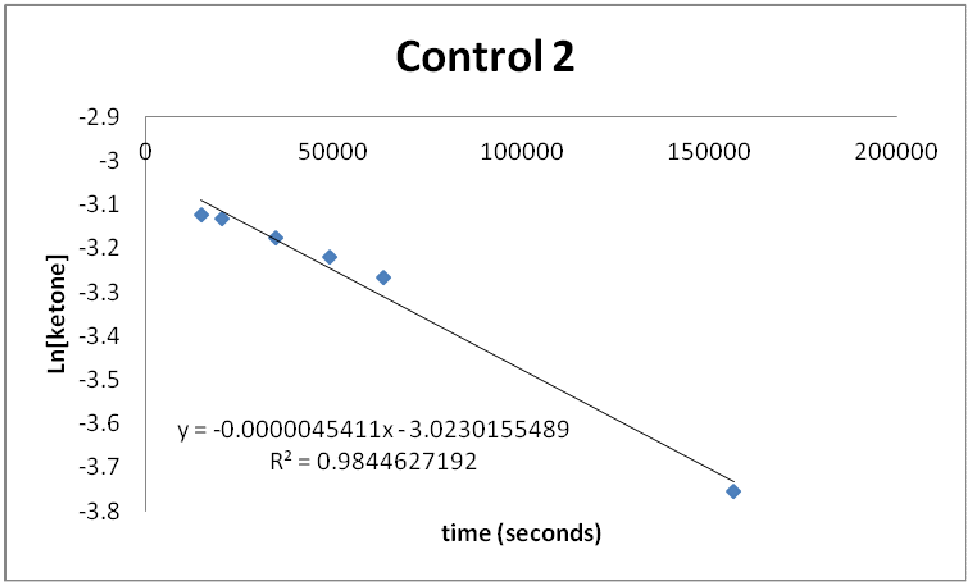


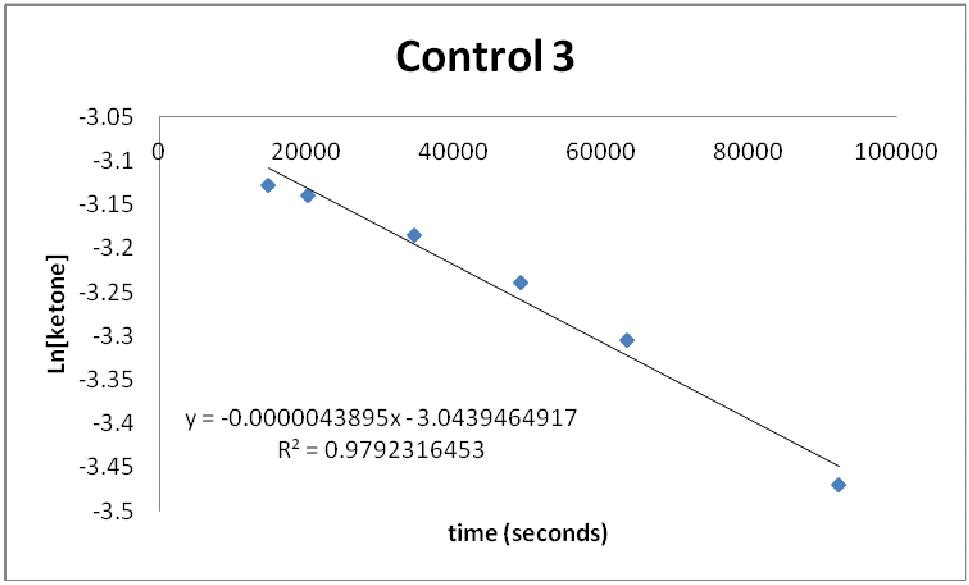
Appendix 20: ^{13}C NMR spectrum of 4-MeO(CO)$C_6H_4PCl_2$



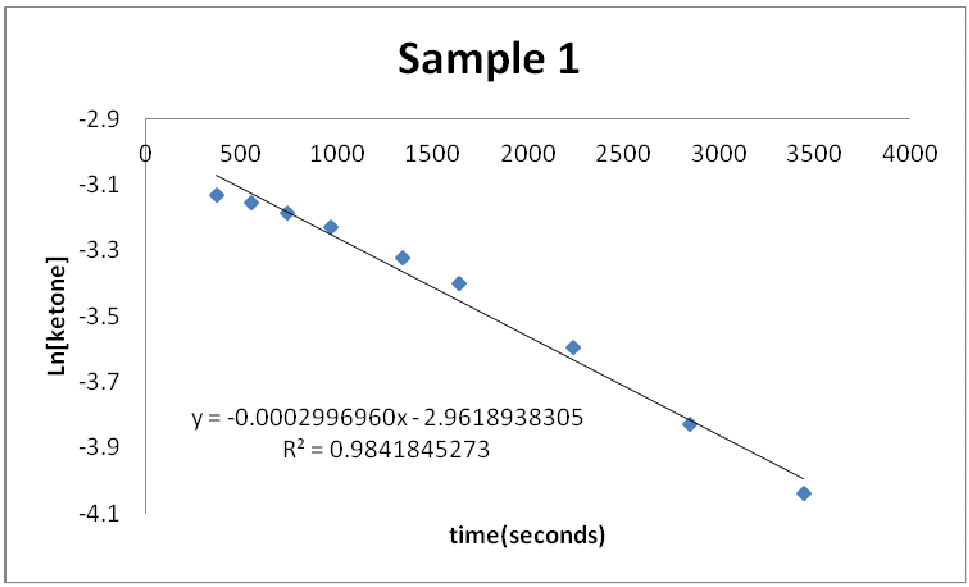
Appendix 21: First order rate plots for control reactions of the Nazarov cyclisation

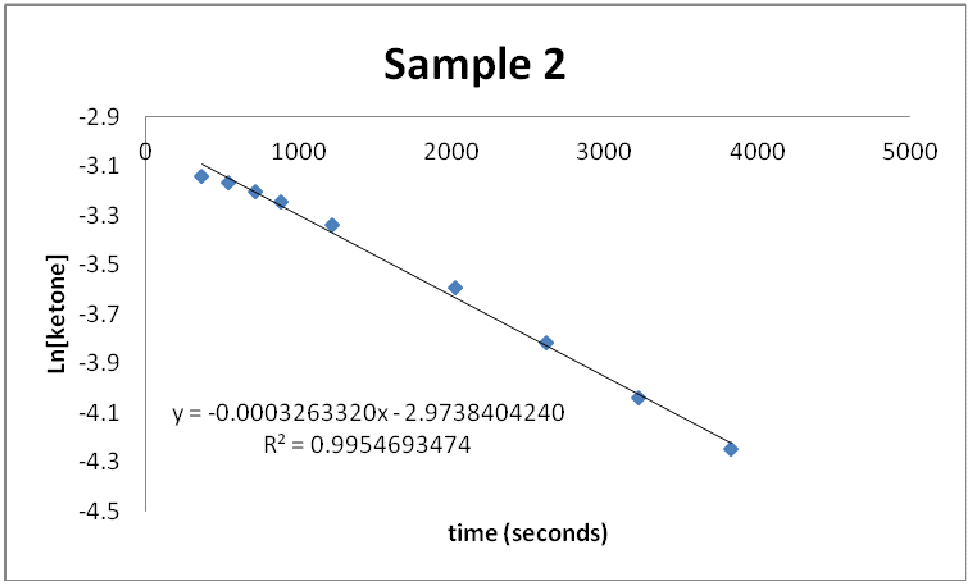


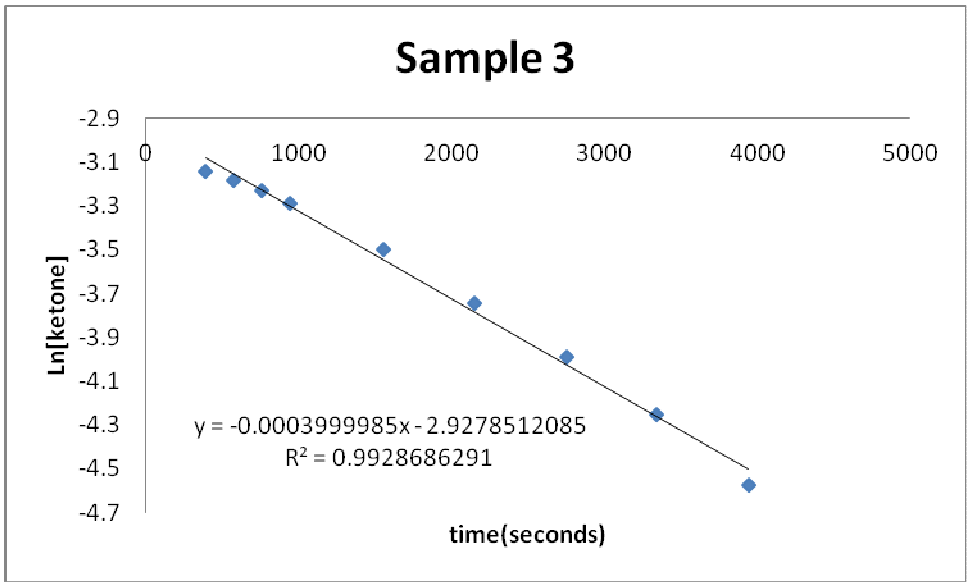




Appendix 22: First order rate plots of the Nazarov cyclisation catalysed by **1**




Sample 2
-2.9
-3.1
-3.3
-3.5
-3.7
-3.9
-4.1
-4.3
-4.5
0
1000
2000
3000
4000
5000
Ln[ketone]
y = -0.0003263320x - 2.9738404240
R² = 0.9954693474
time (seconds)


Sample 3
-2.9
-3.1
-3.3
-3.5
-3.7
-3.9
-4.1
-4.3
-4.5
-4.7
0
1000
2000
3000
4000
5000
Ln[ketone]
y = -0.0003999985x - 2.9278512085
R² = 0.9928686291
time(seconds)