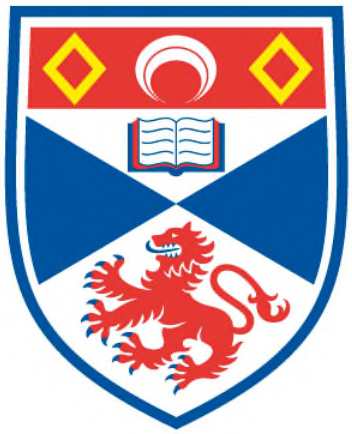
SOLID PHASE STRATEGIES FOR THE PREPARATION OF PHOSPHORUS LIGAND LIBRARIES

Michiel C. Samuels

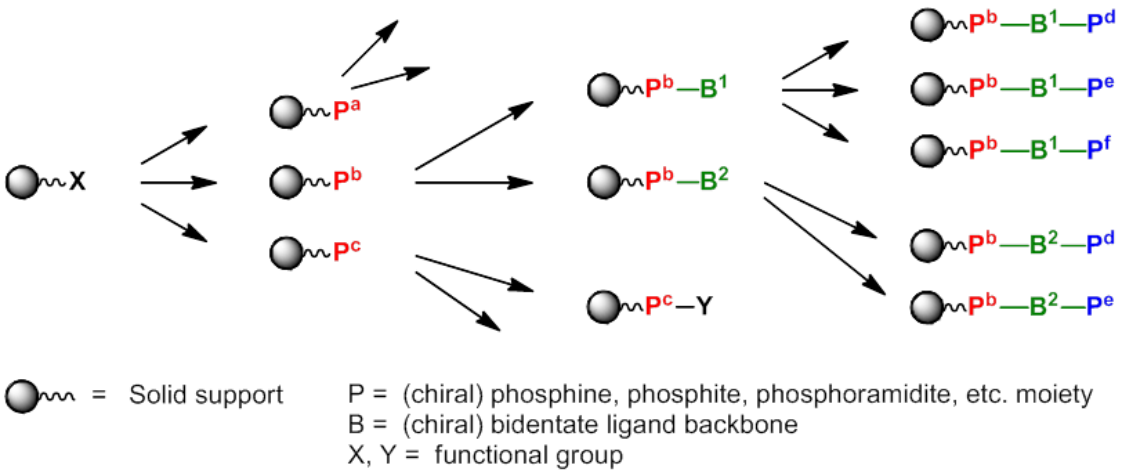
A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



2014

Solid phase strategies for the preparation of phosphorus ligand libraries

A thesis presented to the University of St Andrews
in application for the degree of Doctor of Philosophy



Michiel C. Samuels

Supervised by
Professor Paul C. J. Kamer

February 2014

Table of Contents

Declarations i

Dedication iii

Acknowledgements iv

Abstract v

Abbreviations vi

CHAPTER 1. SOLID PHASE SYNTHESIS OF PHOSPHORUS LIGANDS 1

1.1 Introduction[1] 1

1.2 Insoluble supports in ligand synthesis 6

1.3 Soluble polymeric supports 12

1.4 Supported ligands in catalysis 14

1.5 Solid phase synthesis of non-supported ligands 16

1.6 Conclusions and Outlook 20

1.7 Objectives and outline 21

1.8 References 23

CHAPTER 2. LIGAND SYNTHESIS ON POLYSTYRENE RESIN 26

2.1 Introduction 26

2.1.1 *P*-stereogenic ligands 26

2.1.2 *P*-stereogenic ligands developed by Imamoto 26

2.1.3 *P*-stereogenic ligands developed by Jugé 27

2.1.4 *P*-stereogenic ligands developed by Livinghouse 28

2.2 Solid Phase Synthesis combined with synthesis of P-stereogenic phosphines 29

2.3 Synthesising libraries of immobilised ligands 31

2.4 Solid phase synthesis of immobilised phosphine ligands 33

2.4.1 Synthesis of **PS1** using *t*-BuPCl$_2$ 33

2.4.2 Synthesis of **PS1** using *t*-BuP(NEt$_2$)Cl 39

2.4.3 Synthesis of **PS1** using *t*-BuP(OEt)Cl 42

2.5 Lithiation of PS1 and complex formation with (–)-sparteine 45

2.5.1 Synthesis of immobilised phosphine-phosphinites 47

2.6 Synthesis of immobilised bis(phosphines) 50

2.7 Hydrolysis experiments, towards phosphine-phosphinites 54

2.8 Deprotection of ligands PS26 58

2.9 Conclusions and outlook 60

2.10 General considerations and procedures for working with resins 61

2.10.1 Stirring the resin 61
2.10.2 Swelling and washing of the resin 61
2.10.3 ^{31}P NMR of the resin 63

2.11 Experimental 63
2.11.1 General remarks 63
2.11.1 Optimisation of the ^{31}P NMR spectra of immobilised compounds 64
2.11.2 Synthesis 65

2.12 References 78

CHAPTER 3. LIGAND SYNTHESIS ON *J*ANDA*J*EL™ RESIN 80

3.1 Introduction 80

3.2 Synthesis of secondary phosphines on JandaJel™-Cl 81
3.2.1 Synthesis on Merrifield-Cl resin 85
3.2.2 Synthesis on TentaGel™-OH resin 86

3.3 Synthesis of immobilised bis(phosphines) 88

3.4 Deprotection of immobilised bis(phosphine) ligands 92

3.5 Conclusions and outlook 94

3.6 Experimental 95
3.6.1 General remarks 95
3.6.2 Synthesis 96

3.7 References 102

CHAPTER 4. CATALYTIC STUDIES 103

4.1 Introduction 103

4.2 Rhodium catalysed asymmetric Hydrogenations with polystyrene based ligands 104

4.3 Rhodium catalysed asymmetric Hydrogenations with JandaJel™ based ligands 104
4.3.1 Synthesis of enamides 105
4.3.2 Complex formation with rhodium 106
4.3.3 Asymmetric hydrogenation of substrates B and C 108
4.3.4 Asymmetric hydrogenation of enamides D, E and F 109

4.4 Conclusions and outlook 110

4.5 Experimental 110
4.5.1 General remarks 110
4.5.2 Synthesis 111

4.6 References 115

Declarations

1. Candidate's declarations:

I, Michiel Christiaan Samuels, hereby certify that this thesis, which is approximately 32.000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in August 2009 and as a candidate for the degree of Doctorate of Philosophy in August 2009; the higher study for which this is a record was carried out in the University of St Andrews between 2009 and 2013.

Signature of candidate Date

2. Supervisor's declarations:

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of Doctorate of Philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Signature of supervisor Date

3. Permission for electronic publication:

In submitting this thesis to the University of St Andrews I understand that I am giving permission for it to be made available for use in accordance with the regulations of the University Library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and the abstract will be published, and that a copy of the work may be made and supplied to any bona fide library or research worker, that my thesis will be electronically accessible for personal or research use unless exempt by award of an embargo as requested below, and that the library has the right to migrate my thesis into new electronic forms as required to ensure continued access to the thesis. I have obtained any third-party copyright permissions that may be required in order to allow such access and migration, or have requested the appropriate embargo below.

The following is an agreed request by candidate and supervisor regarding the electronic publication of this thesis:

Access to all of printed copy but embargo of all of electronic publication of thesis for a period of two years on the following ground(s):

Publication would preclude future publication.

Date

Signature of candidate Signature of supervisor

Dedication

To my mother; Mrs. Brigitte Visser
and to my partner; Miss Katie Drummond

Thank you both for your unwavering support,
without you this work would not be completed.

Acknowledgements

I would like to thank Professor Paul Kamer for the opportunity he has given me to do my PhD research in his group and his ongoing support. Thanks also to Dr. Arnald Grabulosa for introducing me to the world of *P*-stereogenic ligands and helping me greatly during my internship. I should not forget the members of the PCJK-group, past and present, who have all helped me in the lab; specifically thanks to Dr. Wouter Laan and Dr. Jason Gillespie for all their wisdom and mental support.

Lorenz Obrecht, Phil Nejman, Dr. Ruben Duque, Dr. Marc Fürst thanks for all the beer & burgers. Dr. Tina Konrad and Melanja Smith for the good games of badminton played. Frank Heutz, good luck continuing my work and hopefully more wonderful results will follow!

And last but definitely not the least, I owe my deepest gratitude to my family and to my fiancée, Katie Drummond, for supporting me during the most stressful times and for keeping faith in me and my work.

Abstract

Catalysis plays a key role in chemical conversions by making them faster and more selective. Despite its widespread use and decades of academic and industrial research, limited catalyst selectivity and stability still call for major improvements in catalyst performance to meet the demands of a sustainable society. Phosphine ligands are ubiquitous in transition metal chemistry and lead to extremely reactive and versatile homogeneous catalysts. Fast development of tailor-made catalysts and catalyst recovery are key issues in (asymmetric) homogeneous catalysis. Therefore libraries of ligands have to be synthesised and screened in an efficient way, which could be facilitated by Solid Phase Synthesis (SPS). Currently, most polymer bound ligands are anchored to the support after the synthesis in solution. However, the main advantages of synthesising the ligands directly on the polymeric support are not only easy catalyst recycling and product separation, but also the ease of purification during the synthesis steps, namely by simple washing and filtration. The use of SPS is very efficient for high throughput synthesis and screening of ligand libraries, however applications of SPS towards libraries of phosphorus ligands are rare, because the synthetic methodologies are still lacking.

Here we present the development of methodologies towards novel immobilised bis(phosphine) ligands synthesised on polystyrene and *J*anda*J*el™ resin. By performing the synthesis steps on a solid support, the advantages of SPS are fully utilised. Successful routes have been developed towards immobilised secondary phosphine-boranes, which were versatile synthons to prepare a variety of new polymer-supported (*C*-chiral) bis(phosphine) ligands. These ligands were then tested for their catalytic activity in rhodium catalysed hydrogenation reactions.

Abbreviations

°C	degrees Celsius
(–)-sp	(–)-sparteine
Ar	aromatic
BDPP	2,4-bis(diphenylphosphino)pentane
BINAP	bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BuLi	butyl lithium
COD	cyclooctadiene
Cp	cyclopentene
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	dichloroethane
DiBAL-H	diisobutylaluminium hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DVB	divinylbenzene
ee	enantiomeric excess
Et	ethyl
Et_2O	diethylether
FID	free induction decay
Fmoc	fluorenylmethyloxycarbonyl
g	grams
GC	gas chromatography
h	hour
HPLC	high-performance liquid chromatography
i-Pr	*iso*-propyl
IR	infra-red
J	coupling constant meassured in Hertz
JJ	*J*anda*J*el™ resin
LDA	lithium diisopropylamide
M	moles per litre
m/z	mass per unit charge
mCPBA	*meta*-chloroperoxybenzoic acid

Me	methyl
MeCN	acetonitrile
MeOH	methanol
mesyl	methane sulfonyl
MF	Merriefield resin
mg	milligrams
μg	micrograms
MHz	mega Hertz
min	minutes
mL	millilitres
μL	microlitre
mmol	millimoles
μmol	micromoles
mol	moles
MW	molecular weight
NMR	nuclear magnetic resonance
PEG	polyethyleneglycol
Ph	phenyl
pK_a	acid dissociation constant
ppm	parts per million
PS	Polystyrene resin
PTHF	polytetrahydrofuran
rt	room temperature
SPS	solid phase synthesis
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TAMA	*N*-methylanilinium trifluoroacetate
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
TG	TentaGel™ resin
THF	tetrahydrofuran
Vitride	sodium bis(2-methoxyethoxy)aluminiumhydride
ν	wavenumber

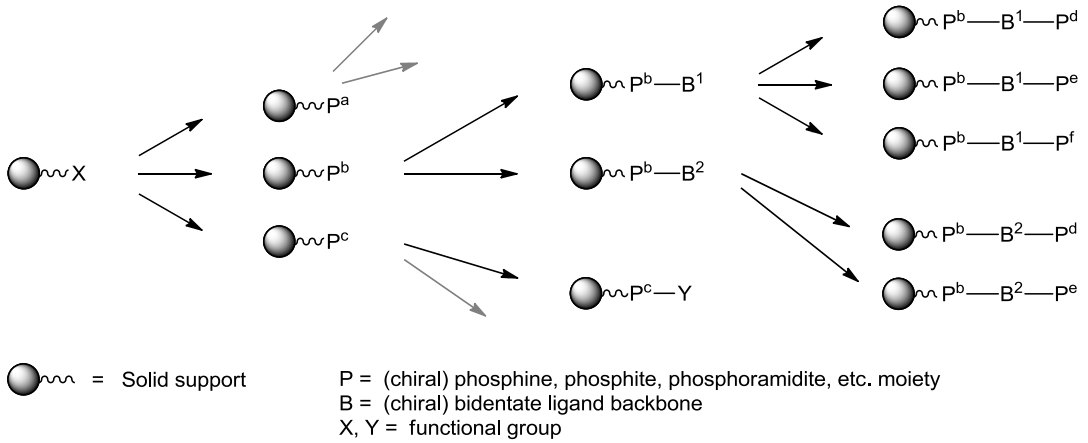
Chapter 1. Solid Phase Synthesis of phosphorus ligands

1.1 Introduction[1]

Homogeneous catalysis plays an increasingly important role in chemical synthesis, both in the production of fine-chemicals and in the bulk industry.[2] Notwithstanding its huge success, there is still a pressing need for novel highly active, selective, stable and reusable catalysts. By far the most important and widespread ligands for (asymmetric) transition-metal catalysis are (chiral) phosphorus based ligands.[2] The electronic and steric properties of these ligands often have a pronounced influence on the activity, stability and selectivity of a catalyst.[3] Consequently ligand design has evolved as a powerful tool in the development of superior catalysts. Despite considerable progress in the last few decades it is often not possible to rationally design ligands and thus the development of new catalysts often relies on 'trial and error'. This in turn necessitates the synthesis and screening of large families of ligands,[4] but due to the reactivity of phosphorus compounds, *e.g.* the moisture sensitivity of phosphites, this can be a laborious and time consuming process.

One way to speed up this process can be the application of Solid Phase Synthesis (SPS). Originally developed for the synthesis of peptides,[5] SPS is based on the covalent attachment of a reactive functionality onto a polymeric support, which can also facilitate a combinatorial approach. The formed immobilised functionality can then serve as the starting point for a sequence of reactions, leading to the desired supported compound. The primary advantage of the solid phase approach is the ease of purification, as the support can be separated from the reaction mixture by simple filtration or decantation. Consequently the use of large excesses of reagents, which can be practical as well as beneficial for the yield, does not complicate the purification of the ligands. Furthermore, the reagents can be neutralised after the filtration step, which may be convenient if reactive reagents like organometallic compounds are used, but can be essential if supported compounds with reactivities similar to those of the reagents are formed. Moreover, as a result of the immobilisation on the support, inter-molecular reactions can be reduced and immobilisation can stabilize reactive intermediates and thus reduce the formation of side-products.

Due to these features, SPS facilitates the use of combinatorial approaches for the synthesis of large libraries of compounds in a fast and efficient manner. When applied to the synthesis of ligands, these combinatorial techniques can facilitate the formation of ligand families and thus SPS can be a powerful tool in the development of novel catalysts. Scheme 1.1 schematically depicts the general approach of the solid phase synthesis of phosphorus based ligands. Reaction of a functionality on the support with a suitable phosphorus reagent allows the loading of this reagent on the support. Subsequently, this intermediate can be converted to the desired supported ligand in a sequence of reactions. Similar to the synthesis of non-supported ligands, structural diversity can be accomplished by using various reagents in one or more phases of the synthesis, allowing the modular synthesis of mono- and bidentate ligands with various electronic, steric, and stereo-chemical properties.



Scheme 1.1. Application of Solid Phase Synthesis for the combinatorial synthesis of ligands

Supported ligands have proven their efficiency in several transition metal catalysed reactions.[6] One of the main disadvantages of homogeneous catalysis is the difficult recovery of the catalysts, which prohibits recycling of the valuable metals and ligands and can lead to contamination of the product with toxic transition metals. Consequently, it is no surprise that the development of techniques to separate the catalyst from the reaction mixture has received considerable attention.[7] The use of supported ligands allows the formation of supported catalysts, which can be easily separated from the reaction mixture by a simple filtration procedure and can subsequently be re-used. Good mixing of the catalyst and the reactants can be maintained by the application of supports with excellent swelling properties (*vide infra*). The approach thus combines the advantages of homogeneous catalysis such as good control over catalyst properties via

ligand design and with the easy catalyst separation and recycling of heterogeneous catalysis.

Despite the advantages of SPS, examples of the combinatorial synthesis of families of phosphorus ligands by multi-step solid phase reactions are still relatively scarce, which can be attributed mainly to the lack of efficient synthetic methodologies.[8] Consequently, the majority of the reviews on polymer supported ligands discuss the application of this class of ligands in catalysis,[4g,6c,6f,6i-k,7b] while the synthetic approaches have received less attention. Outlined below are some practical issues associated with SPS, followed by an overview of the various synthetic methodologies developed to generate libraries of supported-ligands; without claiming to discuss all polymer-bound ligands that have appeared in literature.

Since most of the standard purification techniques such as crystallisation or column chromatography cannot be used, the formation of supported side products should be suppressed necessitating that all synthetic steps are optimised to proceed quantitatively. In general, conditions used for the synthesis of non-supported ligands cannot be simply applied to the synthesis of the supported analogues. Frequently the type of solvent and the applied reaction temperatures need to be adjusted to achieve good conversions, which often can be attributed to the specific swelling properties of the support (*vide infra*). Furthermore, although organometallic chemistry can often be successfully applied to SPS,[9] the high reactivity of some reagents may prohibit their use in combination with a support, necessitating the development of alternative routes.

Solid supports (often referred to as resins) have been initially developed for, and are still extensively used in, DNA and peptide synthesis but SPS has increasingly been applied to other fields of chemistry and consequently a large variety of supports is (commercially) available.[6j] Linear non-cross-linked polystyrenes (PS, Figure 1.1) are soluble in most commonly used organic solvents, but precipitate in protic solvents like water and methanol and are therefore classified as *soluble* supports. If styrene is co-polymerised with divinylbenzene (DVB), cross-linked polymers are formed (PS-DVB, Figure 1.1), which are insoluble in all solvents and therefore are referred to as *insoluble* supports. For these resins, good swelling in the reaction medium is of crucial importance as this impacts the accessibility of the functional groups and consequently the reaction rates and yields. For PS-DVB the swelling is generally very good in THF,

toluene, dioxane and CH_2Cl_2, while the resin contracts in solvents like diethyl ether, methanol and water. This difference in swelling is being utilised in the purification of the support, by alternating washing cycles between solvents in which the support swells and those in which it contracts. One of the most commonly used supports is Merrifield resin, a copolymer of styrene, chloromethylstyrene and DVB, with a chloromethyl reactivity (X = CH_2Cl, Figure 1.1).[5]

The type and percentage of cross-linking, and the type and loading of the functional group determines the swelling properties of the support as well.[6j] For instance, *J*anda*J*el™[6d,e,10] is a support based on a flexible chemically robust polytetrahydrofuran cross-linker, resulting in a polymer with excellent swelling properties in a broad range of solvents. The presence of polyethyleneglycol (PEG) linkers on the polystyrene backbone, as for instance in the TentaGel™ resins (Figure 1.1),[11] also enhances the swelling properties and makes it almost solvent independent. These PEG based linkers can however react with strong bases and organometallic reagents, resulting in "PEG-leakage".[10] Moreover, due to the higher molecular weight of the base structure of these types of support, the loading of functional groups (expressed as mmol per gram resin) can drop considerably in comparison to PS-DVB (0.96 mmol/g for *J*anda*J*el™-Cl vs. 2.17 mmol/g for PS-DVB-Br). This drop in loading is most significant with TentaGel™ (0.24 mmol/g for TentaGel™-OH), due to its long PEG linkers.

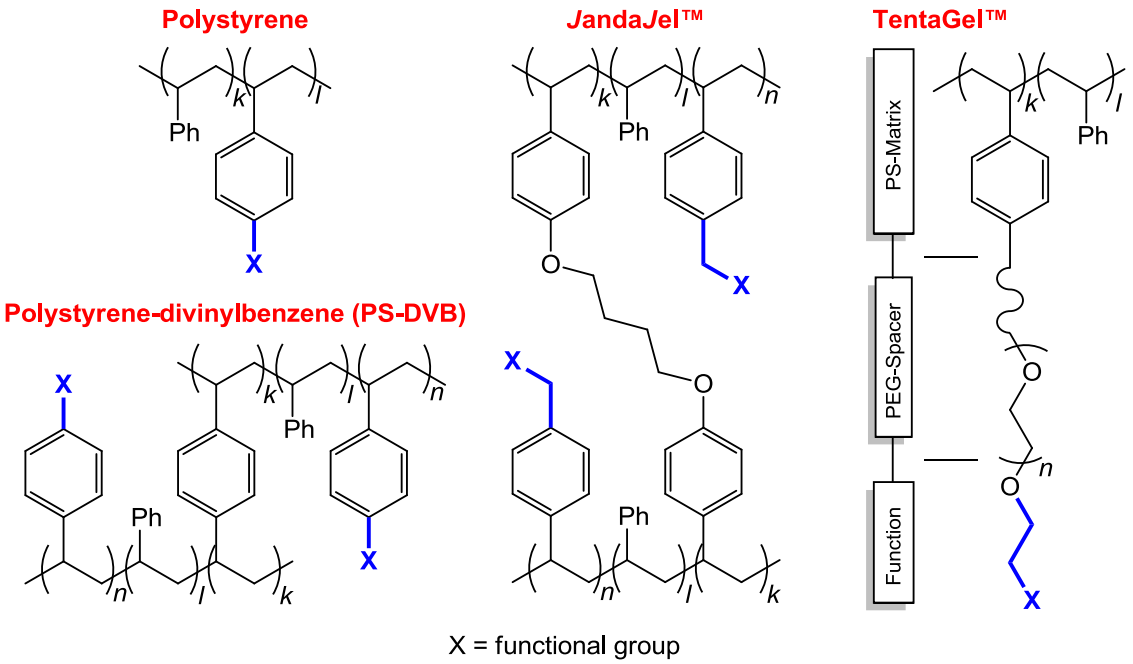


Figure 1.1. General structures of several polystyrene based supports

In addition to commercially available supports, straightforward (co-)polymerisation processes allow the creation of 'custom made' supports with relative ease. Jana *et al.*[12] for instance co-polymerised styrene with a dihydroxy functionalised styrene, in order to synthesize polymer-bound bidentate phosphites, for which the dihydroxy moiety serves as the backbone of the ligand. Bergbreiter *et al.*[13] developed soluble polymeric supports of which the solubility was inversely temperature dependent; *i.e.* they were highly soluble at low temperatures, but insoluble at room temperature. This enabled tuning of the hydrogenation activity of a supported rhodium catalyst by altering the temperature of the reaction mixture. Takaishi *et al.*[14] tuned the properties of polymeric bis-diphenylphosphine ligands by application of hydroxyethyl methacrylate in the co-polymerisation process to create an insoluble resin which, unlike typical PS-based supports, has good swelling properties in alcohol and other polar solvents.

An important requirement for the application of a specific polymer as a support is the stability of both the ligand and the intermediates towards intermolecular side reactions. Several factors influence the occurrence of these; the nature of the ligand, the applied reaction conditions such as solvent and temperature, and the loading and flexibility of the support. Insoluble supports with a high degree of cross-linking may provide more site-isolation than high loading soluble or flexible supports and consequently the latter may be unsuitable for some types of ligands and/or reactions. For instance, aryl exchange in high loading polymer-bound triphenyl phosphites, can result in non-supported phosphites and polymers in which the phosphite moiety acts as a cross-linker. This not only leads to ligand degradation, but can also yield polymers with reduced swelling properties and can result in metal-leaching during catalysis. Replacement of the phenol substituents with a chelating bis-phenoxy group can prevent this reaction.[15]

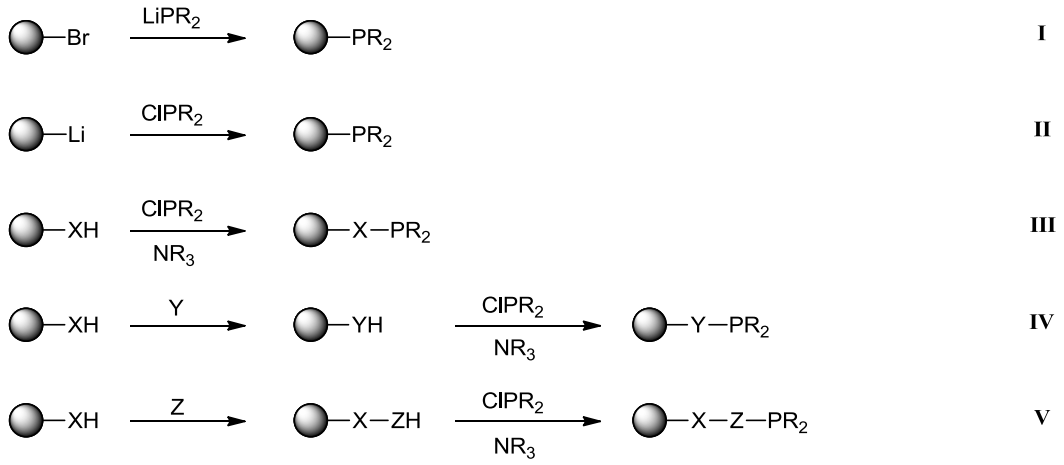
The identification of the supported compounds is often difficult, as standard analysis techniques such as NMR and mass spectrometry are commonly unsuitable. However, supports with excellent swelling properties may allow characterisation by ^{13}C and ^{1}H NMR spectrometry. Conversely, gel-phase ^{31}P NMR spectroscopy can be used in most cases to monitor the reaction progress, to identify the phosphorus species present on the support and to determine the purity of the product.[16] These measurements can be performed in common NMR tubes, as long as the resin is well swollen and is brought into the centre of the probe within the spectrometer, making solvents on which the

supports floats (like dichloromethane for PS-DVB) unsuitable. Generally the resonances of immobilised compounds have broader line widths than those of non-supported analogues, but the broadening of the signals will depend strongly on the swelling of the used support. Elemental analysis can be used to determine the loading of phosphorus on the support and thus to determine the yield of a transformation.

1.2 Insoluble supports in ligand synthesis

The majority of immobilised ligands are synthesised by a single reaction between a support bearing a suitable reactive group and a phosphorus reagent (Scheme 1.2).[6g,8b,c,8h,17] The commercially available polystyrene bound triphenylphosphines (PS-PPh_2) are among the most commonly applied supported ligands and can be formed via several routes. In 1971, Camps *et al*.[18] reported the first preparation by co-polymerisation of styrene with *p*-styryldiphenylphosphine (3:1) and 2% divinylbenzene as the cross-linking agent, but a more common technique is synthesis by the reaction of bromopolystyrene with lithium diphenylphosphide (path **I**)[19] or by lithiation of bromopolystyrene followed by addition of chlorodiphenylphosphine (path **II**).[20] The high reactivity of the organometallic reagents used can however lead to side reactions. For instance, it was observed that not all bromo groups were cleanly converted to the phosphine moiety, as some were simply reduced,[18] while unwanted attack of alkyllithium on the C=C bonds of cross-linked polystyrene can lead to contamination and reduced swelling properties.[6f] Structural diversity can be achieved in routes **I** & **II** by application of structurally different phosphorus reagents. For instance, Le Drain and co-workers[17c,21] synthesised series of eight supported diarylphosphines and six supported *tert*-butylarylphosphines by the straightforward reaction of various lithium phosphides ($LiPAr_2$ and LiP(*t*-Bu)Ar respectively; Ar = Ph, Tolyl, Naphthyl, etc.) with Merrifield resin in THF at room temperature. Although 99% of the chlorine atoms were consumed in the reaction, only ~ 80% of the theoretical maximum of phosphino groups was introduced on the resin. The reaction of lithium *tert*-butylphenylphosphide with *p*-bromopolystyrene proved considerably less efficient, as 98% of the bromine groups were consumed, but only 25% was converted to a phosphino moiety.[17c]

Immobilised phosphoramidites and phosphites are generally prepared by reaction of supports containing, amino- or hydroxy- functionalities with chlorophosphorus compounds in the presence of a tertiary amine as a base (path **III**). Similar to the supported phosphines, structurally diverse ligands can be prepared by the application of different phosphorus reagents.



X = O, NH, NR Y, Z = functional group NR_3 = NEt_3, *i*-Pr_2NEt, etc.

Scheme 1.2. Commonly applied routes towards supported phosphorus ligands

An alternative approach to create families of ligands is by modifying the steric and electronic properties of the functional group on the support (path **IV** and **V**, Scheme 1.2). The group of Waldmann[8c] for example, created a library of seventy-eight phosphoramidites by applying a modular approach based on varying three functionalities (Figure 1.2, **A**, **B** and **C**). The diversity of the ligands was mainly based on the use of twenty-eight different R^1-groups (block **B**), which were systematically varied and included aliphatic and aromatic acyl groups, sulfonamides, urea and thiourea groups, and phosphorus substituents. Moreover, by changes in the amino functionality on the support (block **A**, X = C, N, O, S) and by the use of four BINOL-derivatives (block **C**, R^2 = H, Me, Ph, Br), the library of ligands was extended even further. Portnoy and co-workers[8i] synthesised a variety of amino functionalised supports to create a library of forty borane protected α-aminophosphines (Figure 1.2, top right). Variations were made by connecting different linkers at the *ortho*-, *meta*- and *para*-position and twelve different electron-rich, electron-poor and sterically crowded aromatic amines. Additionally, with the use of various aminoalcohol linkers, the formation of a family of bidentate phosphinite ligands was achieved (Figure 1.2, bottom right, **I**). Moreover,

chlorodehydroxylation of the same aminoalcohol linkers allowed the synthesis of a series of amino-phosphine ligands (Figure 1.2, bottom right, **II**).[8d]

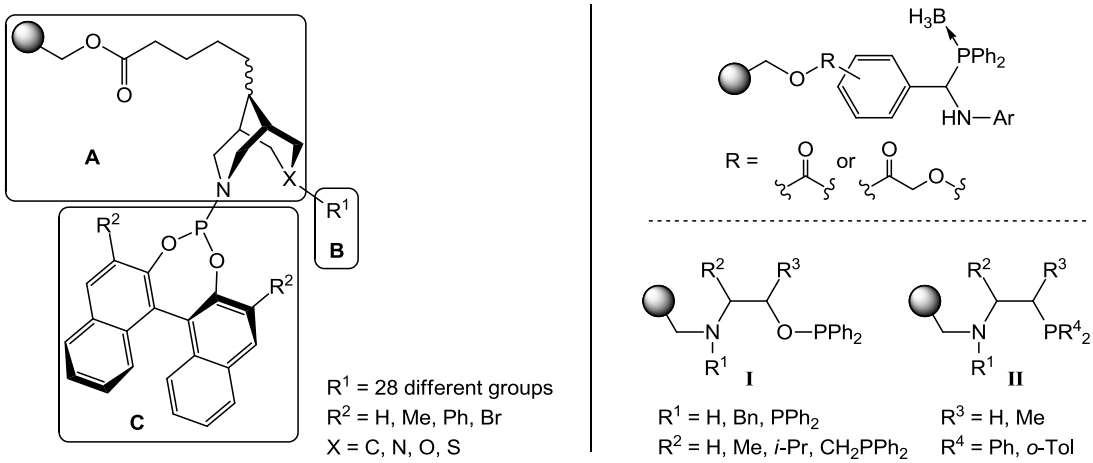


Figure 1.2. General structure of ligands synthesised by Waldmann (left) and Portnoy (right)

Similarly, the groups of Gilbertson[8a,22] and of Meldal,[8e,23] created libraries of immobilised chiral ligands using a series of phosphine-containing amino acids in peptide synthesis (Figure 1.3). By changing the peptide sequence, they varied the incorporation of the phosphine-containing amino acids in the peptide chains linking the phosphorus to the support. Recently, Laan *et al.*[24] have reviewed the synthesis and use of these phosphine containing peptides in more detail.

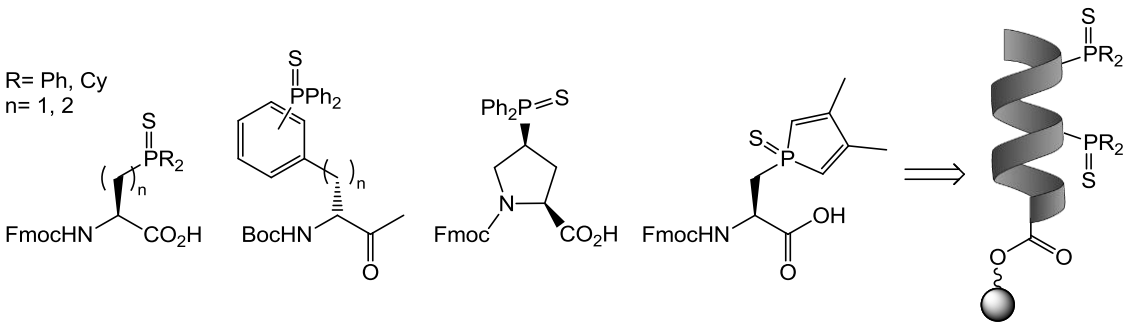


Figure 1.3. Phosphine-containing amino acids in peptide synthesis

To prepare a library of fifteen immobilised (chiral) monodentate ligands with various electronic and steric properties, Kamer and co-workers[8h,25] varied both the functional group on the (commercially) available polystyrene supports, as well as the chlorophosphorus reagent (Figure 1.4). The main advantage of SPS is the ease of purification, which allows the use of excesses of reagents and/or reagents containing impurities. Kamer *et al.*[8h] utilised this feature in the synthesis of the supported

phosphites and phosphoramidites (Figure 1.4), as the use of an excess of partially hydrolyzed (~30%) chlorophosphites did not compromise the work-up or the purity of the immobilised ligand. The synthesis of chlorophosphites from phenols and PCl_3 frequently leads to mixtures containing additional species, such as dichlorophosphites. The authors showed that the presence of a phosphite does not hinder the reaction between a hydroxy-functionalised polystyrene and a chlorophosphite and by pushing the equilibrium toward the formation of a mixture of chlorophosphite and phosphite, the formation of dichlorophosphite, and thus of resin-bound byproducts, could be prevented effectively. The importance of the purity of the support was also discussed. Reaction of the *N*-methylaminomethylated and aminomethylated polystyrene supports with chlorophosphites did not only yield the expected supported phosphoramidites, but also a second species. ^{31}P NMR spectroscopy suggested that alcohol functionalities were also present on the resins, leading to supported phosphites. Since these were covalently bound to the polymer, they could not be separated from the targeted supported phosphoramidites.

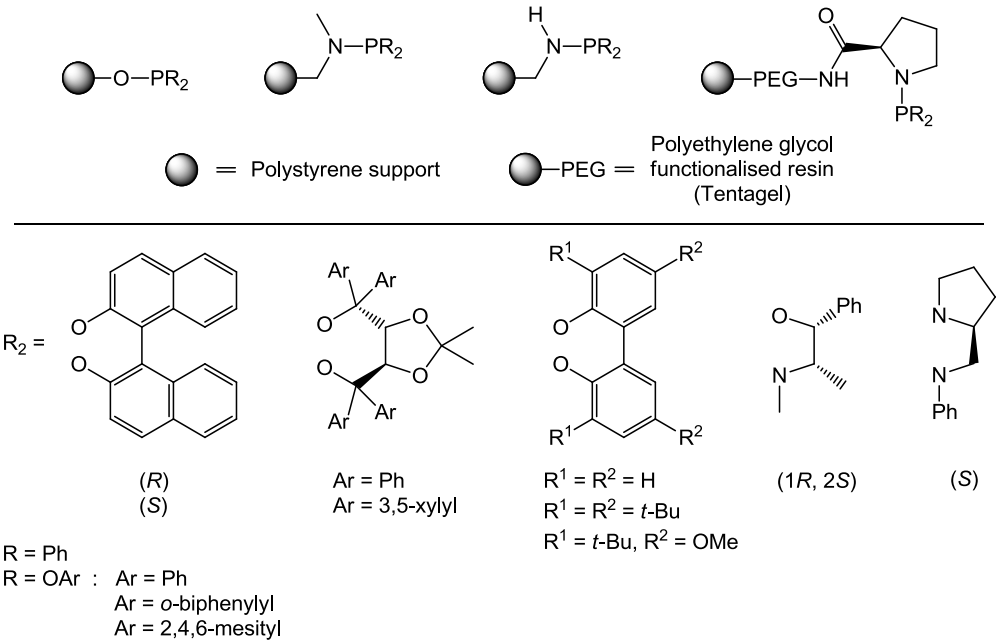


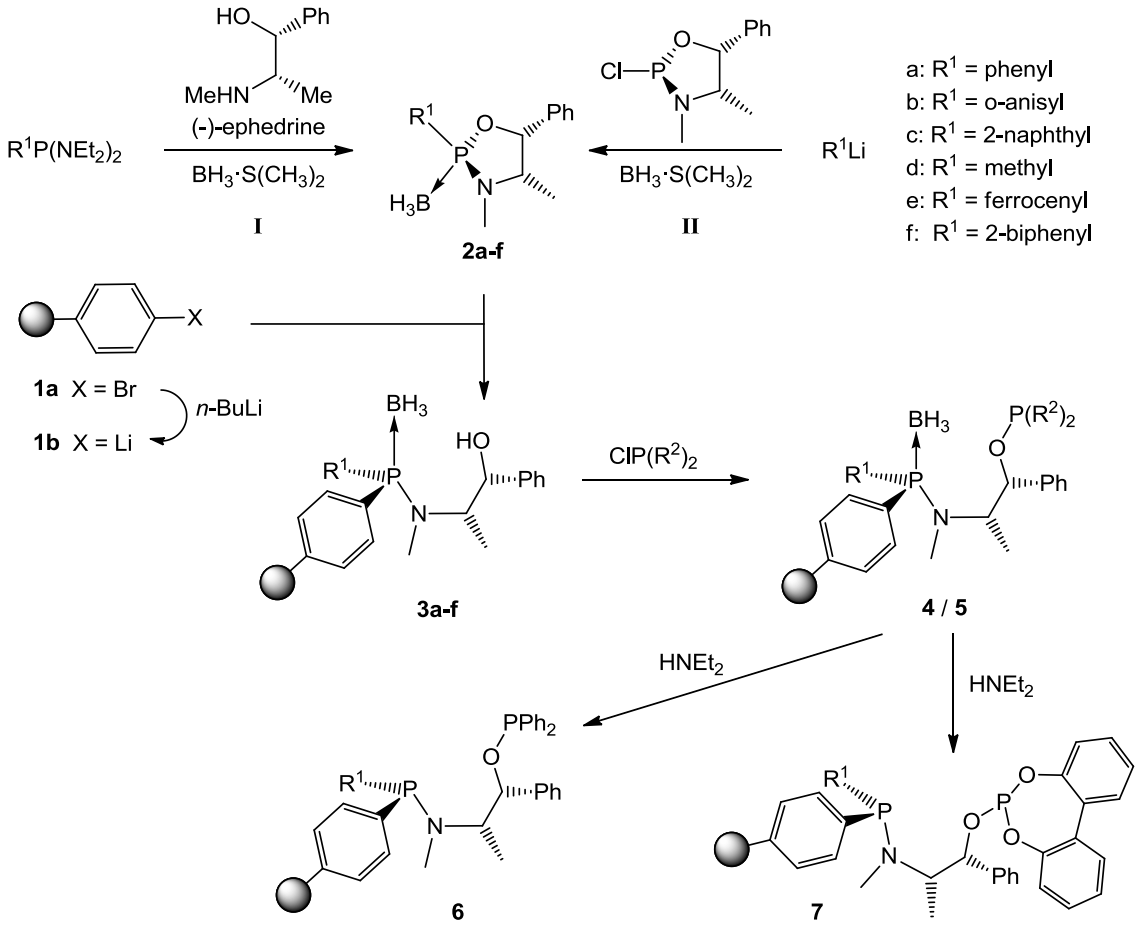
Figure 1.4. Supported monodentate ligands synthesised by Kamer *et al.*

In the routes shown in Scheme 1.2, the structural diversity is created on the phosphorus *prior* to the coupling with the support or on the support *prior* to the coupling with the phosphorus reagent. Examples in which structurally diverse ligands are created from a single polymer supported phosphorus containing precursor ("bottom

up" approach) are considerably more rare. This is surprising, as by synthesizing the ligand on the resin from the start of the reaction sequence, the advantages of SPS can be fully exploited during all steps of the sequence.

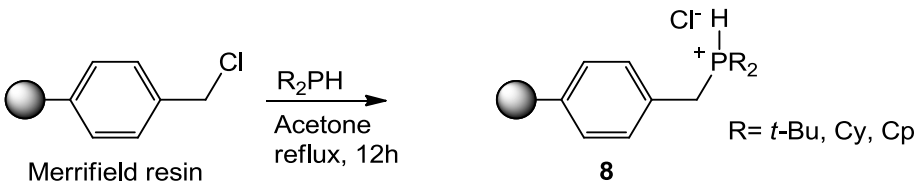
Polystyrene bound chlorophosphorus reagents allow maximum structural diversity, as they can be reacted with large variety of reagents. The group of Kamer[8h] showed that these can be easily accessed using relative simple commercially available reagents and supports and that they are excellent starting materials for the synthesis of supported ligands (Figure 1.4).

The synthesis of supported chiral phosphorus ligands has received considerable attention, but the chirality in the majority of reported ligands originates from a BINOL-moiety. Kamer and co-workers[8g] reported a rare example of the SPS of a family of *P*-stereogenic ligands. Adjusting a method developed by Jugé and co-workers[26] to a polystyrene support enabled the parallel synthesis of supported *P*-stereogenic bidentate ligands. By reacting *para*-lithiopolystyrene **1b**[20] with oxazaphospholidine boranes **2a-f**, six different *P*-stereogenic immobilised aminophosphine boranes (**3a-f**) were synthesised (Scheme 1.3). Analysis by gel-phase ^{31}P NMR showed that these chiral intermediates were formed in excellent yields and purities and with high diastereoselectivities (diastereomeric ratios > 96:4). More precisely, the reaction of the oxazaphospholidine boranes (**2a-f**) with the support proceeds with stereo-selectivities which are comparable to those of the liquid phase reactions. This last fact is particularly significant, as supported chiral ligands can only be applied in the development of efficient enantioselective catalysts if the optical purity of the formed ligands is not compromised by the application of SPS. In fact, the optical purity should ideally be superior to that obtained with solution-phase routes, as further enrichment using, for example, crystallisation is not possible with SPS. The hydroxy moiety in aminophosphines **3a-f** allows the straightforward synthesis of ten bidentate aminophosphine-phosphinite (**6**) and aminophosphine-phosphite (**7**) ligands, by reaction with the appropriate chlorophosphorus reagents, followed by removal of the borane with $HNEt_2$. All ligands were obtained with a (stereo-) chemical purity of more than 92%.



Scheme 1.3. Immobilised Aminophosphine–Phosphinite and Aminophosphine–Phosphite ligands

Recently, Ullah *et al.*[27] reported the synthesis of polymer-supported tri-alkyl phosphine ligands **8** obtained in one step by refluxing Merrifield resin in acetone, in the presence of secondary phosphines for 12 hours (Scheme 1.4). The immobilised phosphines were obtained in quantitative yields after the removal of solvent and reagent, by drying the resin at 80 °C *in vacuo* followed by washing the resin with Et_2O.



Scheme 1.4. Immobilised tri-alky phosphine ligands

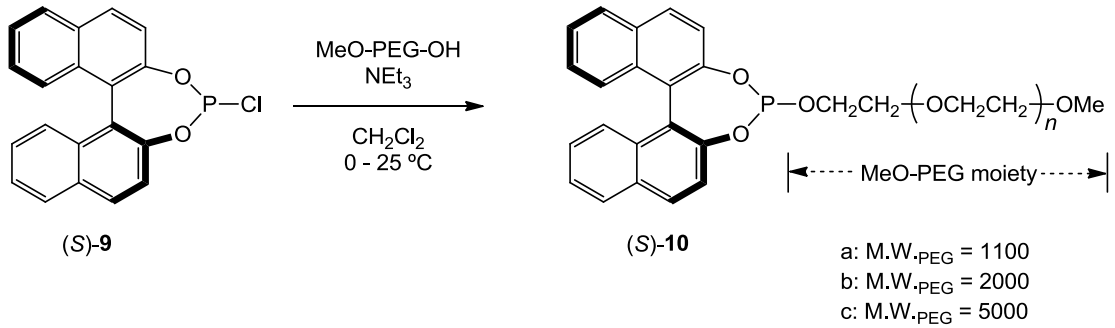
These immobilised ligands were doped with palladium (ratio Pd:L of 1:2) and used in Pd-catalysed Suzuki–Miyaura cross coupling reactions of aryl halides with phenylboronic acids in dioxane obtaining reasonable to high yields (78-94%). They

investigated the reusability of the immobilised catalysts and reported that initially the re-use proved problematic with poor conversions. However, when the immobilised catalysts were washed with degassed water and dry Et_2O before re-use, the results improved dramatically. One batch of catalyst could be re-used four times with only a relatively small drop in efficiency (96 to 80% after four cycles). The authors hypothesise that the aqueous wash is needed to remove inorganic salts formed during the catalysis which were occluding the resin.

1.3 Soluble polymeric supports

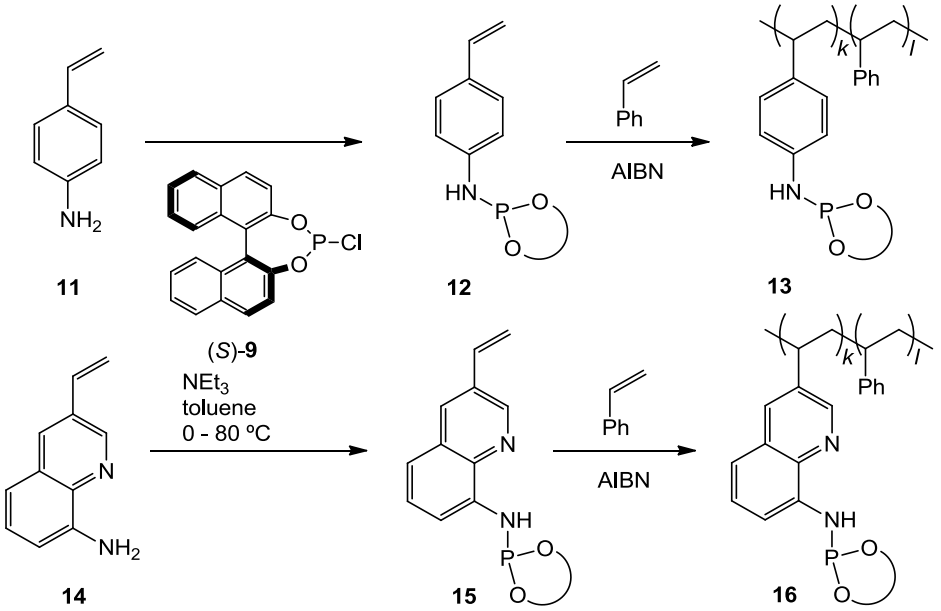
Soluble polymers have received considerable attention as supports for immobilised ligands and catalysts[28] and a number of reviews on this subject have appeared in recent years.[6e,6i,29] They are attractive alternatives to insoluble polymers, as they do not possess some of the limitations associated with the insolubility of the support (*vide supra*). A key difference is that soluble supports allow the synthesis to be carried out under homogeneous conditions, while the phase separation and the associated purification of the immobilised ligand can occur after the reaction. Consequently, the reaction conditions used for the synthesis of non-supported ligands can often be applied to the synthesis of soluble polymer-bound analogues, as long as the support is inert to the applied reagents. However, other restrictions of synthesis on solid support still apply; the reactions must be complete because polymer-bound side products cannot be removed. The solubility of the polymers is highly dependent on the nature of the polymer and the type of solvent, and this property can be used to separate and purify the soluble ligand. Several separation techniques have been developed, but solid/liquid and liquid/liquid techniques are the most commonly applied. An accessible approach is the utilisation of polyethylene glycol (PEG) as support, as it is soluble in water and in common solvents such as toluene, DMF and acetonitrile, but it precipitates in diethyl ether and hexane and this allows the simple separation of the PEG from the reaction mixture by the addition of suitable solvent to precipitate the polymer, followed by filtration.[30] A variety of soluble polymers with a wide range of properties have been developed and several are commercially available. The reported phosphorus ligands are mainly supported di- or triphenylphosphines and BINOL-derived phosphites which are generally prepared by a simple single step reaction between a chlorophosphorus reagent

and the polymer.[6e,6i,29d] For instance, the group of Zheng[29e] reported the synthesis of MeOPEG-monophosphites (**10**) by treatment of the BINOL-based chlorophosphite **9** with an equimolar amount of commercially available PEG-monomethyl ether (MeOPEG-OH) in CH_2Cl_2 at 0 - 25 °C, in the presence of triethylamine (Scheme 1.5). The soluble ligand was separated from the formed ammonium salt (NEt_3HCl) by filtration. Subsequent addition of diethyl ether to the filtrate resulted in precipitation of the polymer. Whittall *et al.*[17a] synthesised several related phosphites by reacting the commercially available PS-PEG_{600}-OH, TentaGel™-OH, MeO-PEG_{2000}-OH, MeO-PEG_{5000}-OH and HO-PEG_{4600}-OH supports with chlorophosphite **9**. The use of trioctylamine as the base turned out to be essential for the purification of the ligands **10**, as trioctylamine hydrochloride is soluble in diethyl ether and therefore can be separated from the ligands by selective precipitation of the latter.



Scheme 1.5. Synthesis of chiral MeO-PEG-monophosphites

Doherty *et al.*[31] investigated an alternative approach to synthesize soluble polymer-bound ligands (Scheme 1.6). Instead of the treatment of a polymer containing a suitable functionality with a phosphorus reagent, the supported ligand **13** was formed by co-polymerisation of a phosphoramidite functionalised monomer **12** with styrene. The solubility properties of the polymer allowed a simple purification procedure (precipitation and washing), yielding the ligand in high purity. It can be noted that the properties of the resulting polymer can be tuned by varying the type and the relative amounts of the monomers used in the co-polymerisation, while cross-linking agents can be applied to create related insoluble supports.[18] A related soluble polymer-bound ligand was formed by co-polymerizing a quinoline based phosphoramidite **15** with styrene and both polymers displayed different activities and enantioselectivities in rhodium catalysed asymmetric hydrogenations.



Scheme 1.6. Supported phosphoramidites by co-polymerisation

1.4 Supported ligands in catalysis

The application of polymer supported ligands in catalysis has been extensively reviewed,[4g,6c,6f,6i-k,7b] and as a result only a few representative examples will be discussed here. The key feature of supported catalysts is the ability to recover (by a simple filtration procedure) and re-use them after a catalytic reaction.[6] This can reduce the presence of metal contaminants in the product and allows the recycling of valuable metals and ligands. Polymer-bound ligands are particularly attractive when the excellent swelling properties of the support allow good mixing of the catalyst and the reactants. The fact that a PEG-based *soluble* polymer supported chiral monodentate phosphite developed by Whittall *et al.*[17a] yields one of the most active rhodium catalyst for the asymmetric hydrogenation of dimethyl itaconate demonstrates this. It is however more commonly encountered that supported catalysts are less active and selective than the non-supported analogues. The polystyrene bound BINOL-based phosphite synthesised by Swennenhuis *et al.*[25] (Figure 1.4) for instance, induced 11 % enantiomeric excess (*ee*) in the rhodium catalysed hydrogenation of dimethyl itaconate, which is in sharp contrast to the 97 % *ee* observed for the non-supported analogue. Despite this commonly encountered disadvantage, polymer-bound ligands can speed up the development of novel catalysts, as SPS allows the rapid synthesis of ligand libraries.[8c,d,8g,8j,21b,32] Gilbertson and co-workers[8j] synthesised a family of ninety-six

supported peptide-based phosphine ligands and tested these in a palladium catalysed asymmetric allylic alkylation reaction. While seventy-seven members of the library gave ≥ 60 % *ee*, an 80% *ee* was observed for only one ligand, showing that in order to find highly efficient catalysts, it is often essential to screen large libraries of ligands, which can be efficiently created by SPS. In addition, screening libraries of supported ligands can provide essential information about the relationships between ligand structure and catalyst performance. Applying the family of ten supported chiral bidentate ligands developed by den Heeten *et al.*[8g] (Scheme 1.3) in the rhodium catalysed hydrogenation of methyl α-acetamidocinnamate, revealed that the nature of the R^1- and R^2-moieties have a decisive influence on the enantioselectivity and the absolute chirality of the product. Application of the biphenol based aminophosphine-phosphite ligands lead predominantly to the *S*-enantiomer, while the aminophosphine-phosphinites lead to the hydrogenation product with the *R* absolute configuration.

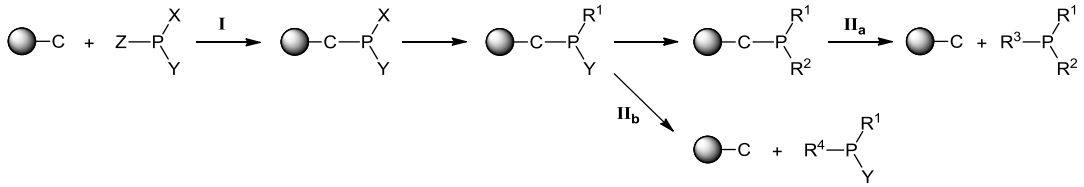
The application of SPS in catalysis research is not restricted to finding efficient supported catalysts. Waldmann and co-workers[8c] showed that the screening of *supported* ligands can be an excellent tool to identify the most efficient *non-supported* ligand. For this purpose a library of seventy-eight polymer-bound phosphoramidites was synthesised by varying the electronic and steric properties of amino functionalised resins. In the enantioselective copper catalysed conjugate addition to enones, the observed *ee* values ranged from 3 to 67 %. A selection of the most efficient supported ligands was synthesised as their soluble non-supported analogues. Application of these homogeneous systems in catalysis revealed that the polymer-bound phosphoramidites mirrored the performance of the analogues ligands in solution. It can be noted that in numerous studies however, no straightforward correlation between the performances of the supported and non-supported analogues was found, which can most likely be attributed to the specific microenvironment created by the support. For instance, Pittman *et al.*[33] observed higher linear to branched selectivities in the hydroformylation of 1-pentene, catalysed by DVB-cross-linked polymer-attached carbonylhydrotris-(triphenylphosphine)rhodium [$(PS\text{-}PPh_3)_3RhH(CO)$] compared to the non-supported analogue, which was attributed to the locally high ligand-rhodium concentration within the swollen resin.

Related to this is the fact that the type of solvent can have a decisive influence on the catalytic performance of polymer supported catalysts, which often can be attributed to the swelling of the support in the applied reaction medium and thus on the microenvironment of the catalyst.[34] An often encountered problem is that a solvent system, in which the swelling properties of the support are optimal, may not be an ideal solvent for the catalyst. To overcome this, a support should be selected that suits the preferred solvent system of the catalyst and this is particularly important if the goal is to find efficient non-supported catalysts through screening libraries of supported ligands. Gilbertson and Yamada studied the performance of palladium allylic allylation catalysts immobilised on various polymeric supports in several commonly used solvents.[34a] The support/solvent combinations displayed a variety of activities and enantioselectivities and for the support/solvent combinations providing good swelling properties, the observed *ee*'s were comparable to those of the non-supported catalyst in that specific solvent. For the combinations where there is an incompatibility between the solvent and the support, no clear correlation between the performances of the supported and non-supported analogues could be found.

1.5 Solid phase synthesis of non-supported ligands

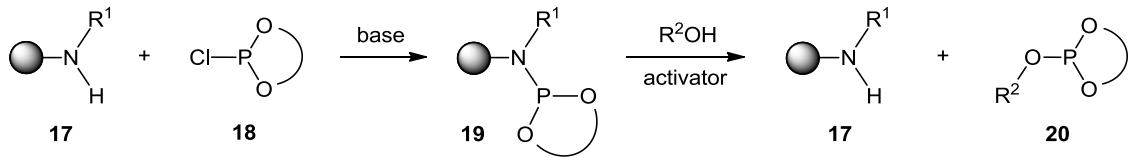
As discussed above, in several catalytic systems the non-supported ligands proved to be superior over their supported analogues, as they yielded more active and selective catalysts. Cleaving the ligands from the support after synthesis is an attractive approach, as it allows utilizing the advantages of solid-phase based synthesis, while yielding non-supported ligands. Surprisingly this methodology has received limited attention, as the majority of supported ligands have been synthesised with the aim to create supported catalysts. The general strategy is based on the use of a functionality (C, Scheme 1.7) that allows loading of phosphorus based reagents on the solid phase (**I**), while it also permits cleavage of the product from the support at a desired stage of the synthetic sequence (**II**). Since analysis of solid supported compounds is not always straightforward, this methodology can assist in the identification of products (**II_a**), as well as intermediates (**II_b**) that are formed during the reactions, as the cleaved compounds can be analysed using standard techniques. A wide variety of linkers, the structural motif which temporarily joins the polymeric support and the ligand, have

been developed, but the suitability of these in a specific synthetic route is highly dependent on the type of reagents and the reaction conditions applied.[35] The linker must allow attachment and cleavage of the phosphorus species under conditions mild enough not to affect the ligand, whilst still tolerating the chemistry involved in the synthesis of the supported ligand. To the best of our knowledge only amine functionalised resins have so far been used in the solid phase synthesis of non-supported phosphorus based ligands. The methodologies exploit the acid lability of P-N bonds, allowing the controlled release of the intermediates or ligands under relatively mild conditions.



Scheme 1.7. Solid phase synthesis of non-supported ligands

Kamer *et al.*[8h] applied phosphoramidites linked to the solid support via an amido functionality as synthetic intermediates for phosphites (Scheme 1.8). Acid-catalysed substitution of the P-N bond of the supported phosphoramidites (**19**) with alcohol, yielded monophosphites (**20**) liberated from the resin (**17**). For this purpose five supported phosphoramidites were formed *in situ*, by reacting amino functionalised resins (**17**) with different chlorophosphites (**18**). A subsequent reaction with various alcohols in the presence of an acid activator allowed the parallel synthesis of a family of twenty (chiral) phosphites (**20**) in high overall yields (82-91 %) and purities (> 97%). The cleavage of the P-N bond re-generates the amine functionalised resin (**17**) and the authors showed that this can be re-used with only a slight drop in yield (88% to 85%) between successive runs.



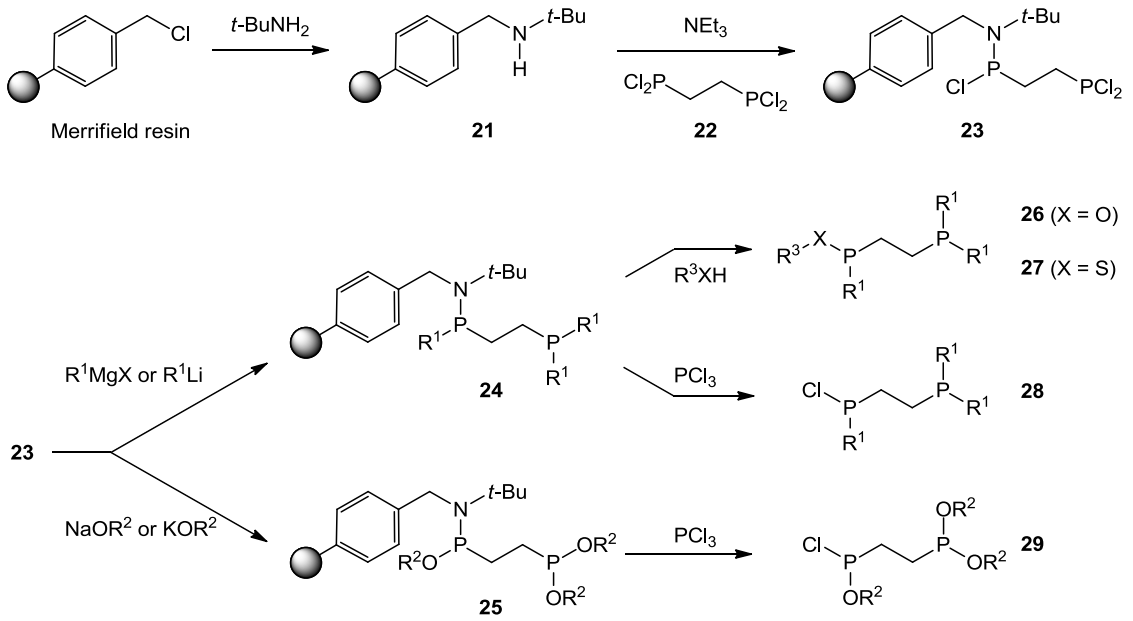
Scheme 1.8. Solid-phase synthesis of phosphites

The leaving group capacity of the amino functionalised resin and the nature of the alcohol and substituents on the phosphorus all influence the efficiency of the cleavage reaction. For instance, bis-aryl phosphites required a good leaving group such as

pyrrolidine as linker, which has a higher basicity (pK_a = 11.3) compared to that of a *N*-methyl-benzylamine moiety (pK_a = 9.7), whereas both linkers could be used for the synthesis of aliphatic TADDOL-based phosphites. Equally important is the acidity of the activator. In the absence of an acid activator, no reaction was observed. With 1*H*-tetrazole, *N*-methyl-imidazolinium trifluoroacetate or pyridinium tetrafluoroborate, the conversion to product was slow or incomplete and the required prolonged reaction times promoted side product formation via oxidation and hydrolysis. *N*-Methylanilinium trifluoroacetate (TAMA) was found to be the most suitable activator, although one equivalent was needed to allow a fast product formation, which necessitates the purification of the phosphite by flash chromatography after cleaving. In the conventional synthetic route, phosphites are synthesised by reaction of a chlorophosphite with an alcohol in the presence of a base, followed by chromatography to purify the ligand. By introducing supported phosphoramidites as intermediates, which are formed from the same chlorophosphites, an advantage over the traditional route is achieved, namely the higher stability of the supported phosphoramidites in comparison to the chlorophosphites. A second advantage is that the supported phosphoramidites can be easily purified and therefore this route does allow the usage of partially hydrolysed chlorophosphites, without complicating the purification of the phosphite.

In the previous approach, two of the three substituents on the phosphorus atom in the non-supported ligand originate from the type of chlorophosphite reagent that is applied in the synthesis of the supported phosphoramidite. The structural diversity of ligands that can be synthesised from one type of supported intermediate is therefore somewhat limited. Li *et al.*[8b] developed an efficient solid phase route that allowed the formation of a large variety of non-supported bidentate ligands, with an immobilised bis(chlorophosphine) as the key intermediate (Scheme 1.9). Reaction of secondary amine functionalised polystyrene support **21**, formed by treating Merrifield resin with an excess of *tert*-butylamine, with the commercially available 2-bis(dichloro-phosphanyl)ethane (**22**) in the presence of triethylamine yielded supported bis(chlorophosphine) **23**. Only one phosphorus atom was linked to the resin and the authors attributed the high selectivity to the steric impediments of the *tert*-butyl group and the use of an excess of **22**. Intermediate **23** allows great structural diversity, as due

to the reactive P-Cl bonds, three of the substituents on the two phosphorus atoms can be introduced by SPS. Polymer-bound **23** can be converted cleanly under mild conditions to intermediates **24** and **25**, by reaction with organomagnesium and organolithium reagents or metal alkoxides, respectively. The inertness of the P-N bond to these reagents ensures that the ligands remain bonded to the resin.



Scheme 1.9. Solid phase synthesis of C1 symmetric bidentate ligands

Cleavage of the bidentate ligands from the resin can be achieved with a variety of reagents, which further expands the structural diversity of ligands that can be synthesised. Reaction of **24** with alcohols or thioalcohols leads to respectively, phosphine-phosphinites (**26**) and phosphine-thiophosphinites (**27**), while reaction with PCl_3 leads to chlorophosphines (**28**). Similarly, non-supported phosphinites-chlorophosphinites (**29**) can be formed by reaction of **25** with PCl_3. The method allowed the synthesis of a family of fifteen different bidentate ligands in good yields (24-75%) and with a high degree of purity (≥ 95%) from a single supported intermediate (**23**). Moreover, it allows the synthesis of C1 symmetric ligands, which are generally difficult to prepare by standard solution chemistry. The utility of the process is evidenced by the synthesis of several ligands on a multigram scale.

1.6 Conclusions and Outlook

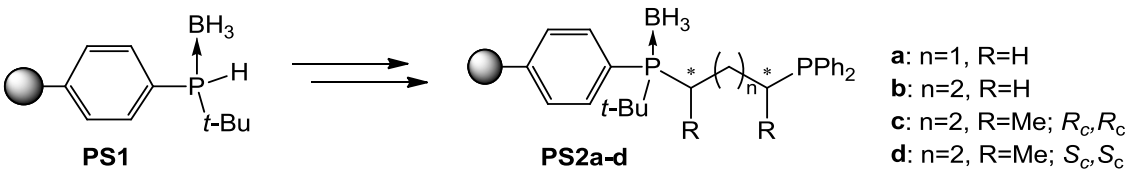
Polymeric supported ligands have proven their efficiency in several transition metal catalysed reactions, as they allow the formation of supported catalysts and thereby facilitate the recovery and reusability of the catalysts. Good mixing of the catalyst and the reactants is maintained by the excellent swelling properties of the polymeric support. These properties also allow polymer-bound ligands to be purified by simple filtration and washing procedures, which is attractive from a synthetic point view, as phosphorus intermediates are in general quite reactive resulting in good conversions, but separation and purification is often the problem in homogeneous systems. Moreover, it allows the use of excesses or even impure reagents. Consequently, application of solid phase synthesis can facilitate the combinatorial synthesis of libraries of ligands in an efficient manner and thus can be a powerful tool in catalysis research. The approach can be utilised to create supported ligands, but also allows the synthesis of non-supported ligands by cleaving them from the support in the final step of the synthetic sequence. Interestingly, the utilisation of polymer supported ligands in homogeneous catalysis has received considerably more attention than the development of efficient synthetic routes to form the ligands. Although a variety of *soluble* and *insoluble* polymeric supports have been applied in the synthesis of phosphorus based ligands, the majority of these were synthesised by a single reaction between a support bearing a suitable reactive group and a phosphorus reagent. Structural diversity thus originates from the type of phosphorus based reagent and/or from the support and not from the application of solid phase synthetic techniques. Examples in which ligands are created by multi-step reactions from a single solid bound phosphorus containing precursor are particularly rare. This can be contributed to the lack of efficient synthetic protocols, which in turn can be contributed to the fact that conditions used for the synthesis of non-supported ligands are not always suitable for the synthesis of supported analogues. Multi-step solid phase routes can not only greatly extend the range of supported ligands which can be formed from a single supported intermediate, but also allow the exploitation of the advantages of solid phase synthesis during all steps of the synthetic sequence. Consequently, the development of efficient and flexible solid phase protocols is a prerequisite to the successful utilisation of solid supports in ligand synthesis and catalysis research.

1.7 Objectives and outline

To combine the best of both worlds, *i.e.* the selectivity of stereogenic phosphorus ligands in catalysis and the synthetic advantages of solid phase synthesis (SPS), the main objective of this thesis is the establishment of new methodologies for the generation of libraries of immobilised bis(phosphine) and phosphine-phosphinite ligands.

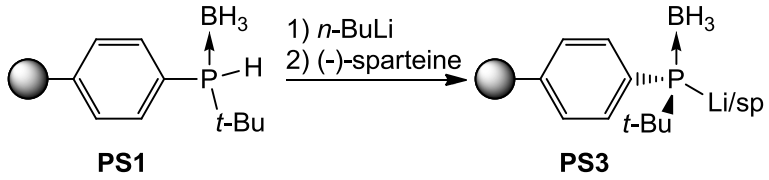
There are ample methods for the immobilisation of ligands on heterogeneous supports, such as anchoring the ligand (non)covalently on silica,[7,36] electrostatic immobilisation,[37] catalyst entrapment within a support and the Sol-Gel process[38] which involves co-condensation of ligand functionalised alkoxysilanes. Other systems utilise ionic liquids,[39] supercritical fluids,[40] fluorous[41] and aqueous biphasic systems[42] for the easy separation of the catalysts from the reaction products. The focus of this project was to anchor the phosphorus moiety covalently to a polymeric support. The most commonly used method of synthesising immobilised phosphine ligands is to prepare a suitable immobilised linker structure and the desired phosphorus compound (R_2PX) separately from each other. In the final step of the synthesis these are then combined, anchoring the phosphorus group to the solid support resulting in the desired immobilised ligand. However our approach was to build the ligands stepwise and systematically, from start to finish, onto a suitable commercially available polymeric support. This approach would fully exploit the advantages of SPS by immobilising all of the compounds and reactive intermediates on the support, the use of excesses of reagents, and 'simple' washing and filtration steps to obtain series of immobilised ligands.

With the wide range of different possible polymeric supports and electrophiles to choose from, there will be a hugely increased number of possibilities once the general synthetic methodology has been developed. In Chapter 2 the synthesis of synthon **PS1** via three different routes and its application towards immobilised bis(phosphines) will be described (Scheme 1.10).



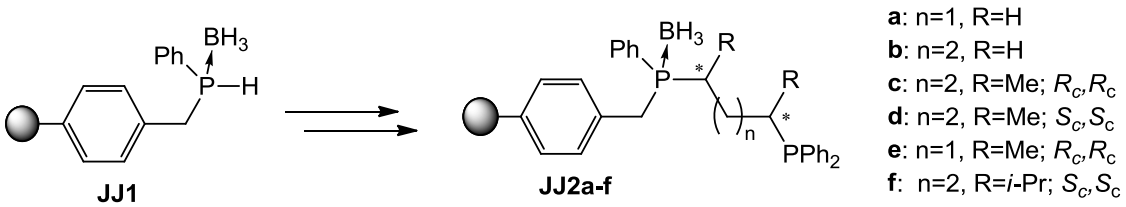
Scheme 1.10. Synthon PS1 and application towards immobilised bis(phosphines)

From this synthon, it was possible to continue stepwise towards immobilised bis(phosphines) **PS2a-d** successfully. Studies towards the synthesis of immobilised phosphine-phosphites will be described as well as the attempts made for resolving the stereogenic centre of **PS1** by performing a kinetic resolution of the immobilised lithium phosphide **PS3** by applying the sparteine method developed by Livinghouse and co-workers[43] (Scheme 1.11). Addition of electrophiles after the resolution should retain the stereogenic centre and thus facilitate immobilised *P*-stereogenic phosphines.



Scheme 1.11. Formation of immobilised *P*-stereogenic phosphide

In Chapter 3, the synthesis and application of synthon **JJ1** will be described (Scheme 1.12). This synthon was synthesised on *J*anda*J*el™ resin which has better swelling properties than PS-DVB and is chemically more robust than TentaGel™ resin. A new method was developed to synthesise secondary phosphines on this support and subsequent reactions were investigated towards immobilised bis(phosphines) **JJ2a-f**.



Scheme 1.12 Synthon JJ1 and application towards immobilised bis(phosphines)

In Chapter 4 the formation of *in situ* rhodium complexes with the immobilised ligands **PS2** and **JJ2** and the rhodium catalysed asymmetric hydrogenation reactions of several substrates (Figure 1.5) with these ligands will be described.

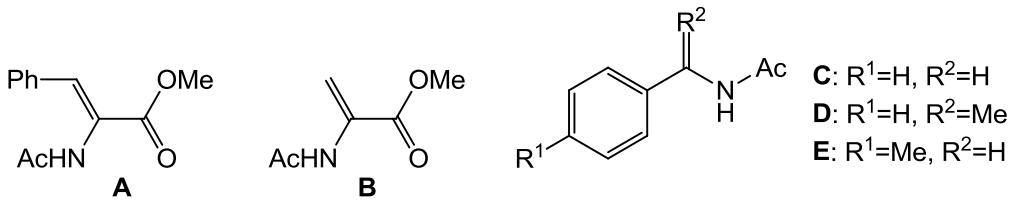


Figure 1.5 Substrates used in rhodium catalysed asymmetric hydrogenations

1.8 References

1. This introduction has been published as a review in a slightly modified form: M. C. Samuels, B. H. G. Swennenhuis, P. C. J. Kamer, (2012), In *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; (Eds. P. C. J. Kamer, P. W. N. M. van Leeuwen), John Wiley & Sons, Ltd, Chichester, UK, pp. 463-479.
2. P. W. N. M. v. Leeuwen, *Homogeneous Catalysis: Understanding the Art*, Kluwer Academic Publishers, Dordrecht etc., **2004**.
3. a) C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313-348; b) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741-2770; c) J. A. Gillespie, D. L. Dodds, P. C. J. Kamer, *Dalton Trans.* **2010**, *39*, 2751-2764.
4. a) M. T. Reetz, *Angew. Chem., Int. Ed.* **2001**, *40*, 284-310; b) J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, *2003*, 799-811; c) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912-2942; d) J. P. Stambuli, S. R. Stauffer, K. H. Shaughnessy, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 2677-2678; e) O. Lavastre, F. Bonnette, L. Gallard, *Curr. Opin. Chem. Biol.* **2004**, *8*, 311-318; f) L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org. Lett.* **2004**, *6*, 1733-1735; g) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071-3100.
5. R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.
6. a) D. C. Sherrington, A. P. Kybett, Editors, *Supported Catalysts and Their Applications*, The Royal Society of Chemistry, Cambridge, **2001**; b) B. M. L. Dioos, I. F. J. Vankelecom, P. A. Jacobs, *Adv. Synth. Catal.* **2006**, *348*, 1413-1446; c) M. Guino, K. K. Hii, *Chem. Soc. Rev.* **2007**, *36*, 608-617; d) B. Clapham, T. S. Reger, K. D. Janda, *Tetrahedron* **2001**, *57*, 4637-4662; e) T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325-3344; f) N. E. Leadbeater, *Curr. Med. Chem.* **2002**, *9*, 2147-2171; g) N. E. Leadbeater, M. Marco, *Chem. Rev.* **2002**, *102*, 3217-3274; h) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275-3300; i) D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.* **2009**, *109*, 530-582; j) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815-838; k) N. Kann, *Molecules* **2010**, *15*, 6306-6331.
7. a) R. T. Baker, W. Tumas, *Science* **1999**, *284*, 1477-1479; b) Thematic issue, *Chem. Rev.* **2002**, *102*, issue no. 10; c) D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702-1706.
8. a) S. R. Gilbertson, S. E. Collibee, A. Agarkov, *J. Am. Chem. Soc.* **2000**, *122*, 6522-6523; b) G. Y. Li, P. J. Fagan, P. L. Watson, *Angew. Chem., Int. Ed.* **2001**, *40*, 1106-1109; c) O. Huttenloch, E. Laxman, H. Waldmann, *Chemistry – A European Journal* **2002**, *8*, 4767-4780; d) A. Mansour, M. Portnoy, *Tetrahedron Lett.* **2003**, *44*, 2195-2198; e) C. A. Christensen, M. Meldal, *Chemistry – A European Journal* **2005**, *11*, 4121-4131; f) Y. Kobayashi, D. Tanaka, H. Danjo, Y. Uozumi, *Adv. Synth. Catal.* **2006**, *348*, 1561-1566; g) R. den Heeten, B. H. G. Swennenhuis, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Angew. Chem., Int. Ed.* **2008**, *47*, 6602-6605; h) B. H. G. Swennenhuis, R. Chen, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Org. Lett.* **2008**, *10*, 989-992; i) B. Bar-Nir Ben-Aroya, M. Portnoy, *Tetrahedron* **2002**, *58*, 5147-5158; j) A. Agarkov, S. J. Greenfield, T. Ohishi, S. E. Collibee, S. R. Gilbertson, *J. Org. Chem.* **2004**, *69*, 8077-8085.
9. a) H. Graden, N. Kann, *Curr. Org. Chem.* **2005**, *9*, 733-763; b) G. Reginato, M. Taddei, *Il Farmaco* **2002**, *57*, 373-384.
10. a) P. H. Toy, K. D. Janda, *Tetrahedron Lett.* **1999**, *40*, 6329-6332; b) P. H. Toy, T. S. Reger, P. Garibay, J. C. Garno, J. A. Malikayil, G.-Y. Liu, K. D. Janda, *J. Comb. Chem.* **2001**, *3*, 117-124.
11. R. Quarrell, T. D. W. Claridge, G. W. Weaver, G. Lowe, *Mol. Diversity* **1996**, *1*, 223-232.
12. R. Jana, J. A. Tunge, *Org. Lett.* **2009**, *11*, 971-974.
13. D. E. Bergbreiter, L. Zhang, V. M. Mariagnanam, *J. Am. Chem. Soc.* **1993**, *115*, 9295-9296.
14. N. Takaishi, H. Imai, C. A. Bertelo, J. K. Stille, *J. Am. Chem. Soc.* **1976**, *98*, 5400-5402.
15. a) T. Jongsma, M. Fossen, G. Challa, P. W. N. M. van Leeuwen, *J. Mol. Catal.* **1993**, *83*, 17-35; b) T. Jongsma, H. van Aert, M. Fossen, G. Challa, P. W. N. M. van Leeuwen, *J. Mol. Catal.* **1993**, *83*, 37-50.
16. a) F. Bardella, R. Eritja, E. Pedroso, E. Giralt, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2793-2796; b) D. E. Bergbreiter, Y.-C. Yang, *J. Org. Chem.* **2010**, *75*, 873-878.
17. a) W. Chen, S. M. Roberts, J. Whittall, *Tetrahedron Lett.* **2006**, *47*, 4263-4266; b) A. Mandoli, M. Calamante, B. L. Feringa, P. Salvadori, *Tetrahedron: Asymmetry* **2003**, *14*, 3647-3650; c) S. Schweizer, J.-M. Becht, C. Le Drian, *Tetrahedron* **2010**, *66*, 765-772.
18. C. R. Harrison, P. Hodge, B. J. Hunt, E. Khoshdel, G. Richardson, *J. Org. Chem.* **1983**, *48*, 3721-3728.

19. H. M. Relles, R. W. Schluenz, *J. Am. Chem. Soc.* **1974**, *96*, 6469-6475.
20. M. J. Farrall, J. M. J. Frechet, *J. Org. Chem.* **1976**, *41*, 3877-3882.
21. a) S. Schweizer, J.-M. Becht, C. Le Drian, *Org. Lett.* **2007**, *9*, 3777-3780; b) S. Schweizer, J.-M. Becht, C. Le Drian, *Adv. Synth. Catal.* **2007**, *349*, 1150-1158.
22. a) S. R. Gilbertson, X. Wang, *Tetrahedron* **1999**, *55*, 11609-11618; b) A. Agarkov, S. R. Gilbertson, *Tetrahedron Lett.* **2005**, *46*, 181-183.
23. a) J. M. Benito, C. A. Christensen, M. Meldal, *Org. Lett.* **2005**, *7*, 581-584; b) C. A. Christensen, M. Meldal, *J. Comb. Chem.* **2007**, *9*, 79-85.
24. R. den Heeten, P. C. J. Kamer, W. Laan, (2012), In *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; (Eds. P. C. J. Kamer, P. W. N. M. van Leeuwen), John Wiley & Sons, Ltd, Chichester, UK, pp. 481-496.
25. B. H. G. Swennenhuis, R. F. Chen, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Eur. J. Org. Chem.* **2009**, *2009*, 5796-5803.
26. a) D. Moulin, C. Darcel, S. Jugé, *Tetrahedron: Asymmetry* **1999**, *10*, 4729-4743; b) C. Darcel, D. Moulin, J.-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey, S. Jugé, *Eur. J. Org. Chem.* **2007**, 2078-2090.
27. E. Ullah, J. McNulty, M. Sliwinski, A. Robertson, *Tetrahedron Lett.* **2012**, *53*, 3990-3993.
28. E. Bayer, V. Schurig, *Chemtech* **1976**, *6*, 212-214.
29. a) P. Wentworth Jr, A. M. Vandersteen, K. D. Janda, *Chem. Commun.* **1997**, 759-760; b) F. Sieber, P. Wentworth Jr, J. D. Toker, A. D. Wentworth, W. A. Metz, N. N. Reed, K. D. Janda, *J. Org. Chem.* **1999**, *64*, 5188-5192; c) P. H. Toy, K. D. Janda, *Acc. Chem. Res.* **2000**, *33*, 546-554; d) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345-3384; e) X. P. Hu, J. D. Huang, Q. H. Zeng, Z. Zheng, *Chem. Commun.* **2006**, 293-295.
30. D. E. Bergbreiter, S. D. Sung, *Adv. Synth. Catal.* **2006**, *348*, 1352-1366.
31. S. Doherty, E. G. Robins, I. Pal, C. R. Newman, C. Hardacre, D. Rooney, D. A. Mooney, *Tetrahedron: Asymmetry* **2003**, *14*, 1517-1527.
32. O. Lavastre, J. P. Morken, *New J. Chem.* **2002**, *26*, 745-749.
33. C. U. Pittman, R. M. Hanes, *J. Am. Chem. Soc.* **1976**, *98*, 5402-5405.
34. a) S. R. Gilbertson, S. Yamada, *Tetrahedron Lett.* **2004**, *45*, 3917-3920; b) H. Nakano, K. Takahashi, Y. Suzuki, R. Fujita, *Tetrahedron: Asymmetry* **2005**, *16*, 609-614; c) A. Leyva, H. García, A. Corma, *Tetrahedron* **2007**, *63*, 7097-7111.
35. a) B. J. Backes, J. A. Ellman, *Curr. Opin. Chem. Biol.* **1997**, *1*, 86-93; b) I. W. James, *Tetrahedron* **1999**, *55*, 4855-4946; c) A. C. Comely, S. E. Gibson, *Angew. Chem., Int. Ed.* **2001**, *40*, 1012-1032.
36. a) J. N. H. Reek, P. W. N. M. Leeuwen, A. G. J. Ham, A. B. Haan, (2006), In *Catalyst Separation, Recovery and Recycling*; (Eds. D. Cole-Hamilton, R. Tooze), Springer Netherlands, *Vol. 30*, pp. 39-72; b) P. B. Webb, D. J. Cole Hamilton, (2012), In *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*, John Wiley & Sons, Ltd, pp. 497-532; c) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267-278.
37. C. Müller, D. Vogt, (2010), In *Handbook of Green Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA.
38. a) L. L. Hench, J. K. West, *Chem. Rev.* **1990**, *90*, 33-72; b) R. Ciriminna, A. Fidalgo, V. Pandarus, F. Béland, L. M. Ilharco, M. Pagliaro, *Chem. Rev.* **2013**, *113*, 6592-6620.
39. a) P. Wasserscheid, M. Haumann, (2006), In *Catalyst Separation, Recovery and Recycling*; (Eds. D. Cole-Hamilton, R. Tooze), Springer Netherlands, *Vol. 30*, pp. 183-213; b) M. Petkovic, K. R. Seddon, L. P. N. Rebelo, C. Silva Pereira, *Chem. Soc. Rev.* **2011**, *40*, 1383-1403; c) H. Niedermeyer, J. P. Hallett, I. J. Villar-Garcia, P. A. Hunt, T. Welton, *Chem. Soc. Rev.* **2012**, *41*, 7780-7802.
40. a) C. Gordon, W. Leitner, (2006), In *Catalyst Separation, Recovery and Recycling*; (Eds. D. Cole-Hamilton, R. Tooze), Springer Netherlands, *Vol. 30*, pp. 215-236; b) C. Aymonier, A. Loppinet-Serani, H. Reverón, Y. Garrabos, F. Cansell, *The Journal of Supercritical Fluids* **2006**, *38*, 242-251; c) B. Subramaniam, M. A. McHugh, *Industrial & Engineering Chemistry Process Design and Development* **1986**, *25*, 1-12.
41. C. Mathison, D. Cole-Hamilton, (2006), In *Catalyst Separation, Recovery and Recycling*; (Eds. D. Cole-Hamilton, R. Tooze), Springer Netherlands, *Vol. 30*, pp. 145-181.
42. a) M. G. Freire, A. F. M. Claudio, J. M. M. Araujo, J. A. P. Coutinho, I. M. Marrucho, J. N. C. Lopes, L. P. N. Rebelo, *Chem. Soc. Rev.* **2012**, *41*, 4966-4995; b) E. Wiebus, B. Cornils, (2006),

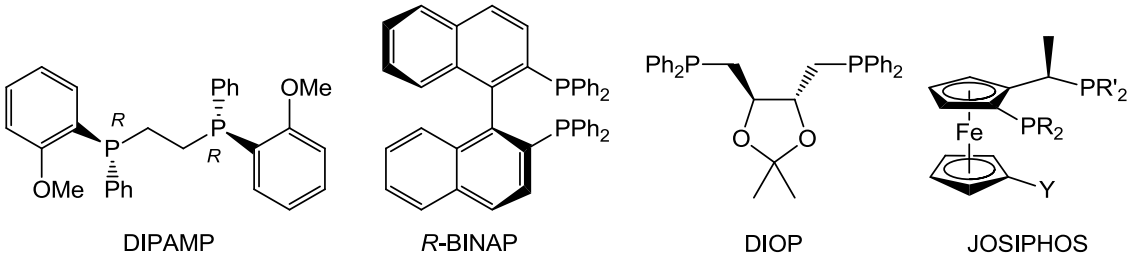
In *Catalyst Separation, Recovery and Recycling*; (Eds. D. Cole-Hamilton, R. Tooze), Springer Netherlands, *Vol. 30*, pp. 105-143.
43. B. Wolfe, T. Livinghouse, *J. Am. Chem. Soc.* **1998**, *120*, 5116-5117.

Chapter 2. Ligand synthesis on polystyrene resin

2.1 Introduction

2.1.1 *P*-stereogenic ligands

Historically, the first type of chiral phosphines contained *P*-stereogenic atoms (such as DIPAMP,[1] Figure 2.1), but were soon supplanted by ligands with other stereogenic elements, often bearing diphenylphosphine-moieties. Among these, three extremely well known examples are BINAP,[2] which contains a stereogenic axis, DIOP,[3] bearing two stereogenic carbon atoms, and JosiPhos,[4] in which planar chirality is key (Figure 2.1).



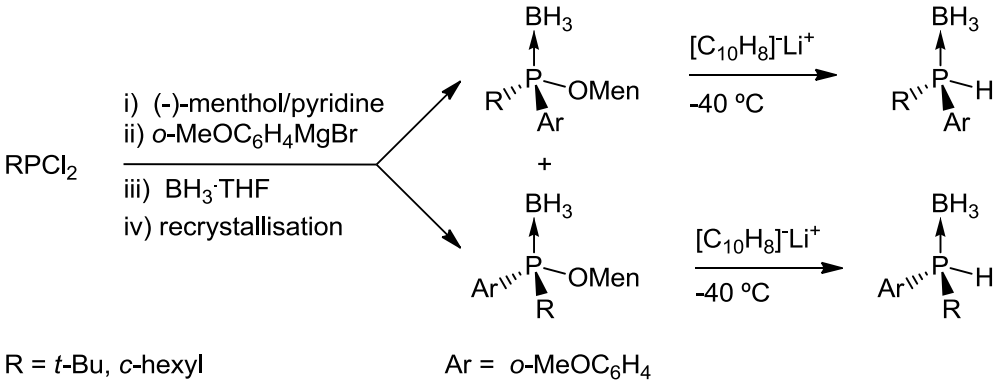
DIPAMP *R*-BINAP DIOP JOSIPHOS

Figure 2.1. Ligands used in asymmetric homogeneous catalysis

However, since then, new efficient methods to synthesise *P*-stereogenic phosphines have been developed. Among which, the most promising methods are those developed by Imamoto *et al.*[5], by the group of Jugé[6] and by Livinghouse and co-workers.[7]

2.1.2 *P*-stereogenic ligands developed by Imamoto

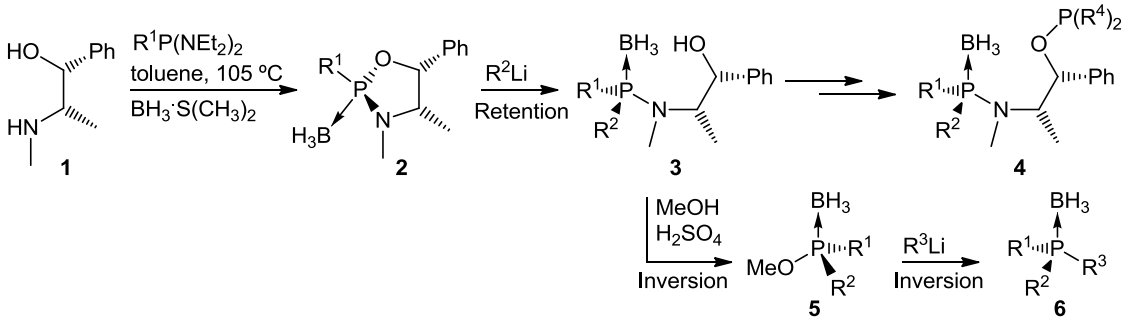
Imamoto *et al.*[5a,b] reported the synthesis of *P*-stereogenic phosphine-boranes. These *P*-stereogenic phosphinite-boranes were synthesised by reacting dichlorophosphines with one equivalent of (−)-menthol, followed by addition of *o*-methoxyphenyl magnesium bromide, and borane-THF complex. The stereoisomers could be separated by recrystallisation in high *ee* (100%) but low yields (12-32%) (Scheme 2.1). Subsequent reduction with lithium naphthalenide at −40 °C resulted in the corresponding *sec*-phosphine-boranes in high yields (93-98%), with retention of the stereochemistry.[5a,b]



Scheme 2.1 Imamoto's method for *P*-stereogenic phosphine synthesis

2.1.3 *P*-stereogenic ligands developed by Jugé

In 1989, the group of Jugé[6a] developed a method for the synthesis of *P*-stereogenic phosphine-boranes via the use of chiral auxiliary (–)-ephedrine **1**. This is one of the most successful methods, in terms of its versatility, stereoselectivity and simplicity, and availability of the chiral auxiliary.[6,8] In this method the key intermediate is oxazaphospholidine borane **2**, which is formed by reacting a bis(diethylamine)arylphosphine with (−)-ephidrine **1** at 105 °C, followed by protection with BH_3 (Scheme 2.2). This ring closure is stereoselective due to the substituents on **1** and only one diastereomer is being formed.



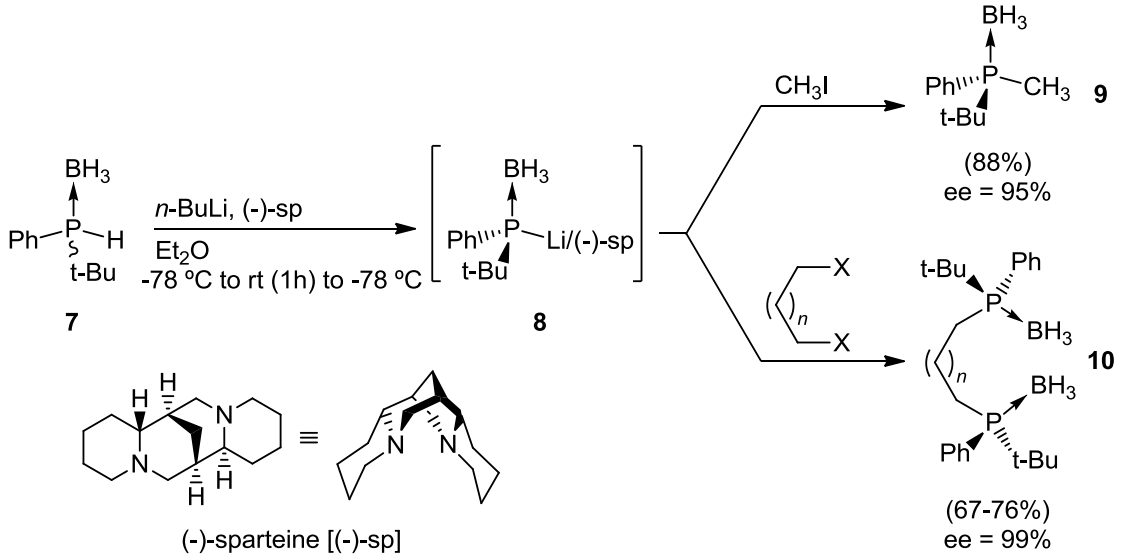
Scheme 2.2 Jugé's method for *P*-stereogenic phosphine synthesis

Clean chemoselective ring opening of the P-O bond by aryl lithium reagents results in phosphinous amide-borane **3** with retention of configuration. Further substitution of the OH-group of **3** with disubstituted chlorophosphines yields aminophosphine-phosphinites **4**.[6d,6f] Treatment of **3** with methanol produces **5** by releasing (−)-ephidrine **1** with inversion of configuration, which can be converted to phosphine **6** by reacting it with organolithium compounds, again with inversion of configuration. The drawback of this method is that the introduction of *o,o*-disubstituted aryllithium

compounds in **2** as R^2 is not possible due to steric hindrance. Moreover, when R^2 is a *tert*-butyl group the methanolysis is unsuccessful even at reflux temperatures. Thus the method is limited with respect to the size of the substituents.[6f]

2.1.4 *P*-stereogenic ligands developed by Livinghouse

In 1998, Livinghouse and co-workers[7] reported a different approach towards *P*-stereogenic phosphines, namely by dynamic kinetic resolution of lithio-phosphides with the use of a chiral diamine, based on preliminary work of Evans and co-workers.[9] Starting from racemic (±)-*tert*-butyl phenylphosphine-borane **7**, enantioselective deprotonation with *n*-BuLi in the presence of chiral diamine (–)-sparteine [(–)-sp] results in the *in situ* formation of optically enriched phosphide-sparteine borane complex **8** (Scheme 2.3).[7-10]



Scheme 2.3 Livinghouse's method for *P*-stereogenic phosphine synthesis

Subsequent addition of electrophiles (*e.g.* methyliodide) results in the formation of enantiomeric pure phosphine-borane **9** in high isolated yield and *ee*. Phosphide-sparteine borane complex **8** reacts readily with other halide-containing electrophiles as well, resulting in their corresponding phosphines in high yields (80-90%) and high *ee* (92-95%). Bis(phosphine) **10** could be obtained after reaction of 2 equivalents of **8** with dihalides in slightly lower isolated yields (67-76%) but in very high *ee*.[7]

The (–)-enantiomer of the chiral diamine (–)-sparteine is only available as a natural oil and isolated by extraction of papilionaceous plants such as Scotch broom (Cytisus

scoparius).[11] Until 2010 it was commercially available however for reasons unknown the production has ceased and currently there is a worldwide shortage of (–)-sparteine. The only other option available is the use the (+)-sparteine surrogate developed by the group of O'Brien (Figure 2.1).[12] However, this surrogate has not been applied to the Livinghouse method and thus it currently is unknown if its performance is similar to (–)-sparteine for this reaction. Additionally, the (+)-surrogate is only commercially available in very small quantities (up to 100 mg) and therefore considered to be too expensive.

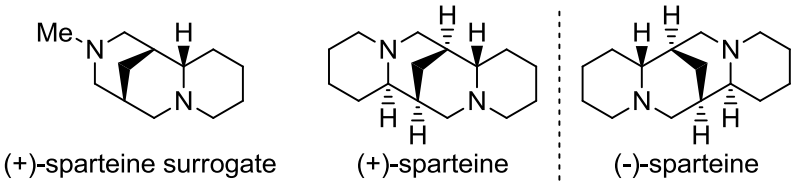


Figure 2.2 (+)-sparteine surrogate

2.2 Solid Phase Synthesis combined with synthesis of P-stereogenic phosphines

The main objective of the project is the development of new methodologies towards the synthesis of libraries of immobilised phosphines, bis(phosphines), phosphine-phosphinites and phosphine-phosphites. The application of solid phase synthesis (SPS) with ligand-development will enable fast synthesis of diverse ligand structures and combine the powerful performance of phosphorus ligands in catalysis with easy separation of the catalyst from the mixture after reaction, due to its immobilisation.

The combination of the methods for the synthesis of *P*-stereogenic ligands discussed above with SPS techniques would provide a powerful approach to create libraries of immobilised *P*-stereogenic ligands in an efficient way. However, the synthetic methodologies towards such libraries are not fully developed yet. The method of Imamoto[4a,b] is not suitable for SPS because it relies on crystallisation for the separation of the stereoisomers which is impossible with the immobilised phosphines.

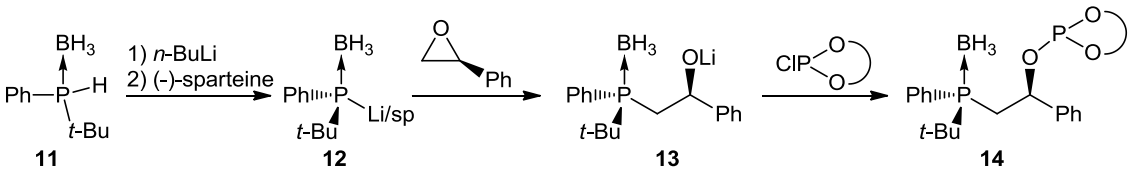
Conversely, the methods developed by Jugé[6a] and Livinghouse[7] are much more promising and somewhat complementary to each other. The method developed by Jugé is successful for the introduction of aryls, but is unsuitable for large aliphatic groups. Recently, by combining the method developed by the Jugé group[6a] with SPS, the Kamer

group[13] has synthesised a small library of ten immobilised bidentate *P*-stereogenic aminophosphane-phosphite and -phosphinite ligands. This example is described in more detail in Chapter 1.

Livinghouse's method requires a large aliphatic group, such as a *tert*-butyl group, and cannot be applied with smaller aryl-groups. However, the kinetic resolution of phosphide-sparteine borane complex **8** that this method utilises does require the precipitation of the least soluble complex in diethylether for it to work. On solid support this required precipitation step is prohibited and cannot be accomplished. Additionally, the reaction cannot be performed in the optimal solvent, *i.e.* diethylether, as the use of diethylether results in poor swelling of most resins and this reduces the accessibility to the reactive sites within the resin beads.

Still, this method or related routes may be interesting to combine with SPS for the synthesis of immobilised *P*-stereogenic aryl-alkyl phosphines, bis(phosphines), phosphine-phosphinites and phosphine-phosphites. The stereoselectivity of the (–)-sp method in supported systems has to be determined via other approaches than reported, as the most commonly used methods for *ee*-determination, *e.g.* by HPLC, GC and/or crystallisation, are not an option for solid supported systems. One approach is to introduce a second stereocenter in the molecule or by complexation of the immobilised ligand to a chiral auxiliary such as the complex developed by Wild *et al.*[14] Both approaches are based on a difference in chemical shift in ^{31}P NMR of the isomers.

In liquid phase Deerenberg *et al.*[10a] have successfully applied the method developed by Livinghouse *et al.*[7] for the synthesis of a series of *P*-stereogenic phosphine-phosphite ligands (Scheme 2.4).



Scheme 2.4 Phosphine-phosphite synthesis by Deerenberg[10a] with the method of Livinghouse[7]

As Deerenberg *et al.*[10] have shown in their survey of similar phosphine-phosphite ligands, the ^{31}P NMR resonances of the phosphite moieties of the R_p,R_c and the R_p,S_c stereoisomers differ by approximately 4 ppm (Figure 2.3), which should be sufficient to

observe even with the generally broad signals of resin bounded phosphines. As the phosphite moiety is located further away from the backbone, the resonance signals will be sharper than the signals of the phosphine moiety. Similar behaviour was observed for the immobilised aminophosphine–phosphinites synthesised by den Heeten *et al.*[13]

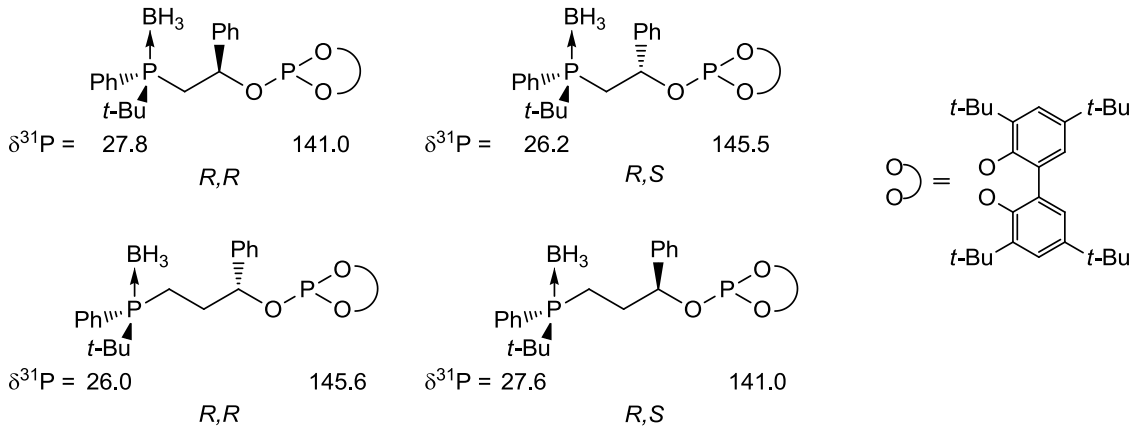


Figure 2.3. Phosphine-phosphite ligands developed by Deerenberg *et al*.

2.3 Synthesising libraries of immobilised ligands

Immobilised secondary phosphine **PS1** (Figure 2.4) was selected as a synthon for the utilisation of Livinghouse's method[7] in SPS of ligands on polymeric support as it closely mimics the liquid phase analogue **11**.

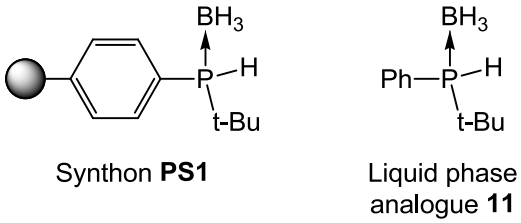
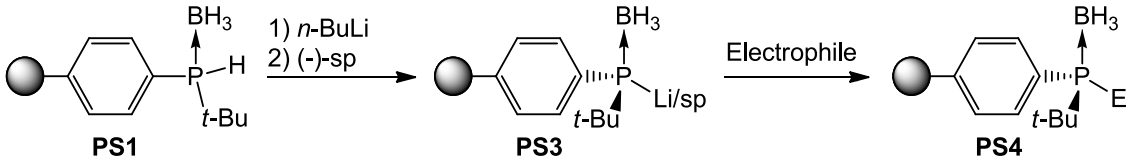


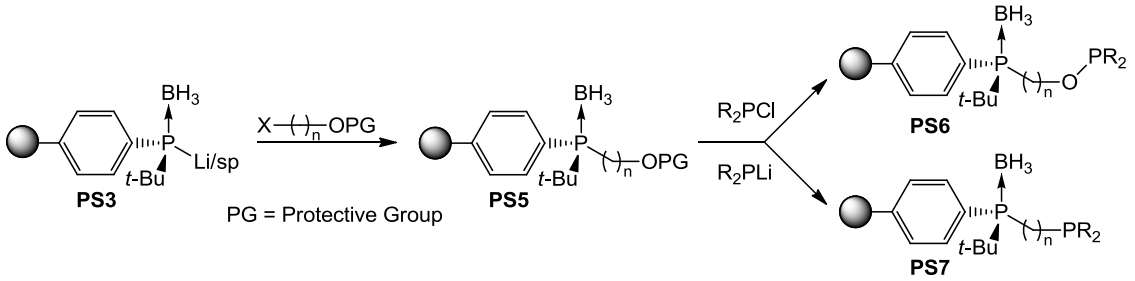
Figure 2.4 Synthon PS1 and its liquid phase analogue 11

The key step in Livinghouse's method[7] would be the precipitation of complex **PS3**, which is required to achieve high enantioselectivity with the kinetic resolution for the liquid phase analogue. Although this is not feasible on solid support, addition of electrophiles to immobilised phosphide **PS3** should facilitate the generation of libraries of immobilised phosphines **PS4** (Scheme 2.5), but *P*-stereogenic purity will most likely not be obtained.



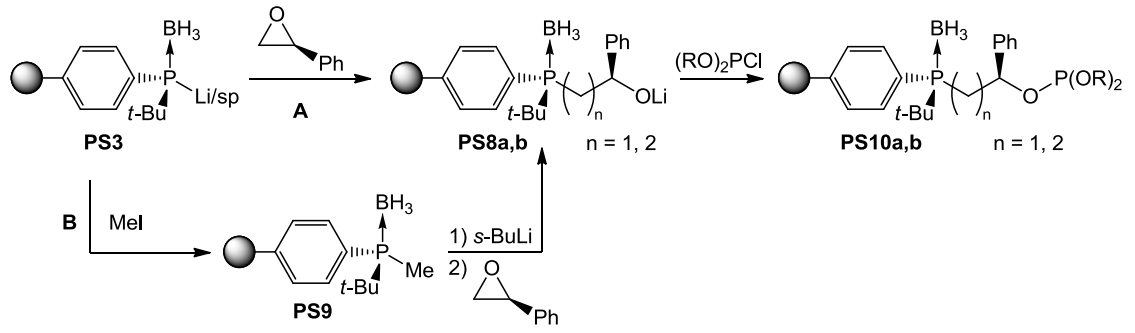
Scheme 2.5 Formation of immobilised *P*-stereogenic phosphines

By utilising electrophiles containing a second functional group, such as an alcohol, a subsequent reaction with chlorophosphines may facilitate the formation of covalently bound phosphine-phosphites or phosphine-phosphinites **PS6**. The synthesis of immobilised bis(phosphine) **PS7** could be envisioned when utilising electrophiles containing a good leaving group (Scheme 2.6).



Scheme 2.6. Proposed synthesis of immobilised phosphine-phosphinites and bis(phosphines)

The following route based on ring-opening of oxiranes was proposed for the synthesis of immobilised analogues of the phosphine-phosphite ligands (Figure 2.3) and as developed by Deerenberg *et al.*[10] (Scheme 2.7). As the chemical shift difference of the phosphite resonance of these immobilised phosphine-phosphites is quite large it would be possible to determine the *ee* of the formation of complex **PS3** by means of ^{31}P NMR spectroscopy.



Scheme 2.7 Resin-bound chiral phosphine-phosphinite ligand synthesis

In this route, addition of (*R*)-styrene oxide (or *S* to obtain the other isomer) to **PS3** would furnish the stereoselective ring opening, which results in **PS8**. Upon addition of a chlorophosphonite, immobilised phosphine-phosphite **PS10a** (n=1) would be formed

(route **A**, Scheme 2.7). Phosphine-phosphites **PS10b** with n=2 can be obtained via route **B**; by firstly reacting **PS3** with methyl iodide to form **PS9**, after which the methyl group can be lithiated, without interfering with the stereogenic centre. This would yield **PS10b** after subsequent reaction with (*R*)-styrene oxide and a chlorophosphonite.

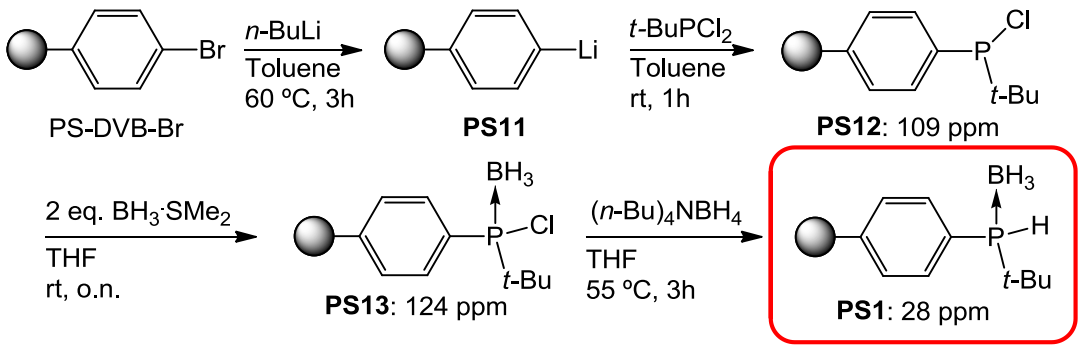
These concepts could be expanded as there is currently such a wide diversity of possible resin structures and electrophiles available. This creates a huge range of possible combinations once the general synthetic methodology is developed. It is therefore a necessity to firstly explore the synthesis routes towards synthon **PS1** and its utilisation towards a small library of immobilised bis(phosphine) ligands. Once the general methodologies have been developed, they can then be applied to different resin structures and combined with several electrophiles to create libraries of new promising ligands structures, which can be tested for catalysis, *e.g.* hydrogenation, hydroformylation and allylic substitution.

2.4 Solid phase synthesis of immobilised phosphine ligands

Since the work-up of solid phase reactions consists of a washing and filtration procedure of the resins (*vide infra*), excess of (impure) reagents can be used, which can boost the yield of the reactions to nearly quantitative. However, care has to be taken with choosing the reagents in such way that the reagents and the formed side-products cannot further interact with the formed products or with the base structure of the resin. The main disadvantage of using SPS is that covalently bound side-products **cannot** be separated or removed from the desired covalently bound products and this formation should therefore be avoided or minimised.

2.4.1 Synthesis of **PS1** using *t*-$BuPCl_2$

The most direct route towards the synthesis of the desired building block **PS1** would be via the reaction of lithiated polystyrene **PS11** with *tert*-butyldichlorophosphine (*t*-$BuPCl_2$) resulting in immobilised chlorophosphine **PS12** (Scheme 2.8). Subsequent protection of the phosphine with $BH_3{\cdot}SMe_2$ complex followed by reduction with (*n*-$Bu)_4NBH_4$ of **PS13** would furnish immobilised secondary phosphine **PS1**.



Scheme 2.8 Synthesis of resin-bound *tert*-butylphosphine borane

Lithiated polystyrene could be obtained from the reaction of commercially available *p*-bromopolystyrene (PS-DVB-Br) with *n*-BuLi in toluene at 60 °C.[15] During this reaction, it was observed that the resin coloured yellow and the swelling of the resin decreased to about half its size and the liquid phase became white and cloudy. When using a standard solution of *n*-BuLi in toluene, the salt formation reduced and the swelling of the resin decreased only slightly. The resin was then washed with toluene until the toluene layer was clear, after which lithiated resin **PS11** was obtained as a bright yellow resin. After resuspending the lithiated resin **PS11** in toluene, an excess of *t*-BuPCl$_2$ was added. This caused the resin to decolourise and the ^{31}P NMR spectrum of the resin displayed one resonance at 109 ppm, corresponding to resin-bound *tert*-butyl chlorophosphine **PS12**. The liquid phase analogue of this compound *tert*-butyl chlorophenylphosphine has a literature value of δ^{31}P = 109.5 in CDCl$_3$.[16] During this synthesis additional resonances at 19 and 1 ppm appeared which did not disappear after washing, indicating that resin-bound side products were formed (Figure 2.5).

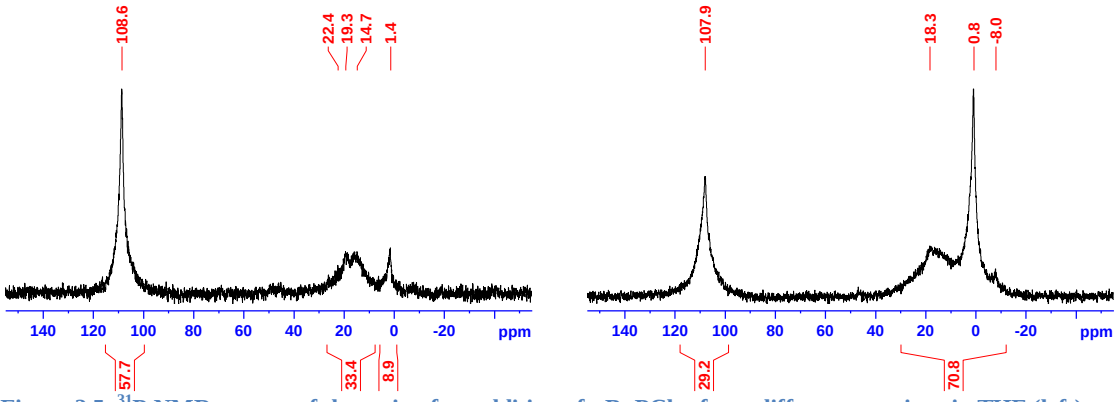


Figure 2.5. ^{31}P NMR spectra of the resin after addition of *t*-BuPCl$_2$ of two different reactions in THF (left) and toluene (right)

The addition of an excess of $BH_3 \cdot SMe_2$-complex in THF to resin **PS12** yielded resin **PS13**, displaying a resonance at 124 ppm in the ^{31}P NMR spectrum. The side product signals, previously at 13 and 1 ppm, had both shifted to approximately the same resonance at 31 ppm (broad signal), however due to the broadness of the resonances it was not possible to distinguish them from each other. Reduction of chlorophosphine **PS13** with $(n\text{-Bu})_4NBH_4$ resulted in a resonance at 28 ppm corresponding to the resin-bound phosphine **PS1**.[17] The broad resonance corresponding to the side products was still visible at 31 ppm (Figure 2.6).

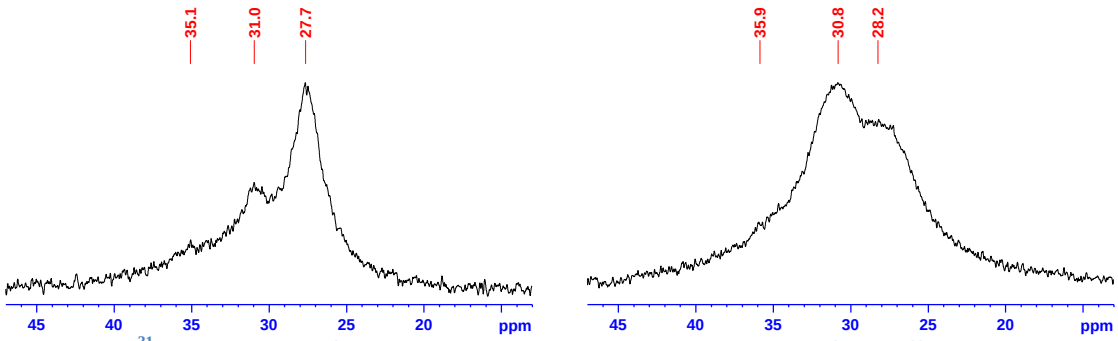


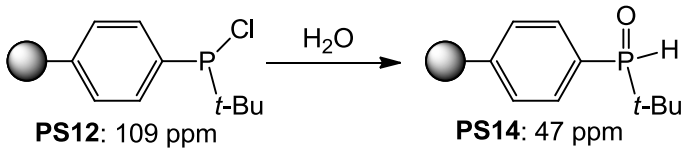
Figure 2.6. ^{31}P NMR spectra of resin-bound *tert*-butylphosphine borane PS13 of two different reactions in THF (left) and toluene (right)

This reaction was performed several times and the ratio between the desired and side products was found to be irreproducible (Figure 2.5 and Figure 2.6). In one case, the final product **PS13** was obtained almost pure, however in most occasions it was notably impure. Moreover, after reduction of **PS13**, the resonance corresponding to **PS1** appeared at similar chemical shift (Figure 2.6), suggesting the side products to be similar in nature as the desired **PS1**.

Although the direct synthetic procedure towards immobilised synthon **PS1** (Scheme 2.8) proved to be possible, the impurities in the resin that were introduced in either the lithiation or the phosphorylation step rendered it unsuitable for further synthesis.

An attempt was made to investigate the nature of these side products. The first hypothesis tested was the possibility of hydrolysis of resin-bound chlorophosphine **PS12**, which is a quite common and often unwanted side reaction in phosphorus chemistry. By addition of H_2O to a small amount of a mixture of resin **PS12** and side products, the phosphine was hydrolysed. This resulted in a resonance in ^{31}P NMR at

47 ppm, which corresponds to the secondary phosphine oxide **PS14** (Scheme 2.9). The resonance of resin **PS12** at 109 ppm disappeared completely after one day. The side product resonances were not affected by the addition of H_2O and were still present.



Scheme 2.9 Hydrolysis of resin-bound *t*-BuPCl PS12

The resin PS-DVB-Br was purchased from two different suppliers. NovaBiochem delivered *p*-bromopolystyrene resins with a loading of 1.9 mmol/g (50-100 mesh, 1% cross-linking DVB). This resin is synthesised by co-polymerisation of styrene with *para*-bromostyrene in the presence of divinylbenzene. The resin purchased from Sigma Aldrich has a loading of 2.17 mmol/g (50-100 mesh, 1% cross-linking DVB) and was synthesised by bromination of polystyrene resin. Although both the resins differ in production method, both yielded side products with the same chemical shifts in the ^{31}P NMR. No significant differences in reactivity were observed, and the reactions were performed with the resin from Sigma Aldrich because of the higher loading and better availability.

To rule out the possibility of the presence of other functionalities (such as hydroxyl or amine) on the resin, a reaction of non-lithiated PS-DVB-Br with *t*-BuPCl$_2$ and NEt$_3$ was performed. This showed no phosphine incorporation onto the resin according to ^{31}P NMR spectroscopy after washing of the resin. Thoroughly washing PS-DVB-Br (Sigma Aldrich) with THF, Et$_2$O, CH$_2$Cl$_2$ and again Et$_2$O respectively before lithiation, did not prevent the formation of the side products. From all these tests, it was concluded that neither hydrolysis of resin-bound chlorophosphine **PS12** nor unwanted functionalisations on the resin were responsible for side product formation. Therefore other possibilities were explored. Initially, the lithiation was performed in toluene and the phosphorylation in THF. The solvent change was introduced because the resin has better swelling properties in THF, however *n*-BuLi is unstable in THF. It was observed that, when the solvent was changed from toluene to THF, the colour of the lithiated resin **PS11** changed from bright yellow to dark yellow; similarly the THF also coloured yellow. By addition of *t*-BuPCl$_2$ both the solvent and the resin decolourised, resulting in white resin **PS12** containing side products. To suppress the colouration of resin **PS11** in

THF, several different methods for addition of *t*-$BuPCl_2$ were attempted. A change from the addition of a stock solution of *t*-$BuPCl_2$ in THF to adding *t*-$BuPCl_2$ as pure solid to resin **PS11**was made as was the order of addition. The latter was performed by first adding solid pure *t*-$BuPCl_2$ to non-suspended resin **PS11**, followed by THF. This suppressed the colouration of the resin, but did not prevent the formation of side products.

Another proposed hypothesis was that the colouration in THF could be caused by a reaction between lithiated resin **PS11** and THF, which could result in the formation of the side products. To eliminate this possibility, the reaction was performed in toluene. During these reactions in toluene, there was no additional colouring of the lithiated resin or of the toluene. However, this change did not suppress the side products formation either.

To investigate the effect of the quantity of *n*-BuLi on the side product formation, resin **PS11** was formed with only one equivalent of *n*-BuLi. This resulted in a decrease of the functionalisation of the resin, as the signals in ^{31}P NMR were of lower intensity. Nevertheless, the formation of side products could not be avoided.

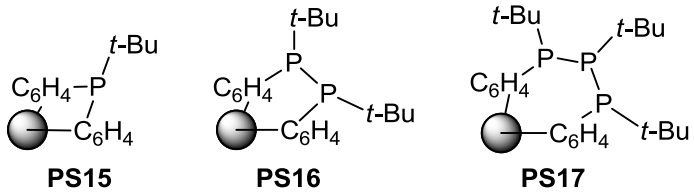
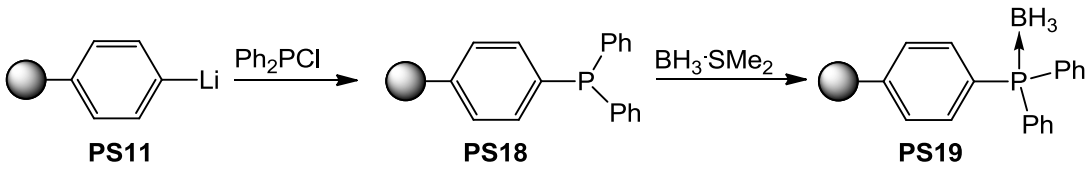


Figure 2.7. Possible cross-linked side products

Another possible source of side-products could be the formation of cross-linked products (Figure 2.7). Product **PS15** can be formed by double nucleophilic attack of the lithiated resin to *t*-$BuPCl_2$. Formation of cross-linked species with P–P bonds can also be envisaged via reductive P–P coupling, producing products such as **PS16** and **PS17**. The formation of these species is a well-known side reaction in substitution reactions of phosphorus halides. Due to the broadness of the resonances in the ^{31}P NMR spectra, it is not known which of the possible side products are formed. To investigate this possibility, the excess of *t*-$BuPCl_2$ was reduced to 1.1 equivalent. This resulted in a decrease of the side product resonances in the ^{31}P NMR spectrum. This reaction was performed in a capped NMR tube. During the lithiation, the tube was regularly mixed on a vortex and after washing, *t*-$BuPCl_2$ was added to the yellow resin, which then fully

decolourised. ^{31}P NMR showed that the reaction was complete within 30 minutes, with only a minimal amount of side product formation. Even after an additional hour, the intensity of the resonances did not change.

To verify the hypothesis of cross-linking due to reductive P–P coupling resulting in side products **PS16** or **PS17**, the same reaction was repeated with 1.1 equivalents diphenyl chlorophosphine (Ph_2PCl) instead of *t*-$BuPCl_2$ (Scheme 2.10). The possible product formed by reductive P–P coupling is $Ph_2P–PPh_2$, which will not be attached to the resin. Therefore its resonance will be visible in the crude ^{31}P NMR spectrum but disappear after washing of the resin.



Scheme 2.10 Verification of cross-linking via reaction with $PhPCl_2$

After addition of the Ph_2PCl to **PS11**, ^{31}P NMR showed only two resonances, at −6.8 ppm and −16.8 ppm in toluene, which corresponds to resin-bound PPh_2 (**PS18**; in comparison: PPh_3 has a resonance at −7 ppm)[18] and to $Ph_2P–PPh_2$ (literature data: $\delta^{31}P = -14.6$ in $CDCl_3$ and $\delta^{31}P = -13.6$ in C_6D_6)[19] and some other small resonances (Figure 2.8, left). After washing the resin, the resonance at −16.8 ppm disappeared together with all the small resonances (Figure 2.8, right). Subsequently, this resin was protected with BH_3·SMe_2 resulting in **PS19** with a resonance at 19.9 ppm.[18]

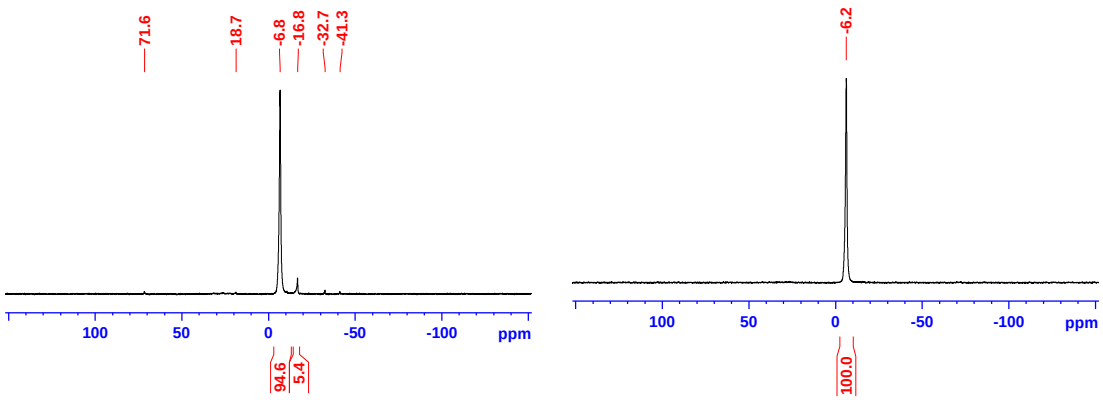
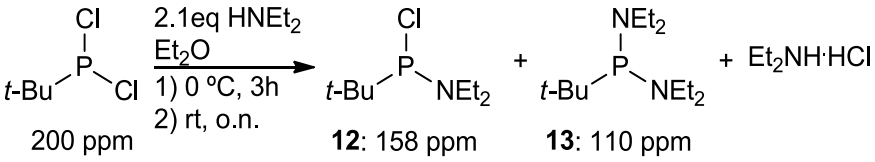


Figure 2.8 Resin-bound diphenylphosphine 18, unwashed (left); washed (right)

These experiments are consistent with cross-linking as the cause of side product formation. To avoid cross-linking completely another strategy was devised, avoiding direct reaction of *t*-BuPCl$_2$ with the lithiated resin.

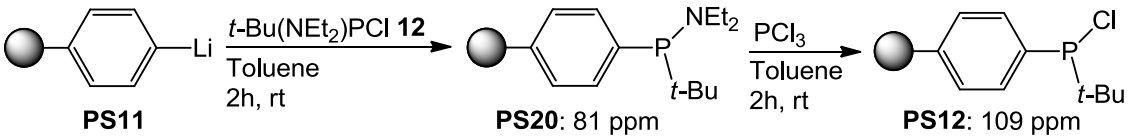
2.4.2 Synthesis of **PS1** using *t*-BuP(NEt$_2$)Cl

To prevent this crosslinking side reaction, *t*-BuPCl$_2$ was first converted into *tert*-butylchloro-*N*,*N*-diethylphosphinous amide **12** (*t*-BuP(NEt$_2$)Cl, δ^{31}P = 157) by reaction with two equivalents of diethylamine (HNEt$_2$) (Scheme 2.11).[20] By using a slight excess of HNEt$_2$ (2.1 eq.), it was ensured that all of *t*-BuPCl$_2$ was converted to **12** and **13**. The minimal amounts of diamine **13** formed due to the excess does not interfere in the next reaction and therefore the crude oil could be used directly after filtration and evaporation of solvent. An attempt to remove **13** by distillation under reduced pressure (20 mbar) resulted in increasing amounts of impurities, probably due to the thermal decomposition at the high distillation temperatures required.



Scheme 2.11 Synthesis of *tert*-butylchloro-*N*,*N*-diethylphosphoramine

Addition of an excess of the oily mixture of **12** and **13** to lithiated polystyrene **PS11** in toluene (Scheme 2.12), yielded **PS20** in pure form according to ^{31}P NMR (δ^{31}P = 81 ppm). In contrast to chlorophosphine **PS12**, this phosphinous amide **PS20** cannot undergo crosslinking, because the amide-group is not reactive towards **PS11**.



Scheme 2.12 General synthesis of resin-bound phosphine

This reaction emphasises the great power of the use of SPS as after addition of the oily mixture of **12** and **13** to the lithiated resin, the excess of reagent and all the other compounds present could be washed away easily, yielding sole immobilised phosphinous amide **PS20** according to ^{31}P NMR spectroscopy (Figure 2.12).

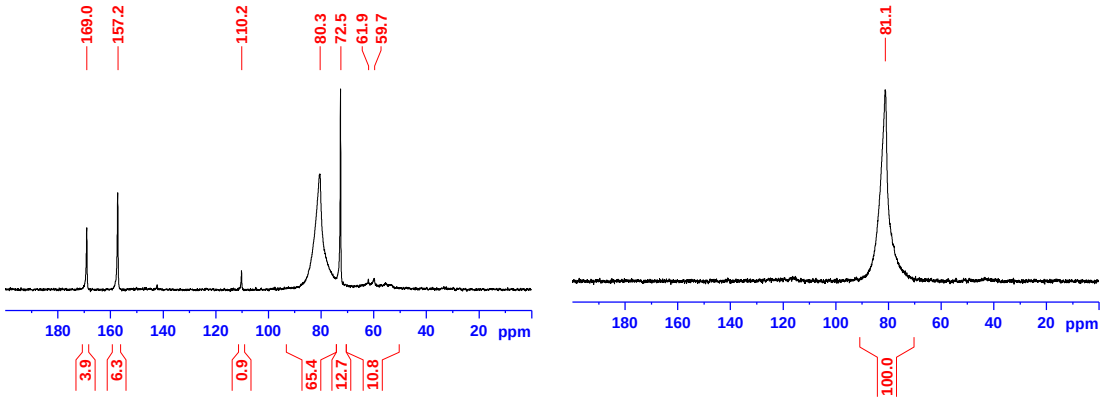


Figure 2.9. Resin PS20 before (left) and after washing (right)

Phosphinous amide **PS20** could then be converted to chlorophosphine **PS12** ($\delta^{31}P$ = 109) using PCl_3. However, during this conversion, in some of the reactions, formation of small amounts of *t*-BuPCl_2 (0.5%) was observed by ^{31}P NMR spectroscopy and resonances that are believed to correspond to resin-Ph-PCl_2 ($\delta^{31}P$ = 162) and to resin-Ph-P(NEt_2)Cl ($\delta^{31}P$ = 142) were observed (Figure 2.10, left). This could occur if alkyl transfer of the slightly acid labile *t*-Bu-group of **PS12** to a second molecule of PCl_3 occurs. Also, a resonance at $\delta^{31}P$ = 44 was observed during the reaction which was still present after washing of the resin and varied in intensity after repeating the experiment (2 to 10%).

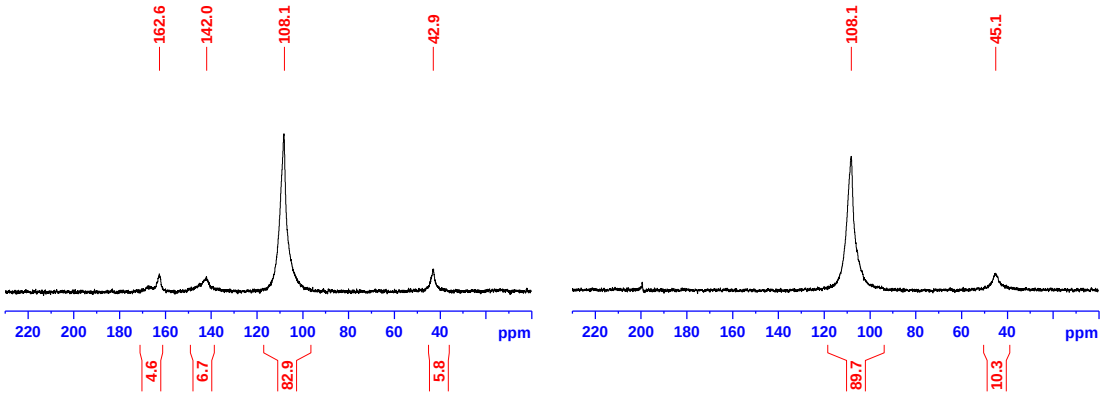
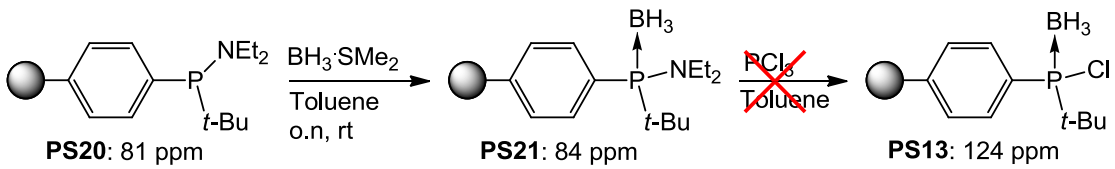


Figure 2.10. Resin PS12 with impurities after washing

In situ protection of **PS20** with borane yielded a single resonance at 84 ppm, but the product **PS21** was totally unreactive as the obtained product could not be converted into **PS13** (Scheme 2.13).



Scheme 2.13 Borane protection of PS20 inhibits the chlorination towards PS13

2.4.2.1 Investigation of the nature of the side product

To investigate the formation of this unknown side-product, NMR test reactions were performed under different conditions and/or with different reagents, directly monitored by ^{31}P NMR. Besides PCl_3, anhydrous HCl solution in Et_2O was also used for the chlorination of phosphinous amides such as resin **PS20**. This led to increased formation of the side product, and the signal was broader and of a higher intensity. The amounts were different for every reaction performed.

One of the obvious structures obtained by hydrolysis is product **PS14** (Figure 2.11), because the resonance of the molecular analogue of **PS14** is at $\delta^{31}P = 47$. However, it is unlikely that there are hydrolysis products formed during this reaction in the presence of PCl_3, due to the higher reactivity of PCl_3 towards H_2O compared to that of **PS12**. Moreover, these products would react with *n*-BuLi in follow-up reactions as well. The resonance of this side product did not shift after the lithiation of PS-DVB-Br and subsequent reactions (*vide infra*), so it was still present and thus seemed to be unreactive.

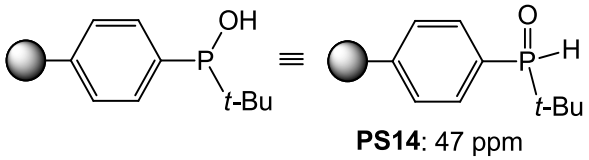


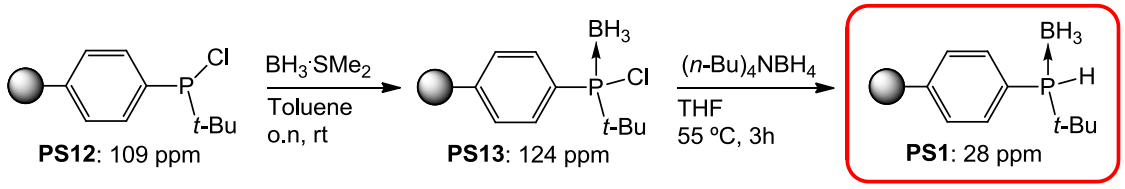
Figure 2.11. Proposed hydrolysed product PS14

Another chlorination agent, oxalyl chloride, was tried as well. This reagent was able to convert the amine-group into the desired chloro group, but side-products were also formed. The side-products formed in the chlorination with the HCl-solution were similar to those formed in the PCl_3 reactions. In the reactions where degassed oxalyl chloride was added to resin **PS20** in THF, the colour of the resin changed from yellow (colour of resin **PS20**) to orange/brown and after 24 hours the resin was black. Besides the change of colour, the swelling of the resin was decreased tremendously as well. More importantly, additional unidentified resonances were observed in the ^{31}P NMR spectra at 55, 70 and 126 ppm next to the signal of resin **PS12** at $\delta^{31}P = 109$. These additional resonances increased after leaving the reaction overnight at room temperature, especially the resonance at 126 ppm, while the signal of resin **PS12** at 109 ppm decreased. Unfortunately, it was not possible to cleave the products of this resin for

analysis and thus it is unknown which products were formed and what kind of side reactions were causing the formation of these products. Thus it was concluded that the use of oxalyl chloride in combination with the resins did not result in the expected clean products, as it decomposed the immobilised phosphorus compounds, and based on the change of resin properties, swelling and colour, the resins are not resistant against this reagent.

*2.4.2.2 Protection and reduction of **3** to obtain phosphine **5***

Although resin **PS12** contained an impurity (5-10%), it could be treated with $BH_3 \cdot SMe_2$ yielding resin **PS13** (Scheme 2.14, $\delta^{31}P = 124$). This reaction proceeds quantitatively and without any problems. For the subsequent reduction reaction, $(n\text{-}Bu)_4NBH_4$ was added to resin **PS13** and heating at 55 °C for 3 hours was required to obtain resin **PS1** ($\delta^{31}P = 29$ ppm), still with the impurity at 44 ppm in the ^{31}P NMR spectrum.



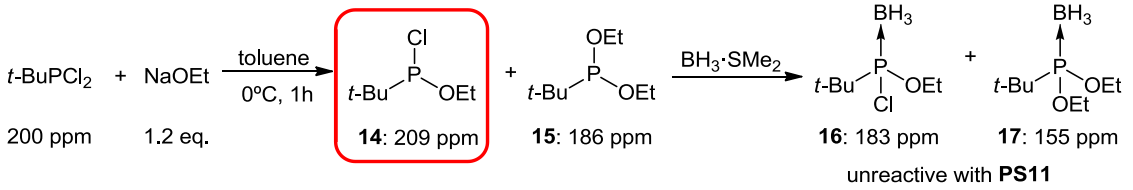
Scheme 2.14 Reactions facilitating immobilised *tert*-butyl phosphine-borane 5

2.4.3 Synthesis of **PS1** using *t*-BuP(OEt)Cl

To avoid the unwanted side product formation obtained from the direct route as well as from the use of aminophosphines a new route was explored to obtain synthon **PS1** in the highest purity possible using *tert*-butylchloroethylphosphinite **14** as reagent, which results in an ethoxy-group on the immobilised phosphorus as second leaving group instead of the diethylamine-group (**PS20**); consequently this would make the chlorination step redundant.

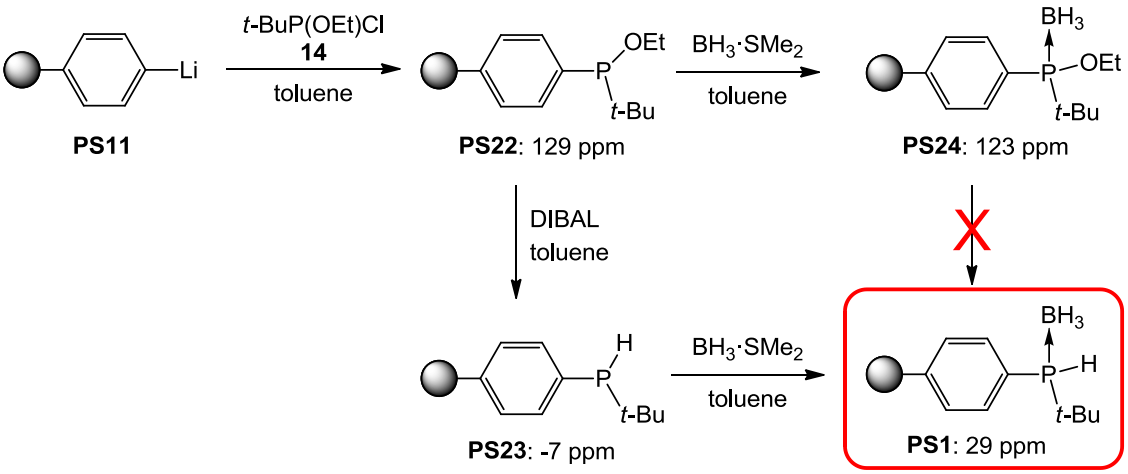
For the synthesis of reagent **14**, commercially available *tert*-butyldichloro-phosphine in toluene was reacted with freshly prepared sodium ethoxide[21] in small excess (1.1 to 1.2 equivalents) at 0 °C (Scheme 2.15). This resulted in a mixture of chloroethoxy-*tert*-butylphosphine **14** with a small amount of diethyl *tert*-butylphosphonite **15**.[22] Purification of **14** was attempted but not achievable as even evaporation of the solvent

under reduced pressure resulted in side-product formation and decomposition of the product; ^{31}P NMR spectroscopy showed only resonances between 40-90 ppm.



Scheme 2.15 Synthesis of *t*-BuP(OEt)Cl

In situ protection of the product mixture with borane to prevent decomposition during purification was carried out, but this did not prevent the formation of some side products (10%; δ = 55-66 ppm) upon evaporation of the solvent. Unfortunately, due to the borane-group, compound **16** became unreactive in the reaction with lithiated polystyrene **PS11**. Therefore, the crude reaction mixture of **14** and **15** was used directly in excess without further purification (Scheme 2.16).



Scheme 2.16 Synthesis of synthon PS1 via ethoxyphosphinite 14

After addition of the reaction mixture to **PS11**, the excess of reagent and all the other compounds present (Figure 2.12, left) were washed away easily, yielding sole phosphinite **PS22** attached to the resin according to ^{31}P NMR spectroscopy (Figure 2.12, right). The immobilised phosphinite **PS22** was protected with borane to prevent the Arbusov reaction as described by Croft *et al.*[22] in their studies during the synthesis of diethyl *tert*-butylphosphonite **15** from *tert*-butyldichlorophosphine and ethanol. Again the reactivity of phosphinite-borane **PS24** in the reduction towards phosphine **PS1** was too low. Very strong reducing agents such as vitride (sodium bis(2-

methoxyethoxy)-aluminium hydride solution in toluene) and DiBAL were tried, but no conversion was obtained, even after heating to 50 ºC.

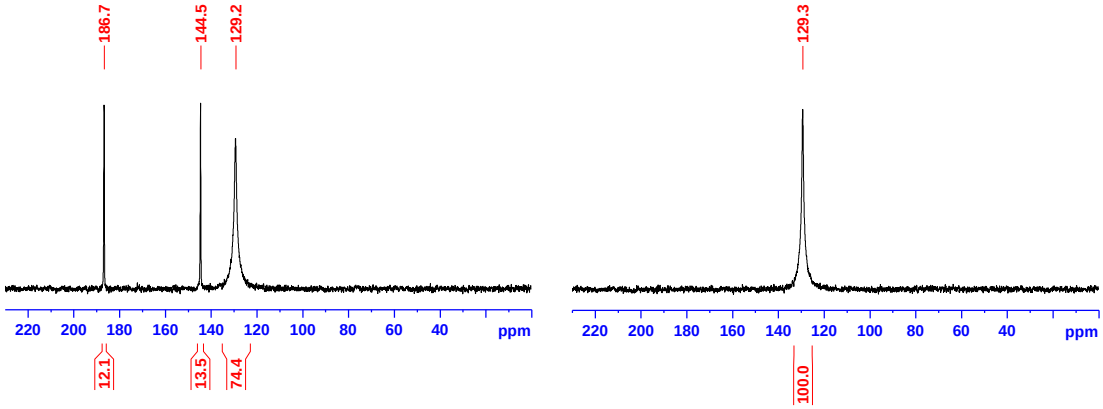


Figure 2.12. Resin PS22 before (left) and after washing (right)

Reduction of the ethoxy-group of phosphinite **PS22** with DIBAL before the protection with borane, yielded secondary phosphine **PS23** in more than 99% purity according to ^{31}P NMR spectroscopy (Figure 2.13). The protection of phosphine **PS23** with borane was quantitative after which the desired synthon **PS1** was obtained without impurities (Figure 2.14). This set of reactions was repeated several times, on small (0.5 g resin) as well as on a large scale (5 g resin) without any immobilised side product formation observed.

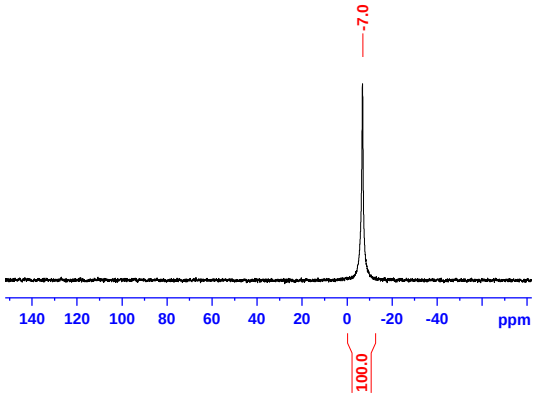


Figure 2.13. Immobilised secondary phosphine PS23

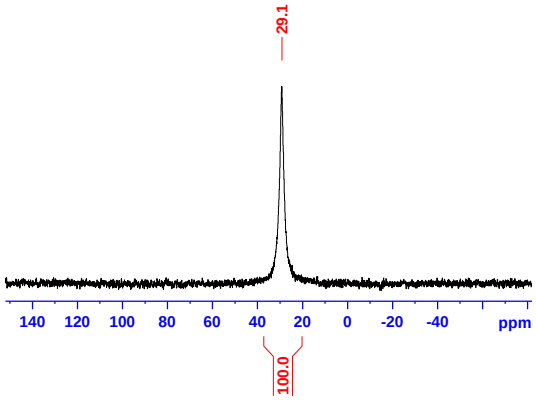
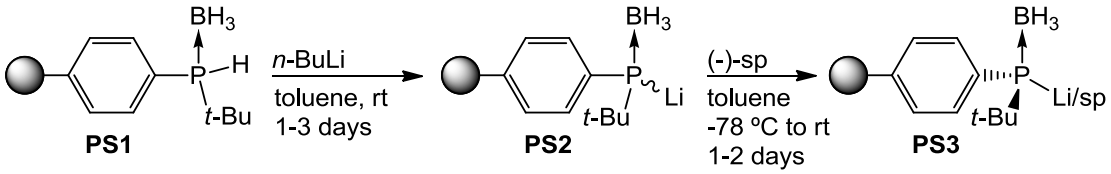


Figure 2.14. Synthon PS1

*2.5 Lithiation of **PS1** and complex formation with (–)-sparteine*

The synthesis of immobilised bis(phosphines) using synthon **PS1** was explored by applying the method developed by the Livinghouse group[7] in SPS, despite the fact that it is unlikely to obtain *P*-stereogenic purity in the solid supported system.



Scheme 2.17 Lithiation of resin PS1 followed by complex formation with (–)-sparteine to form PS3

First of all immobilised phosphide **PS3** had to be generated by lithiation of **PS1** (Scheme 2.17). Small amounts (40-60 mg resin) were used for these reactions which were performed in NMR tubes. The tubes were loaded with **PS1**, suspended in toluene and once the resin was fully swollen, *n*-BuLi was added at room temperature. The reactions were monitored by ^{31}P NMR spectroscopy. During these reactions, the colour of the resin became yellow and the swelling decreased. Interestingly, this resulted in complete disappearance of all resonances in the ^{31}P NMR spectrum in 24-48 hours. This disappearance could be due to solvent effects as later it was observed that by changing the solvent to THF after the formation of **PS2**, a resonance at −16 ppm had appeared.

Higher reaction temperatures of 50 °C for 4 hours did not enhance the reaction rate. The colour of the resin became darker yellow in comparison to the resin that had reacted at room temperature. The spectra of two simultaneously performed reactions, one at room temperature and one at 50 °C, were identical. The intensity of the resonances decreased at the same rate and no other signals were observed. Therefore, it was decided to perform the reactions at room temperature to minimise the colouration of the resin.

When all resonances had disappeared from the ^{31}P NMR, the toluene layer was removed to reduce the excess of *n*-BuLi and fresh toluene was added. Then, the resin was cooled to −78 °C and (–)-sparteine was added. The reaction was allowed to warm slowly to room temperature. Remarkably, as a result of the (–)-sparteine addition, a resonance at $\delta^{31}P = -20$ appeared, purportedly corresponding to lithium phosphide-sparteine complex **PS3**. This process is clearly visible by overlaying the corresponding spectra (Figure 2.15).

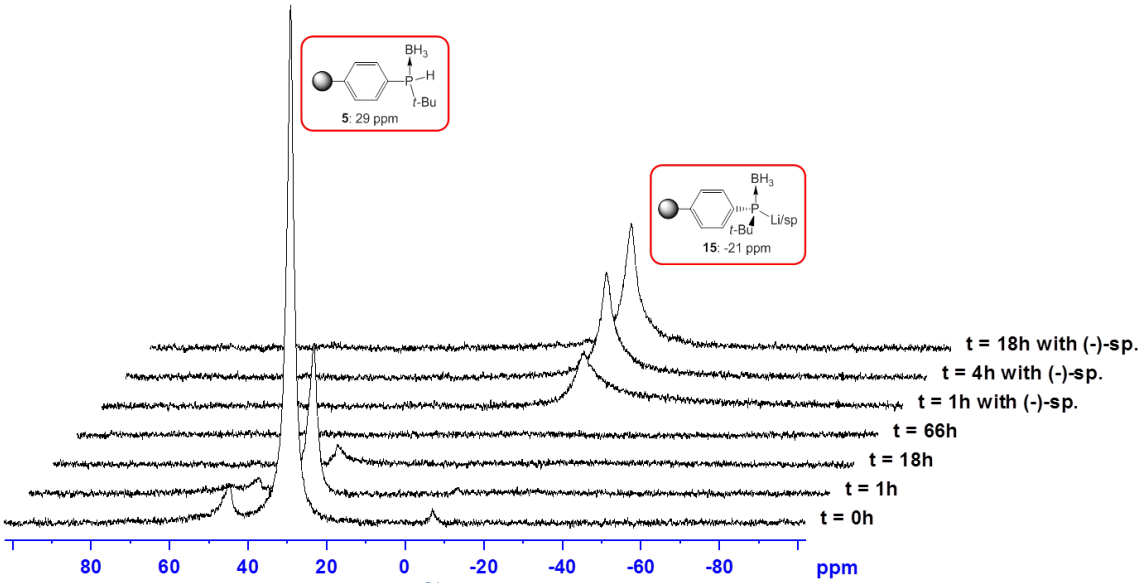


Figure 2.15. ^{31}P NMR spectra of the formation of PS3

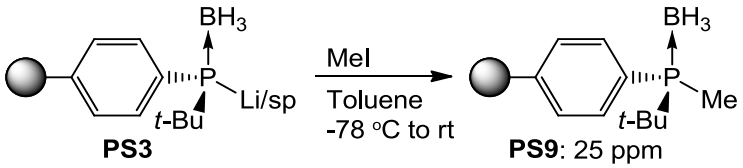
The signals clearly disappear over time after addition of *n*-BuLi to resin **PS1** (t = 0h to t = 66h). After the addition of (–)-sparteine, the new signal appeared at $\delta^{31}P = -20$ and increases in time (t = 1h to t = 18h with (–)-sparteine.). After refreshing the supernatant, this complex was stable for at least one week, stored in the same NMR tube under argon atmosphere at room temperature.

For this study a batch of resin **PS1** was used, which contained small amounts of phosphine-oxide (44.7 ppm, 10%) and unprotected phosphine (−6.9 ppm, 1%). During the lithiation their corresponding signals disappeared, but reaction with (–)-sparteine is unlikely, other explanations could be due to solvent effects or that their chemical shift lies under the product resonance.

2.5.1 Synthesis of immobilised phosphine-phosphinites

2.5.1.1 Reactions of PS3 with methyl iodide

Reaction of lithiated resin-sparteine complex **PS3** with methyl iodide as electrophile proceeded smoothly (Scheme 2.18) and light yellow resin **PS9** was obtained in quantitative yield according to ^{31}P NMR (Figure 2.16).



Scheme 2.18 Synthesis of immobilised tertiary phosphine-borane 30

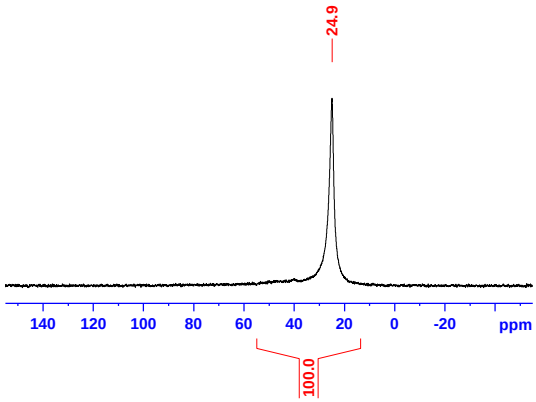
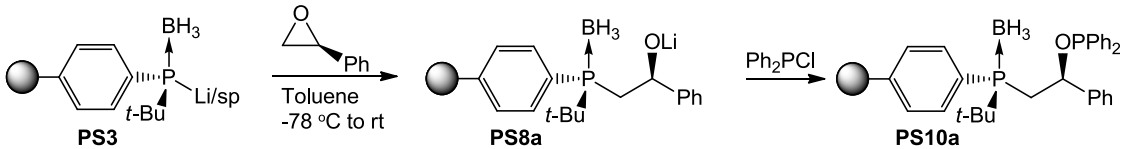


Figure 2.16. Immobilised *tert*-butylmethyphenylphosphine-borane PS9

2.5.1.2 Reactions of PS3 with styrene oxide

The synthesis towards immobilised phosphine-phosphinites/phosphites was started by addition of (*R*)- and (*S*)-styrene oxide to lithium phosphide-sparteine complex **PS3** (Scheme 2.19). The addition was performed in toluene at −78 °C, after which the mixture was shaken briefly on a vortex mixer and then allowed to slowly warm up to room temperature.



Scheme 2.19 Immobilised phosphine-phosphinite synthesis via (*R*)-styrene oxide

The initially yellow resin decolourised slowly over time, but not completely. ^{31}P NMR spectra of resin **PS8a** showed a very broad resonance at 29 ppm (Figure 2.17, left). It is hypothesised that this broadening of the resonance is probably due to the

lithium ions present within the compound. From these spectra it could not be determined whether the reaction was complete or not.

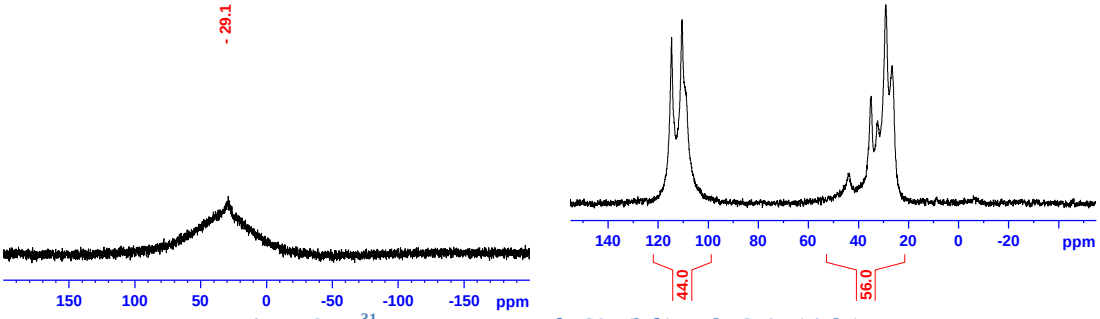


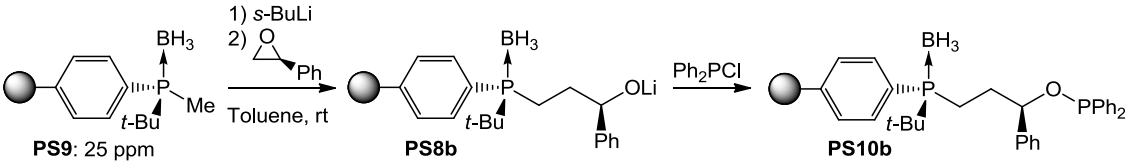
Figure 2.17 ^{31}P NMR spectra of PS8a (left) and PS10a (right)

After a day the supernatant was refreshed and subsequent addition of chlorodiphenylphosphine resulted in the formation of immobilised phosphine-phosphinite-borane **PS10a** (Figure 2.17, right). The resonances of the phosphine-group in the ^{31}P NMR spectrum seems to consist of four resonances and the phosphinite-group of two singlets. It is plausible to assume that there are two different environments on the phosphine-group and that the sparteine did not give the desired stereoselectivity in 100% *ee*. However, this does not explain why the pattern consists of four resonances. Unfortunately, it is impossible to obtain a reliable integration for the resonances to compare the phosphine-group with the phosphinite-group due to the broadness and thus the overlay of the resonances and the side product present in the slope of the resonance.

A possible explanation could be that the multiplicity of the signals is caused by the resin backbone-structure or by unwanted side reactions *e.g.* coupling of a second styrene oxide to **PS8a**, elongating the chain length. In addition, the conditions had to be changed compared to the synthesis reported for the molecular analogues.[7-10] The liquid phase reactions reported were performed at optimal conditions in Et_2O at and only 1.3 equivalents of styrene oxide were added. In our system it is impossible to use Et_2O as solvent due to low swelling of the resin in Et_2O and thus the reactions were performed in toluene and because 100% completion is essential, excesses of three equivalents of reagent were used. Performing the reaction in THF was considered, however the phosphide would then be too soluble to form the lithium phosphide-sparteine precipitate.

When the procedure was repeated in the absence of (–)-sparteine with **PS2**, similar spectra were obtained however, the intensity of the signals was lower and less defined and it appears that the lithiated resin **PS2** was not reactive enough towards the styrene oxide.

2.5.1.3 Reactions of PS9 with styrene oxide



Scheme 2.20 Synthesis of immobilised phosphine-phosphinite-borane 30

Lithiation of the methyl group of resin **PS9** with *s*-BuLi,[5a] followed by addition of (*R*)-styrene oxide and then chlorodiphenylphosphine would furnish resin **PS10b** (Scheme 2.20). During the lithiation of **PS9**, the resonances disappeared in the baseline, similar to the lithiation of **PS1**. The ^{31}P NMR spectrum of **PS8b** showed a very broad signal with a maximum at 25 ppm (Figure 2.18, left). The resonances of resin **PS10b** were singlets but the resonance corresponding to resin **PS9** was observed as well (Figure 2.18, right). Thus the lithiation of resin **PS9** was not complete and the resonance at 25 ppm must have belonged to **PS9** overlapping with the broad signal of **PS8b**.

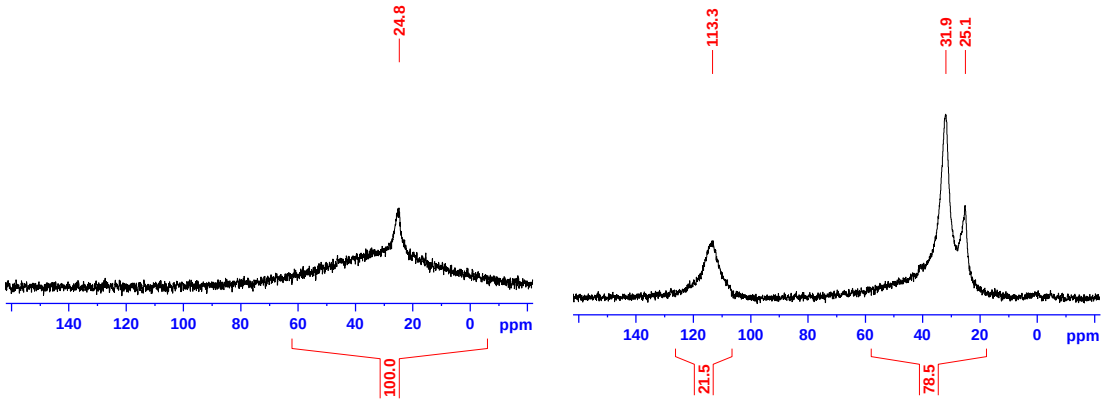
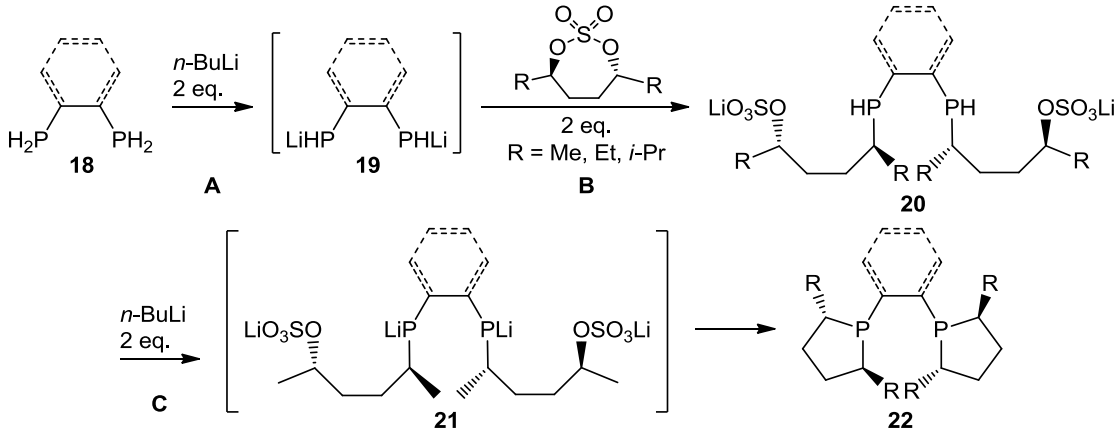


Figure 2.18. Immobilised phosphine PS8b (left) and phosphine-phosphinite-borane PS10b (right)

From these reactions it could be concluded that the synthesis of immobilised phosphine-phosphinites via epoxides was unsuccessful as the desired products could not be obtained in high purity. Therefore the utilisation of different bifunctional electrophiles, such as cyclic sulfates, was investigated.

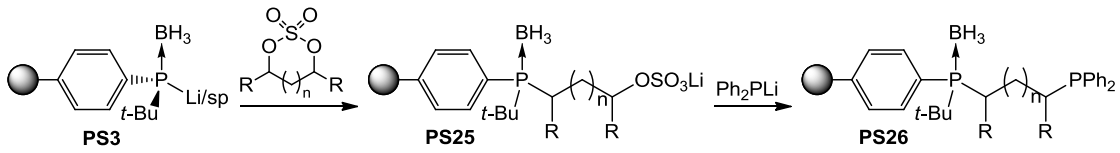
2.6 Synthesis of immobilised bis(phosphines)

Based on the work of Burk[23] on phospholanes (Scheme 2.21), the utilisation of cyclic sulfates was envisioned to be a potential efficient route towards immobilised bis(phosphines). The synthesis of phospholanes **22** is a one pot three-step reaction in which dilithium bisphosphides **19** react readily with the cyclic sulfates (step **B**) and after a second addition of *n*-BuLi (step **C**) the system ring-closes to form the desired phospholanes **22**. The ring-opening of the cyclic sulfates with lithium phosphide proceeds with complete inversion at the stereogenic centre.[24]



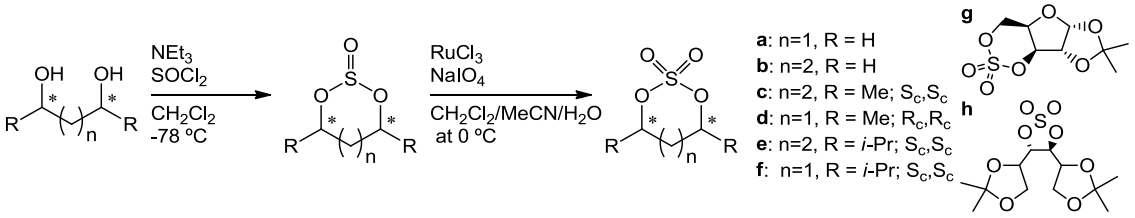
Scheme 2.21 Synthesis of phospholanes by Burk[23]

It was envisaged that after reaction of our immobilised lithium phosphide **PS3** with cyclic sulfates the obtained immobilised sulfate group in **PS25** could be substituted by a second phosphine resulting in immobilised bis(phosphines) **PS26** (Scheme 2.22).



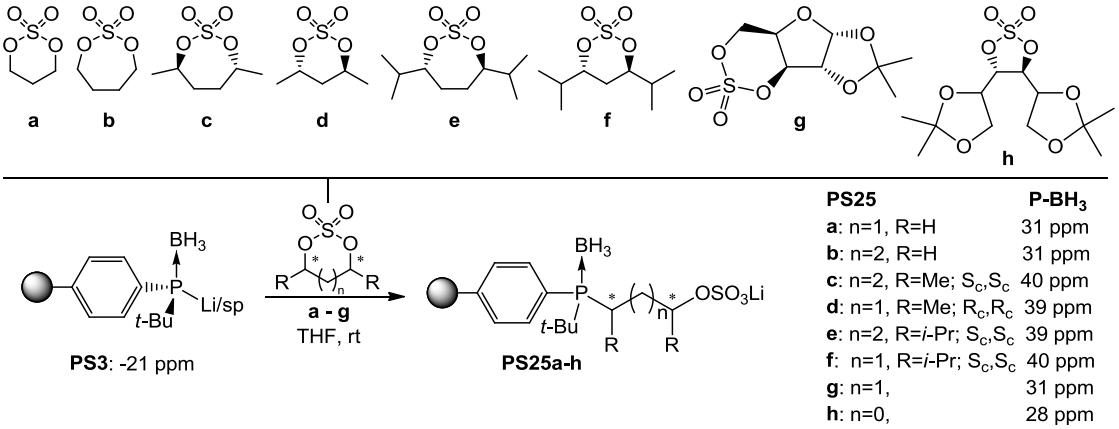
Scheme 2.22 Synthesis of immobilised bis(phosphines) PS26 via cyclic sulfates

To test this hypothesis, a small library of different cyclic sulfates was synthesised from the corresponding diols conforming to literature procedures (Scheme 2.23).[24,29] It was found that these cyclic sulfates when stored at room temperature decomposed over time and therefore had to be stored in the freezer.



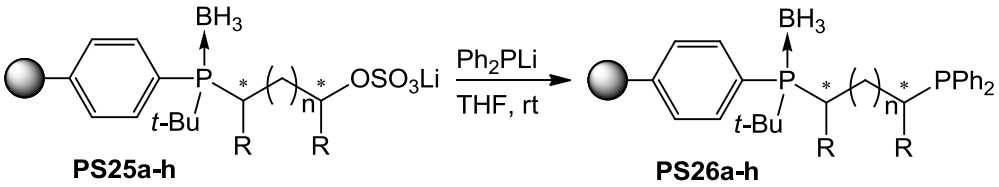
Scheme 2.23 General synthesis of cyclic sulfates

The cyclic sulfates were added to synthon **PS3** and these reactions proceeded readily to form the corresponding immobilised phosphine-sulfates **PS25a-h**. By applying excesses of cyclic sulfate cross-linking of two **PS3**'s with one sulfate could be minimised. The reactions were followed by ^{31}P NMR spectroscopy and the resins were washed after completion of the reactions. The reaction times varied from 1 hour (cyclic sulfates **a-c**) to overnight (**d-h**).



Scheme 2.24 Formation of immobilised phosphines PS25a-h

To convert the obtained immobilised phosphine-sulfates **PS25** to their corresponding bis(phosphines), an excess of freshly prepared lithium diphenylphosphide in THF was added (Scheme 2.25). The use of an excess of lithium diphenylphosphide is necessary as the lithium diphenylphosphide decomposed during the long reaction times needed (15 hours to one week at room temperature).



Scheme 2.25 Synthesis of immobilised bis(phosphines) PS26

This resulted in immobilised bis(phosphines) with resonances of the two phosphorus atoms in a near 1 to 1 ratio in the corresponding ^{31}P NMR spectra for resins **PS26a-c** (Figure 2.19).

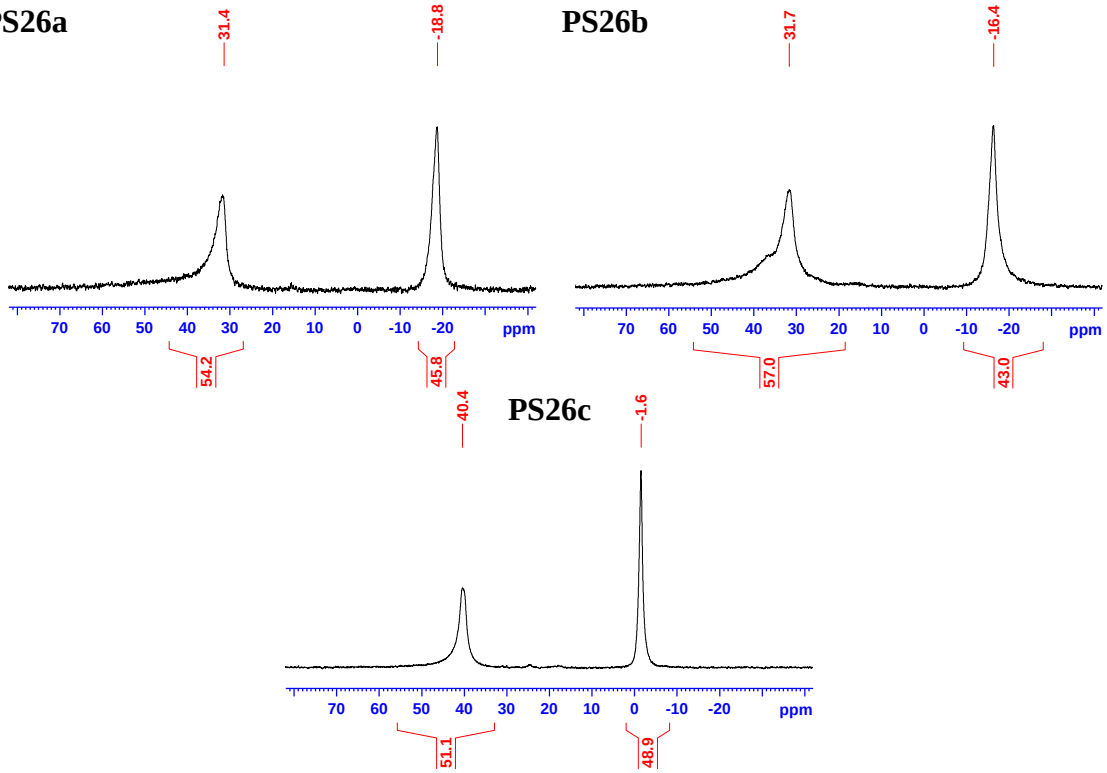


Figure 2.19 Immobilised bis(phosphine)-boranes PS26a-c

The reactions of **PS25d-h** proved to be more difficult and much slower. **PS26d** was formed in 13% when the reaction was performed at room temperature for 3 days (Figure 2.20, left). Heating the reaction mixture for an additional 16 hours did result in more bis(phosphine), however additional resonances were visible in the ^{31}P NMR spectrum as well (Figure 2.20, right). These additional resonances were immobilised on the resin and could be from the borane swapping from one phosphine to the other, or from side-products formed due to the heating of the reaction mixture.

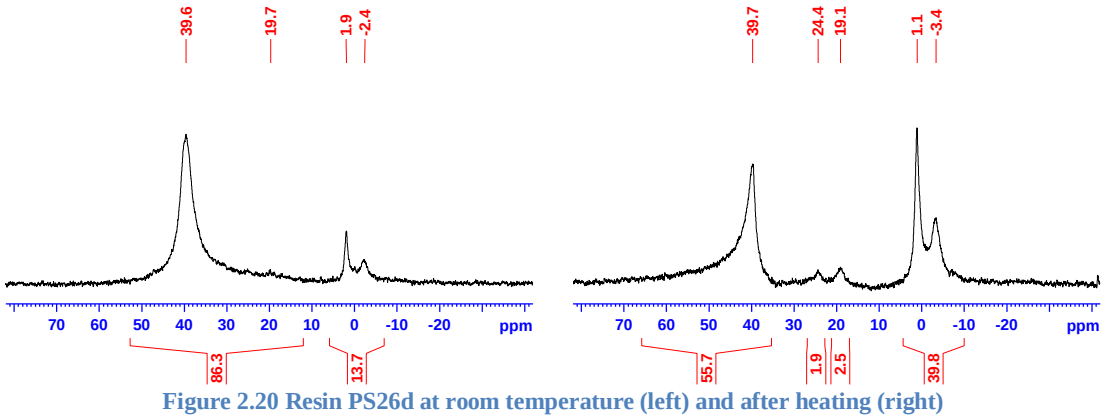


Figure 2.20 Resin PS26d at room temperature (left) and after heating (right)

PS26e-g could not be formed even after heating the reaction mixture (Figure 2.21). It is hypothesised that **PS26e** and **f** could not be formed probably due to steric hindrance from the *iso*-propyl-groups. It is unknown why **PS26g** was not successfully formed as steric hindrance from the furanose-bridge should be similar to **PS26a**. The reaction towards **PS25h** with lithium diphenylphosphide at room temperature did result in the formation of **PS26h**, however other resonances were present of compounds immobilised on the resin as well. In the ^{31}P NMR spectrum, the resonances at 28 and −7 ppm are proposed to belong to the bis(phosphine) and the resonances at 8 and 5 ppm can be explained by the swap of the borane between the two phosphorus donor atoms, but the resonance at −31 ppm could not be explained.

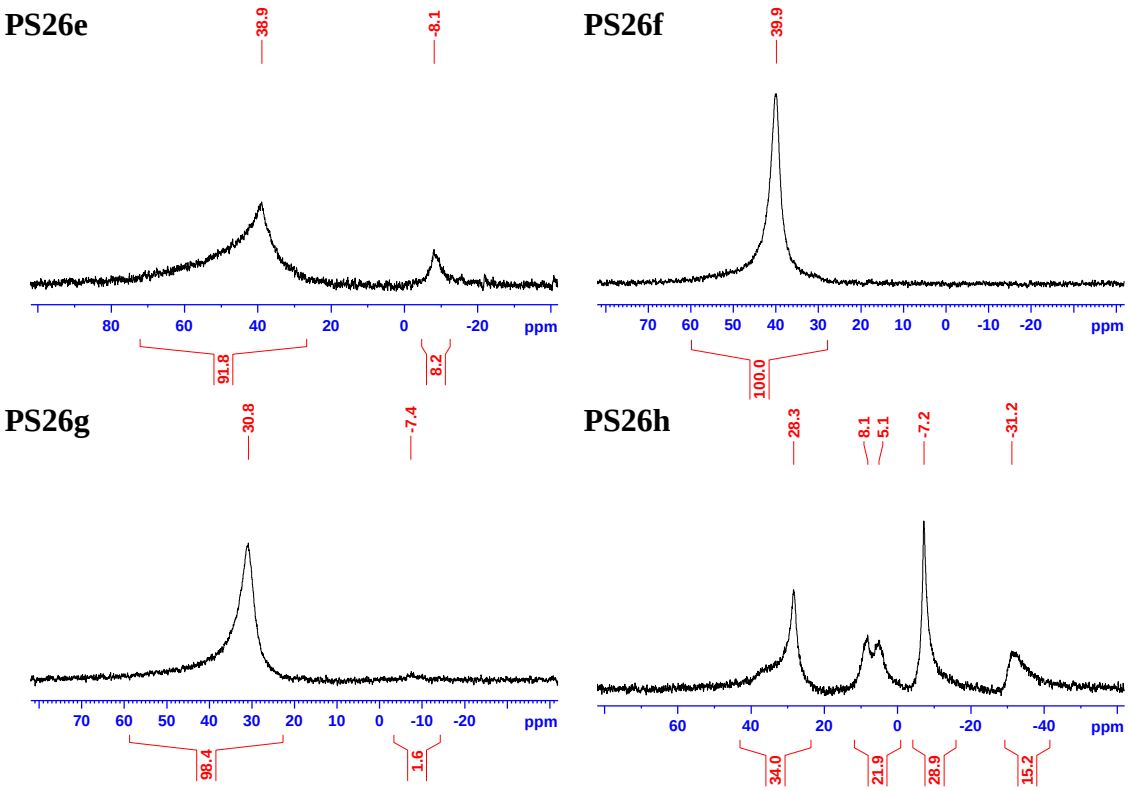
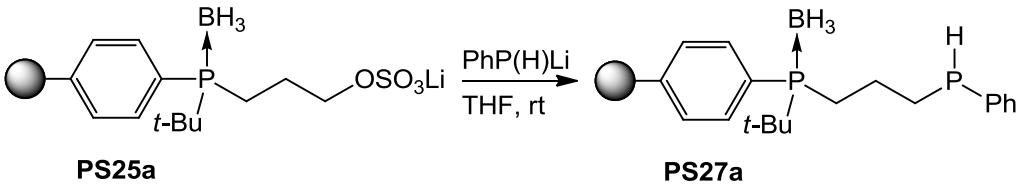


Figure 2.21 Immobilised bis(phosphine)-boranes PS26e-h

Apart from using several different cyclic sulfates, the lithium phosphide structure can be changed as well to expand the scope of the immobilised bis(phosphine) synthesis. In one test reaction with **PS25a**, lithium diphenylphosphide was substituted with lithium phenylphosphide which resulted in the formation of **PS27a** in good yield (Scheme 2.26). The resonance at −55 ppm in the ^{31}P NMR spectrum of **PS27a** (Figure 2.22) corresponds closely to *n*-propyl-phenylphosphine, of which the liquid

phase analogue has a resonance at −53 ppm.[25] This reaction was performed on small scale in an NMR tube as a test reaction. The compound **PS27a** has potential for expansion towards immobilised tridentate ligands and these reactions could be explored in the future.



PS25a **PS27a**

Scheme 2.26 Synthesis of PS27a

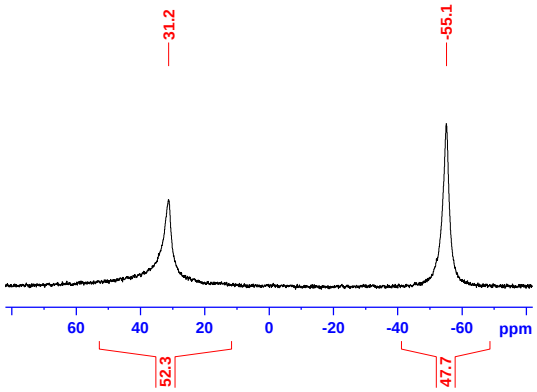


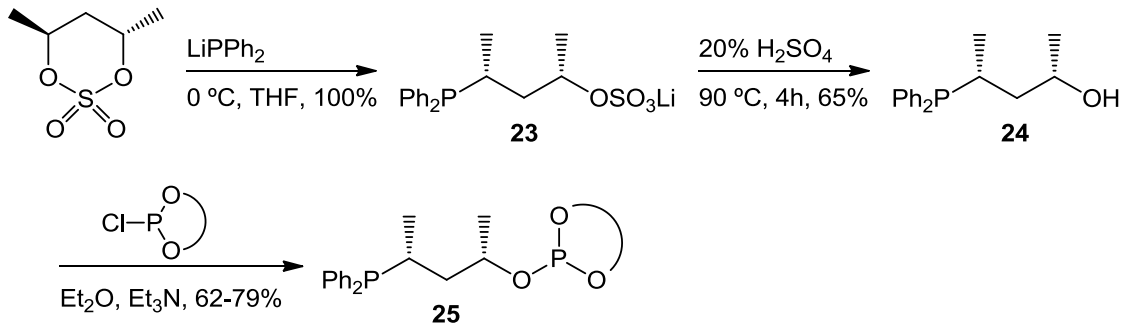
Figure 2.22 NMR spectrum of resin PS27a

The utilisation of several other lithium phosphides, obtained from phosphines such as dicyclohexylphosphine, ditolylphosphine and di-*iso*-propylphospine, could be envisioned; however these reactions have not yet been performed.

2.7 Hydrolysis experiments, towards phosphine-phosphinites

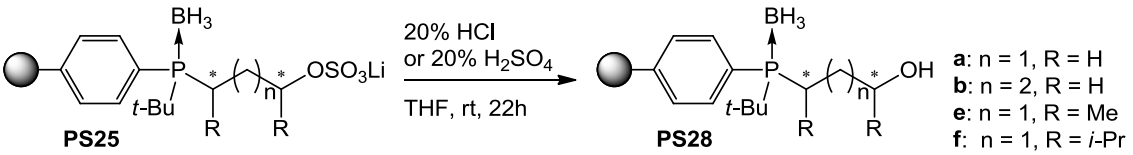
Hydrolysis of the immobilised phosphine-sulfates would result in immobilised phosphines bearing alcohol functionalities. Subsequent addition of chlorophosphines would then yield immobilised phosphine-phosphinites and –phosphites.

The groups of Hegedüs[26] and Farkas[24] both have applied this method for the synthesis of phosphine-phosphites **25** in which they hydrolyse their phosphine-sulfates **23** with 20% H_2SO_4 at 90 °C and react the obtained hydroxyalkyl phosphine **24** with chlorophosphites (Scheme 2.27).



Scheme 2.27 Synthesis of phosphine-phosphites by Farkas *et al*.[24]

The resonances of the immobilised phosphine-sulfate and phosphine-alcohol have the same chemical shift in ^{31}P NMR spectrum and with the limited amount of analysis methods available, it was found that the hydrolysis reactions could only be followed by elemental analysis or by infrared spectroscopy (IR) when focussed on the S=O stretch vibrations belonging to the sulfate group. Following the reaction with elemental analysis would be too time-consuming and expensive; therefore the hydrolysis was followed by IR. Pressing the resin beads into KBr-discs gave the best results. Resin **PS25a** was chosen to investigate the hydrolysis method. The IR spectrum of resin **PS25a** showed a band at 2378 cm^{-1} for the BH_3,[27] and two bands at 1262 cm^{-1} and 1640 cm^{-1}, corresponding to the S=O stretch vibrations,[28] among the many bands belonging to the polystyrene resin.



Scheme 2.28 Hydrolysis of immobilised phosphine-sulfates PS25

The immobilised phosphine-sulfate **PS25a** was stirred in a 20% H_2SO_4 in THF solution for 22 hours at 60 °C (Scheme 2.28). By comparing the IR spectra of the resin **PS25a** before and after the reaction, it was observed that the two bands at 1262 cm^{-1} and 1640 cm^{-1} disappeared over time. To optimise the reaction conditions, the hydrolysis reactions were repeated at room temperature, and with 20% HCl at room temperature and at 60 °C. The results of these reactions were all similar to the initial results. The ^{31}P NMR spectrum confirmed that the chemical shift of the hydrolysed resin **PS28a** was similar to that of resin **PS25a**, but line width was reduced and some minor impurities had formed during the hydrolysis.

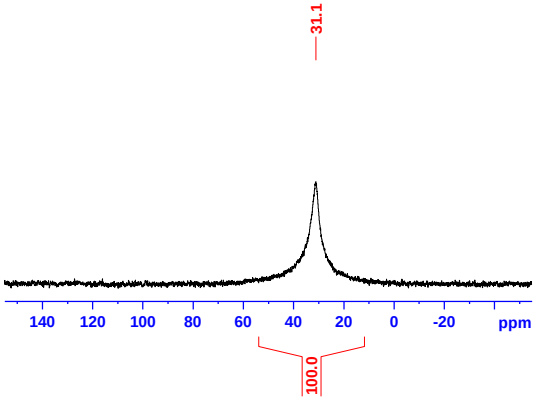


Figure 2.23 Resin PS25a before hydrolysis

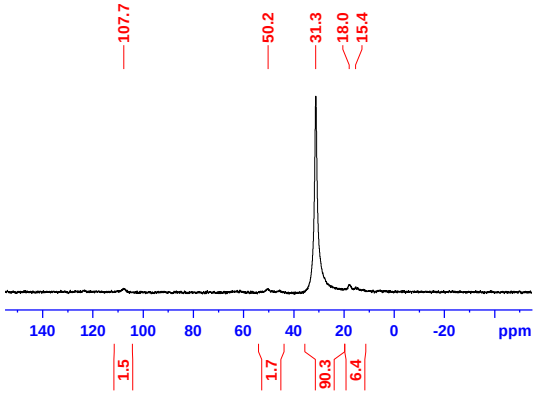
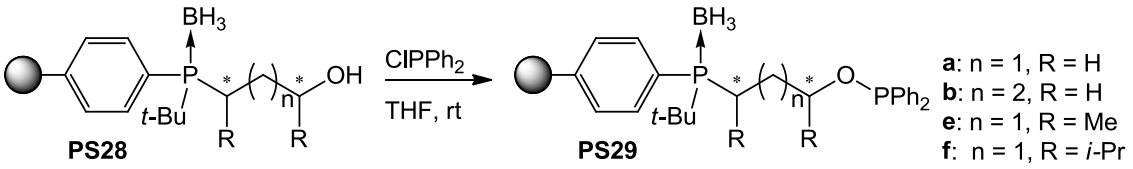


Figure 2.24 Resin PS28a after hydrolysis

The resins **PS15b**, **e** and **f** were also stirred in a 20% HCl-solution for 22 hours at room temperature. Once it was confirmed by IR that the S=O stretch vibration bands had completely disappeared, a slight excess of chlorodiphenylphosphine was added to the three resins (**PS28a**, **b**, **e** and **f**) in the presence of *N*-methylmorpholine, which resulted in the formation of immobilised phosphine-phosphinites **PS29a**, **b**, **e** and **f** (Scheme 2.29).



Scheme 2.29 Synthesis of immobilised phosphine-phosphinites PS29

After 15 hours reaction time at room temperature, the ratio between the signals of the phosphine and phosphinite of resin **PS29e** was 65 to 35, respectively. The reaction mixture was then heated to 60 ºC for 22 hours. However, this did not speed up the reaction, it only caused more impurities to be formed and it was observed that the borane protecting group did swap between the phosphine and the phosphinite group resulting in complicated ^{31}P NMR spectra (Figure 2.26).

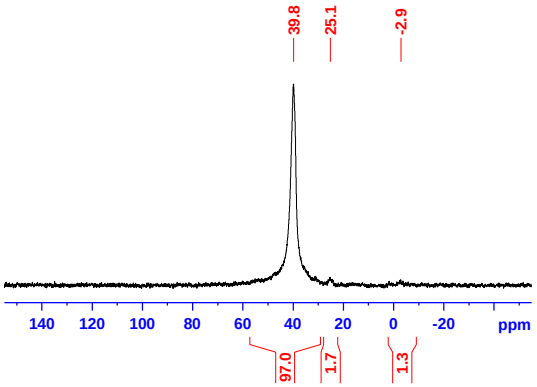


Figure 2.25 Resin PS28e

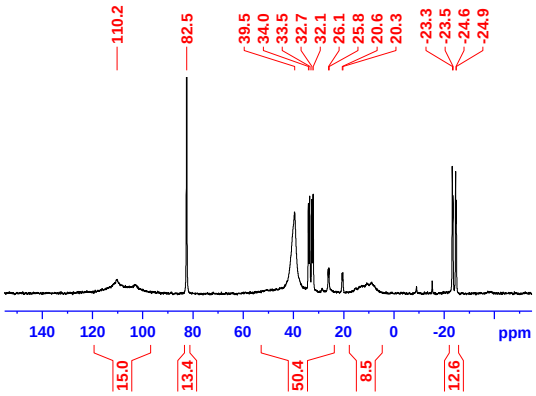


Figure 2.26 Reaction mixture of resin PS28e with Ph_2PCl

The reaction was stopped after an additional week at room temperature even though the excess of chlorodiphenylphosphine was still present and the resin was washed (Figure 2.27). Addition of $BH_3{\cdot}SMe_2$ complex did simplify the spectra considerably by protecting both the phosphine and phosphinite, after which the ratios between phosphine and phosphinite could be determined more accurately (Figure 2.28). The ratio had remained the same (64 to 36 respectively) even after heating and the prolonged reaction time.

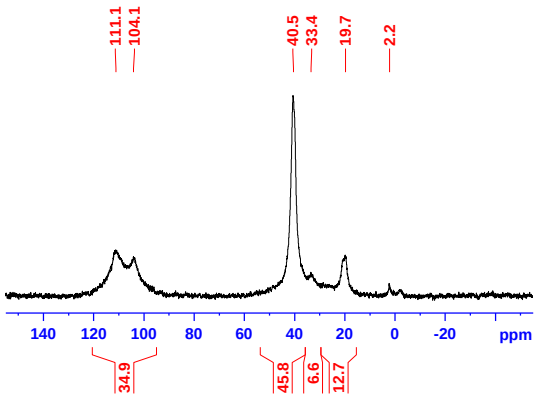


Figure 2.27 Resin PS29e

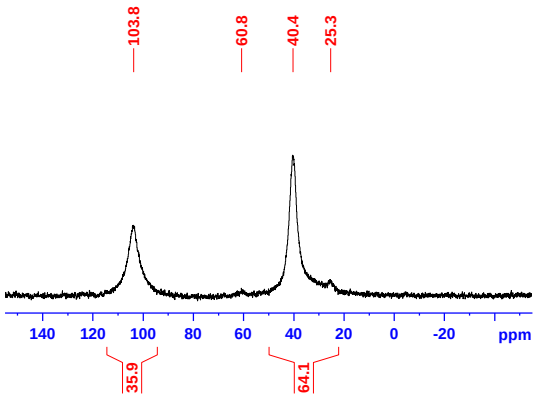


Figure 2.28 Resin PS29e with additional borane

Thus even though the bands corresponding to the sulfate group had fully disappeared according to IR, no full substitution to the phosphinites was obtained. This was the case for all four resins. Resin **PS28a** was formed in a 61 to 39 ratio respectively **PS28b** in a 62 to 35 ratio (Figure 2.29) and after addition of additional borane the ratio of resin **PS28f** was found to be 80 to 20 (Figure 2.30).

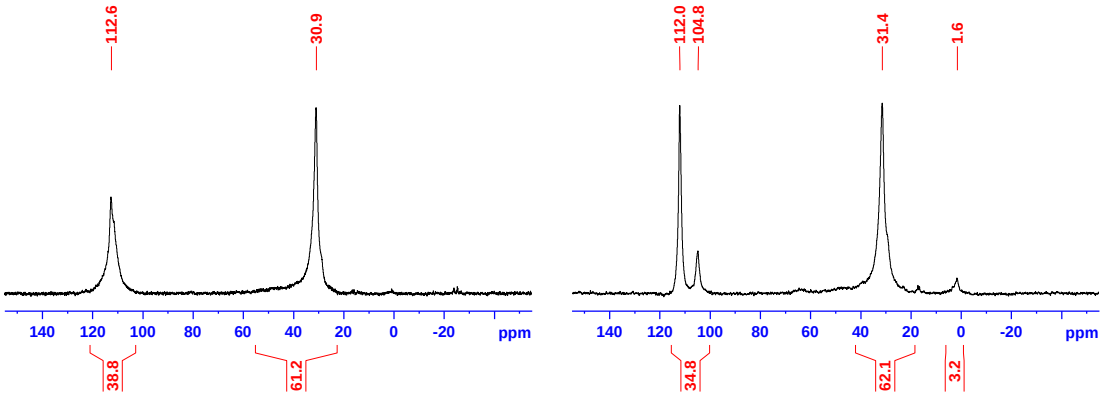


Figure 2.29 Resin PS29a (left) and b (right) after 22 hours reaction time

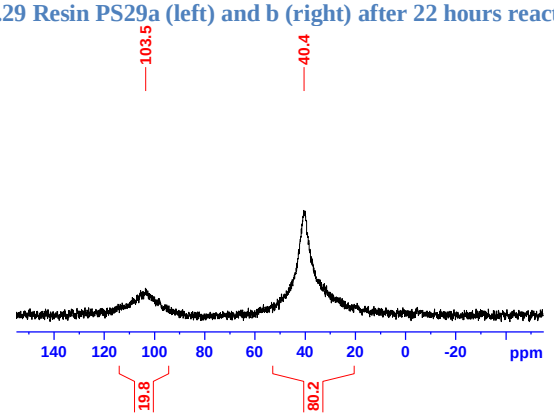
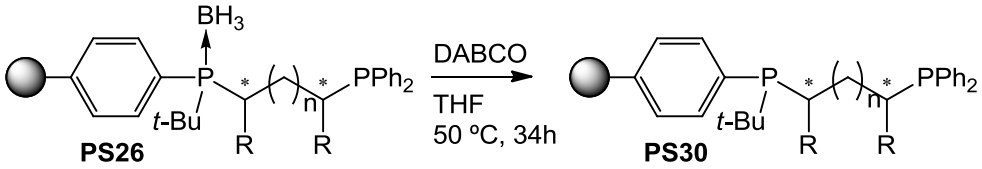


Figure 2.30 Resin PS29f with additional borane

2.8 Deprotection of ligands PS26



Scheme 2.30 Deprotection of PS26

The deprotection of **PS26b** (Figure 2.31) was investigated in toluene at 50 °C with three different deprotection reagents. First to test was a toluene/methanol mixture (1:1). After 60 hours, only a small amount, 3% by integral, of the phosphine was deprotected resulting in a new signal at 1.9 ppm in the ^{31}P NMR spectrum and other resonances had appeared as well at 16 ppm, 25 ppm, 35 ppm and 51 ppm (Figure 2.32). The deprotection with morpholine was more promising. After 42 hours it still had not reached full conversion yet as 2.5% of starting material was still present, however, there were barely any side products as was the case with methanol (Figure 2.33, left). Deprotection with DABCO was tried as well. This yielded fully deprotected phosphine after 40 hours of heating at 50 °C and this method was chosen as deprotection agent in further experiments (Figure 2.33, right).

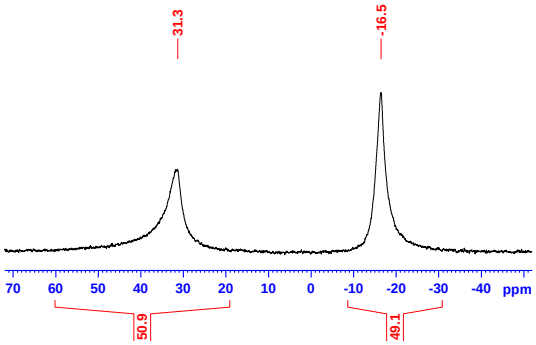


Figure 2.31 Resin PS26b in toluene

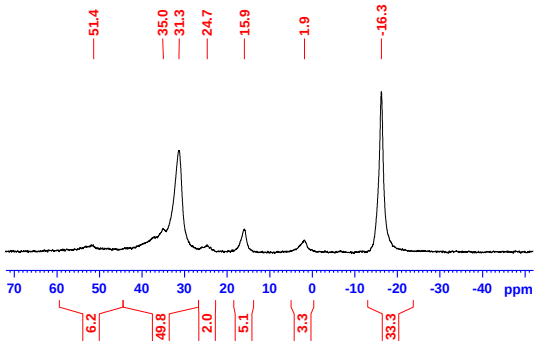
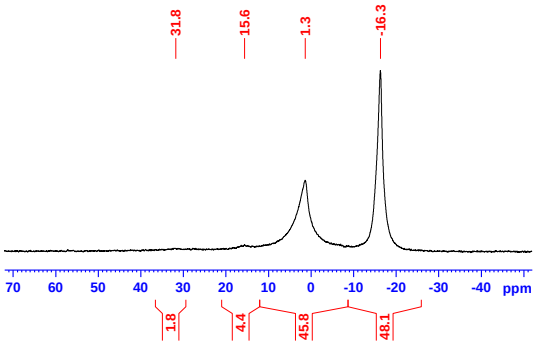


Figure 2.32 Deprotection of resin PS26b with MeOH



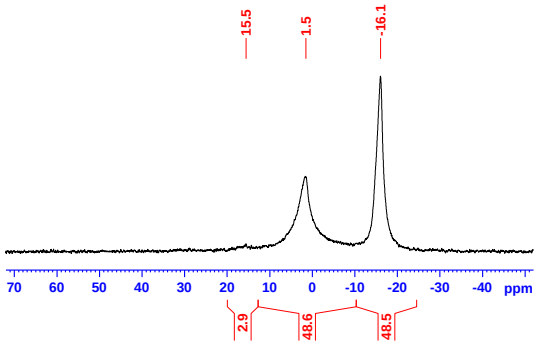


Figure 2.33 Deprotection of resin PS26b with morpholine (left) and with DABCO (right)

Deprotection of immobilised bis(phosphine) **PS26c** resulted in an interesting splitting of the phosphine signal at $\delta^{31}P = 18$ (Figure 2.34), which could correspond to the enantiomers (R_p,*R*,*R*) and (S_p,*R*,*R*) of the immobilised bis(phosphine) **PS26c**, which has one *P*-stereogenic phosphorus and a *C*-chiral bridge between the two phosphorus groups. This result suggests that the sparteine-method had not worked under the conditions that were used during formation of resin **PS25**, and thus had resulted in a racemic mixture instead of the desired enantio-enriched compound. This was to be expected as selective precipitation leading to kinetic resolution is not possible on solid support.

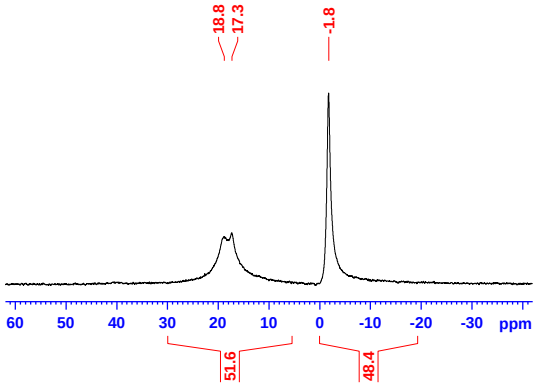


Figure 2.34. Immobilised deprotected bis(phosphine) PS30c

Unfortunately, for unknown reasons the main manufacturer of (–)-sparteine stopped their production line and nowadays there is a worldwide shortage of (–)-sparteine. Therefore, the reaction conditions could no longer be optimised and the project was discontinued.

2.9 Conclusions and outlook

During the synthesis of immobilised bis(phosphine) ligands from start to finish with Solid Phase Synthesis some major difficulties were encountered. The sometimes inevitable formation of immobilised side-product proved to be troublesome, however once the reactions were optimised, isolation and work-up of the immobilised products was straightforward, which is one of the main advantages of SPS.

The synthetic procedure towards resin-bound secondary phosphine-borane **PS1** has been successfully optimised. After investigating three different routes, the best results were achieved by reacting *tert*-butylchloroethylphosphinite **14** with lithiated polystyrene, followed by reduction of the immobilised phosphinite **PS22** and subsequent borane protection. This method yielded the desired product **PS1** pure and without any immobilised side products according to ^{31}P NMR spectroscopy.

Lithiation of **PS1** in combination with (–)-sparteine and subsequent addition of electrophiles, such as styrene oxide and several cyclic sulfates, were investigated. This resulted successfully in the coupling products. The synthesis of immobilised phosphine-phosphinites via the styrene oxide adducts was unsuccessful as immobilised side products were formed as well. The synthesis of bis(phosphines) **PS26** by reaction of the immobilised phosphine-sulfates with lithium diphenylphosphide was only successful in three cases. Deprotection of the synthesised immobilised bis(phosphines) with DABCO was successful. The stereoselectivity of the reactions in the presence of (–)-sparteine proved to be unsuccessful, due to the necessary deviations made in the reaction conditions. With the worldwide shortage of (–)-sparteine, the reaction conditions could no longer be optimised and the project was discontinued.

2.10 General considerations and procedures for working with resins

2.10.1 Stirring the resin

While stirring the reaction mixture particular care must be taken as the polymer supports utilised consist of insoluble beads, however, conventional stirring for prolonged times will crush the resin resulting in its destruction. Moreover, the resin is most vulnerable when it is fully swollen. To minimise the destruction of the resin during reactions, the spinning of the stirring bar must be reduced to the slowest setting or completely switched off. Other alternatives are to shake the reaction flask on a vortex mixer or to manually move the stirring bar inside the reaction flask with the use of a neodymium magnet stuck to the outside of the flask. The latter was a very effective method to mix the resin beads and also to move the resin beads that were stuck to the glass back into the reaction mixture.

In many cases described in this thesis, the stirring of the reaction mixtures was performed either by very slow stirring (about 150 to 200 rpm, slowest setting of the stirring plates), or by placing the reaction flask or NMR tube on a vortex mixer for short periods of time.

2.10.2 Swelling and washing of the resin

The swelling of the resin is extremely solvent-dependent and will differ for each resin. The published swelling properties of the resins utilised in this work in some of the commonly used solvents are depicted in Table 2.1.[29] For *p*-bromopolystyrene (PS-PVB-Br) the most efficient solvents for swelling are THF, toluene, dioxane and CH_2Cl_2. The swelling properties of *J*anda*J*el™ are even better in these solvents, whereas TentaGel™ is a more solvent independent resin.

Table 2.1. Swelling properties of several resins in different solvents

Solvent	THF	Toluene	CH_2Cl_2	Dioxane	Water	MeOH	DMF	MeCN	Et_2O	Benzene
Polystyrene 1% DVB cross-linked	8.8	8.5	8.3	7.8	1.6	1.6	5.6	3.2	4.0	4.4
TentaGel™	5.0	4.8	6.3	5.4	3.6	3.6	4.7	4.2	1.9	4.4
Merrifield	7.7	--[a]	6.0	6.0	--[a]	1.8	4.8	1.8	--[a]	6.6
*J*anda*J*el™-Cl 2% crosslinked	11.6	--[a]	10.8	11.4	--[a]	--[a]	9.0	--[a]	--[a]	10.8

Swelling volume [mL/g] of polystyrene and *J*anda*J*el™ (dry volume: 1.5 mL/g) and TentaGel™ resins (dry volume 1.7 mL/g). [a] no data available

Even though CH_2Cl_2 is a good swelling solvent for most resins, it was less frequently used as reaction solvent. In CH_2Cl_2 the resin does swell well but the resins also have the tendency to float, which can be inconvenient as the resin adheres to the walls of the flask and therefore will no longer be submerged in the reaction mixture. However, CH_2Cl_2 was used during washing sequences as it causes other solids, *i.e.* salts and small pieces of septum, to precipitate to the bottom of the flask while the resin floated at the surface in the solvent phase. The precipitated solids could then easily be removed with a needle without losing the resin.

Solvents in which the resin swells the least, such as Et_2O and MeOH, were mainly used during washing sequences. The resin shrinks in these solvents, forcing all non-covalently bounded substances out of the structure of the resin.

The general procedure to wash the resins was to first remove the reaction mixture with a thin needle (25 Gauge) attached to a plastic or glass syringe. Subsequently, portions of the reaction solvent (THF or toluene) were added and then removed with the same thin needle, followed by portions of Et_2O. This sequence was repeated several times until the solvent stayed clear and no more colour changes of the resin or the solvent were observed. After this washing sequence, the resins were suspended in the suitable solvent used in the subsequent reaction, or the resins were dried under reduced pressure for storage. However, with this procedure small losses of resins are inevitable, the smallest resin beads still could enter the needle, especially with the shrunken resins. In some cases this led to blockages of the needles.

For reactions in which larger quantities of resin (more than one gram) were used, a special Schlenk flask was used, containing a glass filter with tap to easily filter off the solvents under inert atmosphere. Unfortunately, this glassware could not be used for reactions with smaller quantities of resin, due to the amount of resin lost as a result of static electricity causing the resin to adhere to the inside of the glassware.

Due to the inevitable loss of resin during the washing procedures and due to the static nature of the resin itself, it was difficult to determine the yield of a reaction by difference in weight of the resin before and after the reaction. For most of the reactions the yield was found to be quantitative under optimised conditions and determined by conversion of starting material into desired product according to ^{31}P NMR. The exact yields have been confirmed by elemental analysis.

2.10.3 ^{31}P NMR of the resin

^{31}P NMR spectra were recorded on a 400 MHz spectrometer. From the reaction mixture, a small sample of the resin was transferred into a NMR tube with solvent using a 1 mL syringe with a thick needle (18 or 19 Gauge). The resin beads settled on the bottom of the NMR tube forming a plug of resin. The height of the NMR tube sitting in the spinner had to be adjusted to ensure that the plug was in the centre of the coil in the spectrometer. All ^{31}P NMR spectra of resin containing samples were measured proton decoupled and unlocked. Spectra registered on the same NMR machine could be compared with negligible shift in resonances and signal to noise ratio of the base line.

The use of an inner tube (sealed capillary) with D_2O as locking solvent was tested, however, it was observed that gas pockets evolved between the resin beads and the inner tube, and accumulated mostly at the position of the coil, resulting in poor spectra. In addition, these tubes could not be dried in the conventional way and consequently could not be used to record spectra during sensitive reactions. This approach was therefore not applied as the spectra recorded without the inner tube attained a higher quality than of those with the inner tube present.

Many of the reactions described in this thesis were performed directly in NMR tubes under inert atmosphere. Care had to be taken while loading the tubes with resin as an excess of resin would obstruct the mixing within the tube of resin with the reagents, and an insufficient amount of resin would not yield a plug of resin large enough to be brought in the coil of the spectrometer. The optimal amount of resin was found to be around 40 to 50 mg of resin in 1 mL of solvent.

2.11 Experimental

2.11.1 General remarks

All reactions were carried out under strictly oxygen and water free conditions, using standard Schlenk techniques under an atmosphere of purified argon. NMR spectra were recorded at room temperature on a Bruker Avance II 400. The ^{31}P NMR spectra were recorded proton decoupled and the gel-phase resin experiments were run unlocked. Chemical shifts (δ) are reported in ppm and are given relative to tetramethylsilane (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P).

Chemicals were purchased in the highest commercially available purity from Acros Chimica, Aldrich Chemical Co., Biosolve, Fluka and Merck and were used as received, unless stated otherwise. *p*-Bromopolystyrene was ordered from Sigma Aldrich (2.17 mmol/g, 50-100 mesh, 1% cross-linking DVB). Elemental analyses were carried out by Kolbe Mikroanalytisch Labor, Mülheim an der Ruhr (Germany).

Toluene was distilled from sodium, diethyl ether and THF from sodium/benzophenone, tertiary and secondary amines and dichloromethane were distilled from calcium hydride, and methanol and ethanol from magnesium.

2.11.1 Optimisation of the ^{31}P NMR spectra of immobilised compounds

In this thesis, the ^{31}P NMR spectra containing resin were slightly enhanced with Bruker software TopSpin 3.1. As a standard the machines are set to record 64 thousand data points with a line broadening of 2 Hz. The free induction decay (FID) of resin samples was fast and for most samples the signal was reduced to base line within the first five thousand data points (0.02 sec), whereas with standard liquid phase ^{31}P NMR samples this decay is much slower (Figure 2.35).

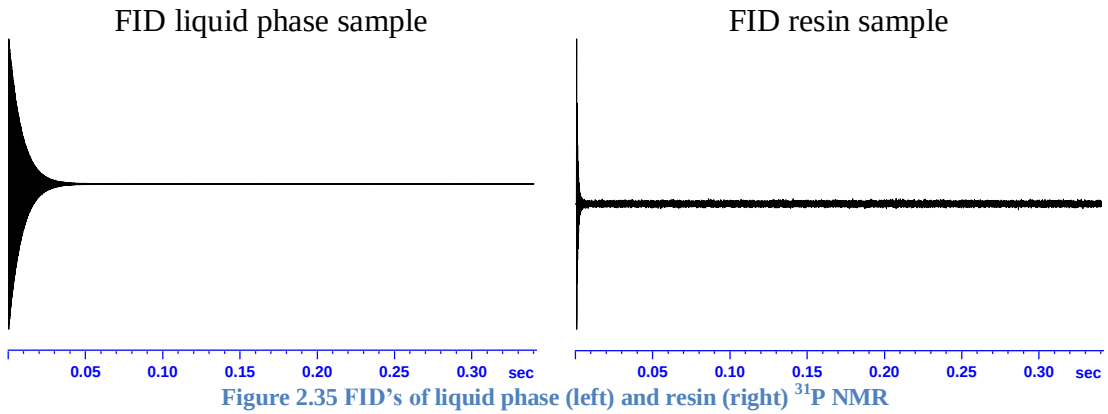


Figure 2.35 FID's of liquid phase (left) and resin (right) ^{31}P NMR

The signal to noise ratio was increased, by instructing Bruker software TopSpin 3.1 to use only the first ten thousand data points with the command 'tdeff 10k', and the line broadening was set to 10 with the command 'lb 10'. The spectrum was then recalculated with the command 'efp'. This was then followed by straightening out the base line with automatic phase correction 'apk' and automatic base line correction 'abs'. For the best results, the commands 'apk' and 'abs' had to be repeated in succession for 3 times or until the base line stayed the same (Figure 2.36).

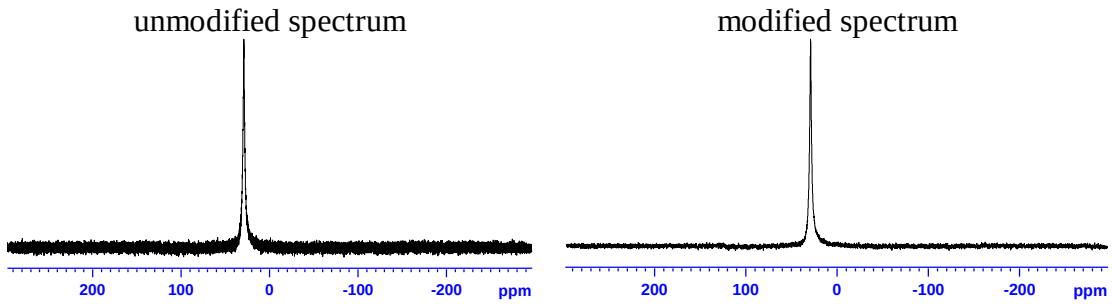
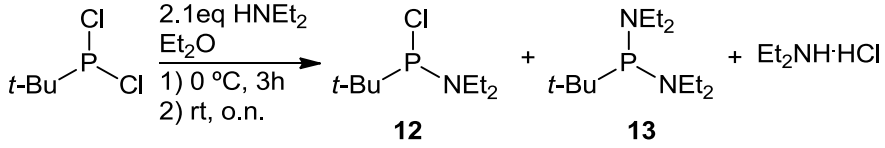


Figure 2.36 Spectrum before (left) and after (right) modification

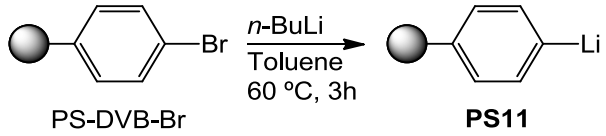
2.11.2 Synthesis

*Synthesis of t-Bu(NEt$_2$)PCl **12*** [20]



To a Schlenk flask, loaded with *t*-BuPCl$_2$ (1.139 g, 7.16 mmol) in 20 mL Et$_2$O, HNEt$_2$ (1.5 mL, 14.56 mmol, 2.03 eq) was added dropwise at 0 °C. The reaction was stirred for 2 hours at 0 °C and subsequently allowed to warm up to room temperature overnight. The white suspension was filtered over a glass filter and the salts were washed with 3x 10 mL Et$_2$O. The solvent was evaporated under reduced pressure, yielding a colourless oil (1.132 g, 5.78 mmol, 81%) which turns yellowish over time, consisting of *t*-Bu(NEt$_2$)PCl **12** (88%), *t*-Bu$_3$P (4.5%) and hydrolysis/oxidation products (7.5%), and was used without further purification. The density of *t*-Bu(NEt$_2$)PCl **12** was determined to be 0.62 g/mL. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 0.98 (t, 6H, *J* = 7.2 Hz), 1.20 (d, 9H, *J* = 14.4 Hz), 2.90-3.10 (m, 4H) ppm. ^{31}P{^{1}H} NMR (162 MHz) (in Et$_2$O) = 157.0 (s).[20b] Known impurities recorded were *t*-Bu(NEt$_2$)$_2$P **13** (δ^{31}P = 111.6) and *t*-Bu$_3$P (δ^{31}P{^{1}H} NMR = 61.1).[25]

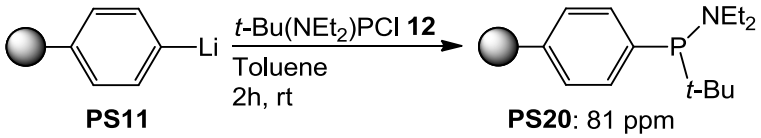
*Synthesis of lithiated polystyrene **PS11*** [15]



p-Bromopolystyrene (5.09 g, 11.04 mmol, loading 2.17 mmol/g) was allowed to swell in 50 mL of toluene for 1 hour. After addition of *n*-butyllithium (30 mL, 78 mmol,

2.6 M in toluene), the suspension was heated for 4 hours at 60 °C with slow stirring, after which the supernatant was removed and the resulting yellow resin **PS11** was washed with toluene (3 x 30 mL).[15] The obtained resin was used as such in a subsequent reaction.

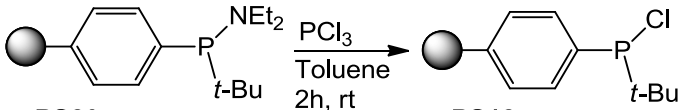
Synthesis of immobilised t-BuP(NEt$_2$) ***PS20***



PS11 **PS20**: 81 ppm

To a suspension of the lithiated resin **PS11** (740 mg, 1.61 mmol) in 5 mL toluene, the crude yellowish oil of *t*-Bu(NEt$_2$)PCl **12** (600 µL, 1.9 mmol) with some minor impurities (less than 10%) was added. The reaction was performed overnight at room temperature, during which the colour of the resin slowly changed colour from yellow to light yellow and salt formation occurred. The resin was washed with 3x 10 mL toluene, followed by 10 mL Et$_2$O and 2x 3 mL toluene. This yielded light yellow coloured resin **PS20**. $\delta^{31}P\{^1H\}$ NMR (162 MHz, in toluene) = 81.4 (br). The obtained resin was used as such in the subsequent reaction.

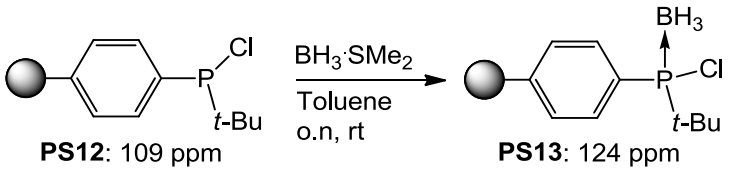
Synthesis of resin-bound chlorophosphine ***PS12***



PS20: 81 ppm **PS12**: 109 ppm

Using a syringe PCl$_3$ (150 µL, 1.72 mmol) was added dropwise to a suspension of the crude *t*-Bu(NEt$_2$)P-functionalised resin **PS20** from the previous reaction in 5 ml toluene at room temperature, while slowly stirring the resin. After 2 hours, the resin was washed with 3x 5 mL toluene, 3x 5 mL Et$_2$O and 3x 3 mL toluene, yielding yellowish coloured resin **PS12**. $\delta^{31}P\{^1H\}$ NMR (162 MHz, in toluene) = 108.3 (90%) and 45.1 ppm (10%). The obtained resin was used as such in the subsequent reaction.

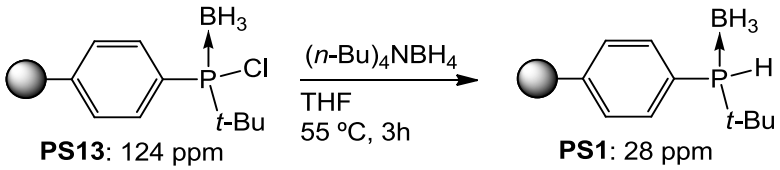
*Synthesis of resin-bound chlorophosphine-borane **PS13***



PS12: 109 ppm **PS13**: 124 ppm

To a suspension of the crude resin **PS12** from the previous reaction in 5 mL toluene, $BH_3 \cdot SMe_2$ (1.5 mL, 3 mmol, 2M in toluene) was added while slowly stirring. The reaction was left overnight at room temperature without stirring. Subsequently, the resin was washed with 3x 5 mL toluene and 3x 5 mL THF, yielding resin **PS13**, as a yellow coloured solid. $\delta^{31}P\{^1H\}$ NMR (162 MHz, in toluene) = 122.8 (93%), and 44.1 ppm (7%). The obtained resin was used as such in the subsequent reaction.

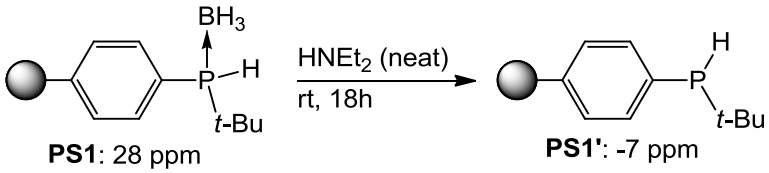
*Synthesis of resin-bound phosphine-borane **PS1** from **PS13***



PS13: 124 ppm **PS1**: 28 ppm

To a suspension of the crude resin **PS13** from the previous reaction in 5 mL THF, $(n\text{-Bu})_4NBH_4$ (600 mg, 2.33 mmol) was added while stirring, upon which the resin coloured orange/brownish and gas evolved. The reaction was heated at 55 °C for 3 hours and overnight at room temperature. During the heating the resin decoloured and white precipitation was visible. After washing with subsequently THF (2x 5 mL), Et_2O (2x 5 mL), CH_2Cl_2 (4x 5 mL) and Et_2O (2x 5 mL), the resin was dried under reduced pressure, affording white resin **PS1** (560 mg, 1.16 mmol; calculated loading: 2.07 mmol/g resin). $\delta^{31}P\{^1H\}$ NMR (162 MHz, in toluene) = 29.02 (94%) and 44.2 ppm (6%). The obtained resin was used as such in a subsequent reaction.

*Deprotection of resin **PS1***

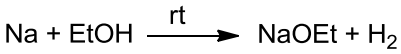


PS1: 28 ppm **PS1'**: -7 ppm

In a screw cap NMR tube, resin **PS1** (62 mg, 128 µmol) was suspended in dry toluene. After sufficient swelling the excess toluene was removed via syringe, to which

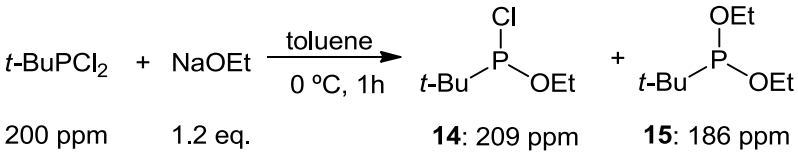
1 mL $HNEt_2$ was added. After an 18 hours reaction at room temperature, deprotected resin **PS1'** was obtained as a white solid. $\delta^{31}P\{^1H\}$ NMR (162 MHz, in $HNEt_2$) = −7.6 (br).

Synthesis of sodium ethoxide[21]



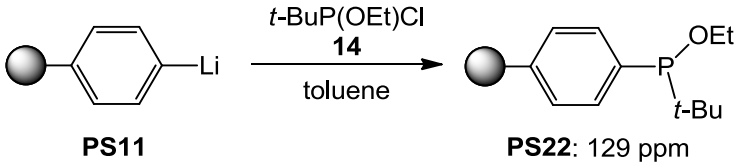
A Schlenk flask was loaded with freshly cut sodium (1.17 g, 50.90 mmol) and cooled to 0 °C. Freshly distilled ethanol (70 mL) was added slowly resulting in gas evolution. After 1 h at 0 °C, the reaction mixture was allowed to warm up to room temperature until all sodium had reacted. After 1 h, the excess of ethanol was removed *in vacuo* at 60 °C. The resulting solid was dried *in vacuo* for an additional 1.5 h at 80 °C, yielding sodium ethoxide as a white fine powder quantitatively (3.46 g, 50.90 mmol).

*Synthesis of tert-butylchloro-ethylphosphinite **14***



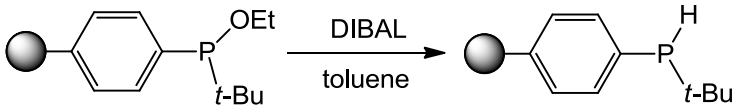
tert-Butylchloroethoxyphosphine **14** ($\delta^{31}P\{^1H\}$ NMR(202 MHz, in toluene) = 208.7 ppm) was prepared by addition of a cooled (0 °C) suspension of freshly prepared sodium ethoxide (3.46 g, 50.90 mmol, 1.1 eq.) in 50 mL of toluene via a Teflon cannula to a cooled (0 °C) solution of *t*-$BuPCl_2$ (46 mL, 46 mmol, 1.0 M in Et_2O) in 75 mL of toluene. The flask was rinsed with toluene (2 x 25 mL) and the reaction was stirred at 0 °C for 2 hours. Resulting in a mixture of *t*-BuP(OEt)Cl **14** (70%, $\delta^{31}P\{^1H\}$ NMR(202 MHz, in toluene) = 209 ppm) and *t*-$BuP(OEt)_2$ **15** (25%, $\delta^{31}P\{^1H\}$ NMR(202 MHz, in toluene) = 187 ppm), which was used as such in the subsequent reaction.

*Synthesis of resin-bound tert-butylethylphosphinite **PS22***



To the lithiated polystyrene resin **PS11** (5.09 g, 11.04 mmol), suspended in 20 mL of toluene, the crude reaction mixture of *t*-BuP(OEt)Cl **14** was added via transfer of the supernatant with a Teflon cannula. The resin decoloured slowly and after overnight stirring at room temperature, the resin was washed with toluene (3 x 30 mL), yielding resin **PS22**. $\delta^{31}P\{^1H\}$ NMR (202 MHz, toluene) = 129 (br). The obtained resin was used as such in the subsequent reaction.

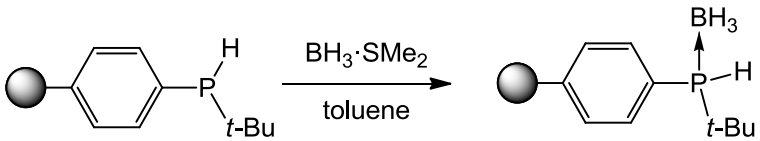
*Synthesis of resin-bound tert-butylphosphine **21***



PS22: 129 ppm **PS23**: -7 ppm

The crude resin **PS22** from the previous reaction was suspended in 10 mL of toluene and diisobutylaluminum hydride (30 mL, 36 mmol, 1.2 M in toluene) was added at room temperature. After 3 days, the resin was washed consecutively with toluene (3 x 30 mL), Et_2O (2 x 30 mL), and toluene (2 x 30 mL), yielding resin **PS23**. $\delta^{31}P\{^1H\}$ NMR (202 MHz, toluene) = −7 (br). The obtained resin was used as such in the subsequent reaction.

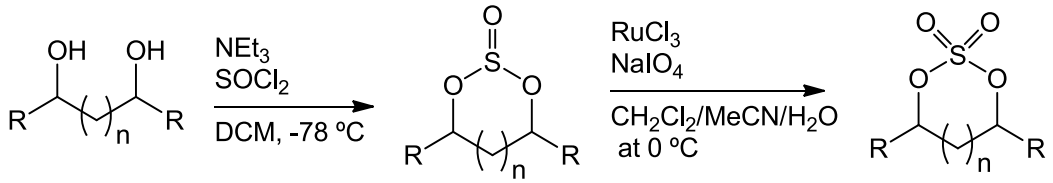
*Synthesis of resin-bound tert-butylphosphine-borane **PS1***



PS23: -7 ppm **PS1**: 29 ppm

The crude resin **PS23** from the previous reaction was suspended in 30 mL of toluene and $BH_3 \cdot SMe_2$ (15 mL, 30 mmol, 2 M in toluene) was added at room temperature. After gentle stirring for 2 hours followed by washing with toluene (3 x 30 mL) Et_2O (2 x 30 mL) and toluene (2 x 30 mL), resin **PS1** was obtained (5.94 g, 12.28 mmol; calculated loading: 2.07 mmol/g resin). $\delta^{31}P\{^1H\}$ NMR (202 MHz, toluene) = 29 (br). IR ν_{max} (KBr)/cm^{-1}: 2365.7 (BH_3); elemental analysis (%): P, 5.13 Calculated: 6.40.

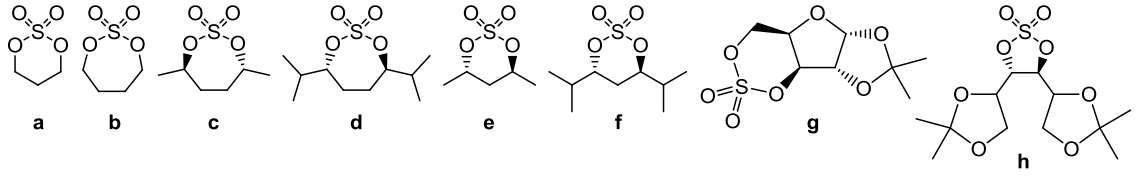
General synthesis of cyclic sulfates[23,30]



Under argon atmosphere, the diol (*e.g.* propanediol, butanediol, 2,4-pentanediol, 2,5-hexanediol) was azeotropically dried with toluene (3 times) before dissolving in CH_2Cl_2 (50 mL per gram diol). Triethylamine (3 eq.) was added and the solution was cooled to −78 °C. Thionyl chloride (1.1 eq.) was added drop-wise to the cooled solution. The reaction mixture coloured slightly yellowish at the end of the addition and a precipitate is formed. After 45 minutes, a small sample (~0.5 mL) of the reaction mixture was transferred into a vial containing 0.3 mL of water to quench the excess of thionyl chloride. The organic layer was filtered over a small plug of Celite and submitted for GC/MS analysis (standard method: 50-300 °C, 15 °C/min ramp and 2 min hold time).

Work-up consisted of quenching the reaction mixture with water (20 mL), transfer of the reaction mixture to a separating funnel with Et_2O followed by washing of the organic layer with 6% $NaHCO_3$ (3g in 50mL H_2O), H_2O and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Under argon atmosphere, the obtained cyclic sulfites were then dissolved in CH_2Cl_2 (10 mL) and acetonitrile (10 mL) and cooled to 0 ºC, after which $RuCl_3$ (0.01 eq.) was added followed by a solution of $NaIO_4$ (1.5 eq.) in water (15 mL). The two layer mixture was stirred at 0 °C for 15 minutes and allowed to warm to room temperature and stirred for an additional 45 minutes. A small sample (~0.5 mL) of the organic layer of the reaction mixture was filtered over a small plug of Celite and submitted for GC/MS analysis (standard method: 50-300 °C, 15 °C/min ramp and 2min hold time). During the reaction the mixture changed colour from dark brown to orange. Work-up of the cyclic sulfates consisted of a transfer of the mixture to a separating funnel with Et_2O followed by washing of the organic layer with 2 x H_2O, $NaHCO_3$ (sat.) and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated. The cyclic sulfates were crystallised from Et_2O with pentane and stored in the freezer as they decompose at room temperature over time (<month). The spectral properties of the obtained cyclic sulfates were in accordance with those reported.[23,30]



a: 1,3-propadiol cyclic sulfate[30a]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.18 (2H, quint, *J* = 5.0 Hz, OCH_2CH_2) and 4.77 (4H, t, *J* = 5.0 Hz, 2xOCH_2) ppm.

b: l,4-butanediol cyclic sulfate[30b]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.07-2.13 (4H, m, 2xOCH_2CH_2) and 4.42-4.49 (4H, m, 2xOCH_2) ppm.

c: (2*S*,5*S*)-2,5-hexanediol cyclic sulfate[23]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.45 (6H, d, *J* = 6.4 Hz, 2xCH_3), 1.87-2.06 (4H, m, 2x$OCHCH_2$) and 4.80-4.88 (4H, m, 2xOCH) ppm.

e: (2*R*,4*R*)-2,4-pentanediol cyclic sulfate[30c]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.62 (6H, d, *J* = 6.6 Hz, 2xCH_3), 2.06 (2H, t, *J* = 5.6 Hz, $OCHCH_2$) and 5.11 (2H, sext, *J* = 6.2 Hz, 2xOCH) ppm.

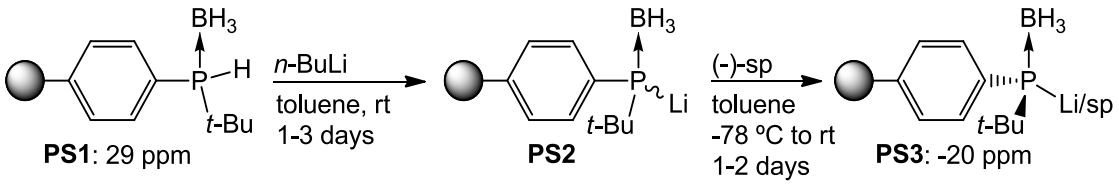
g: 1,2-O-Isopropylidene-a-d-xylofuranose 3,5-O-cyclic sulfate[30d,e]

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.34 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 4.26 (m, 1H), 4.72 (d, 1H, *J*=3.7 Hz), 4.83 (d, 1H, *J*=12.9 Hz), 4.96 (dd, 1H, *J*=2.1, 12.9 Hz), 5.18 (d, 1H, J=2.1 Hz), 6.05 (d, 1H, *J*=3.7 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.1 (CH_3), 26.5 (CH_3), 69.3 (CH) 72.4 (CH_2), 82.8 (CH), 86.5 (CH), 104.7 (CH), 113.1 (C) ppm.

h: 1,2:5,6-diisopropylidene *D*-mannitol cyclic sulfate[30f]

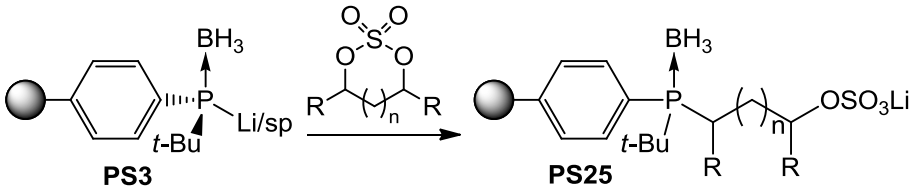
^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.35 (6H, s, 2xCH_3), 1.45 (6H, s, 2xCH_3), 4.06 (2H, AB**X**, J_{AB}=9.6 Hz, J_{AX}=3.5 Hz, OCH_2CH), 4.19 (2H, A**B**X, J_{AB}=9.6 Hz, J_{BX}=6.1 Hz, OCH_2CH), 4.45 (2H, m, $OCHCH_2$), 4.68-4.72 (2H, m, $SOCHCH$) ppm. ^{l3}C NMR (125 MHz, $CDCl_3$) δ = 24.77 (CH_3), 26.76 (CH_3), 66.09 (CH_2), 73.18 (CH), 82.31 (CH), 111.00 (C) ppm.

*General procedure for lithiation of **PS1***



In an NMR tube, to a suspension of resin **PS1** (50-100 mg, 67-150 µmol, loading 2.07 mmol/g) in 0.5 mL toluene, *n*-BuLi (150-250 µL, 2.5M in hexane) was added at room temperature. When all resonances had disappeared according to ^{31}P NMR, the supernatant containing the excess of *n*-BuLi was removed via syringe and fresh toluene was added. The resin was cooled to −78 °C and (–)-sparteine (80 µL, 350 µmol) was added. The reaction was allowed to warm to room temperature and kept at this temperature for 24 hours, resulting in a resonance at $\delta^{31}P = -20$ presumably corresponding to resin **PS3**. The obtained resin was used as such in a subsequent reaction.

General procedure for immobilised phosphine-sulfates



Propanediol cyclic sulfate (129.8 mg, 939.6 µmol, 1.5 eq.) was azeotropically dried with portions of toluene (3 x 0.5 mL) and dissolved in 1 mL of THF. The solution of cyclic sulfate was transferred to the Schlenk tube with the suspension of lithiated resin **PS3** (303 mg, 627.8 µmol, loading: 2.07 mmol/g) in 2 mL of THF. After reacting 18 hours at room temperature, the light yellow resin was washed with portions of THF and Et_2O (3 x 7 mL respectively). The white resin **PS25** was suspended in 7 mL of THF to be used in the subsequent reaction.

PS25a: white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): +31.4 ppm;
IR ν_{max} (KBr)/cm^{-1}: 2380.8 (BH_3), 1640.2 and 1260.3 (S=O);
Elemental analysis (%): P, 3.44 (calculated: 5.06); S, 3.31 (calculated: 5.24).

PS25b: white resin, $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +31.7 ppm;
IR ν_{max} (KBr)/cm^{-1}: 2379.5 (BH_3), 1639.1 and 1262.4 (S=O);
Elemental analysis (%): P, 4.01 (calculated: 4.95); S, 2.89 (calculated: 5.12).

PS25c: white resin, $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +40.4 ppm;
IR ν_{max} (KBr)/cm^{-1}: 2379.9 (BH_3), 1640.3 and 1259.0 (S=O);
Elemental analysis (%): P, 6.01 (calculated: 4.62); S, 2.67 (calculated: 4.78).

PS25d: white resin, $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +38.9 ppm;
IR (KBr): 2379.4 (BH_3), 1645.7 and 1255.4 (S=O).

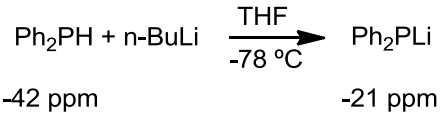
PS25e: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +39.6 ppm.

PS25f: white resin, $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +39.8 ppm;
IR (KBr): 2387.6 (BH_3), 1648.3 and 1252.7 (S=O).

PS25g: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +30.8 ppm.

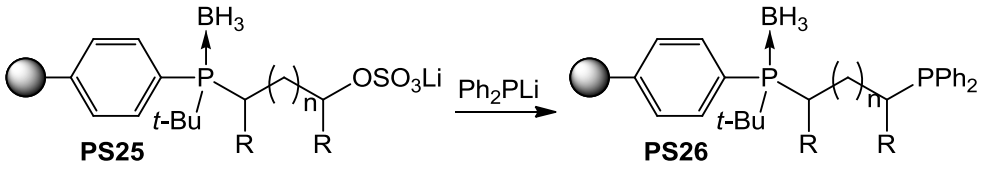
PS25h: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +28.3 ppm.

Synthesis of lithium diphenylphosphide



A pre-weighed Young Schlenk tube (without stirring bar as the formed lithium phosphide reacts with the Teflon coating) was loaded with Ph_2PH (214.1 mg, 200 µL, 1.15 mmol) using a gas-tight microliter syringe. 4 mL of THF was added to obtain an estimated molarity of Ph_2PLi of 0.25 M. Note: With concentrations over 0.4 M the formed Ph_2PLi precipitates as it does not dissolve in the hexanes added with the *n*-BuLi solution. The solution was cooled to −78 °C and *n*-BuLi (2.37 M in hexanes, 480 µL, 1.14 mmol) was added dropwise while shaking the Schlenk at regular intervals on a vortex shaker. This resulted in a bright orange solution of Ph_2PLi which has a ^{31}P NMR resonance at −21 ppm. This solution of Ph_2PLi cannot be stored for extended periods of time and was used immediately in the next reaction and freshly prepared when needed.

General procedure for immobilised bis(phosphine) boranes



To the resin **PS25a** (220 mg, 358.6 µmol, loading: 1.63 mmol/g) suspended in 7 mL of THF was added freshly prepared lithium diphenylphosphide solution (4 mL, 0.25 M, 1 mmol, 2.8 eq.). After reacting 4 days at room temperature, the resin **PS26** was washed with portions of THF and Et_2O (3 x 7 mL respectively). The corresponding integral ratios are the values in between brackets, given in percentages.

The white resin **PS26a-c** was suspended in 7 mL of THF and 1 mL of $BH_3 \cdot SMe_2$ complex (2 M in toluene, 1 mmol) was added. After 18 hours, the white resin **PS26a'-c'** was washed with 5 mL portions of THF, THF/H2O (5:1), THF, Et2O and dried under reduced pressure.

PS26a: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): +31.4 ppm (54%), −18.8 ppm (46%).

PS26a': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): +31.4 ppm, 15.4 ppm;
IR ν_{max} (KBr)/cm^{-1}: 2378.8 (BH_3);
Elemental analysis (%): P, 5.52 (calculated: 8.56).

PS26b: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): +31.7 ppm (57%), −16.4 ppm (43%).

PS26b': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): +31.4 ppm, 15.9 ppm;
R ν_{max} (KBr)/cm^{-1}: 2378.6 (BH_3);
Elemental analysis (%): P, 6.13 (calculated: 8.39).

PS26c: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): +40.4 ppm (51%), −1.6 ppm (49%).

PS26c': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): +40.4 ppm, 24.6 ppm;
IR ν_{max} (KBr)/cm^{-1}: 2380.2 (BH_3);
Elemental analysis (%): P, 5.53 (calculated: 8.09).

PS27a: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): +31.2 ppm (52%), −55.7 ppm (48%).

Prolonged reaction times did not result in further conversions for the following compounds and these reactions were abandoned:

PS26d: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +38.9 ppm (92%), −8.1 ppm (8%).

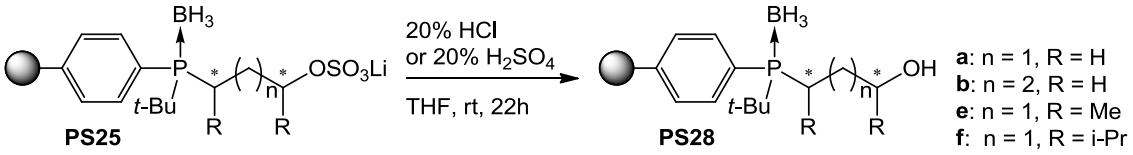
PS26e: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +39.6 ppm (55%), 24.4 ppm (2%), 19.1 ppm (3%), 1.1 and −18.8 ppm (40%).

PS26f: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +39.8 ppm (100%).

PS26g: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +30.8 ppm (98%), −7.4 ppm (2%).

PS26h: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +28.3 ppm (34%), 8.1 and −5.1 ppm (22%), −7.2 ppm (29%), −31.2 ppm (15%).

General procedure for hydrolysis of immobilised phosphine-sulfates



To the resin **PS25a** (79.95 mg, 130.3 µmol, loading: 1.63 mmol/g) was added 3 mL of a solution of 20% HCl in THF. The reaction mixture was heated at 50 °C for 22 hours after which a sample was taken, washed with 1 mL portions of THF and Et_2O and analysed with IR. The hydrolysed resin **PS28a** was washed with portions of THF and Et_2O (3 x 5 mL respectively) and dried under reduced pressure. Without further purification, the obtained resins were used as such in the subsequent reaction.

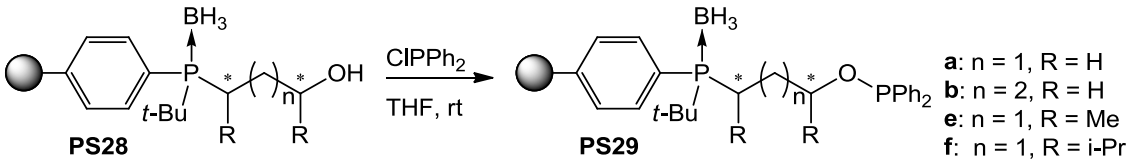
PS28a: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +31.3 ppm (90%).

PS28b: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +31.1 ppm (97%).

PS28e: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +39.7 ppm (97%).

PS28f: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +39.4 ppm (100%).

General procedure for synthesis of immobilised phosphine-phosphinites



In an NMR tube, the resin **PS28a** (70 mg, 130.3 µmol, loading: 1.85 mmol/g) was suspended in 0.9 mL of THF. *N*-methylmorpholine (50 µL, 454.77 µmol, 3.5 eq.) and chlorodiphenylphosphine (50 µL, 270.12 µmol, 2.1 eq.) were added and after 22 hours resin **PS29a** was washed with portions of THF and Et_2O (3 x 5 mL respectively) and dried under reduced pressure. The corresponding integral ratios are the values in between brackets, given in percentages. Prolonged reaction times did not result in further conversions for the following compounds and these reactions were abandoned.

PS29a: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 112.6 ppm (39%), +30.9 ppm (61%).

PS29b: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 112.0 ppm and 104.8 (35%), +31.4 ppm (62%), 1.6 ppm (3%).

PS29e: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 111.1 ppm and 104.1 ppm (35%), +40.5 ppm (46%), 33.4 ppm (6%), 19.7 ppm (13%).

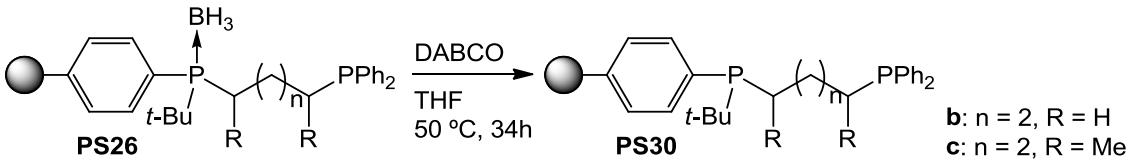
PS29f: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 110.2 ppm and 103.4 ppm (26%), +39.7 ppm (59%), 25.9 ppm (1%), 11.1 ppm (14%).

To resins **PS29e** and **PS29f** additional $BH_3 \cdot SMe_2$ (3 mL, 6 mmol, 2 M in toluene) was added at room temperature to borane-protect both the phosphine and the phosphinite:

PS29e': white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 103.8 ppm (36%), +40.4 ppm (64%).

PS29f': white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 103.5 ppm (20%), 40.4 ppm (80%).

General procedure for deprotection of immobilised bis(phosphine)-boranes



To the resin **PS26b** (110 mg, 151.8 µmol, loading: 1.38 mmol/g) was added 5 mL of a solution of azeotropically dried DABCO (0.19 M in THF). The reaction mixture was heated at 50 °C for 34 hours after which full deprotection was achieved. The deprotected resin **PS30b** was washed with portions of THF and Et_2O (3 x 7 mL respectively) and dried under reduced pressure. Without further purification, the obtained resins were used as such in subsequent reactions.

PS30b: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 1.5 ppm (49%), −16.1 ppm (51%).

PS30c: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 18.8 and 17.3 ppm (52%), −1.8 ppm (48%).

2.12 References

1. a) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106-112; b) W. S. Knowles, *Angew. Chem., Int. Ed.* **2002**, *41*, 1999-2007; c) W. S. Knowles, *Adv. Synth. Catal.* **2003**, *345*, 3-13.
2. A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934.
3. H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.
4. a) A. Togni, *Chimia* **1996**, *50*, 86-93; b) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.
5. a) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5244-5252; b) T. Imamoto, M. Matsuo, T. Nonomura, K. Kishikawa, M. Yanagawa, *Heteroat. Chem.* **1993**, *4*, 475-486; c) T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120*, 1635-1636; d) T. Imamoto, *ChemInform* **2009**, *40*.
6. a) S. Jugé, J. P. Genet, *Tetrahedron Lett.* **1989**, *30*, 2783-2786; b) S. Jugé, M. Stephan, J. A. Laffitte, J. P. Genet, *Tetrahedron Lett.* **1990**, *31*, 6357-6360; c) S. Jugé, M. Stephan, R. Merdes, J. P. Genet, S. Halutdesportes, *J. Chem. Soc.-Chem. Commun.* **1993**, 531-533; d) D. Moulin, C. Darcel, S. Jugé, *Tetrahedron: Asymmetry* **1999**, *10*, 4729-4743; e) C. Darcel, D. Moulin, J.-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey, S. Jugé, *Eur. J. Org. Chem.* **2007**, 2078-2090; f) F. Chaux, S. Frynas, H. Laureano, C. Salomon, G. Morata, M.-L. Auclair, M. Stephan, R. Merdès, P. Richard, M.-J. Ondel-Eymin, J.-C. Henry, J. Bayardon, C. Darcel, S. Jugé, *C. R. Chim.* **2010**, *13*, 1213-1226.
7. B. Wolfe, T. Livinghouse, *J. Am. Chem. Soc.* **1998**, *120*, 5116-5117.
8. A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, *251*, 25-90.
9. A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075-9076.
10. a) S. Deerenberg, H. S. Schrekker, G. P. F. van Strijdonck, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. Fraanje, K. Goubitz, *J. Org. Chem.* **2000**, *65*, 4810-4817; b) S. Deerenberg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **2000**, *19*, 2065-2072.
11. J. F. Couch, *J. Am. Chem. Soc.* **1936**, *58*, 1296-1299.
12. a) M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, *124*, 11870-11871; b) P. O'Brien, *Chem. Commun.* **2008**, 655-667.
13. R. den Heeten, B. H. G. Swennenhuis, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Angew. Chem., Int. Ed.* **2008**, *47*, 6602-6605.
14. J. W. L. Martin, F. S. Stephens, K. D. V. Weerasuria, S. B. Wild, *J. Am. Chem. Soc.* **1988**, *110*, 4346-4356.
15. M. J. Farrall, J. M. J. Frechet, *J. Org. Chem.* **1976**, *41*, 3877-3882.
16. S. Schweizer, J.-M. Becht, C. Le Drian, *Tetrahedron* **2010**, *66*, 765-772.
17. H. Lam, D. J. Aldous, K. K. Hii, *Tetrahedron Lett.* **2003**, *44*, 5213-5216.
18. M. Durand, C. Jouany, G. Jugie, L. Elegant, J. F. Gal, *J. Chem. Soc.-Dalton Trans.* **1977**, 57-60.
19. a) D. L. Dodds, M. F. Haddow, A. G. Orpen, P. G. Pringle, G. Woodward, *Organometallics* **2006**, *25*, 5937-5945; b) M. B. Volker P. W. Böhm, *Angew. Chem., Int. Ed.* **2001**, *40*, 4694-4696; c) A. Dashti-Mommertz, B. Neumuller, *Z. Anorg. Allg. Chem.* **1999**, *625*, 954-960.
20. a) O. J. Scherer, W. Gick, *Chem. Ber.-Recl.* **1970**, *103*, 71-75; b) L. P. Muller, W. W. Dumont, J. Jeske, P. G. Jones, *Chem. Ber.* **1995**, *128*, 615-619.
21. D. Williams, R. W. Bost, *J. Chem. Phys.* **1936**, *4*, 251-253.
22. P. C. Crofts, D. M. Parker, *J. Chem. Soc., C* **1970**, 332-336.
23. M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519.
24. G. Farkas, S. Balogh, Á. Szöllősy, L. Ürge, F. Darvas, J. Bakos, *Tetrahedron: Asymmetry* **2011**, *22*, 2104-2109.
25. J. Tong, S. Liu, S. Zhang, S. Z. Li, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2007**, *67*, 837-846.
26. C. Hegedüs, H. Gulyás, Á. Szöllősy, J. Bakos, *Inorg. Chim. Acta* **2009**, *362*, 1650-1654.
27. B. Khater, J.-C. Guillemin, A. Benidar, D. Bégué, C. Pouchan, *J. Chem. Phys.* **2008**, *129*, 224308.
28. a) L. G. Wade, *Organic Chemistry (5th Edition)*, Prentice Hall, Upper Saddle River, NJ, **2003**; b) M. A. Fox, J. K. Whitesell, *Organic Chemistry (2th Edition)*, Jones & Bartlett Publishers, Sudbury, MA, **1997**.

29. a) http://www.sigmaaldrich.com/chemistry/drug-discovery/resin-explorer/Jandajels.html (Accessed: February 2014); b) http://www.rapp-polymere.com/index.php?id=1218 (Accessed: February 2014); c) P. H. Toy, T. S. Reger, P. Garibay, J. C. Garno, J. A. Malikayil, G.-Y. Liu, K. D. Janda, *J. Comb. Chem.* **2001**, *3*, 117-124; d) R. Santini, M. C. Griffith, M. Qi, *Tetrahedron Lett.* **1998**, *39*, 8951-8954.

30. a) V. Samano, J. A. Ray, J. B. Thompson, R. A. Mook, D. K. Jung, C. S. Koble, M. T. Martin, E. C. Bigham, C. S. Regitz, P. L. Feldman, E. E. Boros, *Org. Lett.* **1999**, *1*, 1993-1996; b) M. S. Berridge, M. P. Franceschini, E. Rosenfeld, T. J. Tewson, *J. Org. Chem.* **1990**, *55*, 1211-1217; c) G. Fries, J. Wolf, K. Ilg, B. Walfort, D. Stalke, H. Werner, *Dalton Trans.* **2004**, 1873-1881; d) É. Bozó, S. Boros, J. Kuszmann, E. Gács-Baitz, L. Párkányi, *Carbohydr. Res.* **1998**, *308*, 297-310; e) C. Hardacre, I. Messina, M. E. Migaud, K. A. Ness, S. E. Norman, *Tetrahedron* **2009**, *65*, 6341-6347; f) B. M. Kim, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 655-658.

Chapter 3. Ligand synthesis on *J*anda*J*el ™ resin

3.1 Introduction

There is currently a wide diversity of support structures with a huge variety of functional groups, loadings, different types of cross-linking and degree of cross-linking available from commercial sources such as Sigma Aldrich and Rapp Polymere. For this project supports were chosen that were identical in functional group, such as Merrifield's resin and *J*anda*J*el™-Cl resin, or that could easily be modified to a similar end result such as TentaGel™-OH resin (Figure 3.1). As mentioned previously in Chapter 1, Merrifield's resin is one of the most commonly used resins in SPS, with benzyl chloride as functional group, crosslinked with divinylbenzene and similar properties as PS-DVB. Standard *J*anda*J*el™ is a support with benzyl chloride groups as functionality as well, but has a more flexible polytetrahydrofuran (PTHF) cross-linker instead of the divinylbenzene (DVB) cross-linker used in PS-DVB and Merrifield's resin.[1] This PTHF cross-linker is chemically robust and can withstand the use of strong acids and bases and organometallic reagents, such as mCPBA, Dibal-H, MeI, Ac_2O, aq. NaOH, aq. HCl, and 50% TFA/CH_2Cl_2 and *n*-BuLi.[1a]

The use of the PTHF cross-linker results in a polymer with excellent swelling properties in a broad range of solvents. The swelling property of a resin is of utmost importance for site accessibility and thus resin functionalisation.[1a,2]

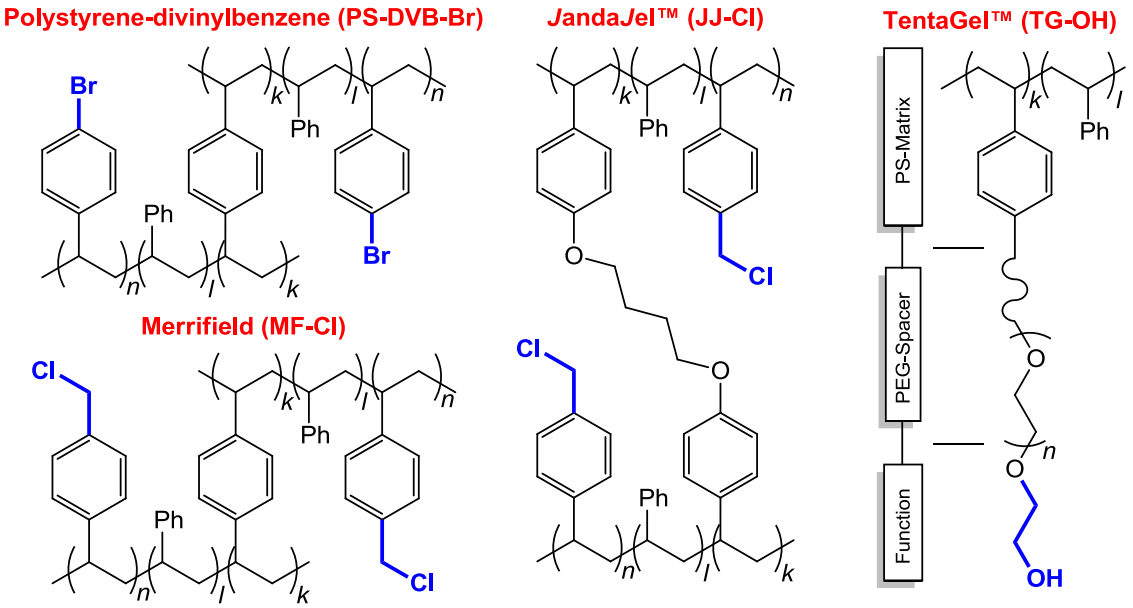


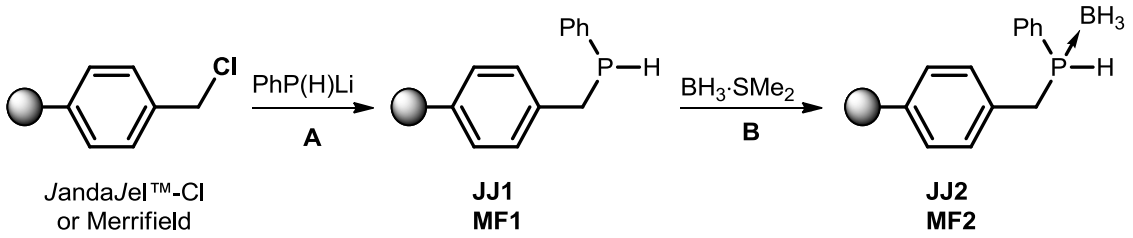
Figure 3.1 Chemical architecture of several resins

In THF the swelling of *J*anda*J*el™ is by far superior to that of polystyrene (11.6 vs. 8.8 mL per gram resin respectively),[3] however, due to the higher molecular weight of the base structure of these types of support, the loading of functional groups (expressed as mmol per gram resin) can drop considerably in comparison to PS-DVB (0.96 mmol/g for *J*anda*J*el™-Cl vs. 2.17 mmol/g for PS-DVB-Br). This drop in loading is most significant with TentaGel™ (0.24 mmol/g for TentaGel™-OH), due to its long PEG linkers. These long PEG linkers between the backbone and the functional groups have the advantage that the reactive sites show more solution like behaviour.[4] In this project this was most noticeable in NMR analysis of the compounds as it resulted in sharper signals in ^{31}P NMR. There are some inherent problems associated with PEG-based cross-linkers as PEG itself is a hygroscopic polymer and the PEG esters are not very stable and easily hydrolysed. PEG can be oxidized along the polyether chain to form peroxides or esters, depending on the storage conditions and storage time. Consequently acid treatment or treatment with bases hydrolyses the formed PEG-esters which results in a small amount of "PEG - leakage", therefore the use of such reagents should be avoided.[4]

*J*anda*J*el™-Cl and Merrifield resin have benzyl chloride as functional group and therefore new strategies towards the immobilisation of phosphines on solid supports had to be developed as the methods developed on polystyrene resin (see Chapter 2) were no longer applicable. Therefore, a more direct approach was followed, namely by the addition of lithium phosphides to an immobilised functional leaving group (such as halogen or a mesyl group) to obtain the desired immobilised phosphines, instead of lithiation of the resin, followed by addition of R_2PX, as described in Chapter 2.

3.2 Synthesis of secondary phosphines on JandaJel™-Cl

Our proposed methodology to synthesise secondary phosphines on Merrifield-Cl or *J*anda*J*el™-Cl was based on modification of these resins by addition of lithiated primary phosphine in slight excess (Scheme 3.1, step **A**), followed by borane protection of the phosphine (step **B**). This proved to be a very successful and time-efficient method of synthesising secondary phosphines on these solid supports.



Scheme 3.1 Synthesis of secondary immobilised phosphines

Lithium phosphides could easily be obtained from a reaction of the corresponding primary phosphine in THF with *n*-BuLi at −78° C. This resulted in a bright yellow solution with a single resonance at −112 ppm in the ^{31}P NMR spectrum for lithium phenylphosphide. The lithium phosphides have to be prepared freshly as they cannot be stored for long periods of time. The reaction on *J*anda*J*el™-Cl was clean, resulting in a broad signal at −42 ppm and two signals at −125 ppm (Figure 3.2). Based on the integrals it could be concluded that the reaction was performed in nearly quantitative yield. The resonance corresponding to lithium phenylphosphide was not observed in ^{31}P NMR spectroscopy after addition in the reaction mixture, even though an excess of lithium phosphide was used. It is presumed that the excess of lithium phenylphosphide was quenched by protons from hydroxyl groups present in the resin as phenyl phosphine has a resonance at −125 ppm. It is plausible that these hydroxyl groups could originate either from the synthesis process of *J*anda*J*el™ resin, by hydrolysis of the polytetrahydrofuran cross-linker or the chloride bonds over time. Elemental analysis on chloride returned a value of 3.22% Cl for *J*anda*J*el™-Cl whereas a value of 3.40% was expected. This shows a decrease in loading from the original loading of 0.96 to 0.91 mmol Cl per gram resin.

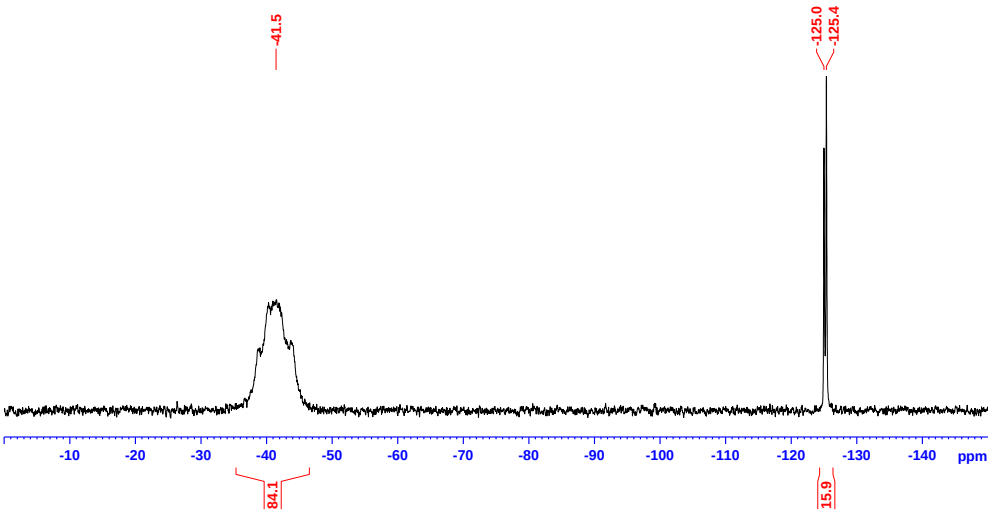


Figure 3.2 Reaction mixture A after 18h at rt in THF

After washing of the resin one broad signal at −42 ppm was observed (Figure 3.3). The reason why this resonance looks like a multiplet is unknown; this spectrum was recorded proton decoupled. In the proton coupled spectrum the signal was likewise broad, half as high, but without visible splitting of the resonance. The *J*anda*J*el™ resin was prepared by suspension copolymerisation of vinylbenzyl chloride, with styrene and PTHF cross-linker as described by Janda *et al.*[1d] This process results in a random distribution of chlorine sites throughout the particles and thus there will be differences in the local surroundings of each functional group. Another hypothesis is that there are π-π interactions between the phenyl groups on the phosphorus atom and the styrene groups in the backbone of the resin structure, which interfere with the rotational freedom of the groups on the phosphorus atom, causing the groups to be fixed in position and therefore individual resonances are visible in the ^{31}P NMR spectrum rather than the average resonance.

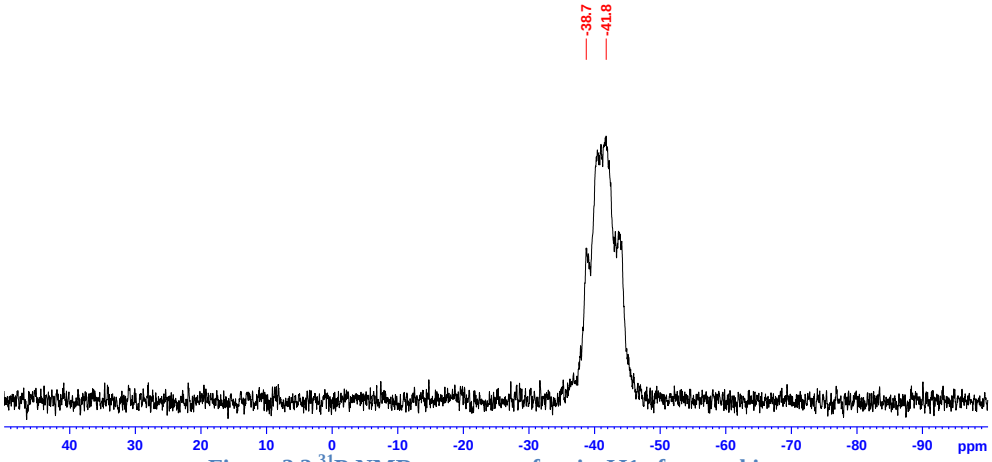


Figure 3.3 ^{31}P NMR spectrum of resin JJ1 after washing

Protection of immobilised phosphine **JJ1** was straightforward by addition of $BH_3{\cdot}SMe_2$ (reaction **B**), resulting in a resonance at $\delta^{31}P = +6.8$ (Figure 3.4). The literature value of the analogue compound benzylphenylphosphine-borane in solution is +6.9 ppm.[5]

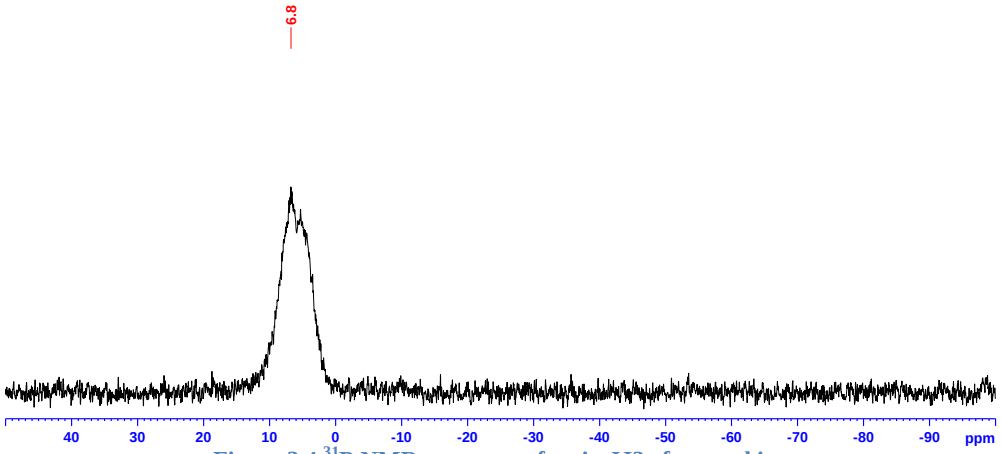


Figure 3.4 ^{31}P NMR spectrum of resin JJ2 after washing

It was observed that the resin phosphine-borane **JJ2** loses its BH_3-group slowly during prolonged storage. When stored under air, this resulted in oxidation of the deprotected phosphine and thus spoiled the resin for further use. Therefore it is advisable to store the immobilised phosphines under inert atmosphere or in a glove box.

It was attempted to determine the loading of the resin by addition of PPh_3 as an internal standard. Observation showed that BH_3-transfer occurs with free phosphine in solution as the BH_3-group moved to the free PPh_3 and signals at +21 ppm (PPh_3-BH_3) and −41 ppm (resin **JJ2**) appear in a ~1:1 ratio in the ^{31}P NMR spectrum. Moreover, in this spectrum the signal for resin **JJ2** had split, which could mean that **JJ2** consists either of two different phosphorus species or that the phosphine of resin **JJ2** appeared to be in two different micro-environments within the resin.

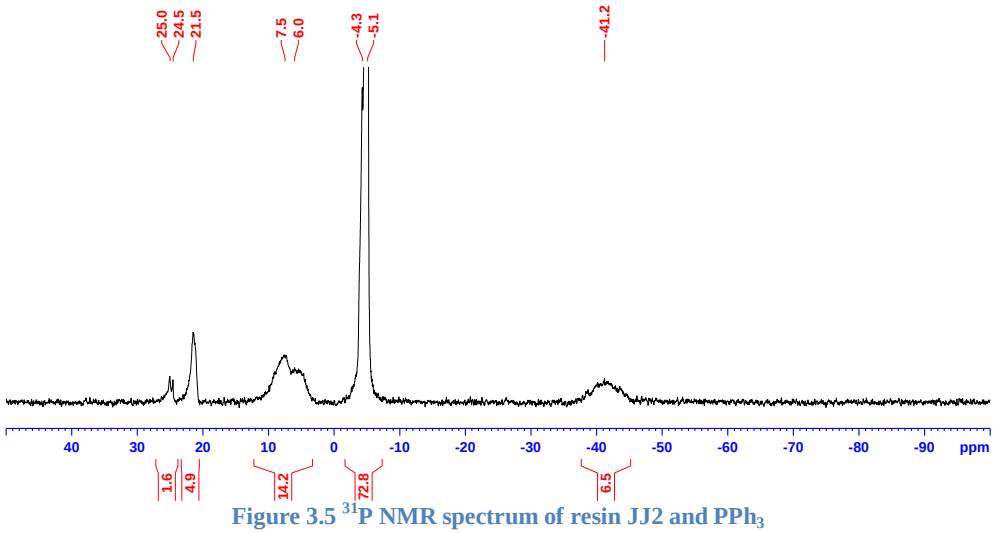


Figure 3.5 ^{31}P NMR spectrum of resin JJ2 and PPh_3

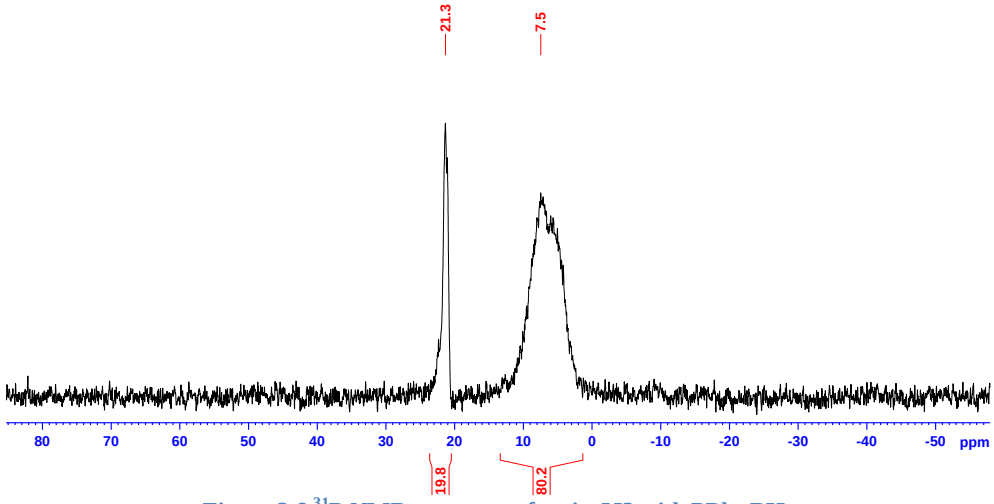


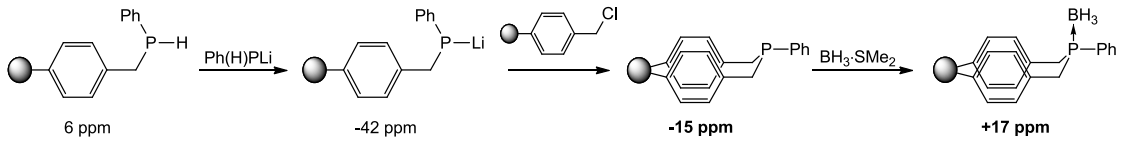
Figure 3.6 ^{31}P NMR spectrum of resin JJ2 with PPh_3-BH_3

Therefore, *in situ* BH_3-protection of PPh_3 was preferred (PPh_3-BH_3 = +21 ppm). For this, PPh_3 (20 µmol) was added to an NMR tube containing resin **JJ2** plus a slight excess of $BH_3{\cdot}SMe_2$ solution. From the ratio of the integrals (Figure 3.6) it should be possible to determine the loading of the resin. The integral ratio suggests that there is 80 µmol of 'P' in the tube, however, the amount of resin present in the sample had a maximum calculated loading of 42 µmol 'P'. Obviously, the resin was not homogeneously dispersed over the solution so no accurate comparison between solution and immobilised phosphorus could be made. Therefore this method of determining the loading is highly unreliable. Elemental analysis on phosphorus of the resin gave a value of 2.37%, which corresponds to a loading of 0.77 mmol P per gram resin, whereas the calculated value would be 0.84 mmol/gram or 2.74% P. Therefore the reaction was not as quantitative as the integrals of the first reaction would suggest (Figure 3.2).

3.2.1 Synthesis on Merrifield-Cl resin

The same procedure for the generation of immobilised phosphines as described above was applied to Merrifield resin. This resulted in the formation of the desired immobilised benzylphenylphosphine and corresponding phosphine-borane, with chemical shifts at −42 ppm (Figure 3.7) and +7 ppm (Figure 3.8) respectively in the ^{31}P NMR spectrum. However a small amount of side product was observed which could be formed by cross-linking the phosphine internally. This could occur when the formed secondary phosphine undergoes a proton-lithium transfer with the excess of lithium phenylphosphide and subsequently reacts with another benzylchloride functionality

within the same resin bead in close proximity. The formed side product has a resonance at −15 ppm and after addition of BH_3 shifted downfield to +17 ppm in the ^{31}P NMR spectrum. These values correspond closely to the literature values of Bn_2PPh ($\delta^{31}P = -12$ ppm),[6] and of the very similar $BnPPh_2$ ($\delta^{31}P = -10$ ppm)[6] and $BnPPh_2(BH_3)$.($\delta^{31}P = +18$ ppm).[5] Therefore it can be concluded that the functionalities within one resin bead must be positioned close enough to each other to react, but far enough apart that they will not cause additional ring tension to the system.[7]



Scheme 3.2 Suggested side product formation on Merrifield-Cl

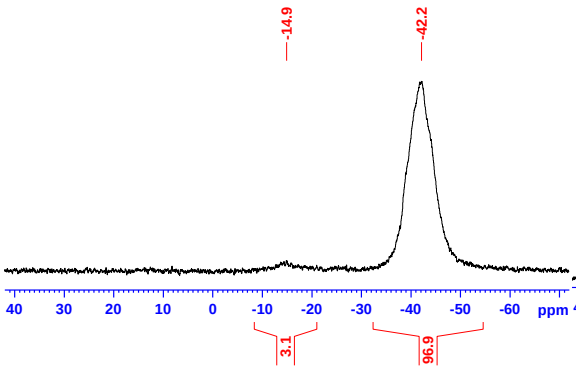


Figure 3.7 MF1 with side product

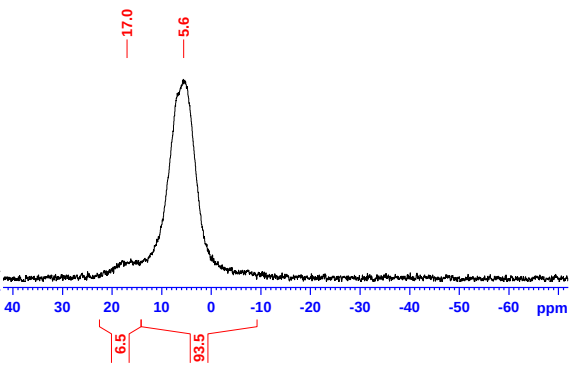


Figure 3.8 MF2 with side product

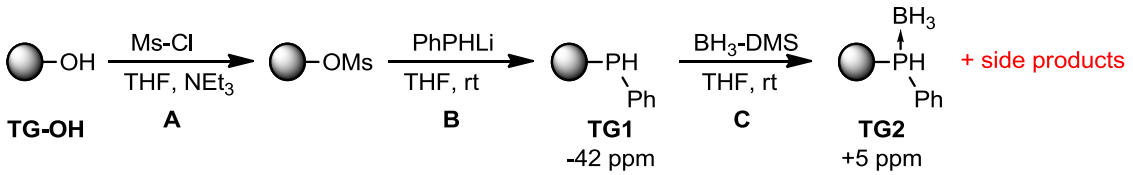
Due to this side product formation on Merrifield's resin and the promising results obtained with *J*anda*J*el™ resin, reactions on the former resin were not continued.

3.2.2 Synthesis on TentaGel™-OH resin

TentaGel™ resins containing a benzyl chloride as functional group or even a suitable other halogenated functionality, are not commercially available. Therefore, TentaGel™-OH was modified by reacting it with a large excess (20 eq.) of methanesulfonyl chloride in the presence of triethylamine in THF (Scheme 3.3, step **A**). The formed mesyl-groups are good leaving groups and are often used in the synthesis of bis(phosphines).[8]

As a test reaction to check if all hydroxyl groups had been fully substituted, the resin was treated with a slight excess of Ph_2PCl. In theory, only free hydroxyl groups should react with the chlorophosphine whereas the mesyl substituted hydroxyl groups are unreactive towards the chlorophosphine. The PCl-treated mesyl substituted resin

showed no signal in ^{31}P NMR after washing of the resin. Hence, it could be concluded that all hydroxyl groups were substituted by mesyl groups.



Scheme 3.3 Synthesis of TG2

Addition of an excess of lithium phenylphosphide did yield the desired phosphine **TG1** (Scheme 3.3, step **B**), however there were also small amounts of covalently bound side products present after washing (Figure 3.9). After protection with borane (step **C**), **TG2** was obtained with a chemical shift of 4.8 ppm and the unidentified side products had also been protected (Figure 3.10).

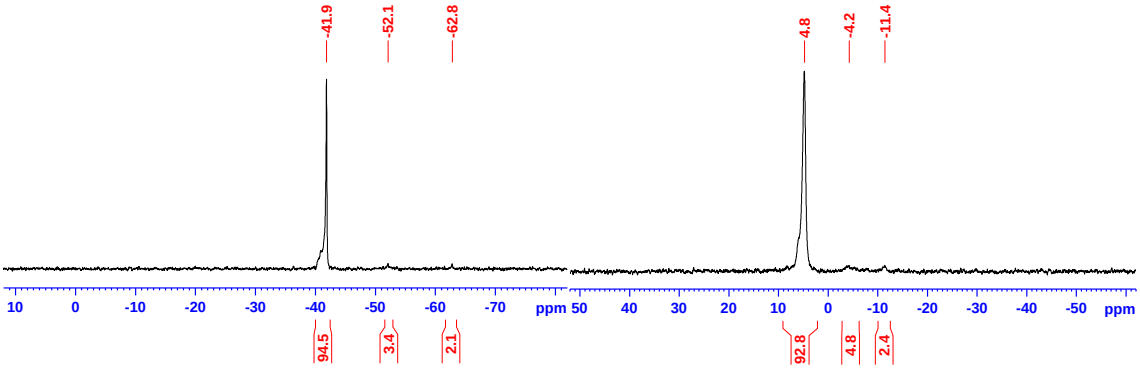


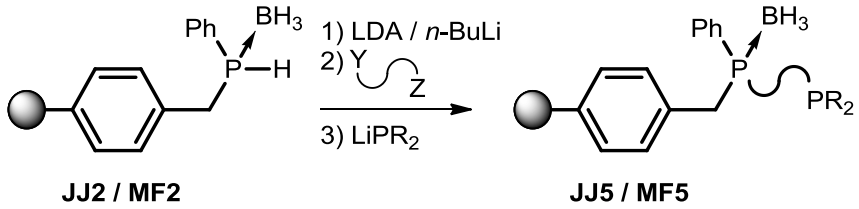
Figure 3.9 TG1 with side product

Figure 3.10 TG2 with side product

Additionally, there were several issues while working with TentaGel™ resin. Mainly, the bead size, even when fully swollen, was much smaller then experienced with PS and JJ resin. This caused problems while washing the resin resulting in blocked washing needles and glass filters, and this slowed the process of washing considerably. Consequently, together with the formation of side products, work on this resin was discontinued, despite the advantage of sharper signals in the ^{31}P NMR spectra.

3.3 Synthesis of immobilised bis(phosphines)

To proceed from the immobilised secondary phosphine towards immobilised bis(phosphines), the method developed on PS-DVB and described in Chapter 2 was initially followed (Scheme 3.4).



Scheme 3.4 Proposed method towards immobilised bis(phosphines)

JJ2 and **MF2** were lithiated with *n*-BuLi, under similar conditions as the reactions on polystyrene resin with **PS1** (Chapter 2). These reactions were performed in toluene which caused the signals of the lithium phosphide to broaden and disappear in the noise in ^{31}P NMR. For **JJ2** its signals had fully disappeared after 18 hours. **MF2** needed a longer reaction time of 3 days for the signals to fully disappear, most likely due to the difference in swelling properties of Merrifield resin in toluene compared to *J*anda*J*el™ resin. After all signals had disappeared, both resins were washed with portions of toluene and THF. In THF the resins coloured red and the ^{31}P NMR spectrum showed full lithiation of **JJ2** and of **MF2** with a signal at −40 ppm. However, there was another signal present at −73 ppm (Figure 3.11). The hypothesis is that, due to its high pK_a (>50) the excess of *n*-BuLi had deprotonated one of the benzylic protons as well, resulting in the second signal in ^{31}P NMR at −73 ppm (Scheme 3.5, step **A**). Subsequent reaction with 2,4-pentanediolcyclic sulfate resulted in two broad signals, namely at 27 ppm and at 43 ppm (Figure 3.12). The 27 ppm signal corresponds to the desired product; the other signal could be from the cyclised phosphane which could possibly be explained by the attack of the benzyl lithium to the opened sulfated group resulting in the cyclised product (Scheme 3.5, step **B**). Unfortunately there are no identical structures found in literature to compare the NMR data. The ^{31}P NMR resonances of three similar structures found in literature[9] (Scheme 3.5) are not conclusive towards the proposed side product.

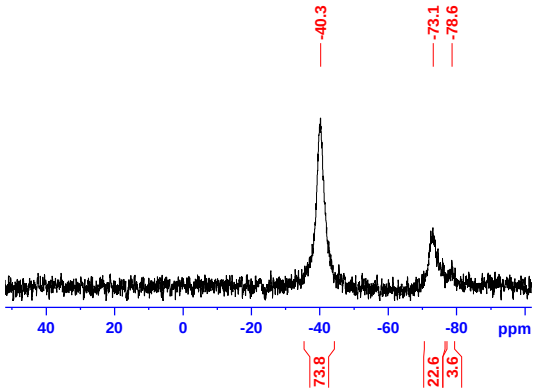


Figure 3.11 JJ3, after lithiation of JJ2 with *n*-BuLi

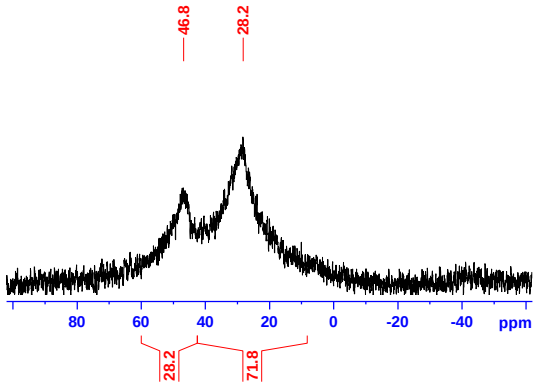
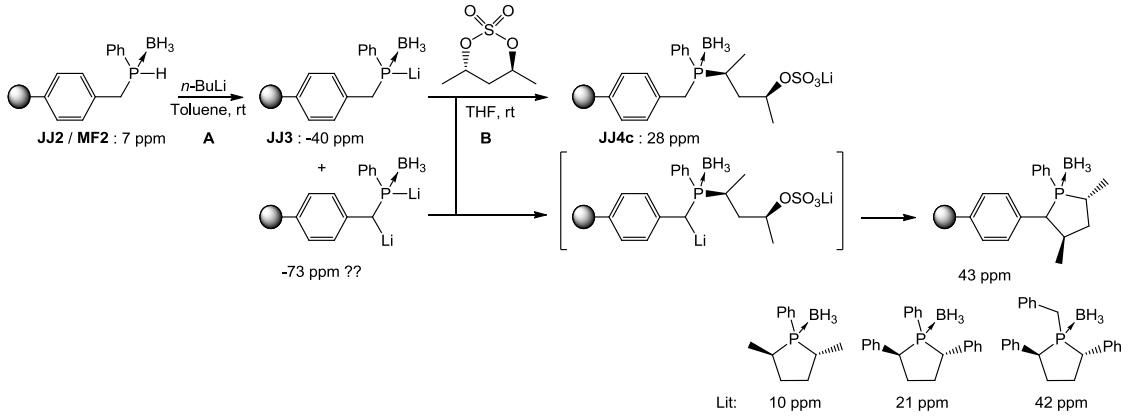


Figure 3.12 JJ4c with side product



Scheme 3.5 Proposed mechanism of side product formation after lithiation with *n*-BuLi

To prevent the deprotonation of the benzylic protons, a lithiation agent with a lower pK_a was chosen, *i.e.* lithium diisopropylamide (LDA). The pK_a of LDA is much lower in comparison to *n*-BuLi (36 for LDA, >50 for *n*-BuLi) and therefore too low to lithiate the benzylic protons (pK_a toluene = 43).[10] Lithiation of **JJ2** with LDA yielded a single broad signal at −40 ppm (Figure 3.13). Additionally, lithiation of the resins with LDA presents a few advantages. As LDA is stable in THF, the lithiation was performed in THF which allows direct monitoring of the reaction by ^{31}P NMR spectroscopy. Moreover, the reaction is much faster due to the better swelling of the resin in THF. On small (NMR tube) scale, full lithiation could be achieved in 1 hour at room temperature for the *J*anda*J*el™-resin and overnight for the polystyrene-resin. On larger scale reactions the reacting times were longer to ensure complete conversion.

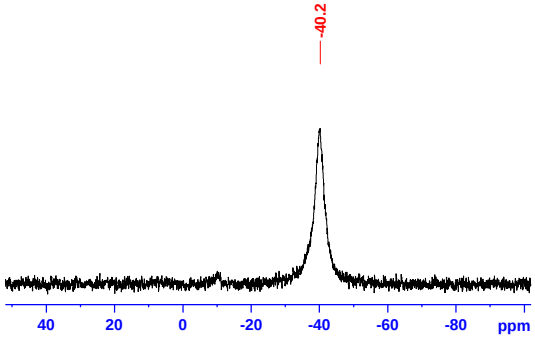


Figure 3.13 JJ3, after lithiation of JJ2 with LDA

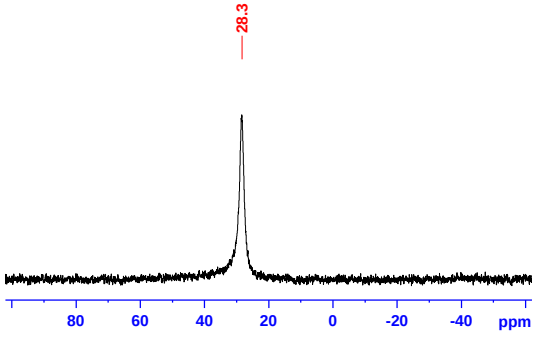
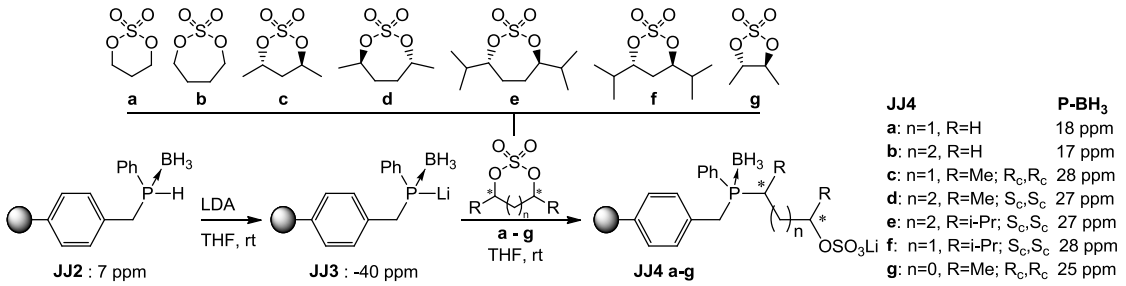


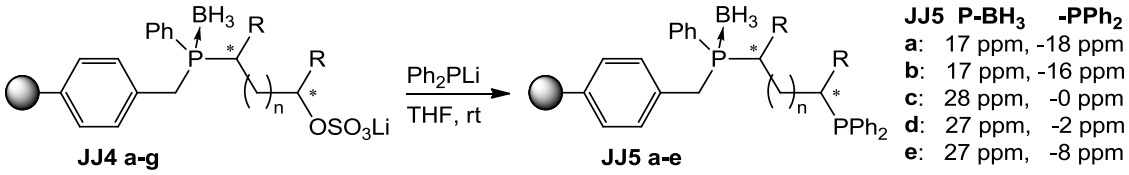
Figure 3.14 JJ4c without side product

In order to obtain a small library of immobilised bis(phosphines), a set of cyclic sulfates **a-g** were synthesised to be added to **JJ3**. All of these cyclic sulfates reacted readily to **JJ3** to form the corresponding immobilised phosphine-sulfates **JJ4a-g** (Scheme 3.6). As an example, the spectrum of **JJ4c** is depicted in Figure 3.14 showing a single signal at +28 ppm.



Scheme 3.6 Formation of immobilised phosphines JJ4a-g

The desired immobilised bis(phosphines) could then be obtained by subsequent addition of an excess of freshly prepared Ph_2PLi to immobilised phosphine-sulfates **JJ4a-g** at room temperature (Scheme 3.7).



Scheme 3.7 Synthesis of immobilised bis(phosphines)

The reactions were followed by ^{31}P NMR spectroscopy and the reaction times varied from 2 days up to 9 days depending on the resin used. The resins were washed once the resonances corresponding to the immobilised phosphine-borane and the newly formed immobilised diphenylphosphine had reached a near 1 to 1 ratio. Figure 3.15 shows that after 5 days the ratio between the two signals was close to 1 to 1 for the reaction of **JJ4c** with Ph_2PLi. The other signals observed in the reaction mixture corresponded to Ph_2PLi

($\delta^{31}P = -22.1$ ppm), Ph_2PH ($\delta^{31}P = -40.5$ ppm), $Ph_2P\text{-}PPh_2$ ($\delta^{31}P = -15.2$ ppm) and side products formed during the formation of Ph_2PLi ($\delta^{31}P$ = 91-86 ppm). After washing of the resin, the ratio had improved to close to 1 to 1 (Figure 3.16). The small shoulder on the right signal is due to the BH_3-group migrating from one phosphorus of the bis(phosphine) to the other.

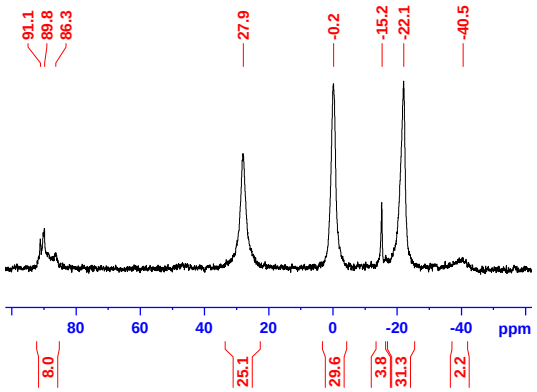


Figure 3.15 Reaction mixture of JJ5c after 5 days

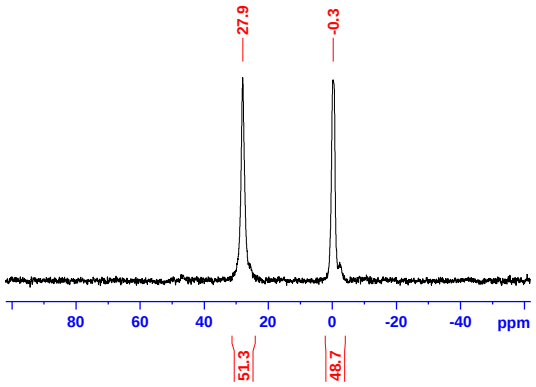


Figure 3.16 JJ5c washed

The reaction of **JJ4c** was also monitored by IR spectroscopy. The sulfate group of **JJ4c** has two vibrations at 1256.8 cm^{-1} and at 1647.5 cm^{-1}, which were no longer present in the IR spectrum of **JJ5c**. As this was a time consuming and non-quantitative method of determining the bis(phosphine) formation, no IR's were recorded of the other resins as ^{31}P NMR spectroscopy was sufficient enough.

Under these conditions only **JJ4a-e** could be converted successfully into bis(phosphines). Only 6% of **JJ4f** had reacted with the Ph_2PLi after 64 hours according to the integrals to from the bis(phosphine). Although the ^{31}P NMR of the reaction mixture **JJ4g** looked promising after one week (Figure 3.17), after washing of the resin there was a multitude of resonances present in the spectrum (Figure 3.18). It is unclear why **JJ4f** and **JJ4g** did not react with Ph_2PLi as they are structurally similar to **JJ4a-e**.

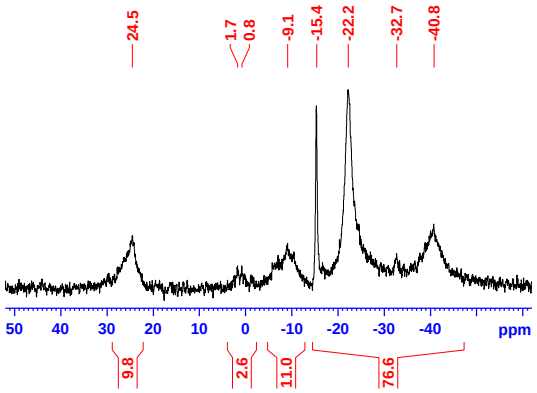


Figure 3.17 Reaction mixture of JJ5g after 7 days

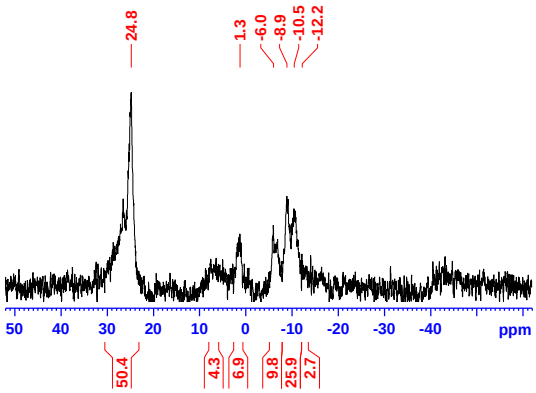
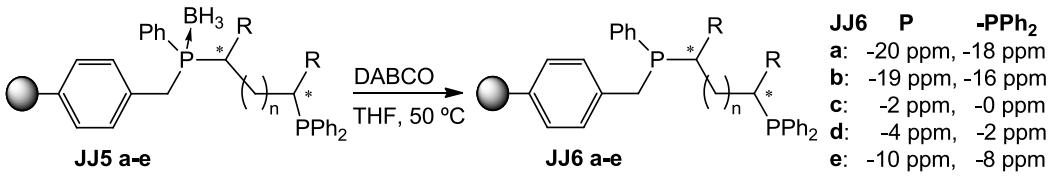


Figure 3.18 JJ5g washed

3.4 Deprotection of immobilised bis(phosphine) ligands

For the deprotection of the immobilised bis(phosphine)-boranes similar conditions were used as for the deprotection of the PS-ligands described in Chapter 2; *i.e.* heating the resins in THF at 50 °C in the presence of an excess of DABCO. This resulted in fully deprotected bis(phosphines) after 40 hours. Unfortunately, a small amount of oxidation of the phosphines (<5%) was observed by ^{31}P NMR. It has not fully been investigated in this project why the oxidation of the deprotected ligands occurred, and the ligands were used as such for the complexation with rhodium. The deprotection was performed under argon atmosphere with azeotropically dried DABCO and dried solvents. It may be that the deprotected ligands were extremely sensitive towards oxidation and therefore it is advisable to deprotect and handle the deprotected ligands in a glove-box.



Scheme 3.8 Deprotection of ligands JJ5a-e with DABCO

Interestingly, both stereoisomers, *i.e.* the R_P,R_C,R_C and the S_P,R_C,R_C isomer, of chiral bis(phosphine) **JJ5d** were visible by ^{31}P NMR after deprotection. The difference between the resonances of the diastereoisomers in the other chiral bis(phosphines) was less pronounced.

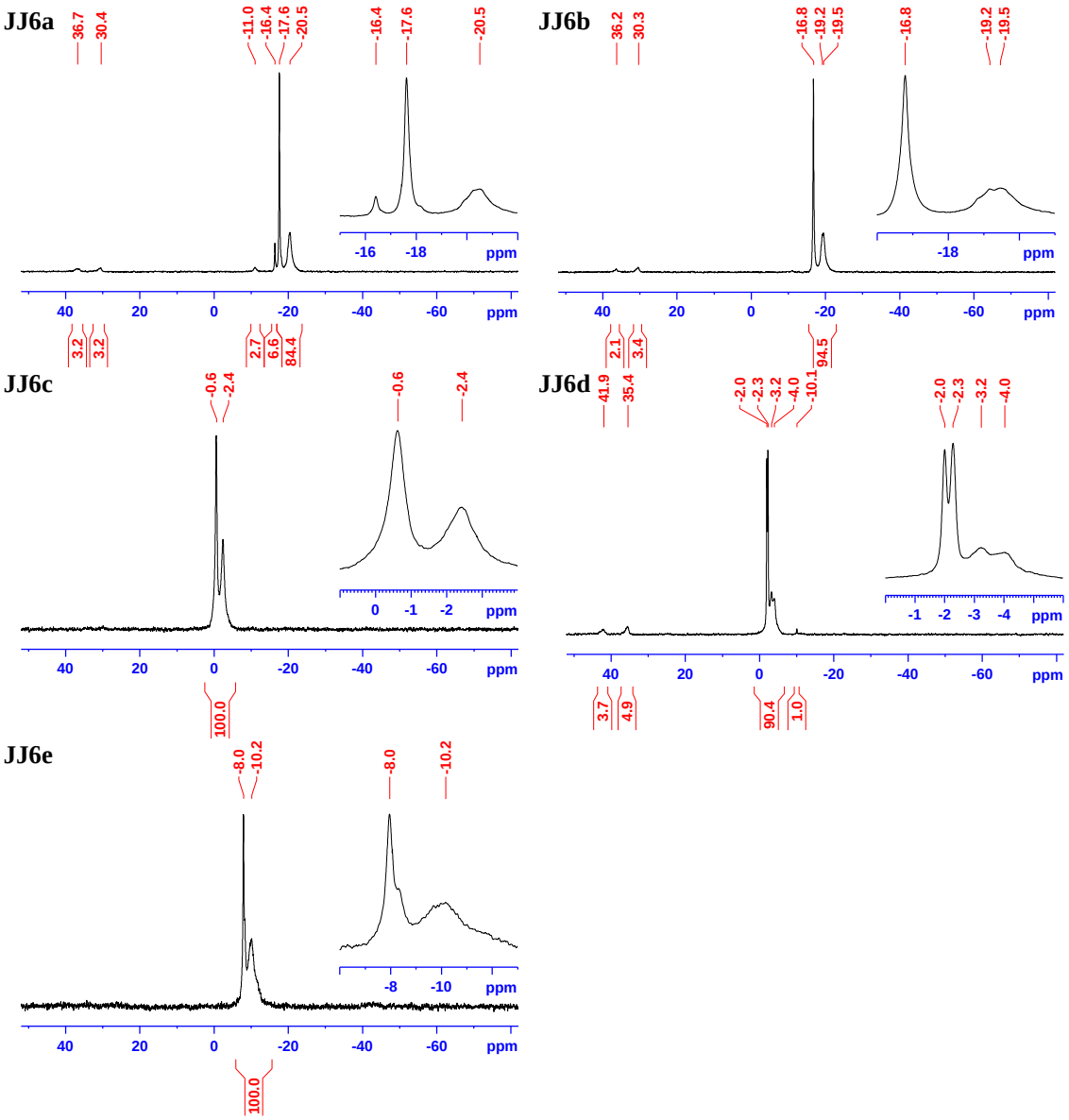
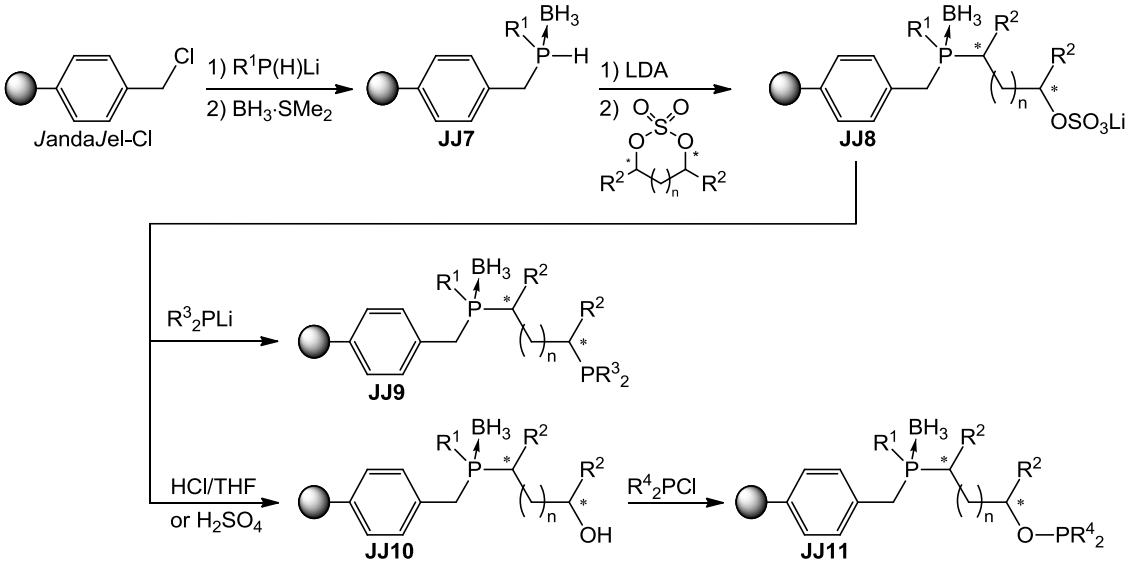


Figure 3.19 Spectra of the immobilised ligands JJ6a-e

3.5 Conclusions and outlook

Successful routes have been developed towards the synthesis of immobilised secondary phosphines on *J*anda*J*el™ resin, Merrifield resin and TentaGel™ resin. However, due to the formation of side products on Merrifield resin as well as on TentaGel™ resin, reactions on these resins were not further investigated. *J*anda*J*el™ resin proved to be the most reliable and best performing resin and was therefore chosen to be used in further optimisations of the reactions towards the formation of immobilised bis(phosphines). By lithiation of immobilised secondary phosphines with LDA and subsequent addition of cyclic sulfates followed by lithium phosphides, several immobilised bis(phosphine) ligands were successfully synthesised. After deprotection, these ligands can be used for asymmetric catalysis reaction, of which rhodium catalysed asymmetric hydrogenation will be discussed in Chapter 4.

In future work, a larger library of immobilised ligands could be generated by using different primary phosphines, for instance cyclohexylphosphine, tolylphosphine and *iso*-propylphospine, resulting in the formation of immobilised secondary phosphines **JJ7**. Reaction of the corresponding lithium phosphides with a large set of different (chiral) cyclic sulfates, followed by a selection of different secondary phosphines, *i.e.* dicyclohexylphosphine, ditolylphosphine and di-*iso*-propylphospine, would result in immobilised bis(phosphines) **JJ9**. The synthesis of immobilised phosphine-phosphinites and –phosphites **JJ11** could be envisaged by hydrolysis of the immobilised sulfates **JJ8** with HCl or H_2SO_4 in THF, followed by addition of chlorophosphines or chlorophosphonites respectively. These reactions are currently under investigation by members of our group.



Scheme 3.9 Proposed synthesis routes towards libraries of immobilised bis(phosphines), phosphine-phosphinites and phosphine-phosphites

3.6 Experimental

3.6.1 General remarks

Unless stated otherwise, reactions were carried out under an atmosphere of argon using standard Schlenk techniques. NMR spectra were recorded at room temperature on a Bruker Avance II 400. The ^{31}P NMR spectra were recorded proton decoupled and the gel-phase resin experiments were run unlocked. Chemical shifts are reported in ppm and are given relative to tetramethylsilane (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P). Elemental analyses were carried out by Kolbe Mikroanalytisch Labor, Mülheim an der Ruhr (Germany).

Unless stated otherwise, all chemicals were obtained from commercial suppliers and used as received. THF and diethyl ether were distilled from sodium/benzophenone. Tertiary and secondary amines, CH_2Cl_2 and acetonitrile were distilled from CaH_2 and toluene was distilled from sodium. Methanol and ethanol were distilled from magnesium. 4-Bromo polystyrene (PS-DVB-Br, 50-100 mesh, 1.9 mmol/g, 1% divinylbenzene/styrene copolymer) and *J*anda*J*el™-Cl (JJ-Cl, 50-100 mesh, 0.96 mmol/g, 2% crosslinked) were purchased from Sigma Aldrich. Merrifield-Cl (MF-Cl, 50-100 mesh, 1.34 mmol/g, 2% crosslinked) from Novabiochem and TentaGel™-OH (TG-OH, 50-100 mesh, 0.24 mmol/g) from Rapp Polymere.

Resin loadings are calculated via the following formula:

$$New\ loading = \frac{Original\ loading}{1 + ((Original\ loading) * (MW_2 - MW_1))}$$

Here '*New loading*' is the adjusted loading obtained after the reaction in mmol/g, '*Original loading*' is the loading of the resin as obtained from the supplier before any modifications. MW_1 is the molecular weight of the functional group on the resin as obtained from the supplier before any modification, and MW_2 is the molecular weight of the newly inserted group after reaction. It is important to adjust the mmol/g into mol/g for the % mass increase (denominator in the formula) to work in similar units as molecular weight which is measured in g/mol.

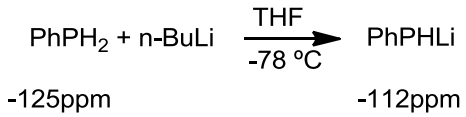
Elemental analysis results are calculated via the following formula:

$$\%Element = (New\ loading) * MW_{Element} * 100\%$$

Here '*New loading*' is the adjusted loading obtained after the reaction in mmol/g. The molecular weights for the elements measured are: MW_{Cl} = 35.45 g/mol, MW_P = 30.97 g/mol and MW_S = 32.06 g/mol.

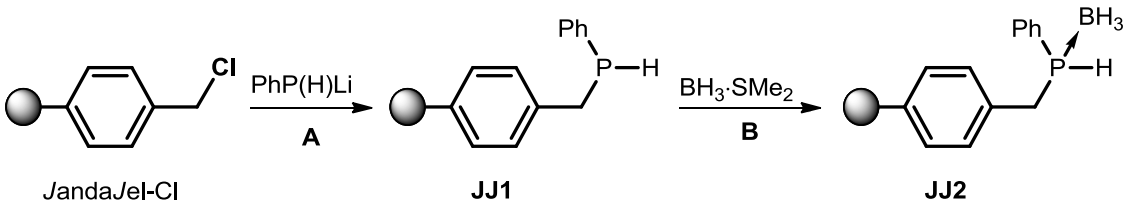
3.6.2 Synthesis

Synthesis of lithium phenylphosphide[11]



A pre-weighed Young Schlenk tube (without stirring bar as the formed lithium phosphide reacts with the Teflon coating) was loaded with $PhPH_2$ (400.8 mg, 400 µL, 3.64 mmol) using a gas-tight microliter syringe. 10 mL of THF was added to obtain an estimated molarity of PhP(H)Li of 0.3 M. Note: With concentrations over 0.4 M the formed PhP(H)Li precipitates as it does not dissolve in the hexanes added with the *n*-BuLi solution. The solution was cooled to −78 °C and dropwise *n*-BuLi (2.37 M in hexanes, 1.5 mL, 3.55 mmol) was added while shaking the Schlenk at regular intervals on a vortex shaker. This resulted in a bright yellow solution of PhP(H)Li which has a ^{31}P NMR resonance at −112 ppm.[12] This solution of PhP(H)Li cannot be stored for extended periods of time and was consequently used immediately in the next reaction and freshly prepared when needed.

General procedure for immobilised phenyl phosphine boranes



Method for JandaJel™-Cl, Merrifield-Cl, or TentaGel™-OMs:

The resin JandaJel™-Cl (1.5 g, 1.45 mmol, loading: 0.96 mmol/g) was suspended in 20 mL of THF for at least 30 minutes before cooling to −78 °C, followed by addition of freshly made PhP(H)Li solution (11.5 mL, 3.52 mmol, 2.4 eq.). The reaction mixture was allowed to warm to room temperature and slowly stirred (~200 rpm) overnight.

A sample of the resin was transferred to an NMR tube by use of a 1 mL syringe fitted with an 18 gauge needle. Enough resin was transferred in this way to obtain a resin plug in the NMR tube of at least 1.5 cm in a total volume of 1 mL.

After confirming the completed formation of **JJ1** by NMR, the resin was washed with 20 mL portions of THF and Et_2O before suspension in THF and addition of $BH_3{\cdot}SMe_2$ complex (2 M in toluene, 5 mL). After slow stirring overnight the resin was washed again with 20 mL portions of THF, Et_2O, MeOH/THF, THF, Et_2O before drying under reduced pressure and the product **JJ2** was stored under argon. The corresponding integral ratios are the values in between brackets, given in percentages.

JJ1: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −42 ppm.

JJ2: white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): +7 ppm;
elemental analysis (%): P, 2.37 Calculated: 2.61;
IR ν_{max} (KBr)/cm^{-1}: 2364.1 (BH_3).

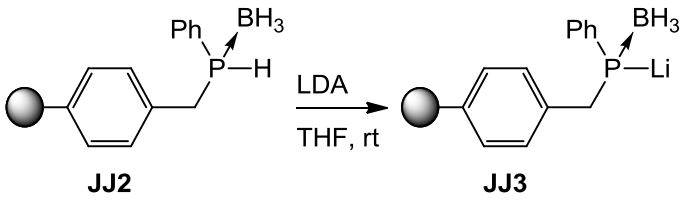
MF1: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −42 ppm (97%), −15 ppm (3%).

MF2: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): +7 ppm (94%), +17 ppm (6%).

TG1: light yellow resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −42 ppm (95%), −52 ppm (3%), −63 ppm (2%).

TG2: light yellow resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): +6 ppm (93%), −4 ppm (5%), −11 ppm (2%).

General procedure for lithiations



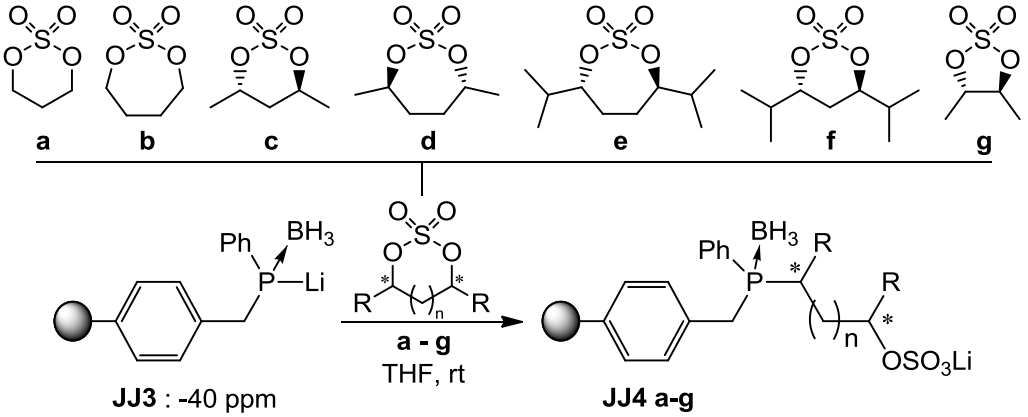
JJ2 **JJ3**

Method for JandaJel™, Merrifield, or TentaGel™:

The resin **JJ2** (220 mg, 195 µmol, loading: 0.89 mmol/g) was suspended in 7 mL of THF for at least 30 minutes, followed by addition of LDA solution (1 mL, 2 M, 10.2 eq.). After reacting 18 hours at room temperature, the brown resin was washed with portions of THF (3 x 7 mL) or until the filtrate was colourless. The brown resin **JJ3** was suspended in 7 mL of THF to be used in the subsequent reaction.

JJ3: brown resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): −40 ppm.

General procedure for immobilised phosphine sulfates



JJ3 : -40 ppm **JJ4 a-g**

Propanediol cyclic sulfate (74.39 mg, 538.5 µmol, 2.76 eq.) was azeotropically dried with portions of toluene (3 x 0.5 mL) and dissolved in 1 mL of THF. The solution of cyclic sulfate was transferred to the Schlenk tube with the suspension of lithiated resin **JJ3** (220 mg, 195 µmol, loading: 0.89 mmol/g) in 7 mL of THF. After reacting 18 hours at room temperature, the light yellow resin was washed with portions of THF and Et_2O (3 x 7 mL respectively). The white resin **JJ4a** was suspended in 7 mL of THF to be used in the subsequent reaction.

JJ4a: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +18 ppm.

JJ4b: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +17 ppm.

JJ4c: white resin, $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +28 ppm;
elemental analysis (%): P, 3.03 Calculated: 2.28;
S, 2.40 Calculated: 2.36;
IR ν_{max} (KBr)/cm^{-1}: 2377.8 (BH_3), 1647.5 and 1256.8 (S=O).

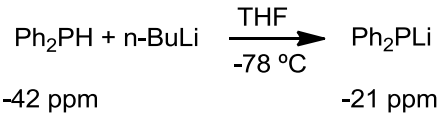
JJ4d: white resin, $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +27 ppm;
elemental analysis (%): P, 2.61 Calculated: 2.25;
S, 2.20 Calculated: 2.33.

JJ4e: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +27 ppm.

JJ4f: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +28 ppm.

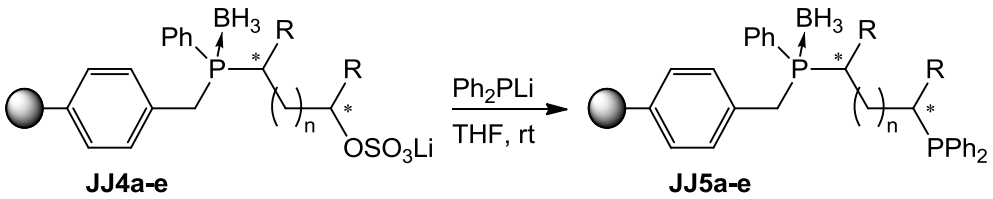
JJ4g: white resin, *in situ* $^{31}P\{^{1}H\}$ NMR (121 MHz, THF): +25 ppm.

Synthesis of lithium diphenylphosphide



A pre-weighed Young Schlenk tube (without stirring bar as the formed lithium phosphide reacts with the Teflon coating) was loaded with Ph_2PH (214.1 mg, 200 µL, 1.15 mmol) using a gas-tight microliter syringe. 4 mL of THF was added to obtain an estimated molarity of Ph_2PLi of 0.25 M. Note: With concentrations over 0.4 M the formed Ph_2PLi precipitates as it does not dissolve in the hexanes added with the *n*-BuLi solution. The solution was cooled to −78 °C and *n*-BuLi (2.37 M in hexanes, 480 µL, 1.14 mmol) was added dropwise while shaking the Schlenk at regular intervals on a vortex shaker. This resulted in a bright orange solution of Ph_2PLi which has a ^{31}P NMR resonance at −21 ppm. This solution of Ph_2PLi cannot be stored for extended periods of time and was used immediately in the next reaction and freshly prepared when needed.

General procedure for immobilised bis(phosphine) boranes



JJ4a-e **JJ5a-e**

To the resin **JJ4a** (220 mg, 195 µmol, loading: 0.89 mmol/g) suspended in 7 mL of THF was added freshly prepared lithium diphenylphosphide solution (4 mL, 0.25 M, 1 mmol, 5.1 eq.). After reacting 4 days at room temperature, the resin **JJ5a-e** was washed with portions of THF and Et_2O (3 x 7 mL respectively). The white resin **JJ5a-e** was suspended in 7 mL of THF and 1 mL of $BH_3{\cdot}SMe_2$ complex (2 M in toluene, 1 mmol) was added. After 18 hours, the white resin **JJ5a'-e'** was washed with 5 mL portions of THF, THF/H_2O (5:1), THF, Et_2O and dried under reduced pressure.

JJ5a: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 18 ppm, −18 ppm.

JJ5a': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): 18 ppm, 15 ppm;
elemental analysis (%): P, 4.10 Calculated: 4.34.

JJ5b: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 17 ppm, −16 ppm.

JJ5b': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): 17 ppm, 16 ppm;
elemental analysis (%): P, 4.07 Calculated: 4.29.

JJ5c: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 28 ppm, −0.3 ppm.

JJ5c': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): 28 ppm, −0.3 ppm;
elemental analysis (%): P, 3.29 Calculated: 4.25;
IR ν_{max} (KBr)/cm^{-1}: 2379.6 (BH_3).

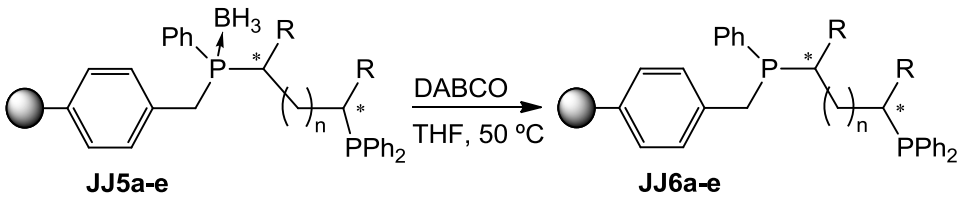
JJ5d: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 27 ppm, −1.6 ppm.

JJ5d': white resin, $^{31}P\{^1H\}$ NMR (121 MHz, THF): 28 ppm, 25 ppm;
elemental analysis (%): P, 3.51 Calculated: 4.21.

JJ5e: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 27 ppm, −8 ppm.

JJ5'e: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): 27 ppm, 26 ppm.

General procedure for deprotection of immobilised bis(phosphine)-boranes



JJ5a-e **JJ6a-e**

To the resin **JJ5a** (110 mg, 80.5 µmol, loading: 0.73 mmol/g) was added 5 mL of a solution of azeotropically dried DABCO (311.4 mg, 2.78 mmol). The reaction mixture was heated at 50 °C for 34 hours after which full deprotection was achieved. The deprotected resin **JJ6a** was washed with portions of THF and Et_2O (3 x 7 mL respectively) and dried under reduced pressure. Without further purification, the obtained resins were used as such in subsequent reactions.

JJ6a: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −20 ppm, −18 ppm.

JJ6b: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −19 ppm, −16 ppm.

JJ6c: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −2.4 ppm, −0.3 ppm.

JJ6d: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −2.3 ppm (d), −1.4 ppm (d).

JJ6e: white resin, *in situ* $^{31}P\{^1H\}$ NMR (121 MHz, THF): −10 ppm, −8 ppm.

3.7 References

1. a) P. H. Toy, K. D. Janda, *Tetrahedron Lett.* **1999**, *40*, 6329-6332; b) B. Clapham, T. S. Reger, K. D. Janda, *Tetrahedron* **2001**, *57*, 4637-4662; c) T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325-3344; d) P. H. Toy, T. S. Reger, P. Garibay, J. C. Garno, J. A. Malikayil, G.-Y. Liu, K. D. Janda, *J. Comb. Chem.* **2001**, *3*, 117-124.
2. R. Santini, M. C. Griffith, M. Qi, *Tetrahedron Lett.* **1998**, *39*, 8951-8954.
3. a) http://www.sigmaaldrich.com/chemistry/drug-discovery/resin-explorer/Jandajels.html (Accessed: February 2014); b) http://www.rapp-polymere.com/index.php?id=1218 (Accessed: February 2014)
4. http://www.rapp-polymere.com/ (Accessed: February 2014)
5. H. Lebel, S. Morin, V. Paquet, *Org. Lett.* **2003**, *5*, 2347-2349.
6. J. Tong, S. Liu, S. Zhang, S. Z. Li, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2007**, *67*, 837-846.
7. P. E. Garrou, *Chem. Rev.* **1981**, *81*, 229-266.
8. Y.-Y. Yan, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 4137-4140.
9. a) M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569-592; b) M. Rivard, F. Guillen, J.-C. Fiaud, C. Aroulanda, P. Lesot, *Tetrahedron: Asymmetry* **2003**, *14*, 1141-1152.
10. a) L. G. Wade, *Organic Chemistry (5th Edition)*, Prentice Hall, Upper Saddle River, NJ, **2003**; b) M. A. Fox, J. K. Whitesell, *Organic Chemistry (2th Edition)*, Jones & Bartlett Publishers, Sudbury, MA, **1997**.
11. Z. Chen, Q. Jiang, G. Zhu, D. Xiao, P. Cao, C. Guo, X. Zhang, *J. Org. Chem.* **1997**, *62*, 4521-4523.
12. F. Garcia, S. M. Humphrey, R. A. Kowenicki, M. McPartlin, D. S. Wright, *Dalton Trans.* **2004**, 977-979.

Chapter 4. Catalytic studies

4.1 Introduction

Rhodium catalysed asymmetric hydrogenation reactions are among the most important tools used in the synthesis of chiral fine chemicals. It all started with the discovery of Wilkinson's catalyst,[1] $Rh(Cl(PPh_3)_3$, which proved to be a highly active and successful catalyst for a wide variety of non-chiral substrates. By now numerous groups have investigated the mechanism and applicability on a plethora of compounds, and several excellent books[2] and reviews[3] have been written on this subject. Because of the successes of chiral bis(phosphines), such as DIPAMP[4] and DIOP,[5] in rhodium catalysed asymmetric hydrogenation of chiral substrates this reaction was chosen to begin the catalytic studies to test the catalytic performance and activity of the synthesised bis(phosphine) ligands immobilised on polystyrene resin and on *J*anda*J*el™ resin. Six model compounds, namely dimethyl itaconate (**A**), methyl 2-acetamidoacrylate (**B**), methyl acetamidocinnamate (**C**) and the three enamides (**D**-**F**) were tested in these studies (Figure 4.1), The asymmetric hydrogenation of these substrates has already been fully investigated in solution by other groups[6] and therefore it can used as benchmark for our immobilised bis(phosphine) ligands.

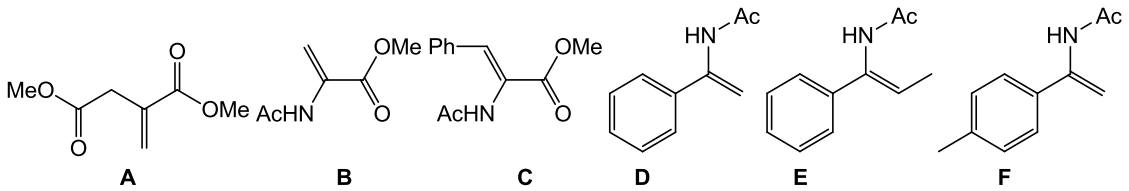


Figure 4.1 Substrates used in preliminary studies

In these preliminary studies, the general catalytic procedure described by den Heeten *et al.*[7] for their immobilised ligand systems on these substrates was followed. The reaction conditions used in the tests were not optimised and were solely used to obtain an indication of the catalytic performance of our immobilised ligands. Once this has been established the conditions should be optimised, but this is beyond the scope of this thesis.

4.2 Rhodium catalysed asymmetric Hydrogenations with polystyrene based ligands

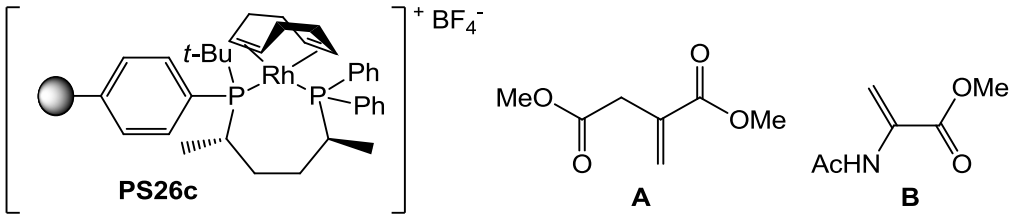


Figure 4.2 Ligand PS26c and substrates used in catalysis

The rhodium complexes were generated *in situ* from $[Rh(COD)_2]^+BF_4^-$ and immobilised chiral ligand **PS26c** and tested for activity and selectivity in asymmetric hydrogenation of dimethylitaconate (Figure 4.2, **A**) and of methyl 2-acetamidoacrylate (**B**).[7]

It was observed that the initially orange resins all had changed colour to dark brown or black during the catalysis under these conditions and the preliminary results proved to be irreproducible. Unfortunately, not enough material of ligand **PS26c** had initially been synthesised and therefore the reactions could not be repeated to meet the optimum conditions.

4.3 Rhodium catalysed asymmetric Hydrogenations with JandaJel™ based ligands

Rajanbabu *et al.*[6f] reported the synthesis of a series of DIOP-type ligands and C4-bridged bis(phosphines) of which ligand **3** and **4** could be seen as the solution-phase analogues of ligands **JJ6d** and **JJ6e** (Figure 4.3). They have successfully used these ligands in the rhodium catalysed asymmetric hydrogenation of several enamides with high conversions and *ee*'s. Ligand **3** performed very well in the hydrogenation of enamides **D**, **E** and **F** with *ee*'s of 91, 96 and 93% respectively. With ligand **4** slightly lower *ee*'s were obtained for enamide **E** (77%), but enamide **D** and **F** were converted successfully with *ee*'s of 95 and 93% respectively.[6f]

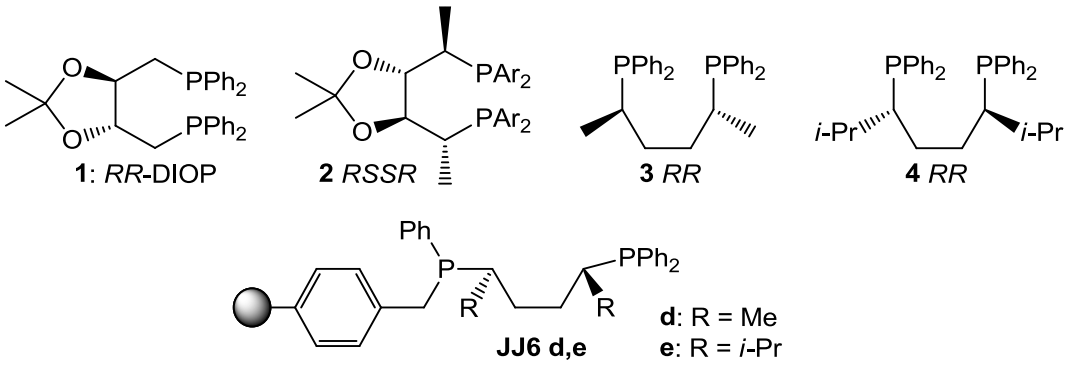
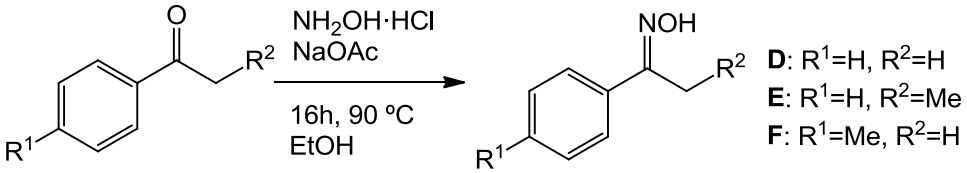


Figure 4.3 Ligands synthesised by Rajanbabu *et al.*[6f] in comparison with immobilised ligands JJ6d,e

These promising high conversions and *ee*'s obtained by the liquid phase analogues could be used as a benchmark to test the catalytic performance of the immobilised ligands synthesised on *J*anda*J*el™ resin.

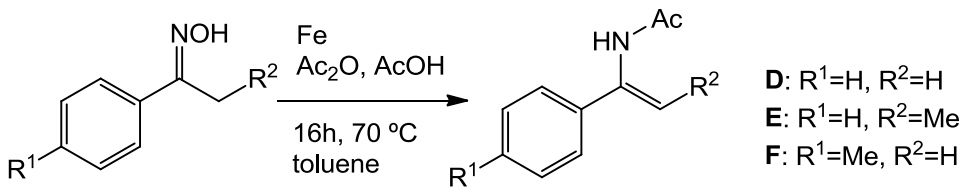
4.3.1 Synthesis of enamides

The enamides were synthesised in two steps from their corresponding ketones. The first step, the synthesis of the oximes from their corresponding ketones, was performed on large scale (20 gram) providing high yields and purity.[8]



Scheme 4.1 Synthesis of the oximes from ketones

To convert the oximes into their corresponding enamides, two different approaches were described in the literature. The first method involved the use of iron powder added in stoichiometric amounts together with excesses of acetic acid and acetic anhydride as described by Burk *et al.*[9] (Scheme 4.2)

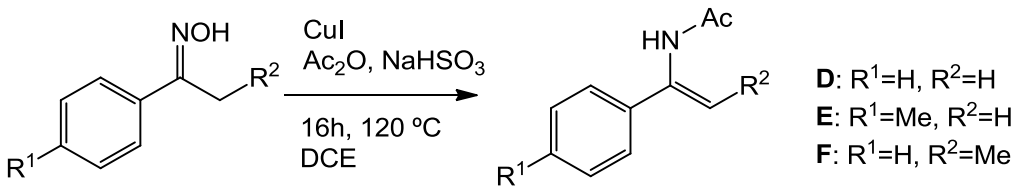


Scheme 4.2 Synthesis of the enamides from oximes with iron powder

The enamides were formed in high yield according to GC/MS analysis, but separation of the products from the suspension of iron oxides particles and other side products proved difficult. After following this procedure, the formed enamides were

fully converted back to their corresponding ketones. Several attempts were made and only the ketones instead of the desired enamides were obtained. It was suspected that during the described workup, which contained an extraction step with NaOH, the enamides decomposed. Hesp *et al.*[10] have reported a slightly different work-up which involved a $NaHCO_3$-wash instead of the use of NaOH. This did not result in any improvement in purity and no pure enamides could be obtained following these procedures.

The second method investigated was developed by Guan *et al.*[11] and they reported successful conversions of oximes to enamide with CuI as catalyst (Scheme 4.3). Via this method the phenylvinylacetamide was formed with considerably less impurities than in the reactions using Fe-powder.

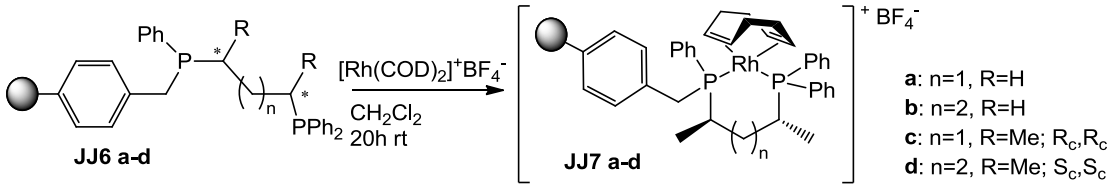


Scheme 4.3 Synthesis of the enamides from oximes with copper iodide

Using this method the enamides were obtained in high purity after column chromatography over silica, followed by crystallisation.

4.3.2 Complex formation with rhodium

The complexation of the deprotected ligands **JJ6a-d** with rhodium was performed *in situ* by suspension of the ligands **JJ6a-d** in CH_2Cl_2 followed by addition of a solution of bis(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate $[Rh(COD)_2]^+BF_4^-$ in CH_2Cl_2 (Scheme 4.4).[7] After 20 hours incubation time the now orange resins were washed with CH_2Cl_2 to remove any excess of rhodium and complex formation was confirmed by ^{31}P NMR (Figure 4.4). It was observed that before addition of the rhodium-solution the resin beads floated under the surface of the CH_2Cl_2. After the incubation time, most of the beads had settled on the bottom of the Schlenk flask. This could be explained either by the difference in solvent effect or swelling of the resin of **JJ6** compared to **JJ7** in CH_2Cl_2, or because the higher weight of complex **JJ7** did increase the density of the resin beads.



Scheme 4.4 Rhodium complex formation of ligands JJ7a-e

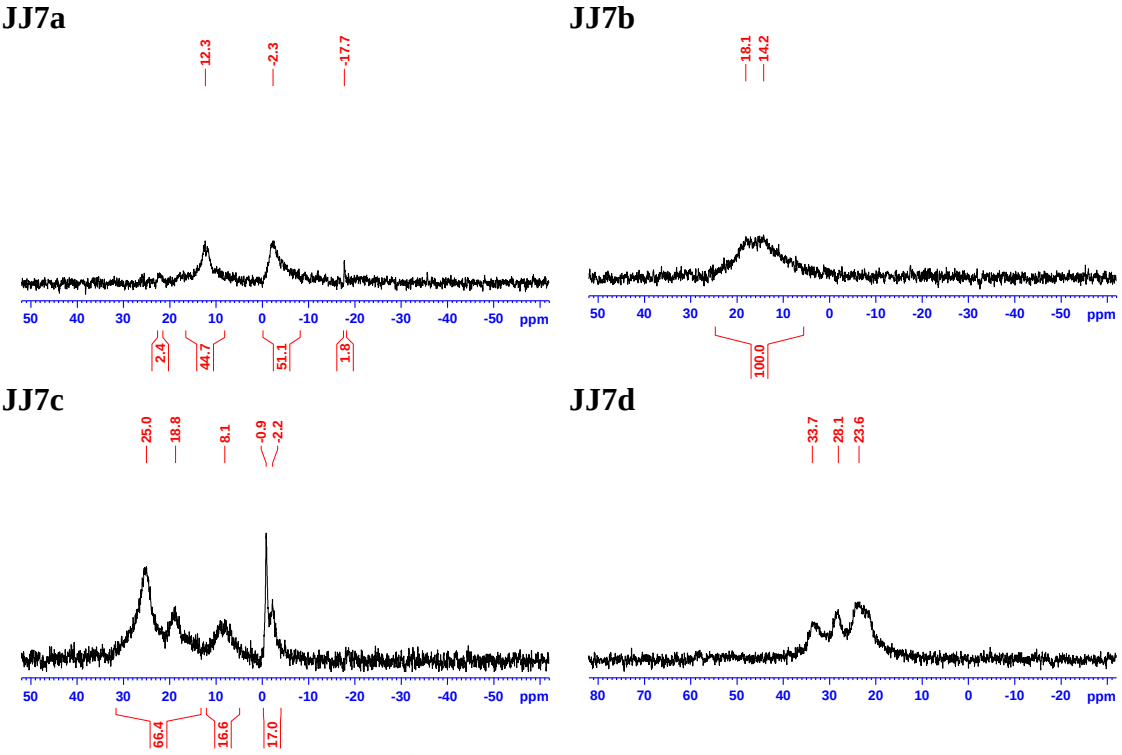


Figure 4.4 Spectra of the immobilised ligand-rhodium complexes JJ7a-d

All complexes were successfully formed as no free phosphine signals were present in the ^{31}P NMR spectra, apart from **JJ7c** which contained 17% of free ligand (−0.9 and −2.2 ppm) after washing of the resin. The ligands contain two different phosphorus groups, *i.e.* −PBzPh and –PPh_2, of which the PBzPh-group is racemic. In the achiral complexes **JJ7a** and **b** this results in two resonances. The chiral complexes **JJ7c** and **d** show three broad signals, two coinciding signals for the PPh_2-group and two for either of the the PBzPh-groups. These specific complexes have not been synthesised in solution as such, but the chemical shifts are in line the resonance of (*S*,*S*)-2,4-bis-(diphenylphosphino)pentane, (S,S)-BDPP, which has a ^{31}P NMR resonance at 29.8 ppm in $CDCl_3$.[12] Due to the broadness of the resonances on solid support, it is impossible to determine the Rh-P coupling constants of the immobilised complexes. It was observed that the resonances of the two different phosphines in complexes of the ligands with a C3-chain length (**JJ7a** and **c**) show larger chemical shift differences than those of the

ligands with a C4-chain length (**JJ7b** and **d**), which could be caused by the difference in ring strain in the complexes.[13]

4.3.3 Asymmetric hydrogenation of substrates B and C

Initially, catalysts **JJ7c-e** (Figure 4.5) were tested for activity and selectivity in rhodium catalysed asymmetric hydrogenation of substrates **B** and **C**. In this preliminary catalytic run, the rhodium complexes were generated *in situ* by loading the reaction vials individually with the immobilised ligands **JJ6c-e**, followed by the addition of a solution of bis(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate $[Rh(COD)_2]^+BF_4^-$ in CH_2Cl_2.[7] After 4 hours incubation time, the resins were washed with CH_2Cl_2 and substrate solutions were added. The vials were transferred to the autoclave and after 20 hours at 15 bar hydrogen pressure, the initially orange resins all had changed colour to dark brown.

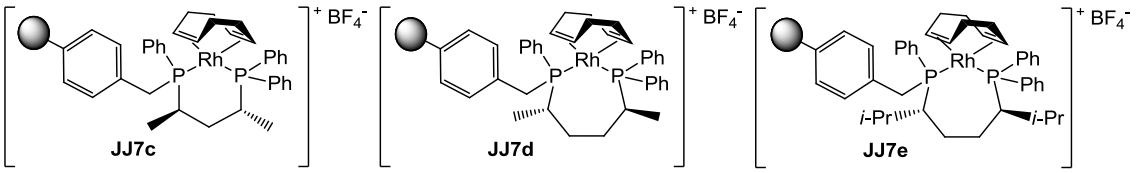


Figure 4.5 Rhodium-ligand complexes used in asymmetric hydrogenation of substrates B and C

Table 4.1 Results of rhodium catalysed asymmetric hydrogenation of substrates B and C

Ligand	Conv.	% *ee* of substrates	
		B	**C**
JJ7c	>99%	26 (*S*)	24 (*S*)
JJ7d	>99%	22 (*R*)	31 (*R*)
JJ7e	>99%	25 (*R*)	33 (*R*)

Ligand/$Rh(Cod)_2BF_4$/Substrate 1:1:30, CH_2Cl_2, 15bar H_2, 20 °C, 20h

The reaction mixtures were filtered over a small plug of silica to remove the resin beads and potentially free rhodium from the samples before analysis by chiral GC. Quantitative conversions were achieved with all three catalysts, but the obtained *ee*'s were very low. The conditions used were not optimised for these reactions. Change of solvent, pressure and temperature might enhance the *ee*'s, however this has not yet been investigated.

4.3.4 Asymmetric hydrogenation of enamides D, E and F

For the asymmetric hydrogenation of enamides **D**, **E** and **F**, the reaction vials were loaded with the immobilised ligand-rhodium complexes, described in Section 4.3.2, in a glove-box under nitrogen atmosphere to exclude the introduction of air into the system. Stock solutions of the substrates **D**, **E** and **F** with diphenylether as internal standard were added to each vial and the vials were transferred to the autoclave. After 20 hours at 15 bar H_2-pressure, it was observed that the colour of all the resins had changed from bright orange to dark orange/brown. Additionally, the reaction solutions of the chiral catalysts **JJ7c** and **d** had become somewhat cloudy, while those of catalysts **JJ7a** and **b** had remained clear.

Full conversion was achieved with catalysts **JJ7a,b,d** at 15 bar H_2 pressure. Chiral catalyst **JJ7d** showed moderate to reasonable *ee*'s for all three substrates. The enantioselectivity of the supported catalyst **JJ7d** is not as high as the selectivity of its non-supported analogue.[6f] This difference in selectivity could be caused by the slightly different structure of the immobilised ligand compared to the non-supported analogue. The analogue is symmetrical and has two diphenylphosphine moieties, while our immobilised system contains one diphenylphosphine and one benzylphenylphosphine moiety. Moreover, differences in enantioselectivities between other supported and non-supported systems, in which the supported system has lower selectivities, have been reported previously.[7,14]

Table 4.2 Results of rhodium catalysed asymmetric hydrogenation of enamides

Ligand	**Conv.**	% *ee* of substrates		
		D	**E**	**F**
JJ7a (15bar H_2)	>99%	0	0	0
JJ7b (15bar H_2)	>99%	0	0	0
JJ7c (5bar H_2)	74%	-	-	17 (*R*)
JJ7c (15bar H_2)	1-8%	16 (*R*) 1% conv.	17 (*R*) 2% conv.	23 (*R*) 8% conv.
JJ7d (15bar H_2) Literature[6f] (5bar H_2):	>99% >99%	63 (*S*) 91	69 (*S*) 96	74 (*S*) 93

Ligand/$Rh(Cod)_2BF_4$/Substrate 1:1:100, CH_2Cl_2, 20 °C, 20h

Catalyst **JJ7c** did not perform as well as **JJ7d** at 15 bar pressure as less than 2% of substrates **C** and **D** were converted with low *ee*'s (16%). Substrate **E** showed the highest

conversion of 8% and 23% *ee*. When the reaction was repeated at a lower pressure of hydrogen (5 bar), the conversion of **E** by catalyst **JJ7c** was increased to 74%, but the *ee* dropped to 17%. The conditions used were not optimised for these reactions. Change of solvent, pressure and temperature might enhance the *ee*'s, however this has not yet been investigated.

4.4 Conclusions and outlook

The rhodium-ligand complexes have been successfully formed as confirmed by ^{31}P NMR. The asymmetric hydrogenation reactions performed with catalysts **JJ7a-e** immobilised on *J*anda*J*el™ were promising, as high conversions were obtained with moderate to good *ee*'s, although not as high as for the liquid phase analogues.[6f] Unfortunately, catalysts **JJ7c** and **PS26c** did not perform as well as expected.

In general the catalytic conditions need to be optimised for these immobilised ligands. The influence of changes in H_2-pressure, solvent and temperatures during catalysis could be investigated. In future experiments the rhodium leaching of the complexes during catalysis should be determined. Once the conditions are optimised, the re-usability of the immobilised ligands could be tested.

4.5 Experimental

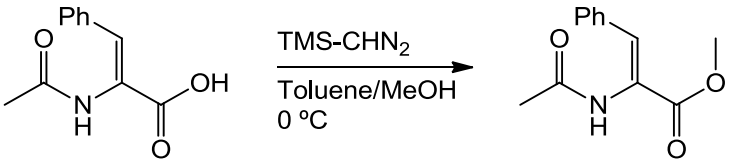
4.5.1 General remarks

Unless stated otherwise, reactions were carried out under an atmosphere of argon using standard Schlenk techniques. NMR spectra were recorded at room temperature on a Bruker Avance II 400. The ^{31}P NMR spectra were recorded proton decoupled and the gel-phase resin experiments were run unlocked. Chemical shifts are reported in ppm and are given relative to tetramethylsilane (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P).

Unless stated otherwise, all chemicals were obtained from commercial suppliers and used as received. THF and diethyl ether were distilled from sodium/benzophenone. Tertiary and secondary amines, CH_2Cl_2 and acetonitrile were distilled from CaH_2 and toluene was distilled from sodium. Dimethyl itaconate and methyl 2-acetamidoacrylate were commercially available and methyl acetamidocinnamate[6a,b] and the enamides[8-11] were synthesised according to literature procedures.

4.5.2 Synthesis

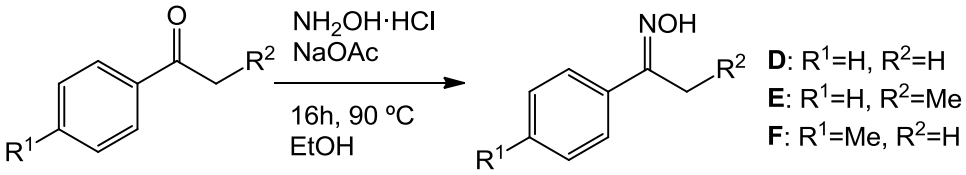
Methyl acetamidocinnamate[6a,b]



In a 50 mL round bottom flask, α-acetamidocinnamic acid (1.3867 g, 6.757 mmol) was dissolved in 15 mL toluene/methanol (3:2 v/v) and cooled to 0 ºC. To the yellow solution was then added trimethylsilyldiazomethane (TMS-CHN_2, 5 mL, 10 mmol) dropwise, resulting in gas evolution. After 3 hours, water was added and the aqueous phase was extracted three times with 20 mL of Et_2O. The organic phases were combined, washed with sat. $NaHCO_3$ and then dried over $MgSO_4$. Et_2O was removed *in vacuo*. Recrystallisation from CH_2Cl_2/pentane yielded 609.62 mg product (2.781 mmol) as off-white small needles (41% yield). The spectral properties were in accordance with those reported.[4a,b]

^{1}H NMR ($CDCl_3$, 300MHz): δ = 2.11 (s, 3H), 3.82 (s, 3H), 7.14-7.46 (m, 7H,) ppm.

General procedure for the synthesis of oximes[9,15]



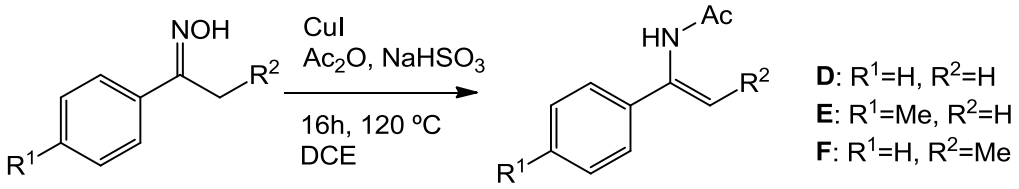
In a 500 mL flask, hydroxylamine hydrochloride (13.2 g, 190 mmol, 1.1 eq.) and sodium acetate (15.5 g, 189 mmol, 1.1 eq.) were suspended in 250 mL EtOH. The white suspension was stirred for 1 hour before addition of acetophenone (20 mL, 171.5 mmol, 1 eq.). The mixture was heated to reflux (90 °C) for 17.5 hours. After cooling the reaction mixture to room temperature, the solvent was removed, water (250 mL) was added and the product was extracted with portions of CH_2Cl_2 (3 x 200 mL). The organic fractions were combined and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The spectral properties of the obtained oximes were in accordance with those reported.[9,15]

D: Yield: 99% of white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.31 (s, 3H), 7.38-7.42 (m, 3H), 7.59-7.63 (m, 2H) ppm.

E: Yield: 99% of white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.18 (t, 3H), 2.84 (q, 2H), 7.37-7.43 (m, 3H), 7.58-7.61 (m, 2H) ppm.

F: Yield: 99% of yellowish clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.30 (s, 3H), 2.37 (s, 3H), 7.19 (d, 2H), 7.50 (d, 2H) ppm.

General procedure for the synthesis of enamides[11]



In an 1 L Schlenk flask equipped with reflux condenser, a mixture of acetophenone-oxime (13.8 g, 101.9 mmol, 1 eq.), acetic anhydride (203.1 mmol, 19.2 mL, 2 eq.), $NaHSO_3$ (307.2 mmol, 31.96 g, 3 eq.) and CuI (10.5 mmol, 2 g, 0.1 eq.) was stirred in 1,2-dichloroethane (DCE, 500 mL, freshly distilled over CaH_2) at 100 °C under argon for 15 hours. The slightly greenish/yellow coloured suspension was cooled to room temperature and filtered over a glass-filter and washed with EtOAc. The volatiles were removed under reduced pressure. The obtained solid was then dissolved in EtOAc (500 mL) and extracted with $NaHCO_3$ (sat., 200 mL) and brine (2 x 100 mL), The organic fractions were dried over $MgSO_4$ and evaporated *in vacuo* at 40 °C, until white crystals started to form. The solution was then allowed to slowly cool to room temperature and the crystals were filtered and recrystallised from refluxing EtOAc. The spectral properties of the obtained oximes were in accordance with those reported.[11]

D: Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.11 (s, 3H), 5.09 (s, 1H), 5.88 (s, 1H), 6.89 (bs, 1H), 7.41-7.35 (m, 5H) ppm.

E: Yield: 48%. ^{1}H NMR (400 MHz, DMSO) δ = 1.62 (d, *J* = 7.2 Hz, 3H), 1.91 (s, 3H), 6.05 (q, *J* = 6.8 Hz, 1H), 7.31-7.27 (m, 3H), 7.40-7.37 (m, 2H), 9.10 (s, 1H) ppm.

F: Yield: 63%. ^{1}H NMR (400 MHz, CDCl3) δ = 2.12 (s, 3H), 2.38 (s, 3H), 5.05 (s, 1H), 5.83 (s, 1H), 6.95 (bs, 1H), 7.18 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H) ppm.

General procedure for rhodium catalysed asymmetric hydrogenation experiments[7]

The hydrogenation experiments were carried out in a stainless steel autoclave (total volume is 150 mL) charged with 2 mL-reaction vials including Teflon mini stirring bars for conducting parallel reactions. In a typical experiment, a reaction vial was charged with polymer-supported ligand (5.0 mg, 3 μmol) and a solution of $[Rh(COD)_2]^+BF_4^-$ (1.52 mg, 3.74 μmol) in CH_2Cl_2 (0.5 mL) and the heterogeneous mixture was allowed to stir gently for 4 hours. The liquid phase was removed using a syringe and washed three times with CH_2Cl_2 (0.5 mL). Subsequently, a solution of substrate (50 mg, 300 μmol) and internal standard (diphenylether, 12 μl, 75 μmol) in CH_2Cl_2 (0.5 mL) was added to the reaction vial. The reaction vials were then capped and transferred to the stainless steel autoclaves, which were purged with argon. The caps of the vials were pierced with two small needles to allow for gas exchange. Before starting the catalytic reactions, the charged autoclave was purged three times with 5 bar of argon followed by three times with 5 bar of H_2 and then pressurised to 15 bar H_2. The reaction mixtures were gently stirred at 25 °C for 20 hours. Next, the autoclave was depressurised and the reaction mixtures were filtered over a small plug of silica with CH_2Cl_2. The enantiomeric excess was measured by chiral GC using the following columns and conditions:

A dimethyl itaconate:

Supelco β-DEX 225 column (T_0 = 70 °C for 60 min, then ΔT = 10 °C min^{-1}, final temp. 180 °C. t_R (*S*) = 54.7 min, t_R (*R*) = 60.7 min, t_R (**A**) = 65.2 min).

B methyl α-acetamidoacrylate:

Chiralsil DEX-CB column (T_0 = 70 °C for 4 min, then ΔT_1 = 4 °C min^{-1} to 140 °C, ΔT_2 = 10 °C min^{-1} to final temp. 200 °C. t_R (decane) = 7.2 min, t_R (**B**) = 13.5 min, t_R (*S*) = 15.4 min, t_R (*R*) = 15.8 min).

C methyl α-acetamidocinnamate:

Chiralsil DEX-CB column (T_0 = 90 °C, then ΔT = 2 °C min^{-1} to final temp. 200 °C. t_R (decane) = 3.7 min, t_R (*R*) = 39.1 min, t_R (*S*) = 39.4 min, t_R (**C**) = 49.2 min).

D-F enamides:

Chiralsil L-Val column (T_0 = 135 °C, then ΔT = 10 °C min^{-1} to final temp.190 °C for 10 min, t_R (diphenylether) = 3.3 min.

D: t_R (*R*) = 10.1 min, t_R (*S*) = 10.6 min, t_R (**D**) = 13.7 min).

E: t_R (*R*) = 14.7 min, t_R (*S*) = 15.5 min, t_R (**E**) = 19.9 min).

F: t_R (*R*) = 15.7 min, t_R (*S*) = 16.3 min, t_R (**F**) = 18.4 min).

4.6 References

1. a) F. H. Jardine, J. A. Osborn, G. Wilkinson, J. F. Young, *Chem. Ind. (London, U. K.)* **1965**, 560; b) J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *Journal of the Chemical Society A: Inorganic, Physical, Theoretical* **1966**, 1711-1732.
2. a) P. W. N. M. v. Leeuwen, *Homogeneous Catalysis: Understanding the Art*, Kluwer Academic Publishers, Dordrecht etc., **2004**; b) P. G. Andersson, I. J. Munslow, *Modern Reduction Methods*, Wiley-VCH, **2008**; c) Y. Chi, W. Tang, X. Zhang, (2005), In *Modern Rhodium-Catalyzed Organic Reactions*; (Eds. Ed.: P. A. Evans), pp. 1-32.
3. a) P. Etayo, A. Vidal-Ferran, *Chem. Soc. Rev.* **2013**, *42*, 728-754; b) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912-2942.
4. a) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106-112; b) W. S. Knowles, *Angew. Chem., Int. Ed.* **2002**, *41*, 1999-2007; c) W. S. Knowles, *Adv. Synth. Catal.* **2003**, *345*, 3-13.
5. H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.
6. a) J. Lee, S. Bernard, X.-C. Liu, *Reactive and Functional Polymers* **2009**, *69*, 650-654; b) P.-A. R. Breuil, J. N. H. Reek, *Eur. J. Org. Chem.* **2009**, *2009*, 6225-6230; c) Y. Wada, T. Imamoto, H. Tsuruta, K. Yamaguchi, I. D. Gridnev, *Adv. Synth. Catal.* **2004**, *346*, 777-788; d) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952; e) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567-2568; f) Y.-Y. Yan, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 4137-4140.
7. R. den Heeten, B. H. G. Swennenhuis, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Angew. Chem., Int. Ed.* **2008**, *47*, 6602-6605.
8. P. Zaware, S. R. Shah, H. Pingali, P. Makadia, B. Thube, S. Pola, D. Patel, P. Priyadarshini, D. Suthar, M. Shah, J. Jamili, K. V. V. M. Sairam, S. Giri, L. Patel, H. Patel, H. Sudani, H. Patel, M. Jain, P. Patel, R. Bahekar, *Bioorganic & Medicinal Chemistry Letters* **2011**, *21*, 628-632.
9. M. J. Burk, G. Casy, N. B. Johnson, *J. Org. Chem.* **1998**, *63*, 6084-6085.
10. K. D. Hesp, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 11430-11433.
11. Z.-H. Guan, Z.-Y. Zhang, Z.-H. Ren, Y.-Y. Wang, X. Zhang, *J. Org. Chem.* **2011**, *76*, 339-341.
12. G. Szalontai, J. Bakos, S. Aime, R. Gobetto, *J. Organomet. Chem.* **1993**, *463*, 223-226.
13. P. E. Garrou, *Chem. Rev.* **1981**, *81*, 229-266.
14. B. H. G. Swennenhuis, R. F. Chen, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Eur. J. Org. Chem.* **2009**, *2009*, 5796-5803.
15. Y.-J. Chen, C. Chen, *Tetrahedron: Asymmetry* **2008**, *19*, 2201-2209.