Chiral Arsenium–Phosphine Complexes

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Declaration

The work described in this thesis is the author's own unless stated otherwise.

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Abstract

The first enantiomerically pure secondary chloro- and iodoarsines based on the 2,2'-bis(methylene)-1,1'-binaphthyl group have been prepared. The seven-membered (a*R*)-iodoarsepine has been prepared by the disproportionation of the corresponding enantiomerically pure (a*R*)-phenylarsepine with one equivalent of triiodoarsine in boiling toluene. The (a*R*)-chloroarsepine was prepared from the iodoarsepine by halide metathesis with silver chloride in dichloromethane. The isolation of these novel compounds facilitated an investigation of the interactions between an enantiomerically pure arsenium ion and symmetrical and *P*-chiral tertiary phosphines.

Phosphine-stabilised arsenium hexafluorophosphates were prepared from the enantiomerically pure (a*R*)-iodoarsepine by reactions with the phosphine in dichloromethane in the presence of aqueous potassium hexafluorophosphate. The complexes have been characterised by X-ray crystallography and NMR spectroscopy. The crystal structure determinations in each case revealed the significant twist in the (a*R*)-binaphthyl framework of the arsenium ion and the coordination of the phosphine orthogonal to the trigonal AsC_2 plane of the arsenium ion. The ^{1}H NMR spectra of the dimethylphenylphosphine and [2-(methoxymethyl)phenyl]dimethylphosphine complexes indicated significant differences in their stabilities. The ^{1}H NMR spectrum of the dimethylphenylphosphine–arsenium complex in CD_2Cl_2 at 25 °C showed diastereotopicity of the P*Me* doublets and broad resonances for the methylene protons of the (a*R*)-arsenium ion because of phosphine exchange. At the slow exchange limit (ca. −50 °C) the reso-

nances for the P*Me* groups sharpened and the methylene protons appeared as AB and A'B' spin systems with additional phosphorus coupling, which was consistent with an asymmetric molecule. The ^{1}H NMR spectrum of the closely related [2-(methoxymethyl)phenyl]dimethylphosphine–arsenium complex in CD_2Cl_2 at 25 °C was sharp, in agreement with the additional stabilisation of the complex by coordination of the methoxymethyl group.

Exploratory work was undertaken concerning the interactions of the (a*R*)-iodoarsepine with racemic *P*-chiral tertiary phosphines with the view to the potential asymmetric synthesis of tertiary phosphines by deracemisation in the presence of iodide.

Contents

Declaration i

Acknowledgements ii

Abstract iv

Abbreviations ix

1 Introduction 1

1.1 Chirality 1

1.2 Tertiary phosphine and arsine inversion barriers 3

1.3 Phosphine-stabilised arsenium salts 5

1.4 Naked arsenium ions 10

1.5 Preparation of optically active phosphines and arsines 12

1.5.1 Resolution via salt formation 12

1.5.2 Resolution by metal complex formation 14

1.6 Synthesis of chiral tertiary phosphines and arsines 18

1.6.1 Synthesis of chiral tertiary phosphines 18

1.6.2 Asymmetric synthesis of tertiary arsines 20

1.7 Asymmetric transformation 24

1.7.1 Examples of asymmetric transformation 25
1.8 Chemical racemisation of chiral tertiary phosphines and arsines . . . 34
1.8.1 Racemisation of tertiary arsines by haloacids 34
1.8.2 Racemisation of tertiary phosphines by iodoarsines 35
1.9 Objectives of current work 39

2 Chiral Haloarsines **40**
2.1 Introduction 40
2.2 Design of a chiral host 41
2.3 Phosphepine synthesis 46
2.4 Synthesis of (a*R*)-**39** (X = I) 50
2.4.1 Direct addition of haloarsines to (a*R*)-**43** 50
2.4.2 Hydriodic acid 51
2.4.3 Disproportionation reactions 57
2.5 Preparation of (a*R*)-**39** (X = Cl) 63

3 Arsenium Complexes of Tertiary Phosphines **66**
3.1 Phosphine-stabilised arsepinenium salts 66

4 Deracemisation of tertiary phosphines **81**
4.1 Attempted deracemisation of a *P*-chiral phosphine 81
4.2 Design of a *P*-chiral phosphine for deracemisation 84
4.2.1 Synthesis of (±)-**35** 84
4.2.2 Deracemisation of (±)-**35** 85
4.3 Synthesis of chiral (1- and 2-naphthyl)
phosphines (±)-**64** and (±)-**65** 94
4.3.1 Deracemisation of (±)-**64** 97
4.3.2 Deracemisation of (±)-**65** 100

5 Conclusions **106**

6 Experimental **108**

6.1 General 108

6.2 Preparations 110

References **142**

Abbreviations

$[\alpha]_D^T$	specific rotation at T °C, sodium D line 589 nm
aq.	aqueous
binaphthyl	1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
bp	boiling point
Bu	butyl
c	concentration in grams per 100 mL
cat.	catalytic amount of
CD	circular dichroism
CIP	Cahn-Ingold-Prelog
dec	decomposition
δ	chemical shift (parts per million)
de	diastereomeric excess
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionisation
Et	ethyl
equiv	equivalents

h	hour(s)
HRMS	high resolution mass spectrum
IUPAC	International Union of Pure and Applied Chemistry
${}^{n}J$(AB)	*n*-bond coupling between nuclei A and B, expressed in Hertz
lit.	literature
Me	methyl
min	minutes
mmHg	millimetres of mercury
mp	melting point
MS	mass spectrum
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf^-	trifluoromethanesulfonate (triflate) ion, $CF_3SO_3^-$
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine
R	aryl or alkyl group
i-R	iso-R
n-R	normal-R
t-R	tertiary-R
R	clockwise (right-handed) sequence
S	counterclockwise (left-handed) sequence
RT	room temperature, $20 - 25\,^{\circ}C$

THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine

List of Figures

1.1 Assignment of R configuration to a tetrahedral stereocentre. 2

1.2 Assignment of aR configuration to chiral biaryl. 3

1.3 Pyramidal inversion of a chiral tertiary phosphine. 4

1.4 Proposed planar transition state for inversion of (±)-methylphenylpropylphosphine. 5

1.5 (a) Arsinophosphonium iodide; (b) phosphine-stabilised arsenium iodide. 5

1.6 P*Me* resonances in CD_2Cl_2 at 25 °C for (R_P*,R_P*)-(±)-**33** (a) and (R_P*,S_P*)-**33** (c) and spectrum of either solution in the presence of (±)-iodomethylphenylarsine (b). 38

2.1 Deracemisation of a chiral tertiary phosphine in the environment of an enantiomerically pure arsenium host of R configuration. 40

2.2 Degenerate bimolecular halide exchange between chloroarsines. . . . 41

2.3 Twist-boat conformation of the seven-membered arsepine ring in (aR)-**40**. 45

2.4 Degenerate axial approach of L to (aR)-**40**. 45

2.5 ORTEP diagram of the independent molecules of (aR)-**53** with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 54

2.6 ^{1}H NMR spectrum of (a*R*)-**39** (X = I) and (a*R*)-**42** arising from reaction of (a*R*)-**53** with boiling hydriodic acid. 56

2.7 Methylene region of ^{1}H NMR spectra in C_6D_6 at 25 °C for synthesis of (a*R*)-**39** (X = I) from (a*R*)-**53** and triiodoarsine in boiling benzene: (a) (a*R*)-**53**; (b) after 2 h; (c) after 8 h; (d) after 52 h reflux, reaction incomplete; (e) (a*R*)-**39** (X = I), after an additional 24 h in boiling toluene. 59

2.8 ORTEP diagram of (a*R*)-**39** (X = I) with atom labelling (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 61

2.9 ORTEP diagram of (a*R*)-**39** (X = Cl) with atom labelling (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 64

3.1 ORTEP diagram of the cation of (a*R*)-**55**·C_4H_8O with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 68

3.2 ORTEP diagram of the cation of (a*R*)-**55**·C_4H_8O with selected atoms labelled (30% ellipsoid probability shown). The selected hydrogen atom indicates the direction of the intramolecular aryl–aryl embrace. 71

3.3 Aliphatic regions of the ^{1}H NMR spectra of (a*R*)-**58**·CH_2Cl_2 in CD_2Cl_2 at 25 °C (a), −30 °C (b), −60 °C (c), −90 °C (d), and the ^{1}H{^{31}P} NMR spectrum at −90 °C (e). 73

3.4 ORTEP diagram of the major (a) and the minor (b) conformers of the cation of (a*R*)-**58** with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 76

3.5 Aliphatic regions of ^{1}H (a) and ^{1}H{^{31}P} (b) NMR spectra of (a*R*)-**58** in CD_2Cl_2 at 25 °C. 80

4.1 Selected region of ^{1}H NMR spectrum (a) and $^{31}P\{^{1}H\}$ NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**59** in CD_2Cl_2 at 25 °C. 83

4.2 Aliphatic region of ^{1}H NMR spectrum (a) and $^{31}P\{^{1}H\}$ NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**62** in CD_2Cl_2 at 25 °C. 88

4.3 ORTEP diagram of (R_C,R_P)-**63** with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 90

4.4 $^{31}P\{^{1}H\}$ NMR spectrum of the unequal mixture of (R_C,R_P)- and (R_C,S_P)-**63** in CD_2Cl_2. 93

4.5 Methylene region of ^{1}H NMR spectrum (a) and $^{31}P\{^{1}H\}$ NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**72** in CD_2Cl_2 at 25 °C. * Impurity. . . 99

4.6 Methylene region of ^{1}H NMR spectrum (a) and $^{31}P\{^{1}H\}$ NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**73** in CD_2Cl_2 at 25 °C. * Impurity. . . 102

4.7 ORTEP diagram of the cation of (aR,R_P)-**73**·0.5C_4H_8O with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity. 104

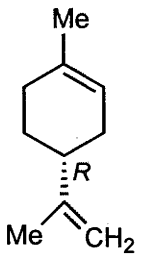
Chapter 1

Introduction

1.1 Chirality

The term chirality stems from the Greek word *cheir*, meaning hand. An object is termed chiral if it is non-superimposable on its mirror image.[1] In the absence of an external chiral influence, individual enantiomers (from the Greek *enantios* – opposite) display identical physical and chemical properties, the exception being their interaction with plane polarised light, where they display an equal and opposite rotation of the incident beam. The introduction of an external chiral influence leads to distinct differences between the enantiomers of a molecule. An example of this influence is observed in the interaction of the human olfactory receptors with the two enantiomers of limonene; naturally occurring (*R*)-limonene, (*R*)-**1**, has the characteristic smell of citrus fruits such as orange and lemon, while the opposite enantiomer (*S*)-limonene has a pine-like smell, similar to other terpenes.

The varied influence of two enantiomers has also been observed in the administration of the chiral drug (±)-thalidomide as a racemate. The two enantiomers of this drug interact with the proteins of the target receptor with different physiological efficacies, (*S*)-thalidomide causing tetratogenic effects on developing fetuses; (*R*)-thalidomine has a beneficial effect on morning sickness in pregnant women. Thus,



(*R*)-**1**

the investigation of the properties of both enantiomers of a chiral chemical is crucial prior to the use of either one in a pharmaceutical application.

The study of molecules possessing chirality requires the establishment of systematic methods for the description of the enantiomorphic arrangements of atoms. The configuration of a chiral molecule is usually assigned by application of the Cahn–Ingold–Prelog (CIP) sequence rules.[2] These rules are commonly applied to organic compounds, where four different groups (ligands) are frequently bound to a tetrahedral carbon stereocentre. The ligands are assigned priorities from one to four ($1 > 2 > 3 > 4$) in the CIP priority sequence. When the tetrahedral molecule is viewed from the side opposite the ligand of lowest priority (4), the sequential arrangement of the remaining ligands can be made from the highest priority to the lowest. In Figure 1.1 the sequence $1 > 2 > 3$ is clockwise, the molecule is assigned the *R* (*rectus*) configuration; the non-superimposable mirror image enantiomer will have an anticlockwise arrangement of these atoms and is assigned the *S* (*sinister*) configuration.

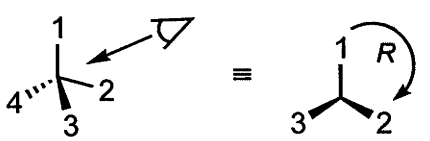


Figure 1.1: Assignment of *R* configuration to a tetrahedral stereocentre.

The assignment of configuration to a molecule containing a chiral axis can also be made with use of the CIP rules. The molecule is viewed down the principle axis and

the priorities 1 and 2 are given to the nearest pair of substituents; the remote pair is assigned similarly and the chirality descriptor a*R* or a*S* is assigned as indicated for the biaryl molecule shown in Figure 1.2.[3] Assignment of chiral planes is more difficult because the chirality arises from a plane containing as many atoms of the molecule as possible, with at least one ligand not being within the chiral plane.[1].

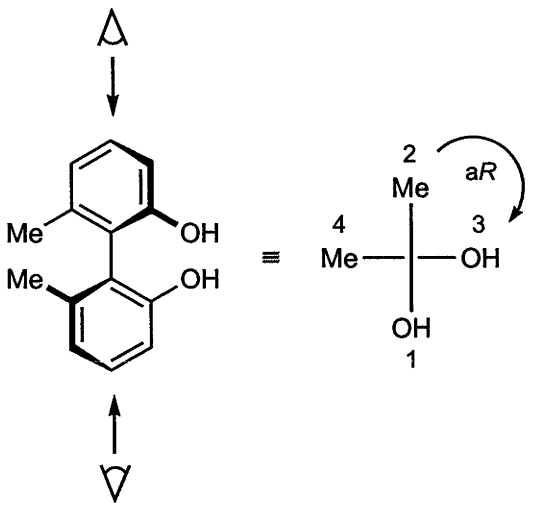


Figure 1.2: Assignment of a*R* configuration to chiral biaryl.

1.2 Tertiary phosphine and arsine inversion barriers

Tertiary phosphines and arsines of the type $ER^1R^2R^3$ (E = P or As) are suitable for resolution into enantiomers because of their stability to racemisation by unimolecular pyramidal inversion. The tertiary phosphine (±)-methylphenyl(*n*-propyl)phosphine has a free energy of activation (ΔG) to inversion of 32.1 kcal mol^{-1} at 130.0 ± 0.3 °C in decalin.[4] The tertiary arsine (±)-ethylmethylphenylarsine is more resistant to pyramidal inversion, having an activation energy for this process of 42.4 ± 2 kcal mol^{-1} at 217.6 ± 0.3 °C in decalin.[5] This barrier for the arsine corresponds to a half-life for racemisation of 740 h at 200 °C. The practical consequence of this higher pyramidal inversion barrier for arsines compared to phosphines means that

many optically active arsines can be distilled without racemisation. A clear trend in the energy barrier for pyramidal inversion of molecules of the type (±)-ER_3 is observed within the Group 15 elements, where amines possess the lowest barrier. The increased activation barriers to pyramidal inversion for trivalent derivatives of the larger Group 15 elements is best considered through analysis of the hybridised orbitals available. The phosphorus atom of a pyramidal phosphine possesses four sp^3 hybrid orbitals, of which three are engaged in σ bonds with the substituents and the other contains a lone pair of electrons. The transition state between one enantiomer and its non-superimposable mirror-image counterpart consists of a trigonal planar arrangement of the substituents, σ bonded through three sp^2 (sp_xp_y) hybrid orbitals, the lone pair of electrons being in a p_z orbital perpendicular to this plane (Figure 1.3). The barrier to inversion can be considered as the energy difference between the pyramidal sp^3 hybridised phosphine and the trigonal planar sp^2p hybridised transition state. As the energy difference for the tertiary arsine [Ar] $4sp^3$ ground state and the [Ar] $4sp^24p$ transition state is larger than the gap between [Ne] $3sp^3$ and [Ne] $3sp^23p$ configurations of the tertiary phosphine, the activation energy increases for the larger elements within the Group.

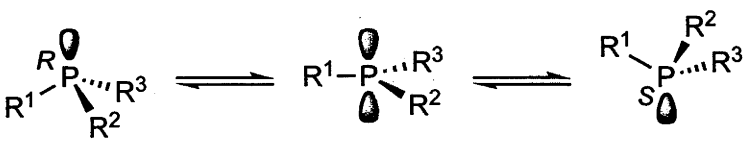


Figure 1.3: Pyramidal inversion of a chiral tertiary phosphine.

Support for a planar intermediate in the racemisation of a tertiary phosphine was provided by the observation that substitution of the cyclohexyl substituent in (±)-cyclohexylmethyl(*n*-propyl)phosphine with a phenyl group increased the rate of inversion 78 fold.[4] Stabilisation of the postulated planar transition state is believed

to occur via conjugation of the phosphorus-centred lone pair of electrons (p orbital) across the delocalised pi system of the phenyl group, as shown in Figure 1.4.

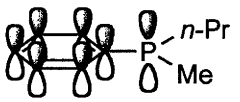


Figure 1.4: Proposed planar transition state for inversion of (±)-methylphenylpropylphosphine.

1.3 Phosphine-stabilised arsenium salts

The initial reports of adducts of tertiary phosphines with chloro- and iodoarsines designated the reaction products as arsinophosphonium salts,[6] the ionic formulation being demonstrated by conductometric titration.[7] More recent publications have made reference to "stibinostibonium salt" and "trimethylstibine adduct of the dimethylstibenium ion",[8] "phosphinophosphonium salts",[9] "phosphine-phosphenium coordination complexes,"[10] and "phosphine-stabilised arsenium salts".[11] The two possible representations of the core intramolecular interaction in a tertiary phosphine–iodoarsine complex are shown in Figure 1.5.

Figure 1.5: (a) Arsinophosphonium iodide; (b) phosphine-stabilised arsenium iodide.

Both representations are reasonable, but the chemical properties of known salts support the ligand-stabilised formulation (Figure 1.5(b)). This representation can be considered as a coordination complex, where the phosphine donates a pair of electrons to the positively charged, two coordinate, six electron arsenium ion (R_2As^+). The coordination of the phosphine can be considered as the dative donation of a

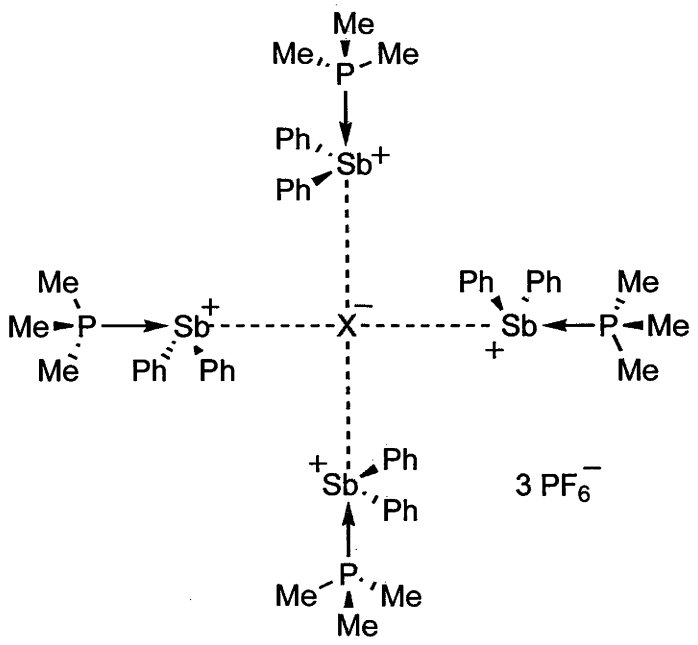
lone pair of electrons on phosphorus into the vacant p orbital of the sp^2 hybridised arsenium centre.

In the initial reports, the compounds $[R_3PAsR_2]I$ were formulated as arsinophosphonium salts, but the addition of alkoxides to the salts resulted in nucleophilic attack at the arsenic, generating arsinous acid esters (Eq 1.1).[7]

$$[Et_3PAsMe_2]I + NaOMe \longrightarrow MeAsOMe + PEt_3 + NaI \qquad (1.1)$$

This nucleophilic attack at arsenic has recently been used for the synthesis of tertiary arsines by the addition of carbanionic reagents such as n-butyllithium to a solution of an (aR)-phosphepine-stabilised methylphenylarsenium hexafluorophosphate, as discussed further in Section 1.6.2.[12,13] Crystallographic analysis of the molecular geometry of triphenylphosphine-stabilised methylphenylarsenium hexafluorophosphate, $[(Ph_3P)AsMePh]PF_6$, supports the formulation shown in Figure 1.5(b).[11] The methyl group, ipso-carbon of the phenyl group, and the lone pair of electrons on the arsenic atom are situated in a trigonal plane. The effect of the lone pair is significant, as the angle between the methyl-carbon atom, arsenic, and ipso-carbon atom of the phenyl group is 101.73(7)°. The triphenylphosphine ligand is coordinated orthogonal to this plane, with angles of 92.31(8)° for the P–As–C angle to the methyl group and 97.04(6)° for the P–As–C angle to the phenyl group. The long P–As distance of 2.3480(5) observed in the complex falls outside the sum of the covalent radii for the two atoms and is consistent with the highly labile nature of the P–As interaction.[14] Orthogonal coordination of the phosphine to the arsenium plane has been observed in a number of related complexes, including phosphine-stabilised arsenium ions derived from 10-chloro-5-hydrophenarsazine[15] and tetra(trimethylphosphine-stabilised diphenylstibenium) halide complexes **2** (X = Cl, Br).[16]

Although the considerations above suggest classification of these compounds as ligand-stabilised salts, analysis of the $^{31}P\{^1H\}$ NMR spectrum of $[(Ph_3P)PPh_2]OTf$



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in CD_2Cl_2 complicates the assignment because the peaks observed at δ +15 and −10 ppm for the PPh_3 and PPh_2 groups, respectively, are similar to those for the tetraphenylphosphonium ion (Ph_4P^+) at δ +20 ppm and tetraphenyldiphosphine (Ph_2PPPh_2) at δ −15 ppm.[9,10] Crystallographic analysis of $[(Ph_3P)PPh_2]OTf$ further supports the view that this compound is a phosphinophosphonium salt because the PPh_2 group has a distorted pyramidal geometry, with the P–P–C angles to the phenyl groups being 100.38(11)° and 100.73(11)°.[9] The corresponding arsenium and stibenium hexafluorophosphates, $[(Ph_3P)EPh_2]PF_6$ (E = As, Sb), have been prepared and a trend is observed where the angles between the phosphorus–arsenic or –antimony bond and the ipso-carbon of the phenyl group decreases from 99.89(6)° and 97.98(6)° in the arsenic compound to 97.61(12)° and 93.70(12)°) in the antimony compound.[9,17] This trend is also observed in the series of related compounds $[(Me_3P)EPh_2]PF_6$ (E = As, Sb, Bi) where the orthogonal coordination becomes more apparent for the heavier elements, the P–E–C angles being 97.33(9)° and 99.60(9)° for As, 90.34(8)° and 100.24(8)° for Sb, 87.030(18)° and 97.51(19)° for Bi.[18] The increasing orthogonality of the P–E bonds in the compounds on proceeding down

Group 15 is considered to indicate an increasing contribution of the sp^2p configuration on the geometry of the planar ER_2 unit.

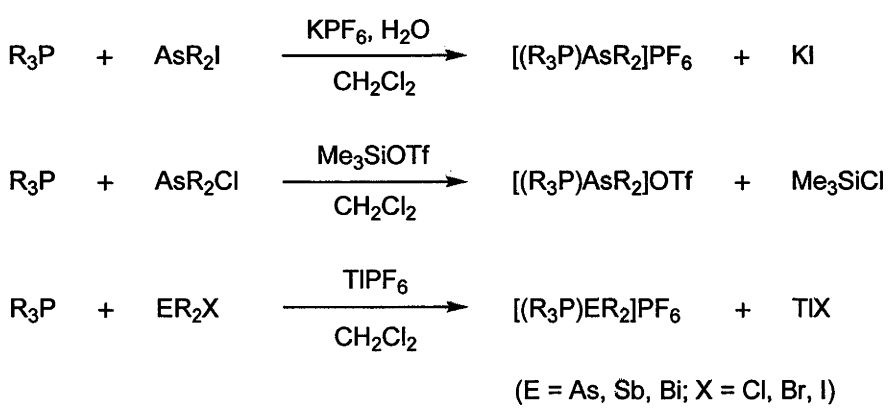
Although there is crystallographic and solution evidence supporting the formulation of $[(R_3P)PR_2]X$ as shown in Figure 1.5(a), the compounds undergo rapid phosphine exchange in solution.[9,10,19,20] This lability of the P–P bond supports the formulation of the complexes as phosphine-stabilised phosphenium salts. Rapid exchange of the triphenylphosphine is also observed in the ^1H and $^{31}P\{^1H\}$ NMR spectra of $[(Ph_3P)AsMePh]PF_6$ at room temperature. Cooling of the solution of the complex slows the exchange process, where the emergence of phosphorus coupling to the protons of the As*Me* group is observed below 8 °C.[11] The lability of the P–As bond was further demonstrated in a crossover experiment between $[(MePh_2P)AsMe_2]PF_6$ and $[(Ph_3P)AsMePh]PF_6$; thus, the mixing together of equimolar CD_2Cl_2 solutions of the two complexes at 20 °C resulted in an equilibrium mixture of the starting materials and the corresponding crossover complexes $[(MePh_2P)AsMePh]PF_6$ and $[(Ph_3P)AsMe_2]PF_6$ within the time taken to prepare the solution and record the spectrum (Eq 1.2).[11]

$$[(MePh_2P)AsMe_2]PF_6 + [(Ph_3P)AsMePh]PF_6 \rightleftharpoons [(MePh_2P)AsMePh]PF_6 + [(Ph_3P)AsMe_2]PF_6 \quad (1.2)$$

Phosphine-stabilised arsenium salts are easily prepared by three methods. One convenient method makes use of a two-phase mixture of a secondary iodoarsine and a tertiary phosphine in dichloromethane and an aqueous solution of ammonium or potassium hexafluorophosphate. Separation of the phases, drying of the organic phase with magnesium sulfate, and recrystallisation of the residue remaining after removal of the dichloromethane affords high yields of the colourless crystals of

the phosphine-stabilised arsenium hexafluorophosphates.[11] Another method makes use of an equimolar solution of a secondary chloroarsine, a tertiary phosphine, and trimethylsilyl trifluoromethanesulfonate in dichloromethane. Removal of the solvent and the volatile by-product chlorotrimethylsilane in vacuo and recrystallisation of the residue from dichloromethane by the addition of diethyl ether furnishes phosphine-stabilised arsenium *triflates*.[15,21] This method is useful when the products or reagents are moisture sensitive, as is the case for phosphine-stabilised phosphenium and arsine-stabilised arsenium salts. A third method involves the addition of excess thallium(I) hexafluorophosphate to a dichloromethane solution of secondary halo-arsine, -stibine, or -bismuthine and tertiary phosphine; the thallium(I) halide precipitates and the complex can be isolated as the hexafluorophosphate after the thallium salts have been filtered off. This is an effective route to the complexes $[(Ph_3P)EPh_2]PF_6$ (E = As, Sb or Bi) and $[(Ph_3P)_2EPh_2]PF_6$ (E = Sb or Bi).[17] The common thread of the three methods is the abstraction of a halide in the presence of a tertiary phosphine and non-nucleophilic counterion to generate the desired complex (Scheme 1.1).

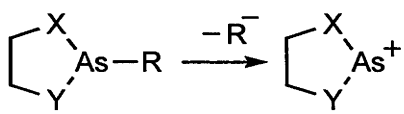
Scheme 1.1: Methods for the synthesis of phosphine-stabilised arsenium, stibenium, and bismuthenium salts



1.4 Naked arsenium ions

Arsenium ions are positively charged, six-electron species in which arsenic(III) is surrounded by two substituents and a lone pair of electrons. Thus, arsenium ions are main group analogues of carbenes, and, based on valence-shell electron-pair repulsion (VSEPR) theory, have distorted trigonal planar geometries. Arsenium ions were first observed in the mass spectra of five-membered heterocyclic arsines where the majority of the compounds investigated readily lost their extra-cyclic substituent, generating the corresponding heterocyclic arsenium ion, generally as the base peak (Scheme 1.2).[22]

Scheme 1.2: Arsenium ions generated by mass spectrometry

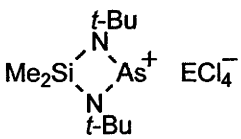


R	X	Y	Relative Intensity Arsenium Ion (%)
Ph	S	S	32
Ph	O	O	2
Ph	O	S	50
Me_2N	S	S	32
Me_2N	O	O	100
Me_2N	O	S	62
Me_2N	NMe	O	100
Et_2N	S	S	17
Et_2N	O	O	100
Et_2N	O	S	100
Et	S	S	100
Et	O	O	100
Et	O	S	100
Et	NMe	O	100

Fragmentation of dimethylphenylarsine, methyldiphenylarsine, and (±)-ethylmethyphenylarsine in the mass spectrometer gives arsenium ions by loss of a methyl group for the first two compounds and an ethyl group for the third compound.[23] Arsenium ions arising from the loss of other groups were also observed, but had lower intensities. The mass spectra of chloromethylphenylarsine

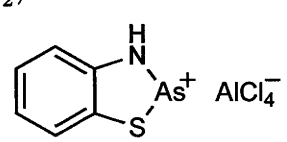
and iodomethylphenylarsine indicated the formation of the methylphenylarsenium ion.[23]

The attempted synthesis of naked arsenium ion salts has focused on the stabilisation of the electron deficient arsenium centre by chelation with electronegative elements. Thus, chloride abstraction from a secondary chloroarsine with ECl_3 (E = Al, Ga, or In) facilitated the synthesis of the four membered arsenium salt **3**.[24,25]



3

The bicyclic salt **4** has been prepared by chloride abstraction from the parent chloroarsine with aluminium(III) chloride.[26,27] Crystallographic data for the salt indicate that the charge on the arsenium ion is delocalised across the conjugated organic framework. The crystallographic analysis revealed the planarity of the core hetereocycle within a mean of 0.0020 Å. The As–N and As–S bonds in the cation were the shortest known for an arsenic(III) system at the time, and it was suggested that there could be double bond character in these bonds because of aromatisation involving a number of resonance structures. Following the isolation of this arsenium salt, other salts were subsequently isolated, viz. **5**, **6** (Y, Z = NMe, NEt, or S and $X^- = AlCl_4^-$, $GaCl_4^-$, or OTf^-) and the acyclic compounds **7** (R = Me, Et, *i*-Pr, Z = NEt_2, Cl and $X^- = AlCl_4^-$, OTf^-).[28–31]



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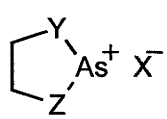

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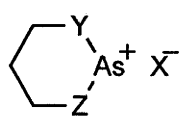

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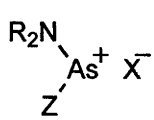
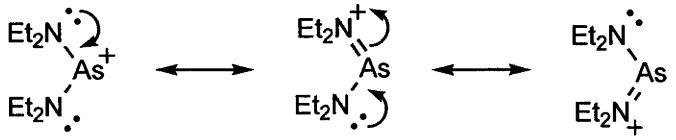


7

Donation of electron density from the heteroatom lone pairs to the arsenium ion in each case is a possible mechanism for the stabilisation of these species. Scheme 1.3 shows some plausible resonance structures for the acyclic species **7** where R = Et and Z = NEt_2.

Scheme 1.3: Resonance stabilisation of an arsenium ion



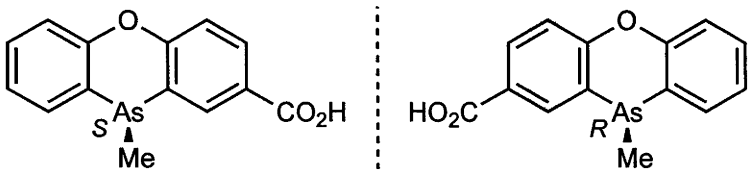
1.5 Preparation of optically active phosphines and arsines

The separation of the enantiomers of a racemate is traditionally achieved by resolution. The separation of a racemate with use of a configurationally stable resolving agent is feasible where there is a sufficient difference in solubility (or retention times on a chromatographic column) between two diastereomers. Removal of the resolving agent from a pure diastereomer provides the resolved enantiomer of the racemate in a maximum yield of 50%. The resolutions of chiral phosphines and arsines have been thoroughly reviewed, but some historically significant examples are presented below.[32–36]

1.5.1 Resolution via salt formation

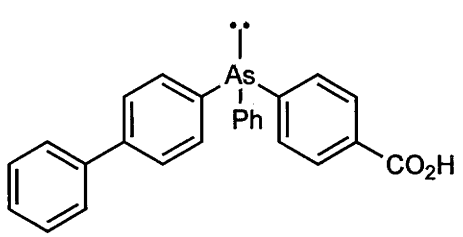
The first resolution of a racemate was achieved by Pasteur by triage of the spontaneously resolved hemihedral crystals of sodium ammonium tartrate tetrahydrate.[37] Since then numerous resolutions have been achieved by the formation of appropriate salts of racemates with enantiomerically pure counterions. Indeed, the first resolution of an optically active tertiary arsine, (±)-10-methylphenoxarsine-2-carboxylic acid ((±)-**8**) was achieved by the fractional crystallisation of the corresponding (−)-strychninium salts.[38] Acidification of the less soluble diastereomer of the salt gave the optically pure tertiary arsine (+)-**8**. The investigators, however, considered the optical activity of the arsine to arise from the conformational rigidity of the folded

ring system rather than the presence of a configurationally stable arsenic stereocentre because of the inability of leading workers in the field at that time to resolve non-cyclic tertiary arsines.[36]



(±)-**8**

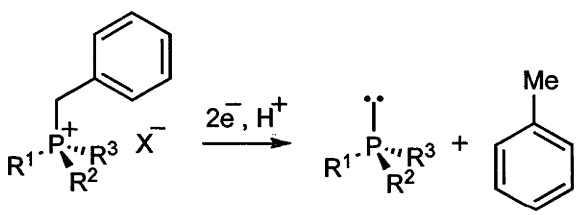
Although crystalline (−)-strychninium and (−)-quininium salts were prepared from these non-cyclic arsine carboxylates, the rotations for the separated diastereomers were similar in each case. The work up of the salts, however, involved the use of chloroform which is now known to racemise chiral arsines if it contains a trace of hydrogen chloride. The mechanism of this process will be discussed in Section 1.8.[39] Regrettably, much of the work concerning the decomposition of diastereomeric ammonium salts of arsine-carboxylates involved the use of dilute aq. hydrochloric acid. The resolution of the first non-cyclic triarylarsine, (±)-**9**, was achieved by the fractional crystallisation of the diastereomeric salts derived from (±)-phenyl-(3-carboxyphenyl)-4-biphenylylarsine and (−)-α-phenylethylamine, which resulted in the isolation of the (+) enantiomer of the tertiary arsine.[40] It should be noted that the less-soluble diastereomeric salt of (+)-**9** was decomposed with *dilute sulfuric acid.* There are available comprehensive reviews concerning the resolution of tertiary arsines.[36,41]



(±)-**9**

The first tertiary phosphine oxide to be resolved, (±)-ethylmethylphenylphosphine oxide, was achieved by the fractional crystallisation of the diastereomers arising from the protonation of the oxide with *d*-bromocamphorsulfonic acid.[42] The first isolation of optically active tertiary phosphines was achieved by the cathodic reduction of resolved phosphonium salts.[43] The electrolytic reduction resulted in cleavage of the functional group most stable as an anion, usually the benzyl group, with retention of configuration at phosphorus (Scheme 1.4). This electrochemical method was also applicable to the reduction of optically active benzylarsonium salts.[44,45]

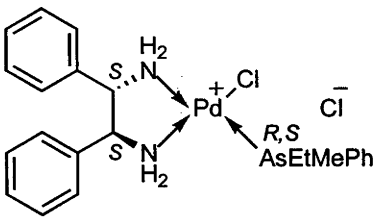
Scheme 1.4: Electrolytic reduction of a phosphonium salt with retention of configuration at phosphorus



1.5.2 Resolution by metal complex formation

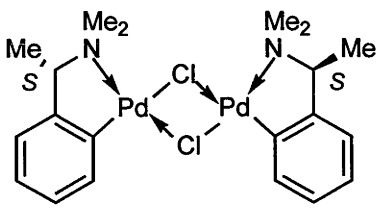
The separation of the neutral diastereomers of dichloroplatinum complexes containing (+)-deoxyephedrine and (±)-(*t*-butyl)methylphenylphosphine was achieved by fractional crystallisation, although the phosphine was not liberated from the metal.[46] The resolution and isolation of the individual enantiomers of (±)-ethylmethylphenylarsine was achieved by fractional crystallisation of the salts **10**.[45] This method was put forward as a general procedure for the resolution of tertiary arsines.

The chloro-bridged palladium(II) dimer (S_C,S_C)-**11** is suitable for the partial kinetic resolution of certain tertiary arsines and phosphines by bridge splitting.[47] The phosphine or arsine coordinates trans to the dimethylamino group, generat-

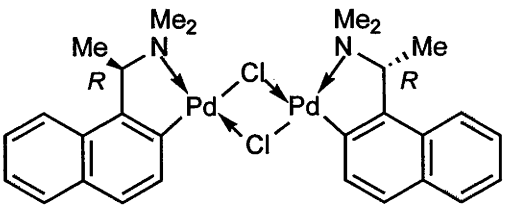


10

ing monopalladium diastereomers that can be separated by fractional crystallisation. The addition of chelating ligands such as 1,2-bis(diphenylphosphino)ethane or 1,2-diaminoethane displaces the resolved phosphine or arsine with retention of configuration at the donor stereocentre (Scheme 1.5).

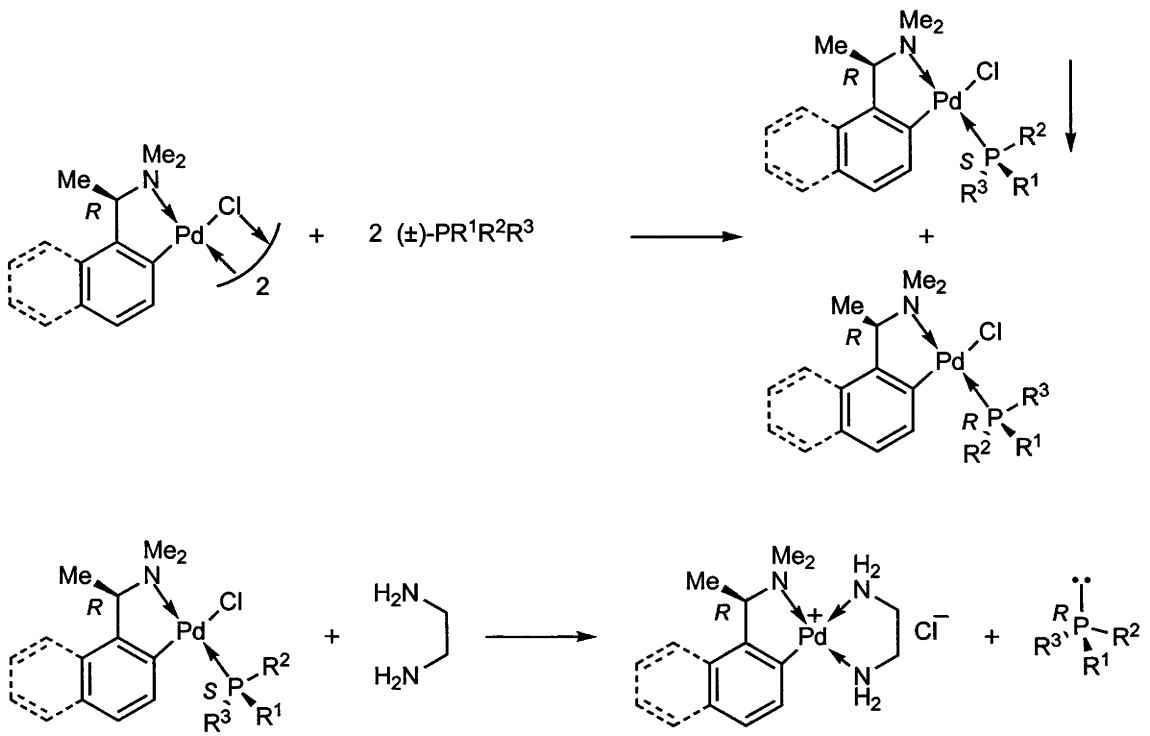


(S_C,S_C)-**11**

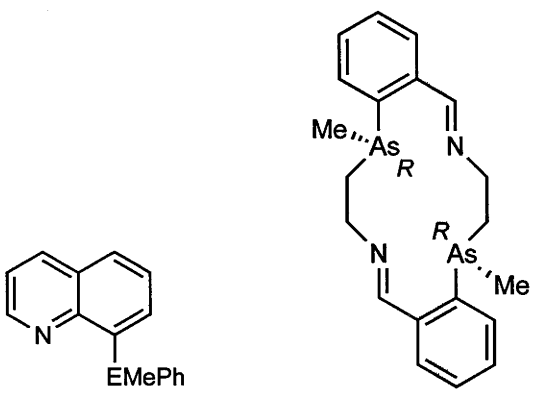


(R_C,R_C)-**12**

Scheme 1.5: Resolution and recovery of chiral tertiary phosphines

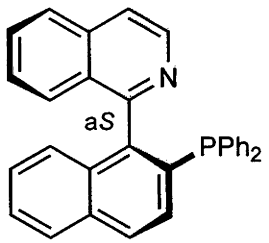


Resolutions of chiral tertiary arsines and phosphines with the enantiomerically pure palladium(II) dimer (R_C,R_C)-**12** have been remarkably successful;[41] bidentate and multidentate ligands can also be resolved with this reagent, for example, (±)-**13** (E = P, As) has been resolved and (R_{As},R_{As})-**14** has been obtained by asymmetric synthesis from the meso *macrocycle* (R_{As}*,S_{As}*)-**14** and (R_C,R_C)-**12**.[48,49]



(±)-**13** (R_{As},R_{As})-**14**

The cheaper *N*,*N*-dimethyl-α-methylbenzylamine-derived reagent (R_C,R_C)-**11** is often employed for the resolution of chiral phosphines and arsines because of the high cost of the naphthalenyl reagent. The use of the naphthalenyl complex, however, can be necessary when there are special structural constraints within the diastereomers containing the chiral ligand and the resolving agent. This has been demonstrated by the resolution of the atropisomers of QUINAP, (±)-**15**. The resolution of this ligand was undertaken by complexation with (S_C,S_C)-**12** and fractional crystallisation of the diastereomers: the (aS,R_C) diastereomer crystallised from chloroform and the (aR,R_C) diastereomer crystallised from 2-butanone upon the addition of diethyl ether.[50] In an earlier publication it was stated that use of (R_C,R_C)-**11** in the resolution of (±)-**15** resulted in formation of a mixture of diastereomeric complexes, as observed by NMR spectroscopy, but that no separation could be obtained by fractional crystallisation. It was later found that the diastereomers derived from (±)-**15** and (S_C,S_C)-**11** formed a quasiracemate.[51] Closer examination of the solid state structure of the cocrystallised diastereomers of the complex indicated significant conformational differences between the orthometallated–amine chelate ring of the two diastereomers, with the δ conformation of the ring placing the chirotopic methyl group in an axial position and the λ conformation of the organometallic ring positioning the methyl group in an equatorial position. Interconversion between the two conformations of this ring can occur by ring-flipping. In the naphthalenyl system, however, a locked asymmetric envelope conformation of the five-membered organometallic ring persists in the diastereomers because of a steric interaction between the chirotopic methyl group and the hydrogen atom on position 8 of the naphthalene ring. The axial disposition of the methyl group in the complex is assured because inversion of the five-membered ring is impossible on steric grounds.

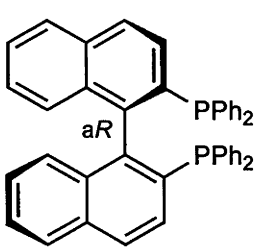


(a*S*)-**15**

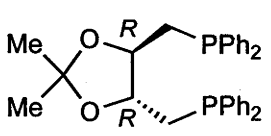
1.6 Synthesis of chiral tertiary phosphines and arsines

1.6.1 Synthesis of chiral tertiary phosphines

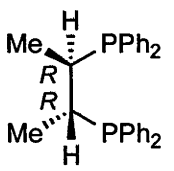
Chiral tertiary phosphines (and to a lesser extent chiral arsines) play an important role in asymmetric synthesis. The field has been dominated by ligands possessing a stereogenic backbone, such as in BINAP, DIOP, Chiraphos and Duphos.[52] Far less attention has been applied to the use of *P*-chiral phosphines (and *As*-chiral arsines) in asymmetric synthesis although there are examples of syntheses where ligands of this type have out-performed those with stereogenic backbones.[53]



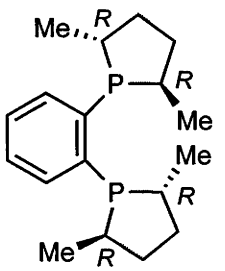
(a*R*)-BINAP



(R_C,R_C)-DIOP



(R_C,R_C)-Chiraphos

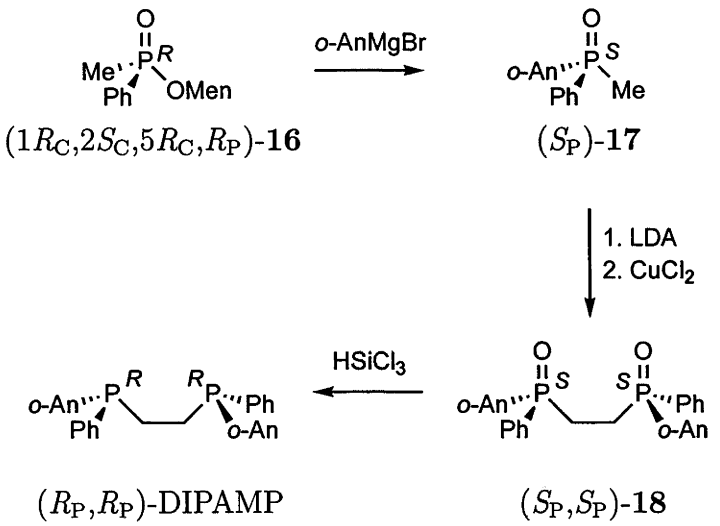


(R_C,R_C,R_C,R_C)-Duphos

In addition to the resolution methods outlined in Section 1.5, there are also examples of the asymmetric synthesis of *P*-chiral phosphines. A recent review has highlighted some of the current methods.[52] The synthesis of enantiomerically pure (R_P,R_P)-DIPAMP from enantiomerically pure ($1R_C$,$2S_C$,$5R_C$,R_P)-

menthoxymethylphenylphosphine oxide ($1R_C,2S_C,5R_C,R_P$)-**16** is shown in Scheme 1.6.[54] Here, ($1R_C,2S_C,5R_C,R_P$)-**16** was isolated by fractional crystallisation of the products of the reaction between (±)-chloromethylphenylphosphine oxide and ($1R_C,2S_C,5R_C$)-(−)-menthol. Treatment of ($1R_C,2S_C,5R_C,R_P$)-**16** with *o*-anisylmagnesium bromide gave the tertiary phosphine oxide (S_P)-**17**, which was coupled by deprotonation of the P*Me* group and subsequent oxidation of the resulting carbanion to give (S_P,S_P)-**18**. Reduction of the diphosphine *dioxide* gave configurationally pure (R_P,R_P)-DIPAMP, which was employed with great success for the asymmetric synthesis of the compound *L*-DOPA, a precursor to the neurotransmitter dopamine, which is capable of crossing the blood-brain barrier.[54] More recent work concerning menthoxyphosphine diastereomers has involved the use of phosphine–borane adducts in preference to phosphine oxides: the phosphine–borane adducts are easily handled in air and can be separated and purified by fractional crystallisation and column chromatography.[55] Removal of the borane from a configurationally pure phosphine–borane adduct is readily achieved by mild heating in an amine such as morpholine. For phosphine oxides and phosphine–borane adducts, attack by a nucleophile results in displacement of the menthoxy group and inversion at phosphorus.

Scheme 1.6: Synthesis of (R_P,R_P)-DIPAMP

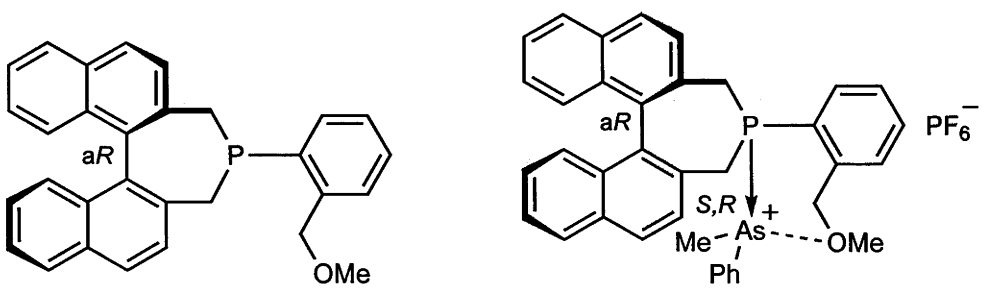


($1R_C$,$2S_C$,$5R_C$,R_P)-**16** (S_P)-**17**

(R_P,R_P)-DIPAMP (S_P,S_P)-**18**

1.6.2 Asymmetric synthesis of tertiary arsines

Recent work within our group has focussed on the asymmetric synthesis of enantiomerically enriched tertiary arsines from phosphine-stabilised arsenium salts containing (a*R*)-4-[2-(methoxymethyl)phenyl]-4,5-dihydro-3*H*-dinaphtho[2,1-c;1',2'-e]phosphepine, (a*R*)-**19**.[12,13,56] Initial investigations dealt with the (a*R*)-**19**-stabilised methylphenylarsenium hexafluorophosphate, (aR,R_{As})/(aR,S_{As})-**20**, which was synthesised by the two-phase method described in Section 1.3.

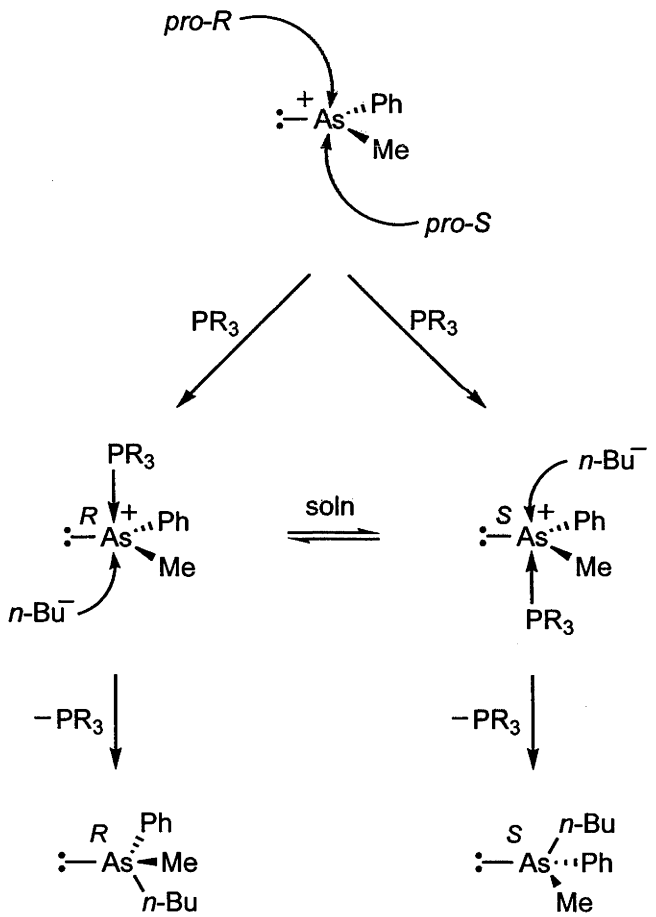


(aR)-**19** (aR,R_{As})/(aR,S_{As})-**20**

The C_1 phosphine (aR)-**19** can bind to either face of the prochiral arsenium ion, generating the diastereomers (aR,R_{As}) and (aR,S_{As})-**20**. The diastereomers of **20** can be observed by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy, where the ratio (aR,R_{As})-**20**/(aR,S_{As})-**20** = 79/21 (58% de) at 20 °C.[11] Cooling of the equilibrating mixture

of diastereomers to −90 °C increases the diastereomeric excess to 88%. Addition of *n*-butyllithium to a dichloromethane solution of the equilibrating mixture of diastereomers at −80 °C gave (*S*)-(*n*-butyl)methylphenylarsine in 77% ee, as determined from the ^{1}H NMR spectrum of the diastereomers formed by bridge splitting of the palladium complex (S_C,S_C)-**12** with the enantiomerically enriched tertiary arsine.[12,13] The influence of the phosphine on the approach of the *n*-butyl ion to the prochiral arsenium ion is shown in Scheme 1.7.

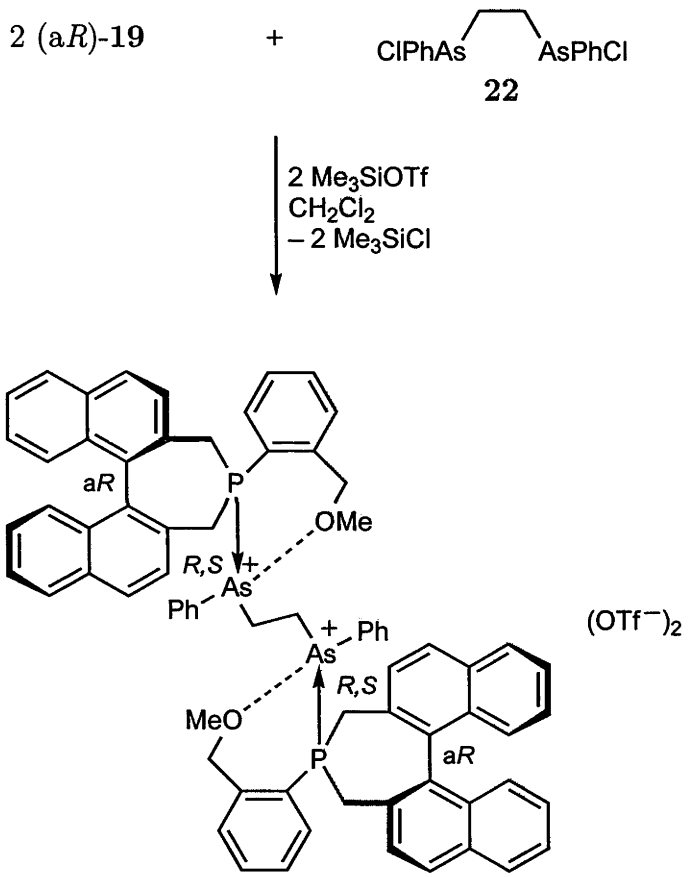
Scheme 1.7: Attack of a prochiral phosphine-stabilised arsenium by the *n*-butyl ion



Recent work has extended this method to the asymmetric synthesis of diarsines, in particular (R_{As}*,R_{As}*)-(±)/(R_{As}*,S_{As}*)-1,2-bis[(*n*-butyl)phenylarsino]ethane, (R_{As}*,R_{As}*)-(±)/(R_{As}*,S_{As}*)-**21**.[56] The reaction of 2 equiv (a*R*)-**19** with 1,2-bis(chlorophenylarsino)ethane (**22**) and 2 equiv trimethylsilyl trifluoromethanesul-

fonate in dichloromethane, followed by removal of chlorotrimethylsilane and the solvent gave a mixture of (aR,R_{As},R_{As},aR)/(aR,S_{As},S_{As},aR)/(aR,R_{As},S_{As},aR)-**23** (Scheme 1.8). Analysis of this equilibrating mixture of diastereomers by $^{31}P\{^1H\}$ NMR spectroscopy at low temperature revealed three overlapping sets of resonances for the three possible diastereomers.

Scheme 1.8: Synthesis of a bis(phosphepine-stabilised)diarsenium triflate

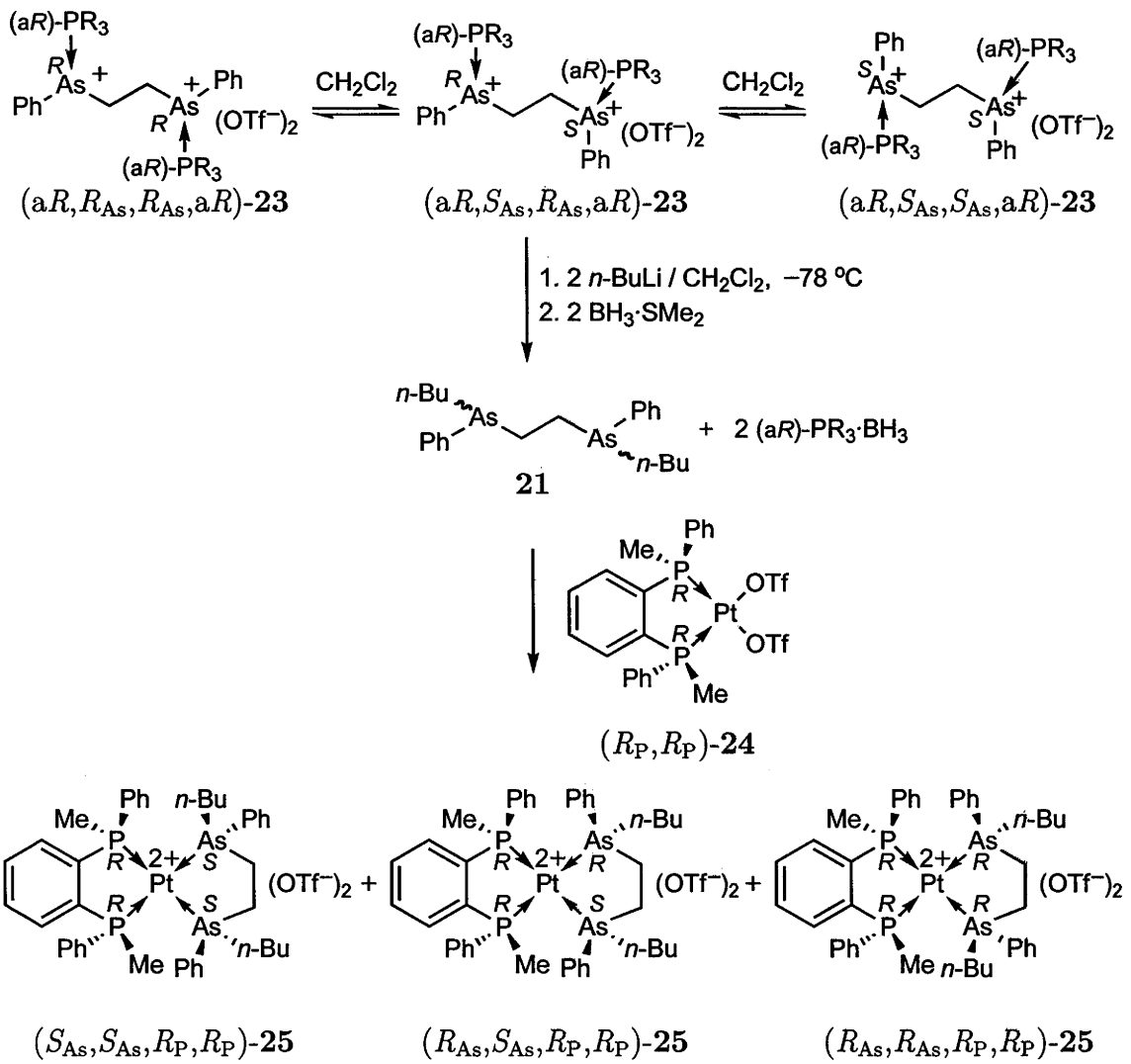


(aR,R_{As},R_{As},aR)/(aR,S_{As},S_{As},aR)/(aR,R_{As},S_{As},aR)-**23**

The reaction of the mixture with n-butyllithium at −78 °C produced (R_{As}*,S_{As}*)/(R_{As},R_{As})/(S_{As},S_{As})-**21**. Complexation of these stereoisomers with the enantiomerically pure platinum(II) ditriflate (R_P,R_P)-**24** gave complexes that could be analysed by $^{31}P\{^1H\}$ NMR spectroscopy to give the diastereomeric and enan-

tiomeric excesses of **21** (Scheme 1.9). Spectroscopic analysis of the platinum–diarsine complexes gave (R_{As},S_{As},R_P,R_P)/(S_{As},S_{As},R_P,R_P)/(R_{As},R_{As},R_P,R_P)-**25** = 29/9/62, which corresponded to a de of 42% for the (R_{As}*,R_{As}*)-(±) diastereomer of the diarsine, which in turn was composed of 87% of the (S_{As},S_{As}) enantiomer and 13% of the (R_{As},R_{As}) enantiomer.[56]

Scheme 1.9: Asymmetric synthesis of a chiral diarsine [(a*R*)-PR_3 = (a*R*)-**19**]

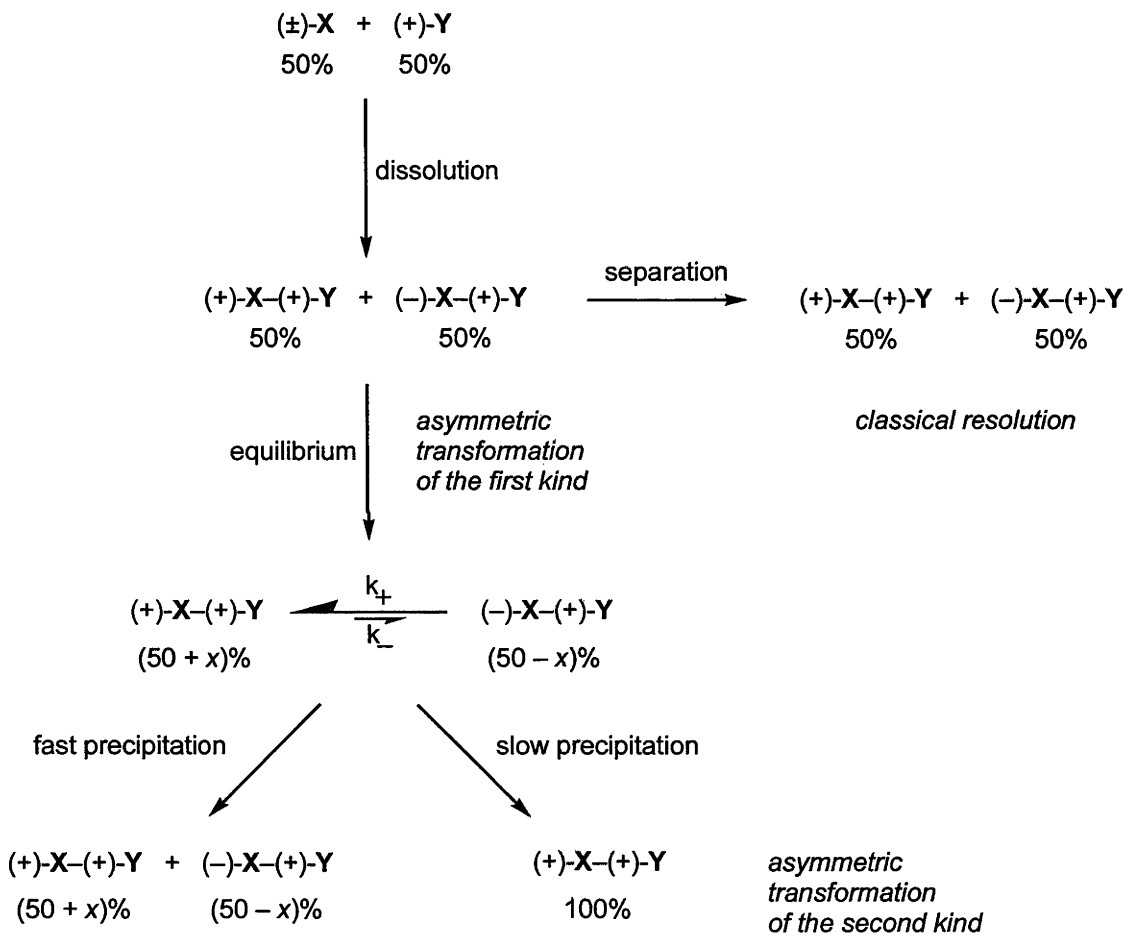


1.7 Asymmetric transformation

Resolutions typically involve the separation of enantiomers that are not capable of interconversion. Asymmetric transformation refers to a process whereby a mixture of enantiomers or diastereomers (generally 50/50) in solution is transformed into a single stereoisomer (or stereoisomer enriched mixture) by the influence of an external chiral reagent on an equilibrium process.[1] Thus, the neutralisation of the configurationally stable acid (±)-**X** by the enantiomerically pure base (+)-**Y** will result in the diastereomeric salts (+)-**X**–(+)-**Y** and (−)-**X**–(+)-**Y**. Separation of the 50/50 mixture of salts by fractional crystallisation amounts to a chemical resolution, where the maximum yield of each diastereomer is 50%. Where the component (±)-**X** is configurationally labile, however, the two diastereomers will be in equilibrium. If the equilibrium constant $K \neq 1$, enrichment in one diastereomer has occurred by asymmetric transformation. The first use of the term *asymmetric transformation* was in relation to the addition of the organic base (−)-brucine to a solution of (±)-2-*o*-carboxybenzyl-α-hydrindone in acetone, where the solid that crystallised was exclusively derived from (−)-brucine and the (+)-acid.[57] The dextrorotatory acid was subsequently recovered from the salt and was found to readily racemise. The transformation of a mixture of diastereomers in solution, followed by the crystallisation of a solid enriched in one diastereomer, is termed a *second-order asymmetric transformation* (or more correctly an *asymmetric transformation of the second kind*).[1] The addition of (−)-hydroxyhydrindamine to (±)-chlorobromomethanesulphonic acid in dry acetone results in a change in the optical rotation (mutarotation), which corresponds to the enrichment of the (−)-amine–(−)-acid salt resulting from a shift in the equilibrium position between the optically active base and the racemising acid.[58] The enrichment of a diastereomer in solution is known as a *first-order asymmetric transformation* (or more correctly as an *asymmetric transformation of the first kind*). This effect is referred to in the literature of coordination chemistry as

the 'Pfeiffer effect', owing to the initial observation of the influence of optically active anions on the proportions of the enantiomers of labile (±)-$[Zn(phen)_3]^{2+}$ (phen = 1,10-phenanthroline) in water.[59] The concepts of resolution and asymmetric transformation are summarised in Scheme 1.10.[60,61]

Scheme 1.10: Overview of asymmetric transformations

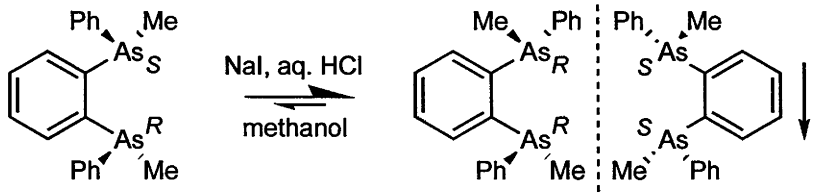


1.7.1 Examples of asymmetric transformation

The (R_{As}*,S_{As}*) diastereomer of the bis(tertiary arsine) **26** undergoes an asymmetric transformation into less soluble (R_{As}*,R_{As}*)-(±)-**26** in methanol in the presence of

a trace of hydrochloric acid and sodium iodide after seeding of the solution with crystals of the (R_{As}*,R_{As}*)-(±) diastereomer (Scheme 1.11).[62]

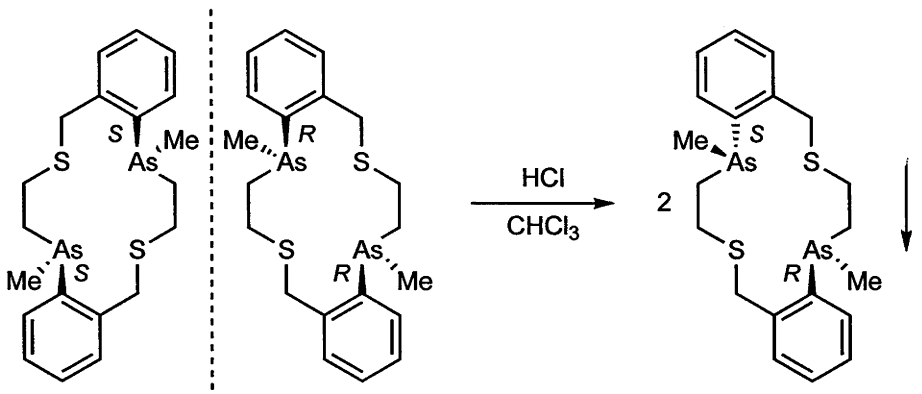
Scheme 1.11: Asymmetric transformation of the second kind



(R_{As}*,S_{As}*)-**26** (R_{As}*,R_{As}*)-(±)-**26**

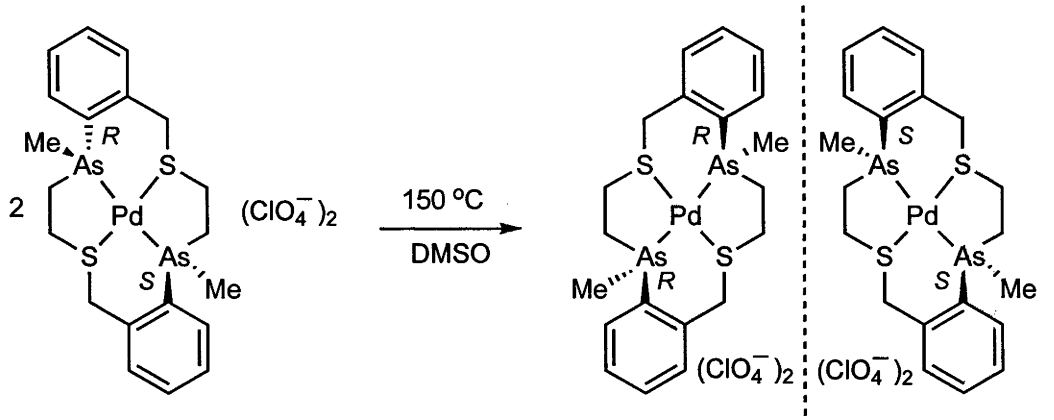
Two interesting examples of asymmetric transformations have been observed in the synthesis of the As_2S_2 macrocycle **27**. The dissolution of (R_{As}*,R_{As}*)-(±)-**27** in chloroform to which a trace of aq. hydrochloric acid had been added furnishes sparingly soluble (R_{As}*,S_{As}*)-**27** in quantitative yield by an asymmetric transformation of the second kind (Scheme 1.12).[63] The meso diastereomer (R_{As}*,S_{As}*)-**27**, however, when complexed to palladium(II) and heated in DMSO at 150 °C furnishes (R_{As}*,R_{As}*)-(±)-**27** in quantitative yield in an asymmetric transformation of the first kind (Scheme 1.13).

Scheme 1.12: Asymmetric transformation of the second kind of (R_{As}*,R_{As}*)-(±)-**27** into (R_{As}*,S_{As}*)-**27**



(S_{As},S_{As})-**27** (R_{As},R_{As})-**27** (R_{As}*,S_{As}*)-**27**

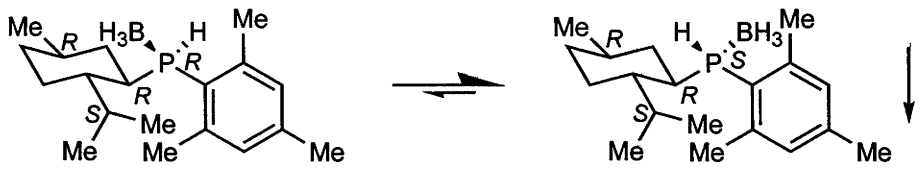
Scheme 1.13: Asymmetric transformation of the first kind of [Pd(R_{As}*,S_{As}*)-**27**](ClO$_4$)$_2$ into [Pd(R_{As}*,R_{As}*)-**27**](ClO$_4$)$_2$



[Pd(R_{As}*,S_{As}*)-**27**](ClO$_4$)$_2$ [Pd(R_{As},R_{As})-**27**](ClO$_4$)$_2$ [Pd(S_{As},S_{As})-**27**](ClO$_4$)$_2$

An asymmetric transformation of the second kind has been demonstrated for the resolution of a borane adduct of a *P*-chiral secondary phosphine.[64,65] An (R_P/S_P) 54/46 mixture of the diastereomers of (1R_C,2S_C,5R_C)-menthylmesitylphosphine (**28**) in benzene was treated with borane–dimethylsulfide; the corresponding borane adducts were initially formed in a similar ratio but the solution became enriched in one diastereomer over 18 h (Scheme 1.14). Removal of the benzene and redissolution of the residue in *n*-hexane brought about the crystallisation of the major diastereomer in 66% yield and 97% diastereomeric purity. The mother liquor was enriched in the isolated diastereomer. The crystal structure of the less-soluble borane adduct indicated the *S* configuration at phosphorus. Liberation of the borane from the pure adduct gave the secondary phosphine in 97% diastereomeric purity.

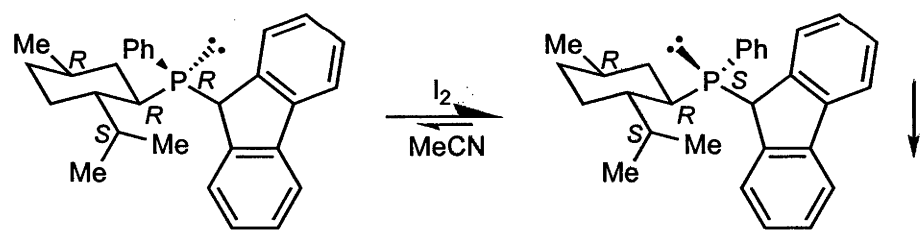
Scheme 1.14: Asymmetric transformation of the second kind of ($1R_C$,$2S_C$,$5R_C$,R_P)-**28** into ($1R_C$,$2S_C$,$5R_C$,S_P)-**28**



($1R_C$,$2S_C$,$5R_C$,R_P)-**28** ($1R_C$,$2S_C$,$5R_C$,S_P)-**28**

The asymmetric transformation of tertiary phosphines has also been demonstrated for (R_P/S_P)-9-fluorenyl[($1R_C$,$2S_C$,$5R_C$)menthyl]phenylphosphine (**29**), where a 20/1 mixture of ($1R_C$,$2S_C$,$5R_C$,S_P)/($1R_C$,$2S_C$,$5R_C$,R_P)-**29** was obtained by recrystallisation of a 3/1 mixture in acetonitrile containing 4 mol % iodine (Scheme 1.15).[66]

Scheme 1.15: Asymmetric transformation of the second kind of ($1R_C$,$2S_C$,$5R_C$,R_P)-**29** into ($1R_C$,$2S_C$,$5R_C$,S_P)-**29**

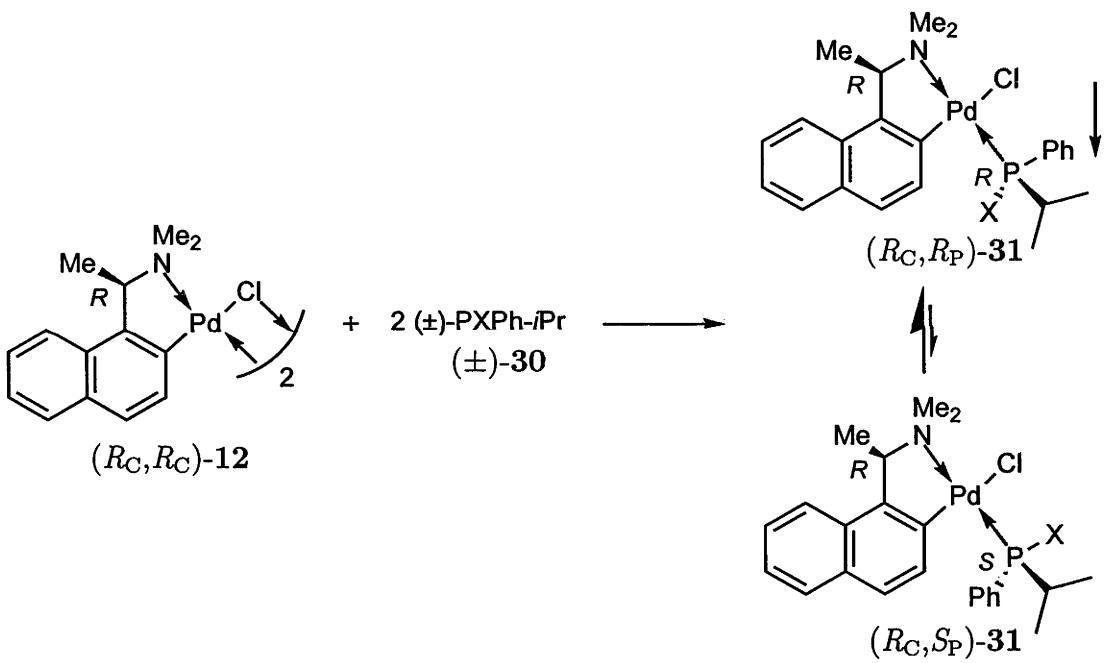


($1R_C$,$2S_C$,$5R_C$,R_P)-**29** ($1R_C$,$2S_C$,$5R_C$,S_P)-**29**

The attempted resolutions of secondary halophosphines has also revealed asymmetric transformations of the second kind (Scheme 1.16).[67,68] (±)-Chlorophenyl(*i*-propyl)phosphine (±)-**30** (X = Cl) reacts with (R_C,R_C)-**12** in dichloromethane to give the diastereomers (R_C,R_P)/(R_C,S_P)-**31** (X = Cl). Analysis of the mixture of complexes in solution by $^{31}P\{^1H\}$ spectroscopy indicated a 22/78 mixture of the two diastereomers, which persisted over several days. The isolation of the major diastereomer of the complex was achieved by successive crystallisations from enriched solutions, with four crystallisations providing (R_C,R_P)-**31** (X = Cl) in 82% yield.[67]

The fluorophosphine (±)-**30** (X = F) combines with (R_C,R_C)-**12** in a similar manner to give (R_C,R_P)/(R_C,S_P)-**31** (X = F) (Scheme 1.16). Observation of the mixture by $^{31}P\{^1H\}$ spectroscopy indicated the presence of the two diastereomers in almost equal amounts; upon standing of the solution for 18 h, however, the proportion of one diastereomer increased to 75%. Isolation of the crystalline solid by the addition of diethyl ether to the solution gave the major diastereomer (R_C,R_P)-**31** (X = F) in 64% yield by an asymmetric transformation of the second kind.[68]

Scheme 1.16: Asymmetric transformation of the second kind of coordinated ((±)-**30** (where X = F or Cl)

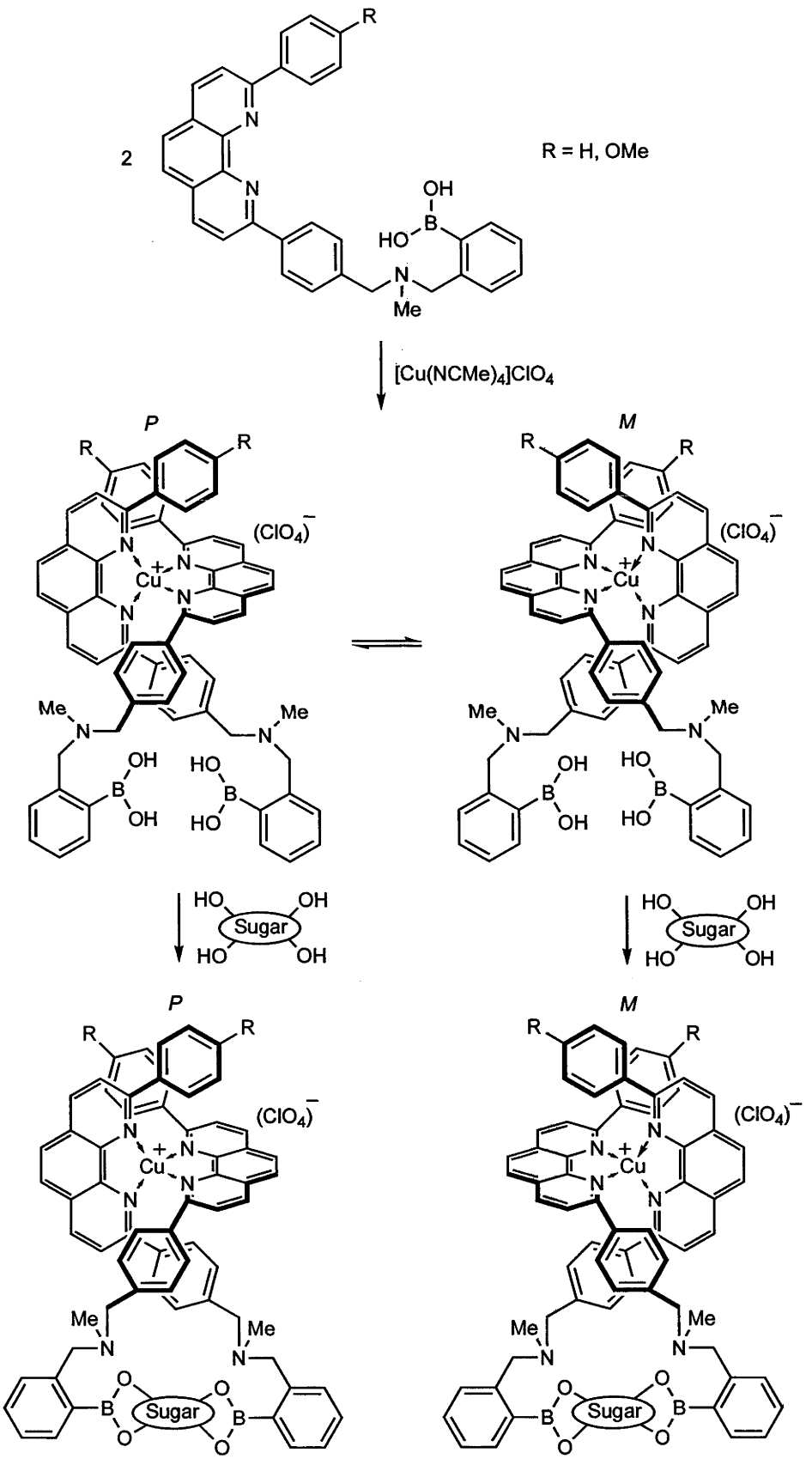


Complexes of the type Λ-[Co(en)$_2$AA]Cl$_2$ (AA = (*S*)-valine, (*S*)-alanine) are configurationally stable at cobalt. The addition of a small quantity of base to the complexes deprotonates the coordinated amino acids at the α-carbon, which results in the establishment of an equilibrium mixture of the two possible diastereomers by rapid inversion at carbon. The equilibrium constants for the reactions indicate the ratio 63/37 for the diastereomers Λ-[Co(en)$_2$(*R*-val)]$^{2+}$/Λ-[Co(en)$_2$(*S*-val)]$^{2+}$ and 50/50 for the diastereomers Λ-[Co(en)$_2$(*R*-ala)]$^{2+}$/Λ-[Co(en)$_2$(*S*-ala)]$^{2+}$.[69] The con-

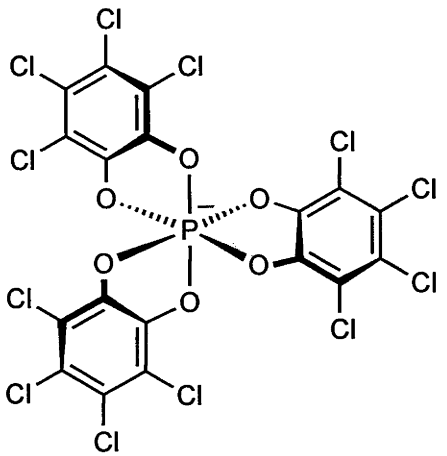
figuration at cobalt(III) is stable under these conditions. This procedure was further explored by reactions of a variety of tetraamine–cobalt(III) complexes with a range of amino acids, where diastereomeric ratios of up to 91/9 were observed.[70–72] The asymmetric transformations of the first kind were monitored by CD and NMR spectroscopy.[72]

The configurations of metal complexes can also been influenced by external components, such as chiral anions and other chiral additives. An interesting asymmetric transformation of the first kind was observed for the addition of (±)-$[Fe(bipy)_3]^{2+}$ (bipy = 2,2'-bipyridine) to an aq. solution of double-stranded DNA.[73] The CD spectrum of the mixture resembled that of (+)-$[Fe(bipy)_3]^{2+}$, which indicated the transformation of the racemate by association with the anionic surface of the DNA double helix. The asymmetric transformation of helices containing achiral ligands has also received attention. The binding of sugars to boronic-acid functionalised 1,10-phenanthroline–copper(I) complexes induces helicity at copper (Scheme 1.17).[74,75] In this example, the enrichment in the *P* or *M* helicate is dependent on the sugar used for the asymmetric transformation, as determined by CD spectroscopy.

Scheme 1.17: Asymmetric transformation of the first kind of a boronic acid-functionalised 1,10-phenanthroline–copper(I) complex



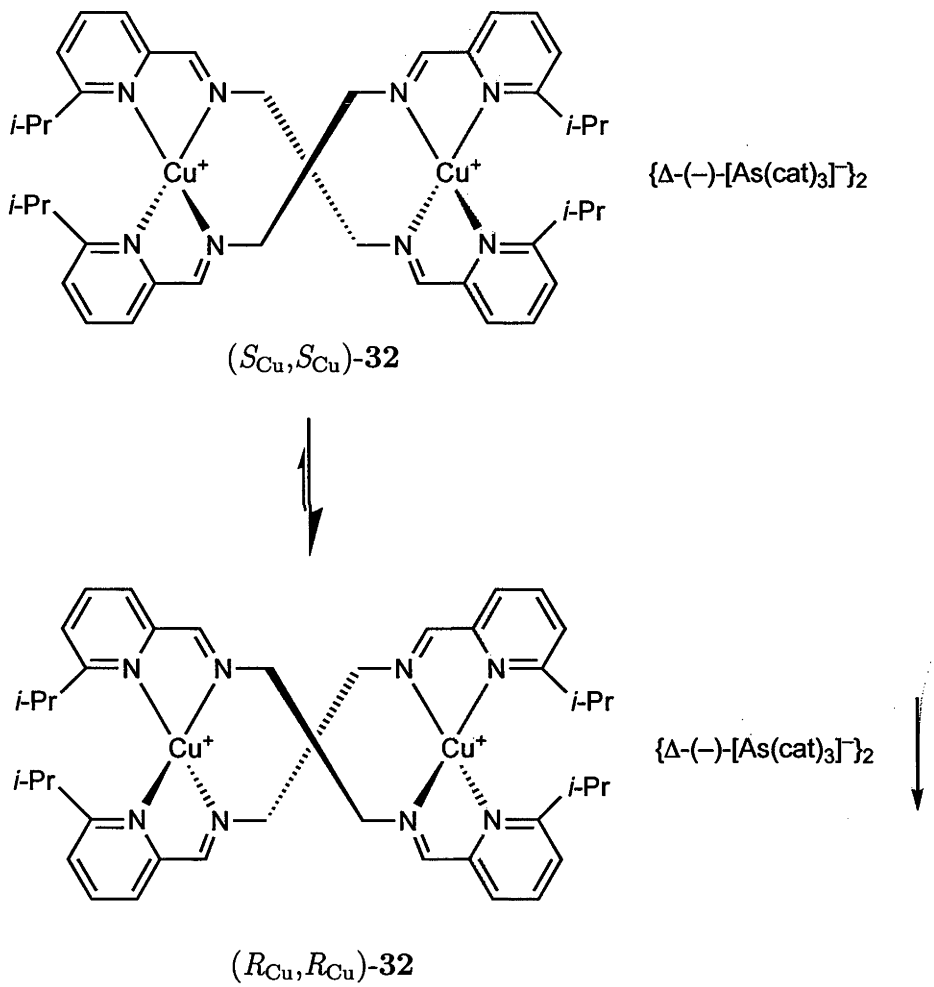
Many successful asymmetric transformations have been effected with use of the enantiomers of the (±)-*tris*(tetrachlorobenzenediolato)phosphate(V) ion (TRISPHAT), including axially chiral ammonium and diammonium salts,[76–78] supramolecular systems,[79,80] helicates,[81] metallospiranes,[82,83] and three-bladed propeller complexes.[84–86] The subject has recently been reviewed.[87]



(Λ)-TRISPHAT

An asymmetric transformation of the second kind has been demonstrated in our group for a double-stranded, dicopper(I) helicate containing achiral bis(bidentate) Schiff base ligands (Scheme 1.18).[88] The diastereomer [(R_{Cu},R_{Cu})-**32**] crystallises upon the addition of an aqueous solution containing 2 equiv of Δ-(−)-tris(catecholato)arsenate(V) to an equilibrium mixture of the (±)-helicate in dichloromethane. Crystal structure determinations on two individual crystals of the complex indicated crystallisation of a single diastereomer. Confirmation of the asymmetric transformation of the second kind was given by X-ray powder diffraction on the bulk solid, with the collected data corresponding to the data obtained for the two single crystals. Interconversion between the two enantiomers of the helicate in solution occurs by an intramolecular process, since intermolecular ligand crossover between similar helicates are slow compared to the rate of racemisation of the resolved helicate.

Scheme 1.18: Asymmetric transformation of the second kind for a double-stranded, dicopper(I) helicate



(S_{Cu},S_{Cu})-**32**

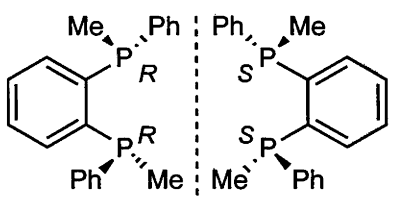
(R_{Cu},R_{Cu})-**32**

1.8 Chemical racemisation of chiral tertiary phosphines and arsines

As described in Section 1.2, chiral tertiary phosphines and arsines racemise by unimolecular pyramidal inversion at elevated temperatures. There are also a number of chemical conditions under which tertiary phosphines and arsines racemise.

1.8.1 Racemisation of tertiary arsines by haloacids

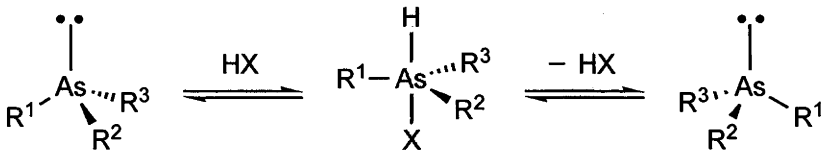
Tertiary phosphines are strong bases and form stable salts with strong acids. For example (R_P*,R_P*)-1,2-phenylenebis(methylphenylphosphine) ((R_P*,R_P*)-(±)-**33**) is protonated stereospecifically by dilute aqueous tetrafluoroboric acid with retention of configuration at phosphorus; the mono-protonated phosphonium salt is stable to racemisation, as indicated by recovery of the free (R_P*,R_P*)-(±)-**33** by neutralisation. Indeed, optically pure (R_P,R_P)-**33** can be recovered unchanged after three weeks in concentrated hydrochloric acid.[89,90]



(R_P*,R_P*)-**33**

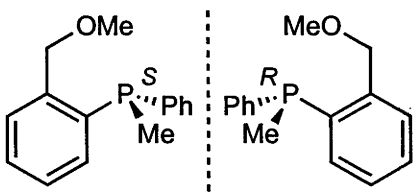
Tertiary arsines, however, are weak bases and cannot be isolated as protonated salts under normal conditions.[91] Nevertheless, optically active tertiary arsines chiral at arsenic racemise rapidly in the presence of halo acids, purportedly by a five-coordinate intermediate as shown in Scheme 1.19.

Scheme 1.19: Racemisation of tertiary arsines by haloacids

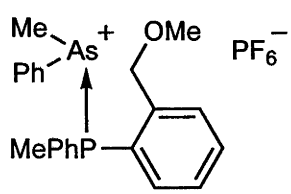


1.8.2 Racemisation of tertiary phosphines by iodoarsines

The asymmetric synthesis of tertiary arsines has been achieved with use of the phosphepine ligand (a*R*)-**19**, as outlined in Section 1.6.2. The racemic phosphine-stabilised arsenium salt (R_{As}*,R_P*)-(±)-**34** was prepared to determine the suitability of the ligand for the asymmetric synthesis of tertiary arsines.[12] It was hoped that the enantiomerically pure form of the phosphine would coordinate selectively to one face of the prochiral arsenium cation; subsequent addition of *n*-butyllithium to the equilibrating mixture of diastereomers of the complex, one diastereomer being in excess, would produce an enantioselectively enriched tertiary arsine by a novel method of asymmetric synthesis.



(±)-**35**

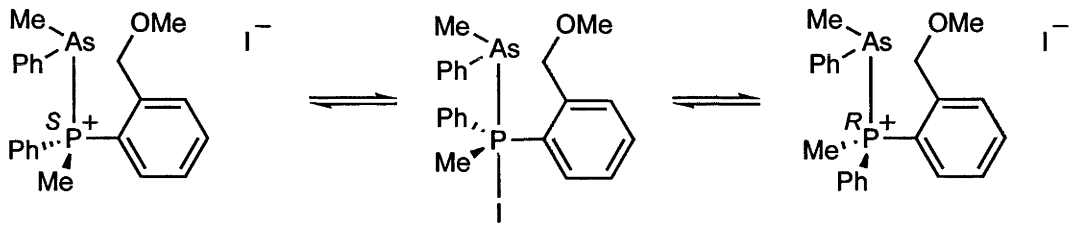


(R_{As}*,R_P*)-**34**

In this earlier work, the racemic phosphine (±)-**35** and (±)-iodomethylphenylarsine in dichloromethane was treated with aqueous sodium hexafluorophosphate; (R_{As}*,R_P*)-(±)-**34** was isolated in 59% yield from the organic phase. Analysis of the recrystallised complex by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy in CD_2Cl_2 indicated two diastereomers in a 64/36 ratio or 28% diastereomeric excess. The de of the more stable complex increased to 38% when the solution was cooled to −50 °C. The phosphine (±)-**35** was then resolved with use of the palladium(II) dimer (S_C,S_C)-**12** and the two-phase synthesis of the

phosphine-stabilised arsenium hexafluorophosphate described above was repeated with the optically pure (+)-**35**, (±)-iodomethylphenylarsine, and aqueous ammonium hexafluorophosphate. Disappointingly (at the time), the optical activity of the resolved phosphine was lost during the synthesis and workup.[12] The racemisation of the phosphine by the iodoarsine was considered to proceed via a five-coordinate intermediate (Scheme 1.20). Psuedorotation of the five coordinate intermediate will result in rapid racemisation of the phosphine by the mechanism proposed for the racemisation of tertiary arsines in the presence of haloacids.

Scheme 1.20: Racemisation of (+)-**35** by (±)-iodomethylphenylarsine



The confirmation of the racemisation of the phosphine by the secondary iodoarsine was made by the addition of a trace of (±)-iodomethylphenylarsine to a dichloromethane solution of (R_P*,R_P*)-(±)-**33**.[12] Epimerisation† of (R_P*,R_P*)-(±)-**33** into an equimolar mixture of (R_P*,R_P*)-(±)/(R_P*,S_P*)-(±)-**33** was observed by ^{1}H NMR spectroscopy to be complete within the time taken to prepare the solutions and record the NMR spectrum. The experiment was repeated with (±)-chloromethylphenylarsine as the possible racemising agent; no racemisation of (R_P*,R_P*)-(±)-**33** was observed. I reinvestigated this work by treating a solution of (R_P*,R_P*)-(±)-**33** in CD_2Cl_2 with 0.2 equiv (±)-iodomethylphenylarsine. The epimerisation occurred, but at a considerably slower rate than originally reported. The addition of 1 equiv of (±)-iodomethylphenylarsine to a CD_2Cl_2 solution of (R_P*,R_P*)-(±)-**33** resulted in complete epimerisation at phosphorus into the 1/1

†The term epimerisation is defined as follows: The interconversion of diastereomers by change of configuration at one or more than one stereogenic centre.[1]

(R_P*,R_P*)-(±)/(R_P*,S_P*)-**33** equilibrium mixture within the time taken to prepare the sample and record the ^{1}H and ^{31}P{^{1}H} NMR spectra. ^{1}H NMR spectra showing P*Me* resonances for the (R_P*,R_P*)-(±) and (R_P*,S_P*) diastereomers of **33**, as well as the mixture generated by the addition of the iodoarsine, are shown in Figure 1.6.

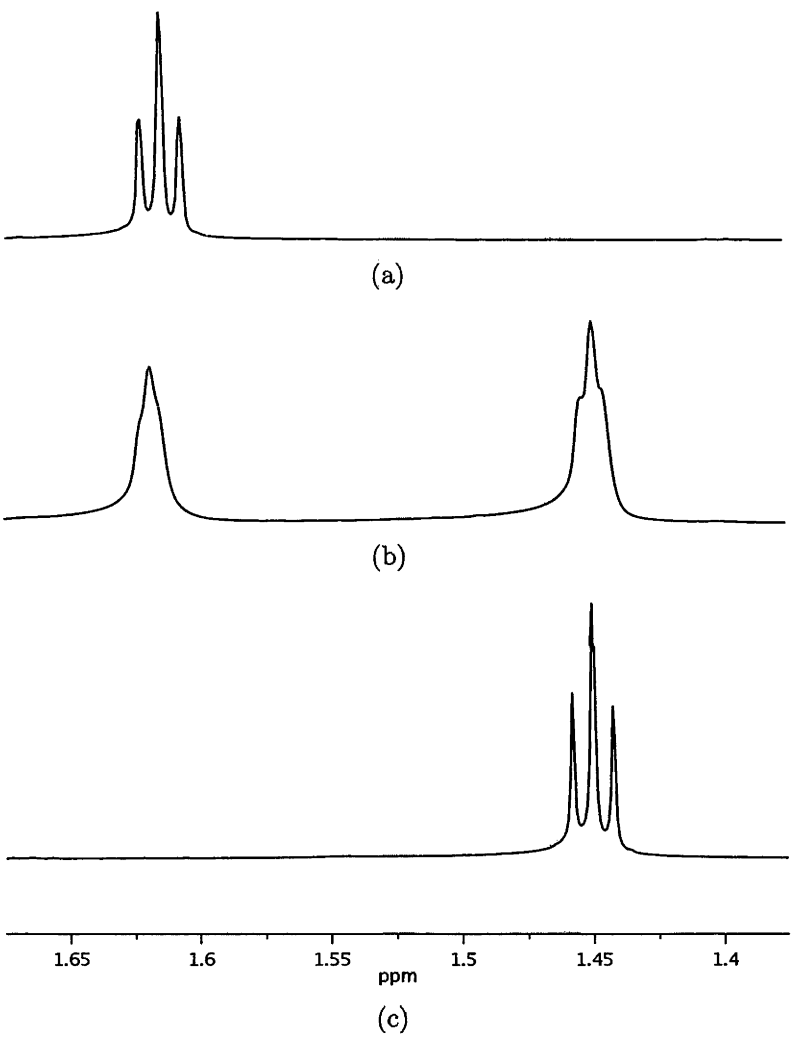
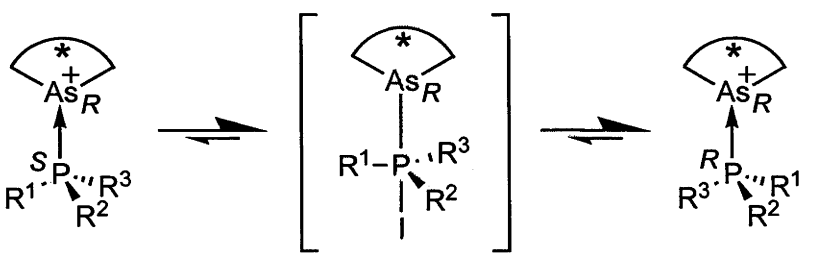


Figure 1.6: P*Me* resonances in CD_2Cl_2 at 25 °C for (R_P*,R_P*)-(±)-**33** (a) and (R_P*,S_P*)-**33** (c) and spectrum of either solution in the presence of (±)-iodomethylphenylarsine (b).

1.9 Objectives of current work

The resolution of tertiary phosphines chiral at phosphorus by complexation with an enantiomerically pure, chloro-bridged orthometallated (α-methyl)benzylamine or -naphthylamine–palladium(II) resolving agent is an extremely effective route to chiral phosphines of high enantiomeric purity (>99%). Nevertheless, the maximum yield of an enantiomer that can be obtained by resolution of a racemate is 50%. We have therefore explored in this thesis a new method for the asymmetric synthesis of chiral phosphines, where the maximum yield of the enantiomerically pure phosphine could be 100%. The primary goal of the work was the synthesis of a configurationally stable haloarsine and to generate from this by methods known within the group the first phosphine-stabilised arsenium salt containing an enantiomerically pure arsenium auxiliary. Because secondary haloarsines lack configurational stability due to rapid intermolecular halide exchange it was necessary to devise a system in which the chirality was not at arsenic but was within the framework of the molecule. It was envisaged that a phosphine bound to the chiral arsenium ion could be racemised under the influence of iodide, resulting in the enrichment of one diastereomer in solution by an asymmetric transformation. Subsequent isolation of the enantiomerically enriched tertiary phosphine would provide a new asymmetric synthesis of *P*-chiral tertiary phosphines.



Chapter 2

Chiral Haloarsines

2.1 Introduction

Arsenium ions, AsR_2^+, can be generated from tertiary arsines and secondary haloarsines by ionisation in a mass spectrometer,[22,23] can be isolated as ligand-stabilised species by reactions of secondary iodoarsines in the presence of aqueous hexafluorophosphates, or by the addition of trimethylsilyl triflate or thallium(I) salts to a chloroarsine.[11,21] The primary aim of this project was the synthesis of an enantiomerically pure haloarsine that could be used for the possible asymmetric transformation of racemic, *P*-chiral tertiary phosphines into an enantiomerically enriched tertiary phosphine, as indicated in Figure 2.1 for an arsenium ion of *R* configuration.

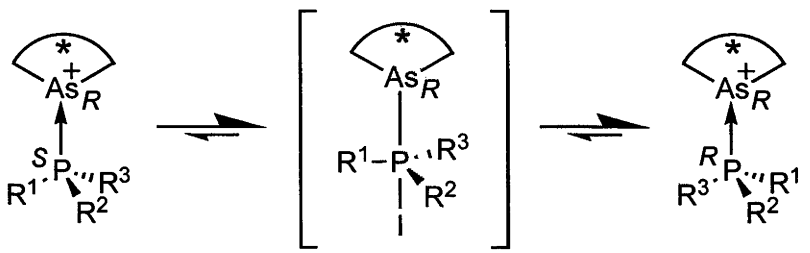


Figure 2.1: Deracemisation of a chiral tertiary phosphine in the environment of an enantiomerically pure arsenium host of *R* configuration.

A suitable chiral haloarsine was therefore required for the synthesis of appropriate phosphine-stabilised arsenium salts. Halo-arsines and -phosphines of the type (±)-ERR'X are configurationally labile because of rapid intermolecular halogen exchange (Figure 2.2).[68,92] A number of mechanisms have been proposed for degenerate halide exchange in chloroarsines and chlorophosphines, with kinetic investigations indicating bimolecular exchange as the most likely mechanism.[93]

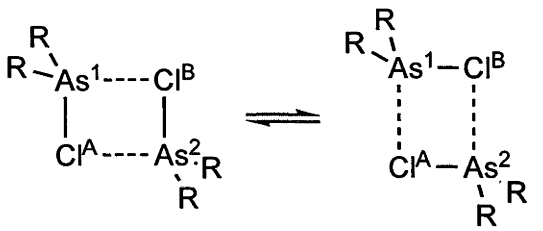
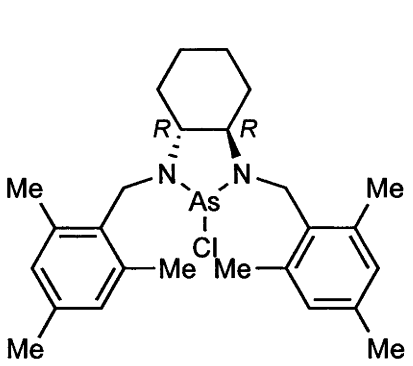


Figure 2.2: Degenerate bimolecular halide exchange between chloroarsines.

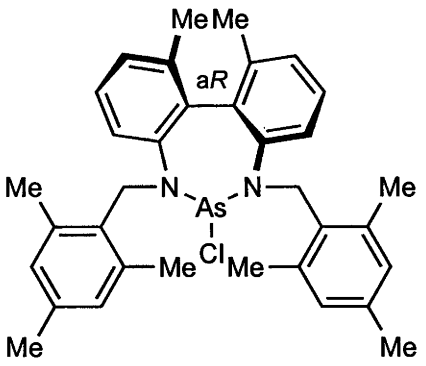
The two-phase method used for the preparation of phosphine-stabilised arsenium salts from iodoarsines and tertiary phosphines in dichloromethane in the presence of aqueous potassium hexafluorophosphate requires stability of the resulting phosphine-stabilised arsenium salt to aqueous hydrolysis; the hydrolysis of a ligand-stabilised arsenium salt was observed in the attempted two-phase synthesis of triphenylarsine-stabilised methylphenylarsenium hexafluorophosphate.[21]

2.2 Design of a chiral host

Arsenium ions of C_2 symmetry were considered attractive possibilities for this investigation because of the degeneracy of the axial sites to coordination above and below the angular AsC_2 plane of the arsenium ion. Initial investigations were directed towards the use of enantiomerically pure diamines as chelating components of heterocyclic chloroarsines. The chloroarsines chosen for this investigation were the bis(mesitylmethyl)-functionalised diamino derivative (R_C,R_C)-**36** and the related atropisomeric compound (aR)-**37**.



(R_C,R_C)-**36**

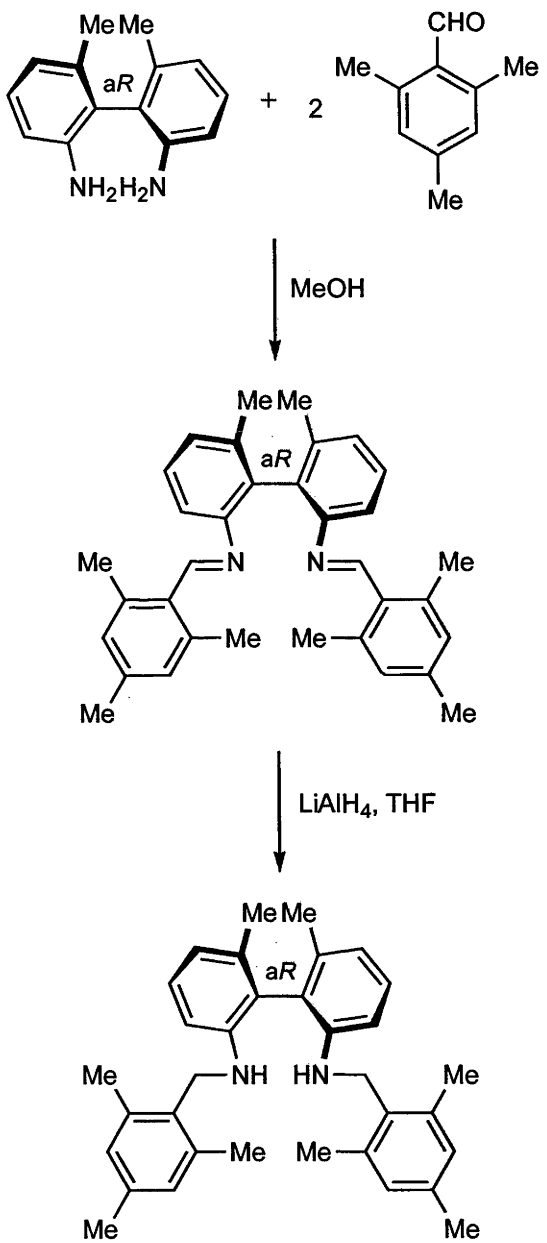


(aR)-**37**

The resolutions of the two parent bis(primary diamines) required for the syntheses of the above compounds are described in the literature.[94,95] Mesitylation of each bis(primary amine) was achieved by condensation with two equiv of mesityl aldehyde. Reductions of the resulting Schiff bases with $NaBH_4$ or $LiAlH_4$ furnished the desired bis(secondary diamines). The synthesis of (aR)-*N*,*N*'-bis(2,4,6-trimethylbenzylidene)-6,6'-dimethyl-1,1'-biphenyl-2,2'-diamine, (aR)-**38**, is shown in Scheme 2.1.

The synthesis of (R_C,R_C)-**36** by the addition of trichloroarsine to a solution of the diamine in the presence of excess 1,8-bis(dimethylamino)naphthalene was evident from the ^{1}H NMR spectrum of the crude product, but attempts at isolating the pure compound were unsuccessful. No formation of (aR)-**37** was observed under similar conditions.

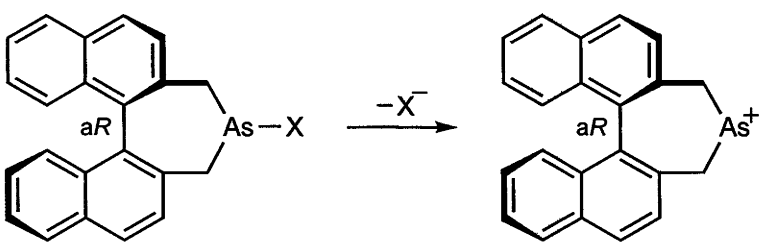
Scheme 2.1: Synthesis of (aR)-**38**



(aR)-**38**

Arsenium ions derived from haloarsines containing the 2,2'-bis(methylene)-1,1'-binaphthyl group will be configurationally stable because rotation about the 1,1'-bond of the binaphthyl group is prevented by steric hindrance between the methylene groups in the 2,2' positions and the hydrogen atoms in the 9 and 9' positions. The abstraction of a halide ion from (a*R*)-**39** (X = Cl, I) will generate (a*R*)-**40** (Scheme 2.2). The axial chirality of (a*R*)-**40** under normal experimental conditions will be assured because hindered rotation about the C–C bond of the 1,1'-binaphthyl group will lock the seven-membered arsepine ring into a chiral twist-boat conformation. This ring can only be inverted by racemisation of the 1,1'-binaphthyl framework. Figure 2.3 shows a representation of the twist-boat conformation of (a*R*)-**40** when the molecule is viewed down the C_2 axis. Locking of the conformation of the arsepinenium ring by steric resistance ensures that no additional conformers are present for (a*R*)-**39** (X = I) or (a*R*)-**40** in solution or in the solid state. Intermolecular halide exchange or pyramidal inversion at arsenic in (a*R*)-**39** (X = Cl, I) does not result in racemisation because of the C_2 symmetry of the rigid 2,2'-bis(methylene)-1,1'-binaphthyl framework. The coordination of a phosphine (L) to either face of (a*R*)-**40** is degenerate because of its C_2 symmetry, but lowers the symmetry of the resulting phosphine-stabilised arsenium complex to C_1 (Figure 2.4).

Scheme 2.2: Formation of (a*R*)-**40** from (a*R*)-**39** (X = Cl, I)



(a*R*)-**39** (X = Cl, I) (a*R*)-**40**

Unlike the As–N bonds in (*R*,*R*)-**36** and (a*R*)-**37**, the As–C bonds in (a*R*)-**40** will be stable to hydrolysis and the conditions usually applied to the synthesis and

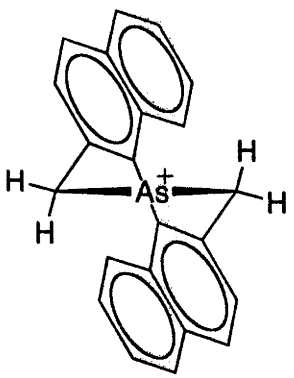


Figure 2.3: Twist-boat conformation of the seven-membered arsepine ring in (a*R*)-**40**.

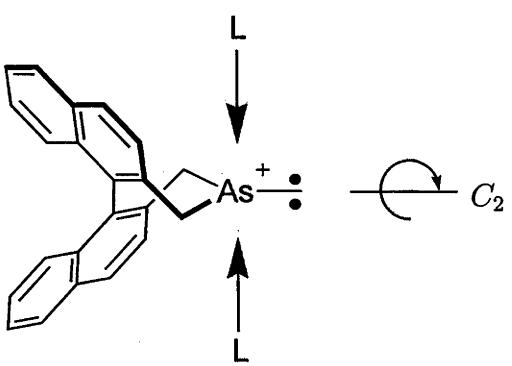


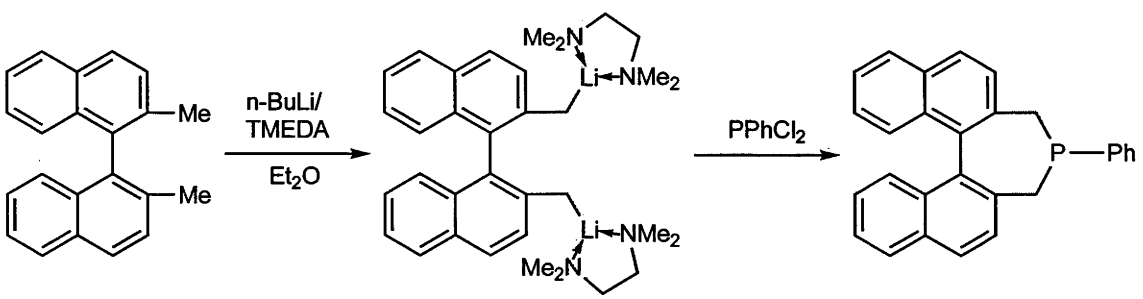
Figure 2.4: Degenerate axial approach of L to (a*R*)-**40**.

reactions of phosphine-stabilised arsenium salts. These include attack at arsenic by strong nucleophilic reagents such as *n*-butyllithium and alkali metal alkoxides.[11] The framework in (a*R*)-**40** is also attractive because of the success of the related phosphepine (a*R*)-**19** in the asymmetric synthesis of enantiomerically enriched tertiary arsines by the addition of *n*-butyllithium to appropriate phosphine-stabilised arsenium salts, as discussed in Section 1.6.2.

2.3 Phosphepine synthesis

Axially dissymmetric phosphepines possessing the 2,2'-bis(methylene)-1,1'-binaphthyl framework have been employed for a number of asymmetric syntheses, such as the asymmetric hydrogenation of methyl α-acetamidocinnamate with dihydrogen in the presence of $[Rh(COD)_2]BF_4$.[96] The substrate in this reaction was reduced quantitatively in up to 96% enantiomeric excess (ee). The synthesis of the phosphepine (±)-**41** was achieved by metallation of (±)-2,2'-dimethyl-1,1'-binaphthyl, (±)-**42**, with *n*-butyllithium/potassium *t*-butoxide/TMEDA in *n*-hexane, which gave (±)-**43**; addition of dichlorophenylphosphine to the dilithium complex (±)-**43** gave the crude phosphepine (±)-**41** (Scheme 2.3). The pure phosphepine was isolated in 30% yield by flash chromatography of the crude material.[97]

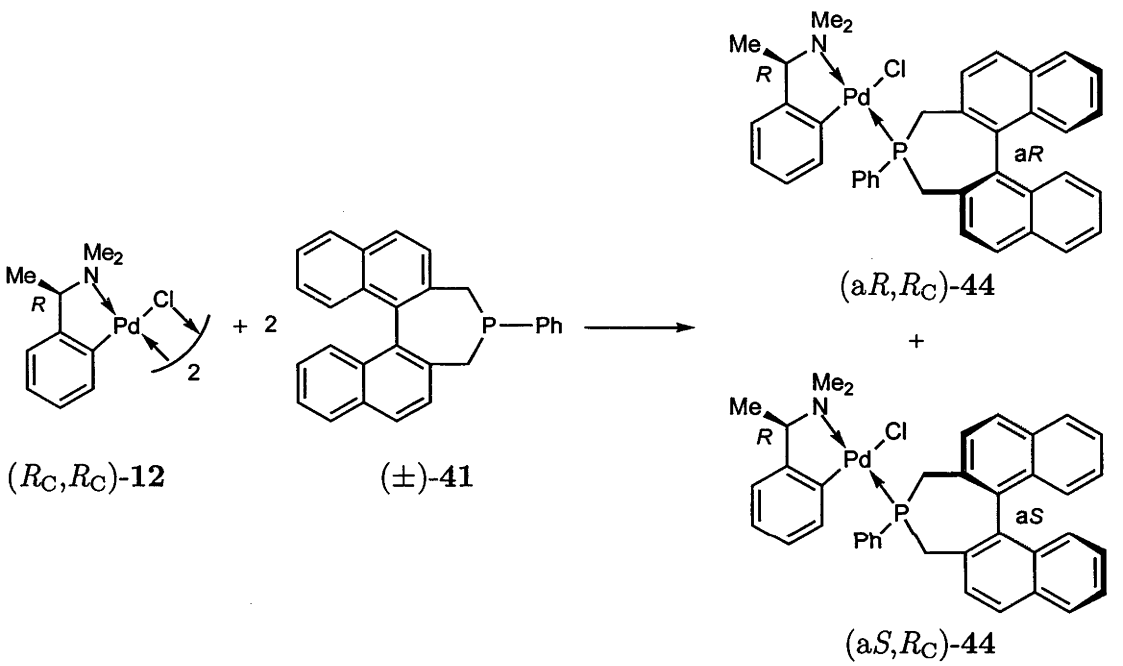
Scheme 2.3: Synthesis of (±)-**41**



(±)-**42** (±)-**43** (±)-**41**

The resolution of (±)-**41** was achieved by complexation with the enantiomerically pure palladium complex (R_C,R_C)-**12**; the diastereomer (a*S*,R_C)-**44** was the least soluble of the two formed and was isolated in 47% yield by recrystallisation of the 1/1 mixture from dichloromethane/*n*-hexane (Scheme 2.4).

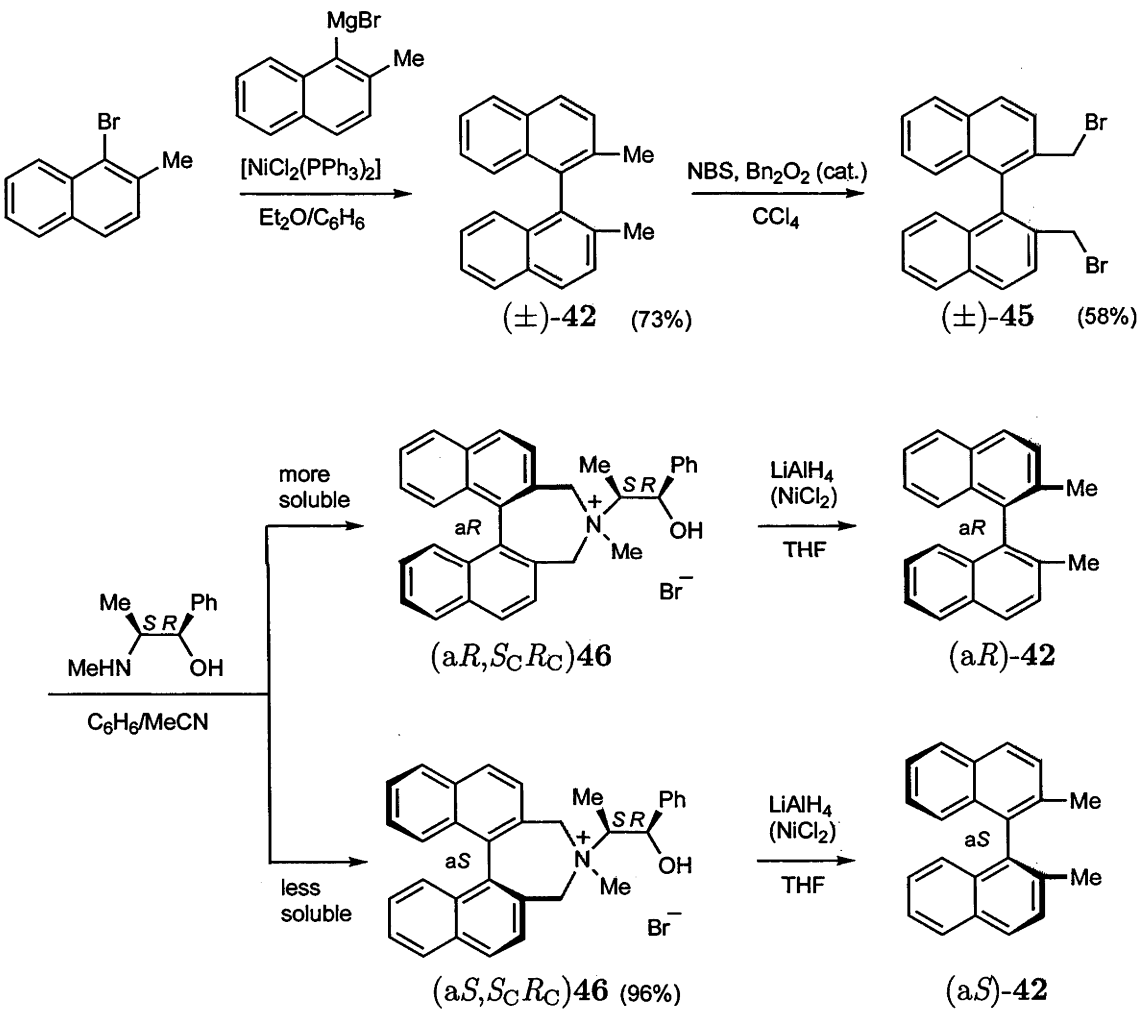
Scheme 2.4: Synthesis and resolution of (a*S*)-**41**



The preparation of the enantiomerically pure precursors (a*R*)-**42** and (a*S*)-**42** began with the coupling of 1-bromo-2-methylnaphthalene to give the racemate (±)-**42** (Scheme 2.5). The resolution of (±)-**42** was accomplished by cyclisation of the corresponding bis(bromomethyl) derivative (±)-**45** with (−)-ephedrine and fractional crystallisation of the diastereomeric azepinium bromides (±)-**46** from ethanol. Reductions of the individual diastereomers (±)-**46** with $LiAlH_4$ in the presence of anhydrous nickel(II) chloride as catalyst gave the resolved atropisomers of (±)-**42**.[98]

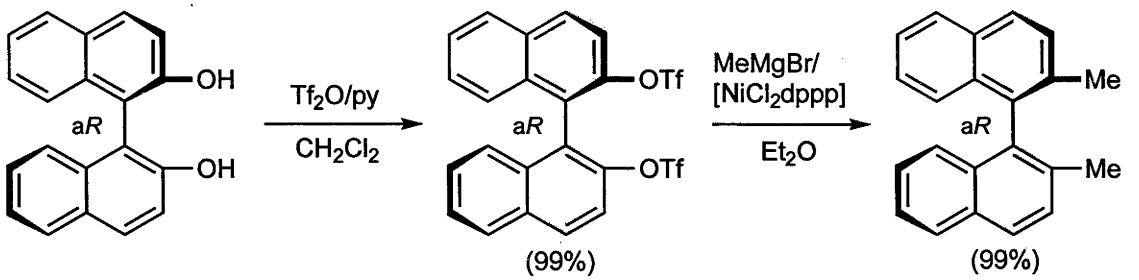
Although this method was effective for the production of (a*R*)- and (a*S*)-**42**, the large number of steps required made a simpler procedure more desirable. An alternative route to (a*R*)- and (a*S*)-**42** begins with the commercially available enantiomers

Scheme 2.5: Synthesis and resolution of (±)-**42**



of BINOL, (a*R*)- and (a*S*)-**47**.[99] The preparation of the enantiomers of (±)-**42** from the enantiomers of BINOL is readily accomplished, as shown in Scheme 2.6. Thus, the diester (a*R*)-**48**, which was prepared and isolated in 99% yield as a crystalline solid, was treated with an excess of methylmagnesium bromide in the presence of the transfer catalyst [Ni(dppp)Cl_2] to give (a*R*)-**42** in a similarly high yield.

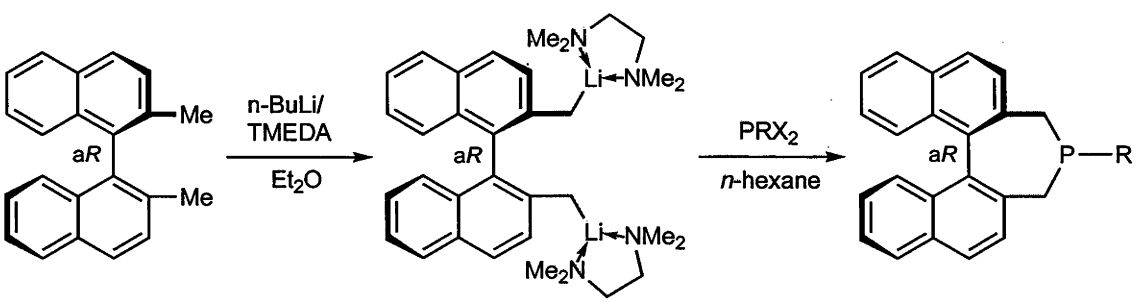
Scheme 2.6: Synthesis of (a*R*)-**42** from (a*R*)-**47**



(a*R*)-**47** (a*R*)-**48** (a*R*)-**42**

The metallation of (a*R*)-**42** with *n*-butyllithium in the presence of TMEDA in diethyl ether gives (a*R*)-**43** as dark red crystals.[13,100] Subsequent reactions of sparingly soluble (a*R*)-**43** suspended in *n*-hexane with a secondary dihalophosphine or dihaloarsine furnishes phosphepines and arsepines in modest yields (Scheme 2.7).[96,97,101]

Scheme 2.7: Synthesis of (a*R*)–**41**

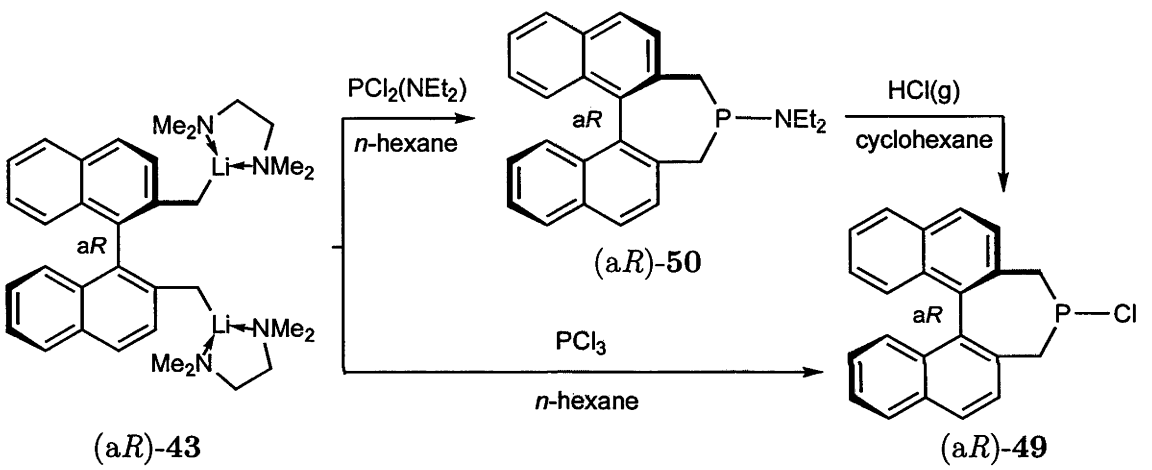


(a*R*)-**42** (a*R*)-**43** (a*R*)–**41**

Although there is no literature synthesis of (a*R*)-**39** (X = Cl, I), there are syntheses available for the corresponding chlorophosphepine (a*R*)-**49**, which is a pre-

cursor to a number of enantiomerically pure tertiary phosphepines by reactions with Grignard reagents.[96,102–105] The synthesis of (a*R*)-**49** has been achieved directly by the reaction of (a*R*)-**43** with trichlorophosphine,[102] and by treatment with (diethylamino)dichlorophosphine followed by removal of the amino group from (a*R*)-**50** with anhydrous hydrogen chloride (Scheme 2.8).[96,103–105] It was envisaged that the synthesis of (a*R*)-**39** (X = Cl, I) could be accomplished by similar routes to those used for the phosphepine analogues.

Scheme 2.8: Synthesis of (a*R*)-**49** from (a*R*)-**43**



2.4 Synthesis of (a*R*)-39 (X = I)

2.4.1 Direct addition of haloarsines to (a*R*)-43

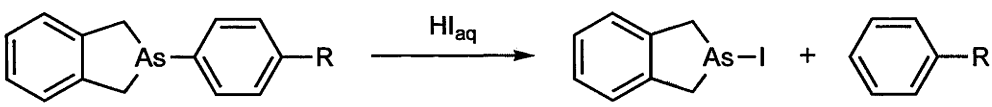
The direct additions of trichloroarsine or triiodoarsine to (a*R*)-**43** in *n*-hexane were unsuccessful. Analysis by ^{1}H NMR spectroscopy of the product in each case indicated a mixture of compounds, although mass spectrometry showed molecular ions corresponding to the desired products. The attempted preparation of (a*R*)-**39** (X = Cl) by the addition of (diethylamino)dichloroarsine to a suspension of (a*R*)-**43** in *n*-hexane, followed by treatment of the reaction mixture with anhydrous hy-

drogen chloride, also appeared promising by EI mass spectrometry and ^{1}H NMR spectroscopy, but the pure product could not be isolated from the reaction mixture.

2.4.2 Hydriodic acid

A model system for a synthesis of (a*R*)-**39** (X = I) has been demonstrated by the synthesis of 2-iodoisoarsindoline (**51**) in quantitative yield by the reaction of either 2-phenylisoarsindoline **52** (R = H) or 2-(*p*-methoxyphenyl)isoarsindoline **52** (R = OMe) with boiling hydriodic acid (57%, constant boiling azeotrope) (Scheme 2.9).[106] No further cleavage of the arsenic–carbon bonds by the hydriodic acid was observed in either reaction.

Scheme 2.9: Aryl–arsenic bond cleavage by HI

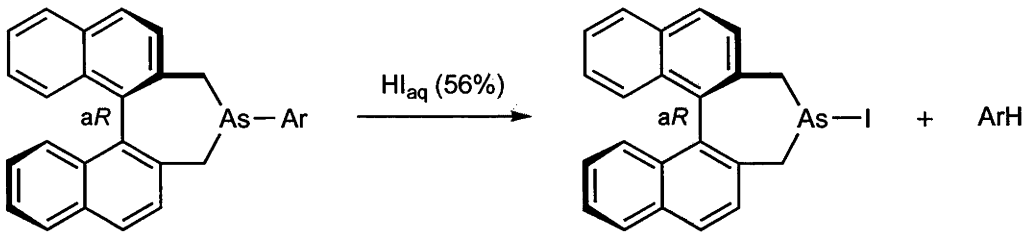


52 **51**

An examination of the reactivity of anisyl-functionalised tertiary arsines has been undertaken where tris(*p*-anisyl)arsine was heated with aqueous hydriodic acid, which resulted in complete cleavage of all three As–C bonds in the tertiary arsine with formation of triiodoarsine and 3 equiv of anisole.[107] Anhydrous hydriodic acid has also been used for the conversion of arylarsines into iodoarsines in good yields.[108,109] It was envisaged that a reaction similar to the one used for the successful synthesis of 2-iodoisoarsindoline could be used for the synthesis of the iodoarsepine (a*R*)-**39** (X = I), as indicated in Scheme 2.10.

The only known arylarsine containing the 2,2'-bis(methylene)-1,1'-binaphthyl group is the phenylarsepine (a*S*)-**53**; quaternisation of (a*S*)-**53** with methyl bromoacetate gives the arsonium salt (a*S*)-**54**, which can be deprotonated to an ylide that

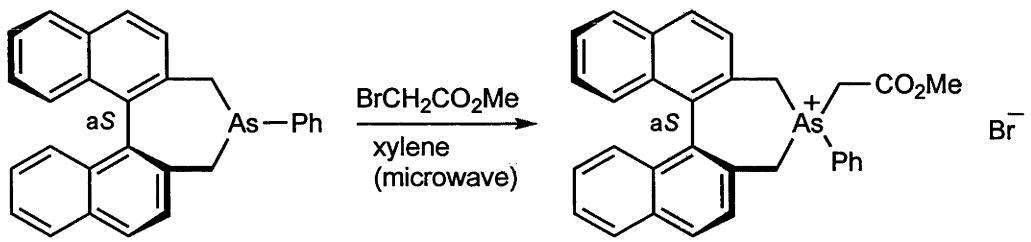
Scheme 2.10: Aryl–arsenic bond cleavage by HI



(a*R*)-**39** (X = I)

undergoes Wittig-type reactions with 4-substituted cyclohexanones to give enantiomerically enriched olefins (Scheme 2.11).[101]

Scheme 2.11: Synthesis of the arsonium bromide (a*S*)-**54** from (a*S*)-**53**



(a*S*)-**53** (a*S*)-**54**

The structure of the arsonium salt (a*S*)-**54** was confirmed by an X-ray crystal structure determination, but the details for the synthesis and characterisation of (a*S*)-**53** were not given. To examine the potential use of (a*R*)-**53** for the synthesis of (a*R*)-**39** (X = I) by treatment with aqueous hydriodic acid, (a*R*)-**53** was prepared by the reaction of (a*R*)-**43** with dichlorophenylarsine in *n*-hexane at 0 °C. Work up of the reaction mixture under Schlenk conditions and crystallisation of the crude product from toluene by the addition of methanol gave pure, crystalline (a*R*)-**53** in reasonable yield (57%). ^{1}H NMR spectroscopy of (a*R*)-**53** in $CDCl_3$ indicated a tertiary arsine of C_1 symmetry, where the C_2 symmetry of the 2,2'-bis(methylene)-1,1'-binaphthyl group was reduced to C_1 by the phenyl substituent at the pyramidally stable tertiary arsenic stereocentre. (Pyramidal inversion at arsenic generates the equivalent C_1 molecule.) The arsepine (a*R*)-**53** is highly resistant

to oxidation in the solid state, with no oxidation being observed in the ^{1}H NMR spectrum of the compound after two months exposure to the atmosphere. A single crystal X-ray diffraction analysis of (a*R*)-**53** was undertaken to confirm the absolute configuration of the molecule and to examine structural features of the arsepine ring. The arsine (a*R*)-**53** crystallises in the monoclinic space group $P2_1$ with two independent molecules in the asymmetric unit and four molecules in each unit cell (Table 2.1). An ORTEP diagram of the two independent molecules in the unit cell is shown in Figure 2.5. The molecules are arranged into alternating layers within the crystal lattice, with each layer being composed exclusively of symmetry related molecules. The two independent molecules display an edge-to-face aryl–aryl embrace at a distance of 2.512(2) Å (C(112)H(1121)$\cdots$C(214-219)); indeed, a number of these interactions are observed within the crystal lattice. The coordination geometry around the arsenic centre in both molecules is pyramidal with the angles approximating those of a tetrahedron, as listed in Table 2.2. The torsion angles of the binaphthyl groups in the two molecules are $-72.2(5)^\circ$ and $-71.4(6)^\circ$. The absolute configuration of the molecule was correlated with the known configuration of (a*R*)-**47** and refinement of the Flack parameter, which was 0.017(9).

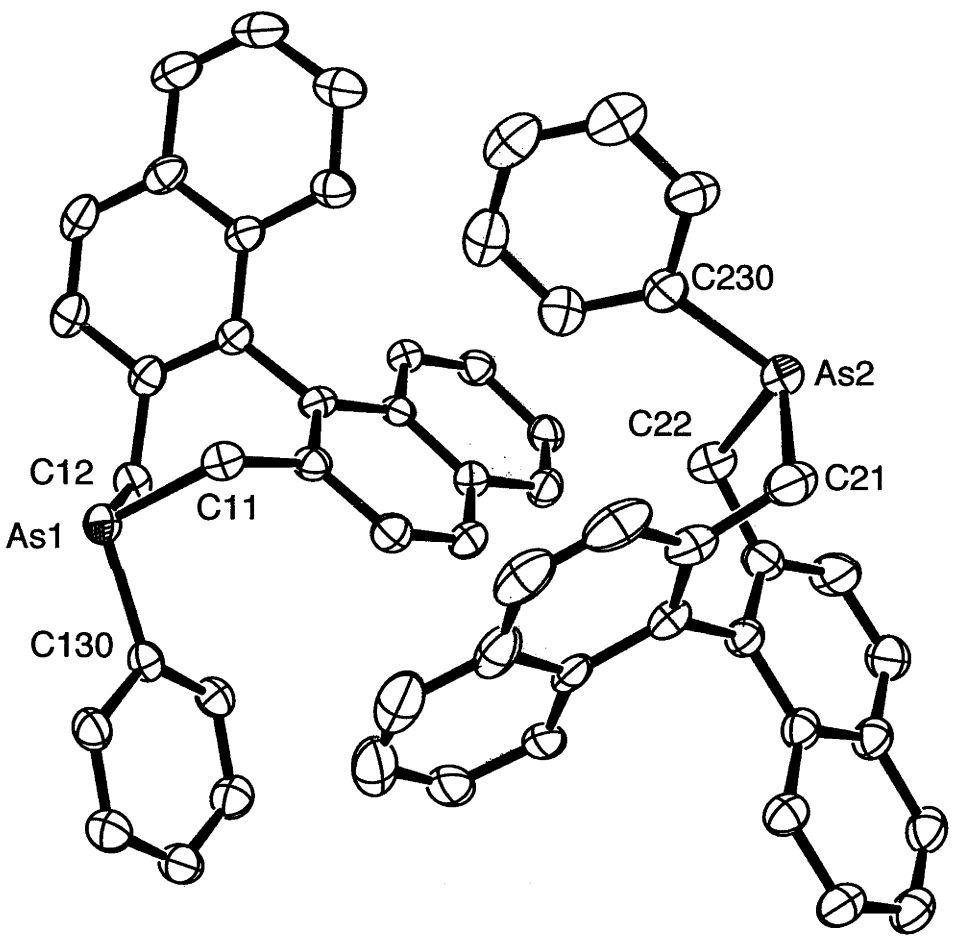


Figure 2.5: ORTEP diagram of the independent molecules of (a*R*)-**53** with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 2.1: Crystallographic data and experimental parameters for X-ray structural analysis of (a*R*)-**53**

empirical formula	$C_{28}H_{21}As$
fw, (g mol^{-1})	432.395
cryst syst	monoclinic
space group	$P2_1$
a, Å	9.5841(5)
b, Å	14.0425(6)
c, Å	15.6167(6)
V, Å^3	2101.55(16)
Z	4
D_{calcd}, (g cm^{-3})	1.367
cryst size, mm	0.26 × 0.21 × 0.03
μ, mm^{-1}	1.628
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique refins	9600
no. of refins obsd ($I > 3\sigma(I)$	4162
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0284, 0.0298
Flack parameter	0.017(9)

Table 2.2: Selected bond lengths (Å) and angles (°) in (a*R*)-**53**

As(1)–C(11)	2.011(4)	C(11)–As(1)–C(130)	101.11(17)
As(1)–C(12)	1.982(4)	C(12)–As(1)–C(130)	100.68(18)
As(2)–C(21)	1.994(6)	C(21)–As(2)–C(230)	100.3(2)
As(2)–C(22)	1.971(5)	C(22)–As(2)–C(230)	100.7(2)
As(1)–C(130)	1.964(4)	C(11)–As(1)–C(12)	96.71(18)
As(2)–C(230)	1.968(5)	C(21)–As(2)–C(22)	95.1(2)
		C(119)–C(110)–C(120)–C(129)	−72.2(5)
		C(219)–C(210)–C(220)–C(229)	−71.4(6)

The attempted synthesis of the iodoarsine (a*R*)-**39** (X = I) was undertaken by the addition of an excess of freshly distilled aqueous hydriodic acid (57%, constant boiling azeotrope) to solid (a*R*)-**53** under nitrogen. The suspension was heated under reflux; an orange colouration typical of iodoarsines appeared within 5 min.

After 2 h, dichloromethane was added to the cooled suspension to extract the sticky orange product. Analysis by ^{1}H NMR spectroscopy of the extract indicated the presence of (a*R*)-**39** (X = I) and 2,2'-dimethyl-1,1'-binaphthyl (a*R*)-**42** (Figure 2.6).

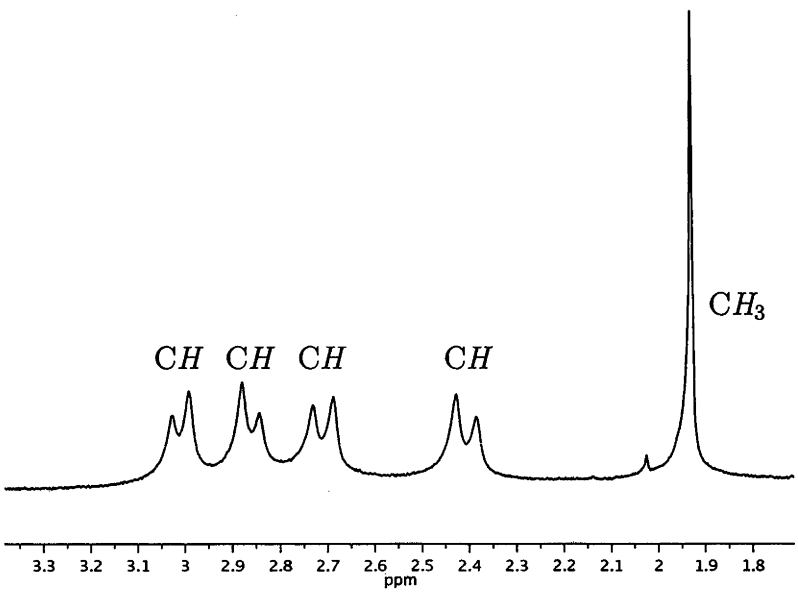


Figure 2.6: ^{1}H NMR spectrum of (a*R*)-**39** (X = I) and (a*R*)-**42** arising from reaction of (a*R*)-**53** with boiling hydriodic acid.

The experiment was repeated, this time by maintaining the heating with hydriodic acid for 24 h; under these conditions, complete cleavage of all three arsenic–carbon bonds in (a*R*)-**53** occurred to give triiodoarsine and (a*R*)-**42**. Many adjustments were made to the reaction conditions in attempts to cleave only the arsenic–phenyl group in (a*R*)-**53**. At best, a ratio of 14/1 of (a*R*)-**39** (X = I) to (a*R*)-**42** was obtained by heating (a*R*)-**53** with a small excess of hydriodic acid over 3 h at reflux. Recrystallisation of the 14/1 mixture from diethyl ether brought about the removal of the (a*R*)-**42** impurity, but the remaining by-product, triiodoarsine, could not be separated from the desired product. The reaction of (a*R*)-**53** was also attempted with freshly distilled hydrochloric acid (20%, constant boiling azeotrope) and hydrobromic acid (48%, constant boiling azeotrope). No reaction was observed

when (a*R*)-**53** was heated under reflux in hydrochloric acid for 24 h; a similar reaction with hydrobromic acid generated a mixture of products. The treatment of a dichloromethane solution of (a*R*)-**53** with anhydrous hydrogen chloride or hydrogen bromide for 1 h brought about no bond cleavage.

2.4.3 Disproportionation reactions

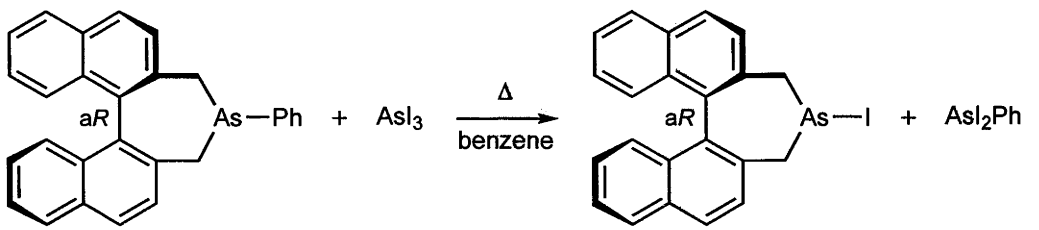
Disproportionation reactions are common in antimony(III) and bismuth(III) organometallic chemistry, an example being the synthesis of chlorodiphenylstibine at room temperature by the solvent free reaction of 1 equiv of trichlorostibine with 2 equiv of triphenylstibine.[111] The mixing of the two components in an inert atmosphere leads to localised formation of a melt phase. This phase extends throughout the solid mixture, ultimately giving a free flowing liquid that solidifies on standing as pure $SbClPh_2$, which can be recrystallised from dichloromethane or used without further purification (Eq 2.1). Changing the stoichiometry of the reactants to 2 equiv trichlorostibine and 1 equiv triphenylstibine furnished dichlorophenylstibine, also in high yield. A similar reaction between trichlorobismuthine and triphenylbismuthine in diethyl ether affords chlorodiphenylbismuthine.[112] The reactions of trialkyl or triarylbismuthines with trihalobismuthines in varied stoichiometries provide a means of synthesising mixed halo(organyl)bismuthines.[111–113]

$$SbCl_3 + 2\,SbPh_3 \longrightarrow 3\,SbClPh_2 \qquad (2.1)$$

Such disproportion reactions are less common for arsenic(III), where they are usually undertaken at high temperatures, often producing mixtures of mono and dihalogenated arsines.[114,115] Thus, the disproportionation of (a*R*)-**53** and triiodoarsine was attempted for a 1/1 mixture in boiling benzene (Scheme 2.12). Aliquots were removed from the reaction mixture after 2, 8, and 52 h and the solvent was removed in vacuo. Analyses of the solutions by ^{1}H NMR spectroscopy in C_6D_6

indicated the growth of new, broad methylene and aromatic signals corresponding to (a*R*)-**39** (X = I) with a corresponding decrease in the much sharper methylene signals of (a*R*)-**53** (Figure 2.7).

Scheme 2.12: Formation of (a*R*)-**39** (X = I) from (a*R*)-**53** and triiodoarsine



(a*R*)-**53** (a*R*)-**39**

Since the reaction in boiling benzene was not complete after 52 h, the benzene was removed from the reaction mixture and toluene was added to the residue and the resulting solution was brought to reflux: an aliquot was concentrated to dryness and the ^{1}H NMR spectrum of the solution (C_6D_6) indicated complete conversion of (a*R*)-**53** into the desired (a*R*)-**39** (X = I) within 24 h. The reaction rate was further increased in boiling xylenes; complete conversion of (a*R*)-**53** into (a*R*)-**39** (X = I) being observed after 2 h at reflux, but the reaction was accompanied by thermal decomposition of the product. The reaction of (a*R*)-**53** with triiodoarsine in boiling toluene over 24 h is quantitative, as determined by ^{1}H NMR spectroscopy. Removal of the toluene from the reaction mixture left a dark orange oil, that, when dissolved in dichloromethane and the solution allowed to evaporate under a stream of dry nitrogen, afforded copious crystals of (a*R*)-**39** (X = I) that were coated with diiodophenylarsine. The latter was removed from the product by covering the crude product with *n*-hexane and triturating and sonicating the mixture to assist in the dissolution of the diiodophenylarsine. The crude (a*R*)-**39** (X = I) was recrystallised from dichloromethane by the addition of methanol, providing yellow crystals of pure compound in 75% yield.

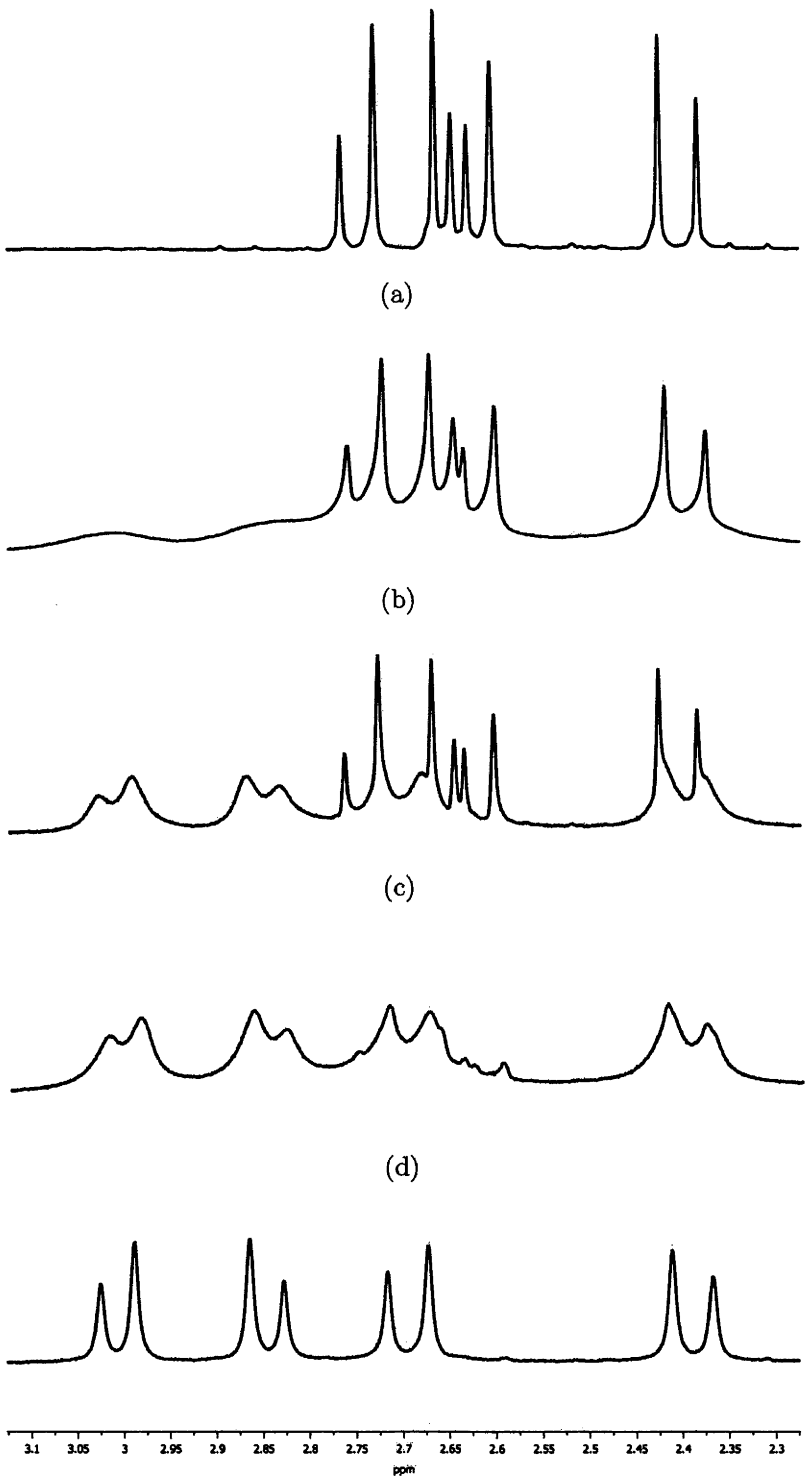


Figure 2.7: Methylene region of ^{1}H NMR spectra in C_6D_6 at 25 °C for synthesis of (a*R*)-**39** (X = I) from (a*R*)-**53** and triiodoarsine in boiling benzene: (a) (a*R*)-**53**; (b) after 2 h; (c) after 8 h; (d) after 52 h reflux, reaction incomplete; (e) (a*R*)-**39** (X = I), after an additional 24 h in boiling toluene.

The iodoarsepine (a*R*)-**39** (X = I) crystallises in the hexagonal space group $P6_5$ with six molecules in the unit cell (Table 2.3). An ORTEP diagram of the compound is shown in Figure 2.8. Analysis of the crystal structure solution revealed a solvent accessible void of 184 Å^3. Further analysis of the structure with Squeeze in PLATON indicated electron density corresponding to 22 electrons, ca. 3.7 electrons per (a*R*)-**39** (X = I). The coordination geometry around arsenic is pyramidal, although the interatomic angles indicate a significant deviation from those observed in (a*R*)-**53** (Table 2.4). The C(19)–C(10)–C(20)–C(29) dihedral angle in (a*R*)-**39** (X = I) is 118.5(5)°, which is smaller than the corresponding angle in (a*R*)-**53**. The absolute configuration of the 1,1'-binaphthyl framework was assigned on the basis of the known configuration of the starting material (a*R*)-**47** and was confirmed by refinement of the Flack parameter, which was 0.008(12).

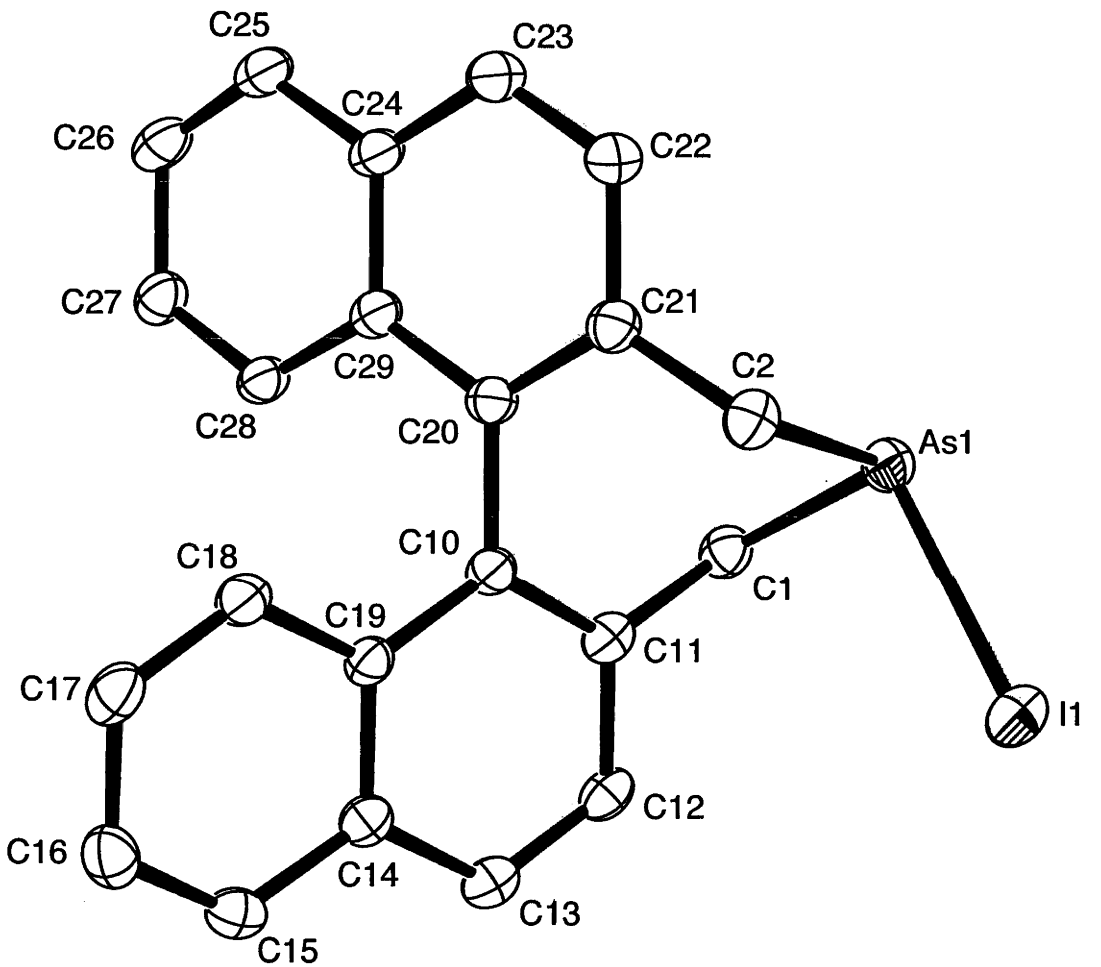


Figure 2.8: ORTEP diagram of (a*R*)-**39** (X = I) with atom labelling (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 2.3: Crystallographic data and experimental parameters for X-ray structural analysis of (a*R*)-**39** (X = I)

empirical formula	$C_{22}H_{16}AsI$
fw, (g mol^{-1})	482.20
cryst syst	hexagonal
space group	$P6_5$
a, Å	16.8728(5)
c, Å	11.2567(2)
V, Å^3	2775.34(13)
Z	6
D_{calcd}, (g cm^{-3})	1.731
cryst size, mm	0.23 × 0.07 × 0.05
μ, mm^{-1}	3.505
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique reflns	4121
no. of reflns obsd ($I > 3\sigma(I)$	2929
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0285, 0.0301
Flack parameter	0.008(12)

Table 2.4: Selected bond lengths (Å) and angles (°) in (a*R*)-**39** (X = I)

As(1)–I(1)	2.5751(5)	I(1)–As(1)–C(1)	99.38(12)
As(1)–C(1)	1.983(4)	I(1)–As(1)–C(2)	96.51(13)
As(1)–C(2)	1.992(4)	C(1)–As(1)–C(2)	94.82(16)
		C(19)–C(10)–C(20)–C(29)	118.5(5)

The success in synthesising (a*R*)-**39** (X = I) by disproportionation of triiodoarsine and (a*R*)-**53** encouraged us to examine disproportionation reactions between (a*R*)-**53** and trichlorophosphine, trichloroarsine, and trichlorostibine. Thus, equimolar amounts of the two reactants in each case were dissolved in toluene and the solutions were heated under reflux for 24 h. Analyses of the reaction mixtures by ^{1}H NMR spectroscopy indicated no reactions between the components under these conditions.

2.5 Preparation of (a*R*)-39 (X = Cl)

Another method for the preparation of a particular haloarsine involves the exchange of one halogen for another with use of a silver halide.[92,116] Thus, (a*R*)-**39** (X = I) was dissolved in dichloromethane and 5 equiv of silver chloride were added. The suspension was stirred overnight in the absence of light; a colourless solution resulted, which was accompanied by the precipitation of yellow silver iodide. Filtration of the reaction mixture to remove the silver halides, followed by evaporation of the solvent and recrystallisation of the residue from a small quantity of boiling ethyl acetate, gave (a*R*)-**39** (X = Cl) as colourless needles (76% yield).

The chloroarsepine (a*R*)-**39** (X = Cl) crystallises in the hexagonal space group $P6_5$ with six molecules in the unit cell, and is isomorphous with (a*R*)-**39** (X = I) (Table 2.5). An ORTEP diagram of the compound is shown in Figure 2.9. Selected bond distances and angles in the molecule are listed in Table 2.6.

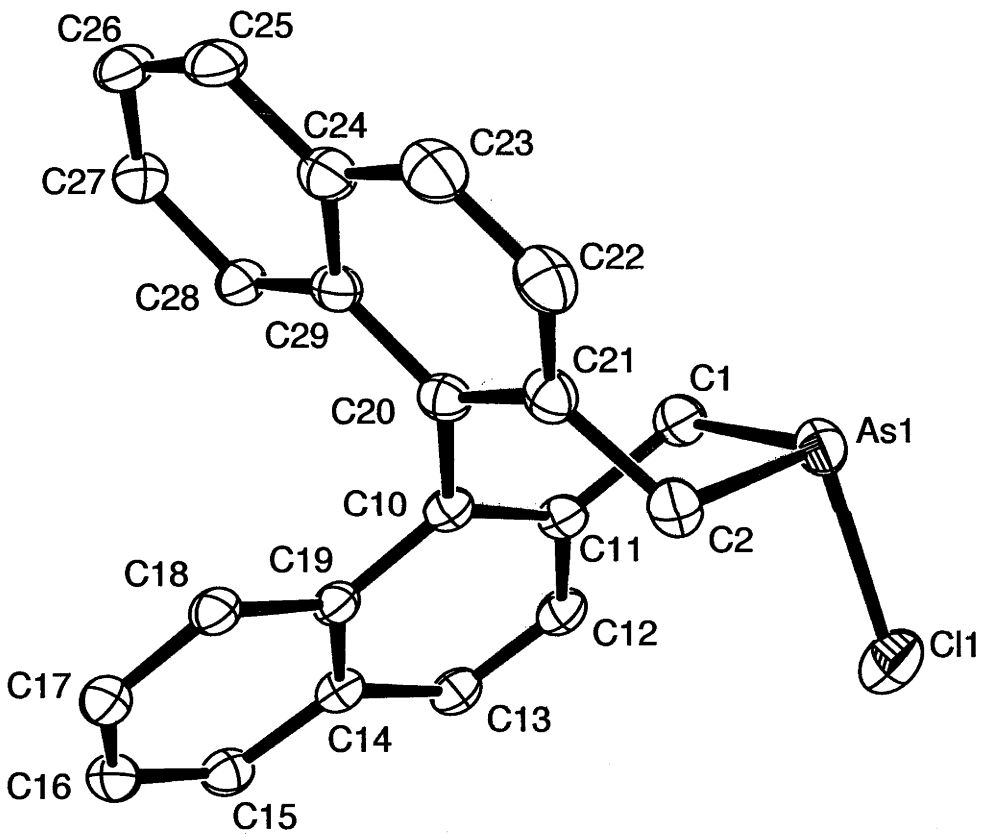


Figure 2.9: ORTEP diagram of (a*R*)-**39** (X = Cl) with atom labelling (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 2.5: Crystallographic data and experimental parameters for X-ray structural analysis of (a*R*)-**39** (X = Cl)

empirical formula	$C_{22}H_{16}AsCl$
fw, (g mol^{-1})	390.74
cryst syst	hexagonal
space group	$P6_5$
a, Å	16.7760(4)
c, Å	11.0926(2)
V, Å^3	2703.59(10)
Z	6
D_{calcd}, (g cm^{-3})	1.440
cryst size, mm	0.18 × 0.08 × 0.08
μ, mm^{-1}	2.033
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique reflns	4113
no. of reflns obsd ($I > 3\sigma(I)$)	2972
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0382, 0.0423
Flack parameter	0.007(12)

Table 2.6: Selected bond lengths (Å) and angles (°) in (a*R*)-**39** (X = Cl)

As(1)–Cl(1)	2.5126(13)	Cl(1)–As(1)–C(1)	98.34(12)
As(1)–C(1)	1.981(4)	Cl(1)–As(1)–C(2)	95.91(13)
As(1)–C(2)	1.992(4)	C(1)–As(1)–C(2)	95.17(14)
		C(19)–C(10)–C(20)–C(29)	−63.2(4)

Chapter 3

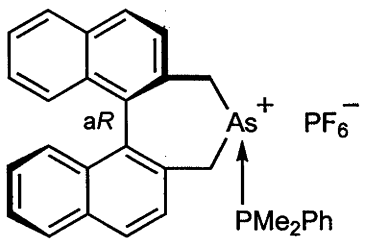
Arsenium Complexes of Tertiary Phosphines

3.1 Phosphine-stabilised arsepinenium salts

Phosphine-stabilised arsenium salts were synthesised from the iodoarsepine (a*R*)-**39** (X = I) and achiral phosphines by the two-phase method. An examination of model complexes was undertaken to provide details about the structure and bonding of the previously uncharacterised arsepinenium group (a*R*)-**40** and its interactions with tertiary phosphines.

Dimethylphenylphosphine was chosen as the model ligand for the arsepinenium system because the methyl groups of the phosphine become diastereotopic in a chiral environment. Thus, dimethylphenylphosphine was added to a dichloromethane solution of (a*R*)-**39** (X = I); the addition of the phosphine resulted in decolouration of the initial yellow solution of the iodoarsepine. An aqueous solution of potassium hexafluorophosphate was then added and the mixture was stirred vigorously for 30 min. The almost colourless organic phase was separated, dried with anhydrous magnesium sulfate, filtered, and the filtrate evaporated to dryness. The colourless solid that remained was crystallised from dichloromethane by the addition of diethyl ether.

Colourless needles of (a*R*)-(dimethylphenylphosphine-*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] hexafluorophosphate 1-dichloromethane, (a*R*)-**55**·CH_2Cl_2, were thus obtained in 92% yield.



(a*R*)-**55**

Recrystallisation of this material from 2-butanone/diethyl ether provided needles of (a*R*)-**55**·C_4H_8O suitable for X-ray crystallography. The solvate crystallised in the orthorhombic space group $P2_12_12_1$ with four formula units within the cell (Table 3.1). The cation of (a*R*)-**55**·C_4H_8O is shown in Figure 3.1. The 2-butanone molecule of crystallisation is disordered, with high thermal parameters being observed for the refined atoms. Attempts to model the disorder did not provide a satisfactory model. The absolute configuration of the (a*R*)-2,2'-bis(methylene)-1,1'-binaphthylarsepinenium group was assigned on the basis of the knowledge of the absolute configuration of the starting material (a*R*)-**47** and was confirmed by refinement of the Flack parameter (0.032(11)).

Principle bond lengths and angles for the cation are given in Table 3.2. The As(1)–P(1) distance of 2.3382(9) Å is longer than the sum of the covalent radii of the two elements (2.22 Å[14]) and is similar in length to the arsenic–phosphorus distance in [(Ph_3P)AsMePh]PF_6 (2.3480 Å).[11] The coordination geometry around the arsenic centre is best described as a distorted trigonal pyramid in which the six-electron AsC_2 group of atoms and the lone pair of electrons occupy the base and the phosphorus atom the apex. This is evident from the angles P(1)–As(1)–C(1), 102.08(11)°, and P(1)–As(1)–C(2), 99.46(10)°, which align the phosphine orthogonal

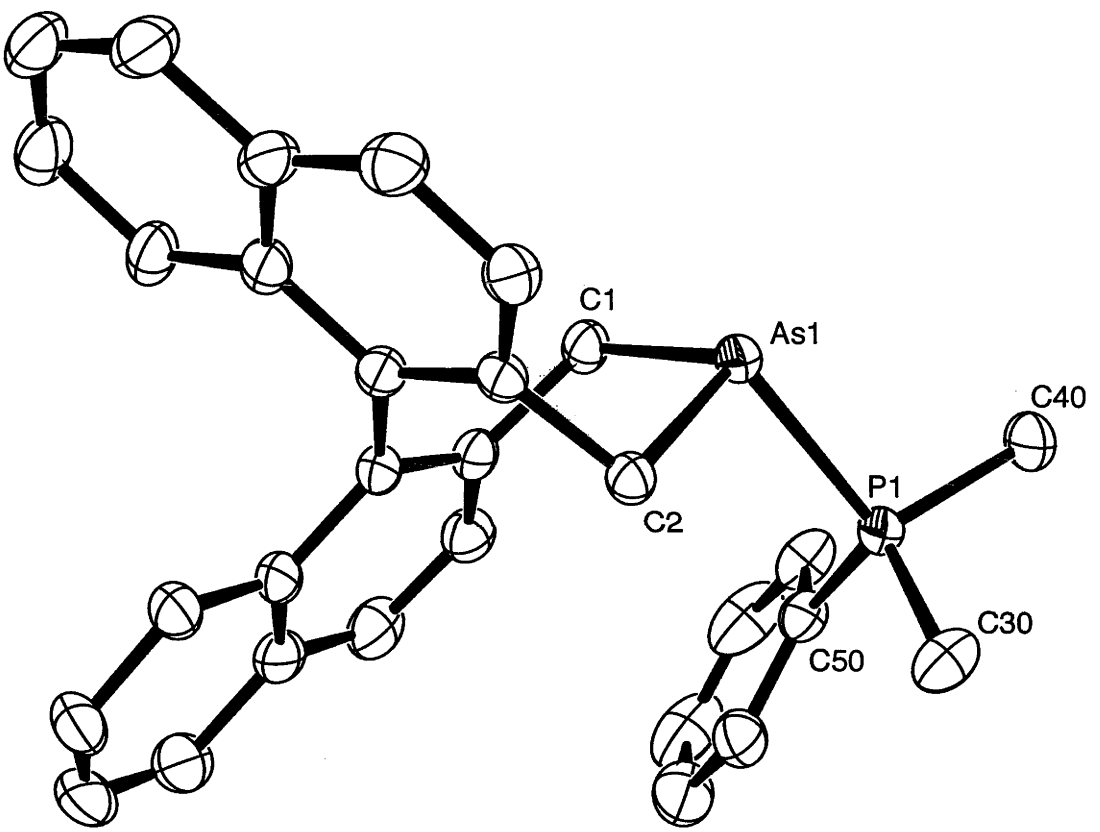


Figure 3.1: ORTEP diagram of the cation of (a*R*)-**55**·C_4H_8O with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 3.1: Crystallographic data and experimental parameters for X-ray structural analysis of (a*R*)-**55**·C_4H_8O

empirical formula	$C_{34}H_{35}AsF_6OP_2$
fw, (g mol^{-1})	710.51
cryst syst	orthorhombic
space group	$P2_12_12_1$
a, Å	8.2770(1)
b, Å	13.4613(2)
c, Å	29.0898(4)
V, $Å^3$	3241.16(8)
Z	4
D_{calcd}, (g cm^{-3})	1.456
cryst size, mm	0.35 × 0.19 × 0.09
μ, mm^{-1}	1.209
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique reflns	7730
no. of reflns obsd ($I > 3\sigma(I)$	4937
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0287, 0.0367
Flack parameter	0.032(11)

Table 3.2: Selected bond lengths (Å) and angles (°) in (a*R*)-**55**·C_4H_8O

As(1)–P(1)	2.3382(9)	P(1)–As(1)–C(1)	102.08(11)
As(1)–C(1)	2.000(3)	P(1)–As(1)–C(2)	99.46(10)
As(1)–C(2)	1.987(3)	C(1)–As(1)–C(2)	97.38(13)
P(1)–C(30)	1.800(4)	As(1)–P(1)–C(30)	109.98(13)
P(1)–C(40)	1.803(4)	As(1)–P(1)–C(40)	105.12(14)
P(1)–C(50)	1.792(4)	As(1)–P(1)–C(50)	116.06(11)
		C(10)–C(19)–C(20)–C(29)	−70.0(4)

to the AsC_2 plane of the arsenium ion. These angles are notably larger than those of previously characterised [(Ph_3P)AsMePh]PF_6, where the equivalent angles are 92.31(8)° and 97.04(6)°.[11] The increase in these angles may be caused by the steric influence of the (a*R*)-2,2'-bis(methylene)-1,1'-binaphthyl group on phosphine coordi-

nation. An additional point of interest in the structure is the C(1)–As(1)–C(2) angle of 97.38(13)°, which is smaller than the corresponding angles in $[(Ph_3P)AsMePh]PF_6$ and $[(Ph_3P)AsPh_2]PF_6$, (101.73(7)° and 105.11(9)°, respectively).[11,17] The seven-membered twist–boat arsepine ring apparently constrains this angle because it is close to the corresponding angles in the tertiary arsine (a*R*)-**53**, where the angles 96.71(18) and 95.1(2)° are observed for the two molecules in the unit cell. It was previously observed for the $MePhAs^+$ cation that the substituent groups and the lone pair of electrons appear to be coplanar, with the methyl group deviating by 0.192 Å from the plane of the phenyl group. It is considered that this coplanarity stabilises the arsenium ion through conjugation of the donated electrons with the phenyl ring, thus delocalising the positive charge on arsenic. Coplanarity of the phenyl groups and the arsenic atom was not observed in $[(Ph_3P)AsPh_2]PF_6$; in this complex, the phenyl rings show significant dihedral displacement.[17] The planarity of the arsenium cation in (a*R*)-**55**·C_4H_8O was analysed within CRYSTALS by defining a plane comprised of As(1), C(1) and C(2) and calculating the angle between the normal of this plane to the line between As(1) and P(1): the deviation is 16.53°. Other features of interest within the crystal structure of (a*R*)-**55**·C_4H_8O are the interaction between As(1) of the cation and F(5) of the hexafluorophosphate ion at 3.347(3) Å and the embrace between C(12)–H(121) of a naphthalenyl group and the phenyl ring of the dimethylphenylphosphine group at 2.7228(3) Å. This embrace appears to be the major influence on the preferred rotamer of the coordinated phosphine (Figure 3.2).

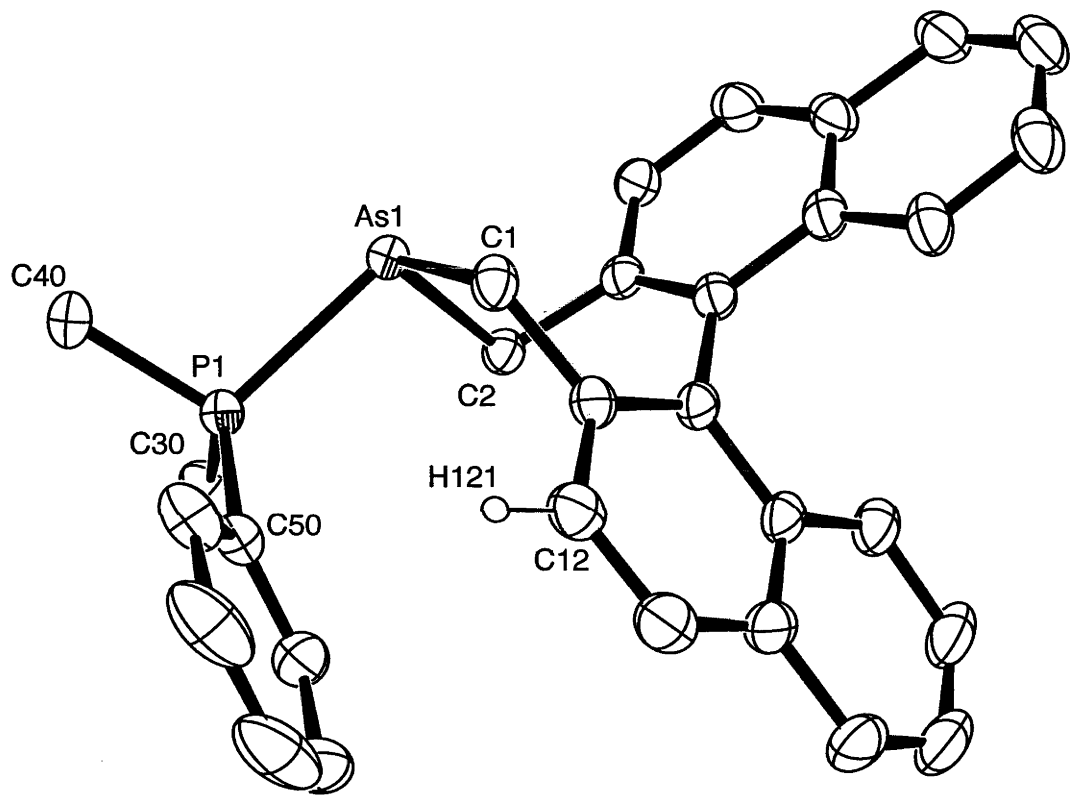


Figure 3.2: ORTEP diagram of the cation of (a*R*)-**55**·C_4H_8O with selected atoms labelled (30% ellipsoid probability shown). The selected hydrogen atom indicates the direction of the intramolecular aryl–aryl embrace.

The ^{1}H NMR spectrum of (a*R*)-**55**·CH_2Cl_2 in CD_2Cl_2 at 25 °C shows diastereotopicity of the P*Me* groups due to the influence of the chiral arsenium ion (Figure 3.3(a)). Although diastereotopicity of the P*Me* doublets ($^{2}J(^{1}H^{31}P)$ = 11.10 Hz) is observed at 25 °C, exchange of the phosphine is still fast at this temperature because the resonances for the methylene protons in the arsepine ring appear as an averaged AB quartet, which is indicative of a C_2 system; at the slow exchange limit for phosphine coordination, AB and A'B' spin systems with additional coupling to the ^{31}P nuclei are expected for the two sets of methylene protons. The coalescence temperature for the methylene protons and P*Me* resonances will not necessarily be the same because of variations in the magnitude of their chemical shift differences and in the unequal population of the rotameric sites of the phosphine substituents. Dissociative exchange of the phosphine in this complex is consistent with the results of crossover experiments with a pair of closely related complexes (Section 1.3).[11] Variable temperature ^{1}H NMR spectra of (a*R*)-**55**·CH_2Cl_2 in CD_2Cl_2 were recorded between 25 and −90 °C to investigate the symmetry of the complex at the slow exchange limit for phosphine coordination. Cooling of the solution of the complex to −30 °C resulted in broadening of the arsepine methylene resonances and an increase in the separation of the pair of P*Me* doublets (Figure 3.3(b)). Further cooling of the solution resulted in the appearance of a complex multiplet between −50 and −60 °C (Figure 3.3(c)), with baseline separation of the P*Me* resonances and resolution of a greater number of the multiplet peaks at −90 °C (Figure 3.3(d)). The $^{1}H\{^{31}P\}$ spectra at −90 °C, revealed distinct AB and A'B' spin systems (Figure 3.3(e)).

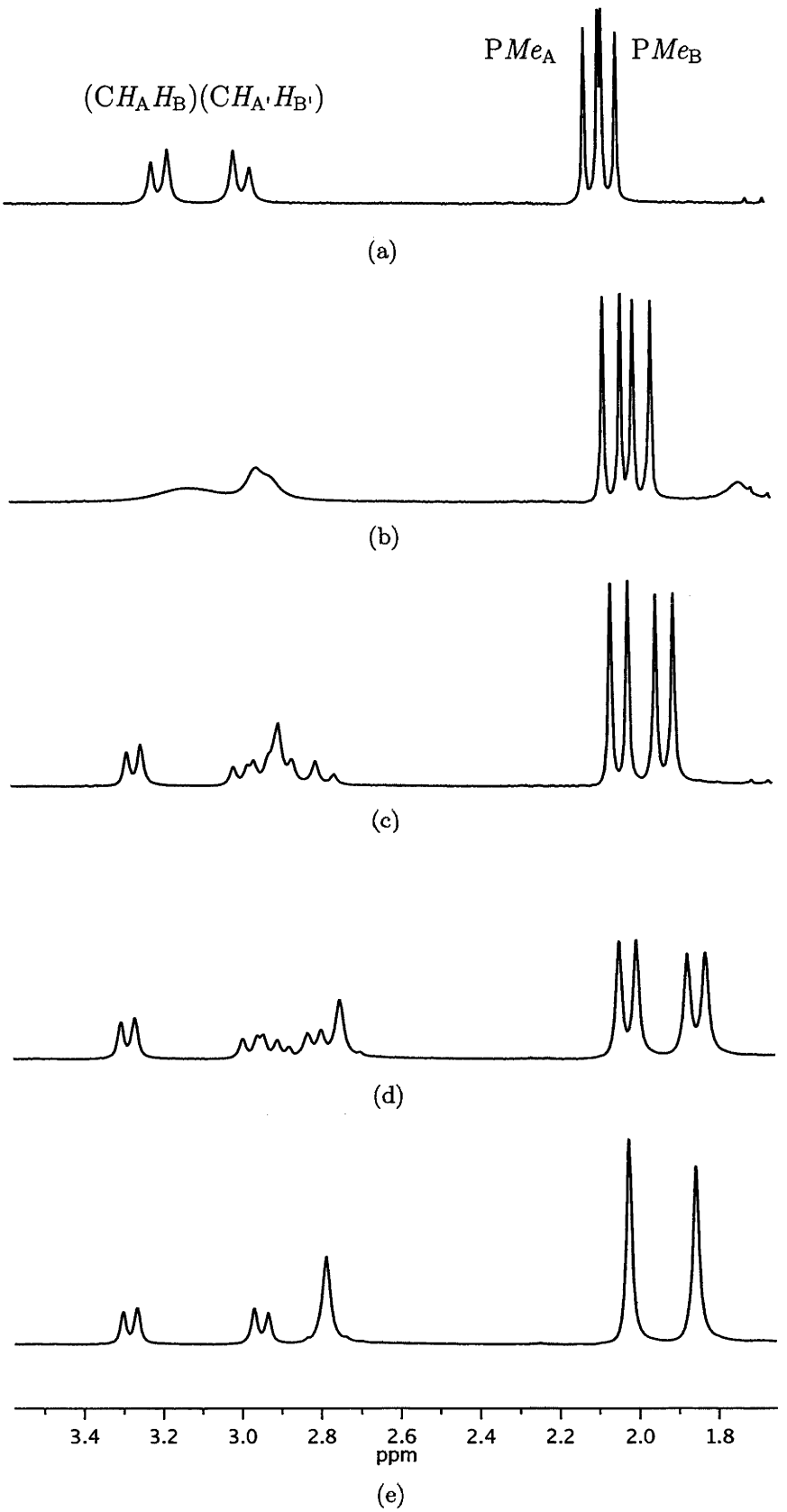
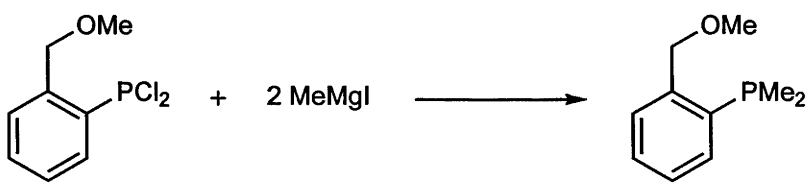


Figure 3.3: Aliphatic regions of the ^{1}H NMR spectra of (a*R*)-**58**·CH_2Cl_2 in CD_2Cl_2 at 25 °C (a), −30 °C (b), −60 °C (c), −90 °C (d), and the $^{1}H\{^{31}P\}$ NMR spectrum at −90 °C (e).

Previous work in our group concerned with the asymmetric synthesis of tertiary arsines by the additions of organolithium reagents to phosphine-stabilised arsenium salts identified the [2-(methoxymethyl)phenyl] group on phosphorus as an important element in the orientation and diastereofacial selection of the prochiral methylphenylarsenium ion (Section 1.6.2). It was therefore appropriate to examine the interaction of a [2-(methoxymethyl)phenyl]-substituted phosphine with the chiral arsepinenium ion. [2-(Methoxymethyl)phenyl]dimethylphosphine was chosen as the ligand to examine this interaction because the coordinated phosphine will show diastereotopic P*Me* resonances in the ^{1}H NMR spectrum below the fast exchange limit for phosphine coordination. [2-(Methoxymethyl)phenyl]dimethylphosphine (**56**) was prepared by the reaction of 2 equiv of methylmagnesium iodide with dichloro[2-(methoxymethyl)phenyl]phosphine, (**57**); the product was isolated in 70% yield by distillation as a colourless oil, bp 78 °C (0.7 mmHg) (Scheme 3.1).

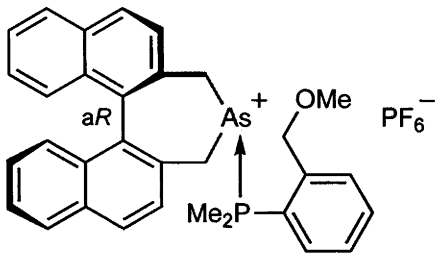
Scheme 3.1: Synthesis of **56**



57 **56**

The coordination of the phosphine **56** to the arsepinenium ion was achieved under conditions similar to those employed for the synthesis of (a*R*)-**55**·CH_2Cl_2; recrystallisation of the crude product from dichloromethane by the addition of diethyl ether furnished the pure product as off-white prisms suitable for X-ray crystallography.

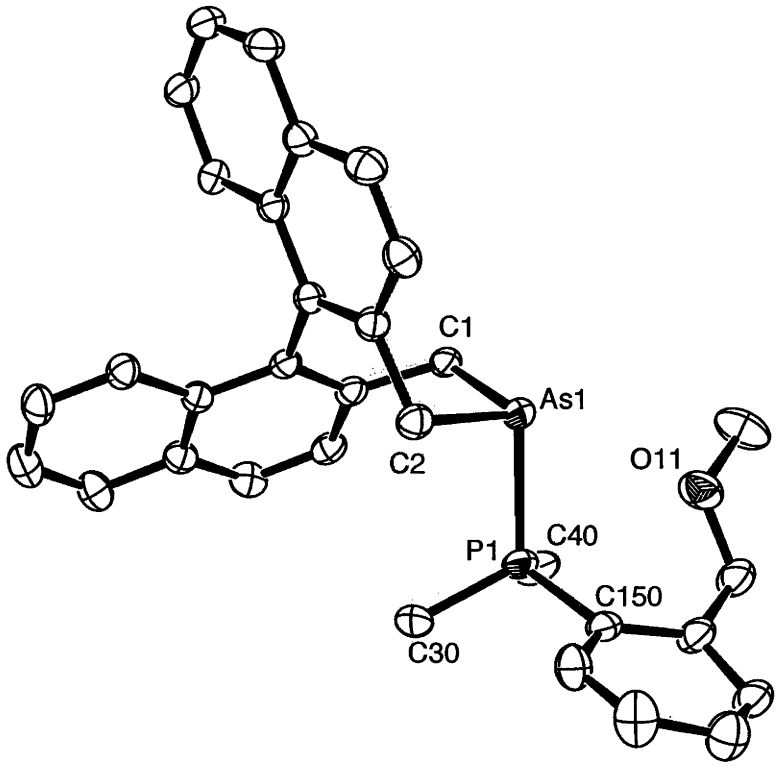
The phosphine-stabilised arsenium salt (a*R*)-**58** crystallises in the monoclinic space group *C*2 with four formula units within the unit cell (Table 3.3). The asymmetric unit contains one $C_{32}H_{31}AsOP$ cation and one PF_6^- ion. The fluorine atoms of the hexafluorophosphate ion are disordered and were modelled as



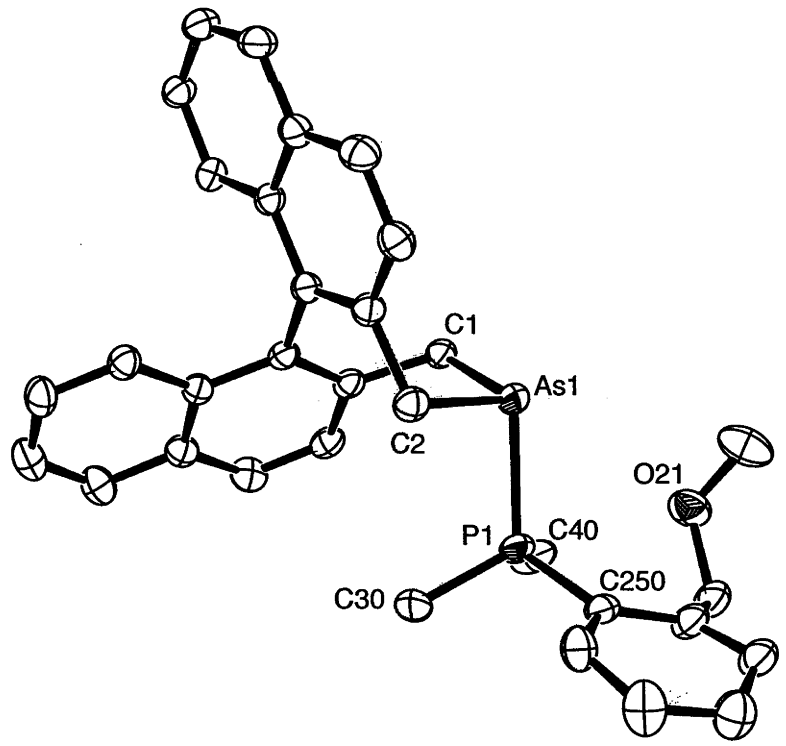
(a*R*)-**58**

two sets of six fluorine atoms by refinement of their relative occupancies. The [2-(methoxymethyl)phenyl] group was also disordered and was modelled as two components having occupancies of 64.2% and 35.8%. The ORTEP diagram of the major conformer of the molecule is shown in Figure 3.4(a) and the minor conformer is shown in Figure 3.4(b). The two conformers are related by rotation about the phosphorus–carbon bond of the [2-(methoxymethyl)phenyl]phosphine group. Relevant bond lengths and angles in the cations are given in Table 3.4.

The two conformers of the cation of (a*R*)-**58** exhibit distinct oxygen–arsenic and oxygen–phosphorus interactions. The major conformer shows interactions of the oxygen with the arsenic atom, where As(1)···O(11) is 3.111(4) Å, and with the phosphorus atom, where P(1)···O(11) is 2.944(4) Å. In the minor component, the oxygen is further away from the P–As bond, viz. As(1)···O(21) 3.721(8) Å, P(1)···O(21) 3.039(8). It is interesting to note that the oxygen atom in both conformers is closer to the phosphorus atom than the arsenic atom, which suggests a greater positive charge on the phosphorus or steric hinderance between the methoxymethyl group and the arsenic. The source of the disorder is unclear, but a phenyl–phenyl embrace can be seen between the [2-(methoxymethyl)phenyl] groups of symmetry related molecules within the crystal lattice. Previously characterised phosphine-stabilised arsenium salts containing the [2-(methoxymethyl)phenyl] group have indicated a weakening of the arsenic–phosphorus bond by a destabilising chelate effect, but this was not observed in the present structure where the As(1)–P(1) distance of 2.3358(8) Å compares very



(a)



(b)

Figure 3.4: ORTEP diagram of the major (a) and the minor (b) conformers of the cation of (a*R*)-**58** with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 3.3: Crystallographic data and experimental parameters for X-ray structural analysis of (a*R*)-**58**

empirical formula	$C_{32}H_{31}AsF_6OP_2$
fw, (g mol^{-1})	682.46
cryst syst	monoclinic
space group	*C*2
a, Å	20.4881(3)
b, Å	7.9518(1)
c, Å	19.5861(3)
V, Å^3	2992.92(7)
Z	4
D_{calcd}, (g cm^{-3})	1.514
cryst size, mm	0.25 × 0.15 × 0.09
μ, mm^{-1}	1.306
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique reflns	7079
no. of reflns obsd ($I > 3\sigma(I)$	4555
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0262, 0.0300
Flack parameter	0.009(7)

Table 3.4: Selected bond lengths (Å) and angles (°) in the two conformers of (a*R*)-**58**

As(1)–P(1)	2.3359(8)	P(1)–As(1)–C(1)	99.58(9)
As(1)–C(1)	1.988(3)	P(1)–As(1)–C(2)	97.94(9)
As(1)–C(2)	1.990(3)	C(1)–As(1)–C(2)	95.66(11)
P(1)–C(30)	1.800(4)	As(1)–P(1)–C(30)	113.51(13)
P(1)–C(40)	1.791(4)	As(1)–P(1)–C(40)	111.33(12)
P(1)–C(150)	1.810(9)	As(1)–P(1)–C(150)	106.8(4)
P(1)–C(250)	1.811(15)	As(1)–P(1)–C(250)	109.0(8)
As(1)···O(11)	3.111(4)	C(10)–C(19)–C(20)–C(29)	−67.5(4)
P(1)···O(11)	2.943(4)		
As(1)···O(21)	3.721(8)		
P(1)···O(21)	3.039(8)		

closely with that of As(1)–P(1) in (a*R*)-**55**·$C_4H_{10}O$ (2.3382(9) Å). The structures of [((2-$MeOCH_2C_6H_4$)Ph_2P)AsMePh]PF_6 and [(Ph_3P)AsMePh]PF_6 revealed As–P distances of 2.3703(5) and 2.3480(5) Å, respectively, indicating a significant lengthening upon anchimeric chelation by the oxygen and phosphorus (Δ_{As-P} 0.0223 Å).[11] This lengthening effect is also seen in the arsine-stabilised arsenium salts [((2-$MeOCH_2C_6H_4$)Ph_2As)AsMePh]PF_6 and [(Ph_3As)AsMePh]PF_6, where an increase of 0.0363 Å is observed for the As–As bond in the methoxymethylphenyl-containing compound.[21] Comparison of the structures [((2-$MeOCH_2C_6H_4$)Me_2E)AsMePh]OTf and [($PhMe_2E$)AsMePh]OTf were also made. The As–E bond lengths in [($PhMe_2P$)AsMePh]OTf and [($PhMe_2As$)AsMePh]OTf of 2.3402(8) and 2.4448(6) Å, respectively, are similar to the corresponding bond lengths in the adducts [((2-$MeOCH_2C_6H_4$)Me_2P)AsMePh]OTf and [((2-$MeOCH_2C_6H_4$)Me_2As)AsMePh]OTf, which are 2.3482(6) and 2.4394(3) Å, respectively. A comparison of the structures of the two phosphine complexes indicates a lengthening of the As–P bond by 0.008 Å, whereas the As–As bonds in the arsine complexes reveals a *decrease* by 0.0054 Å. These variations are considerably smaller than those observed in the triaryl systems and are accompanied by a lengthening in the distance between the oxygen atom and the arsenium arsenic atom, and the oxygen atom and the Lewis donor atom. The extent of the influence of the anchimeric oxygen coordination on the arsenic–phosphorus distance appears to be dependent on the Lewis basicity of the electron pair donor – it is considered that the increased Lewis base character of the phosphine results in a greater donation of electron density to the arsenium ion through the coordinate bond, which decreases the influence of the electronegativity of the oxygen on the arsenium ion.

The ^1H NMR spectrum of (a*R*)-**58** in CD_2Cl_2 at 25 °C indicated that the system is at the slow exchange limit, as indicated by the baseline separation of the diastereotopic P*Me* resonances and the coupling of the diastereotopic pairs of methylene protons to the ^{31}P nuclei, as shown in Figure 3.5(a). The $^1H\{^{31}P\}$ spectrum

of (a*R*)-**58** in CD_2Cl_2 at 25 °C indicated AB and A'B' spin systems for the methylene protons as expected for a C_1-symmetric phosphine-stabilised arsenium cation at the slow exchange limit (Figure 3.5(b)). The observation of slow exchange of the phosphine at 25 °C indicates a significant influence of the methoxymethyl group on the strength of the phosphine coordination to the arsenium ion by chelation. The [2-(methoxymethyl)phenyl] substituent on the phosphine has been shown elsewhere to facilitate face discrimination of the prochiral methylphenylarsenium ion.[11]

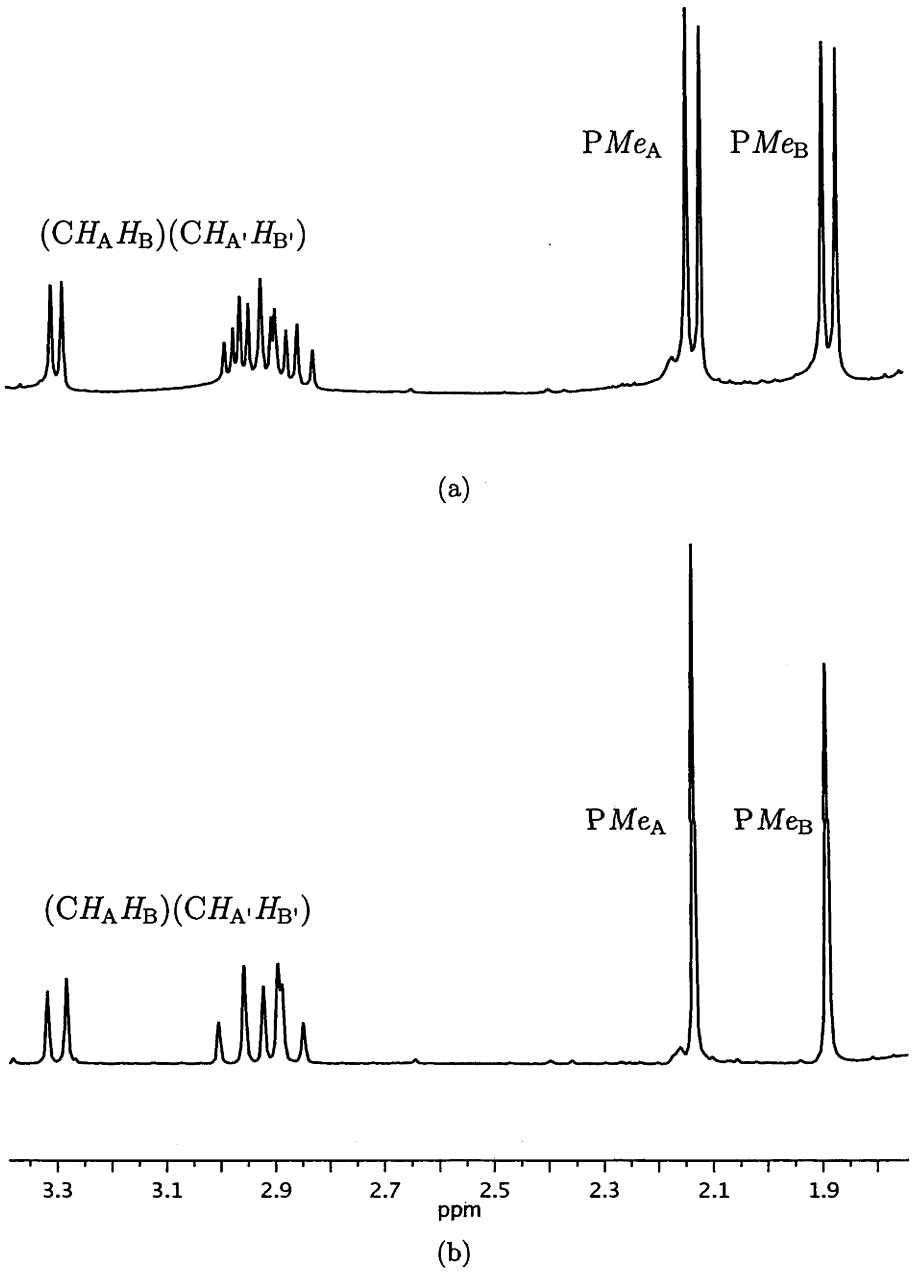


Figure 3.5: Aliphatic regions of ^{1}H (a) and $^{1}H\{^{31}P\}$ (b) NMR spectra of (a*R*)-**58** in CD_2Cl_2 at 25 °C.

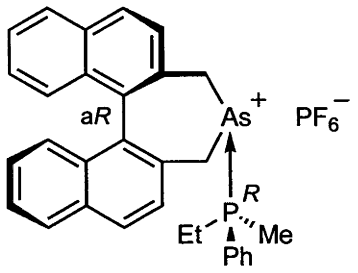
Chapter 4

Deracemisation of tertiary phosphines

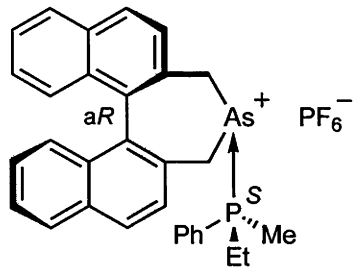
4.1 Attempted deracemisation of a *P*-chiral phosphine

An investigation of the ability of (a*R*)-**39** (X = I) to deracemise (±)-ethylmethylphenylphosphine was undertaken by isolation of the diastereomers of (aR,R_P)/(aR,S_P)-(ethylmethylphenylphosphine-*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] hexafluorophosphate, (aR,R_P)/(aR,S_P)-**59**. Thus, the racemic phosphine was added to a dichloromethane solution of (aR)-**39** (X = I); after 5 h, a solution of potassium hexafluorophosphate in water was added to exchange the iodide for hexafluorophosphate. The dichloromethane solution was dried with magnesium sulfate, filtered, and evaporated to dryness. The powder that remained was redissolved in a small quantity of dichloromethane and diethyl ether was added, which led to the precipitation of a colourless powder in 47% yield.

The ^{1}H and ^{31}P{^{1}H} NMR spectra of the powder at 25 °C indicated a 1/1 mixture of the (aR,R_P) and (aR,S_P) diastereomers of the complex, as indicated by the

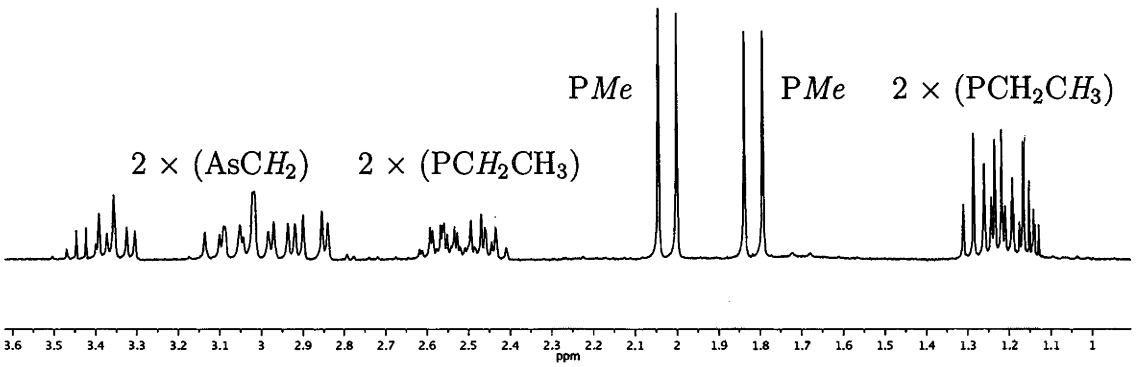


(aR,R_P)-**59**

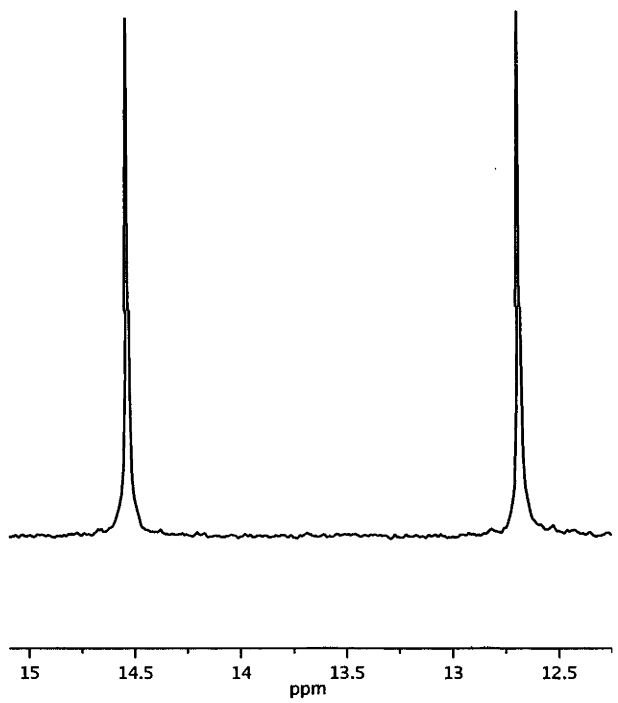


(aR,S_P)-**59**

intensities of the P*Me* doublets (Figure 4.1(a)) and the phosphine-*P* singlets (Figure 4.1(b)). These data are consistent with simple coordination of each enantiomer of the phosphine to the arsepinenium ion, but do not rule out iodide-induced racemisation of the phosphine because the coordination of the two enantiomers could be non-diastereoselective. In order to explore further the stabilities and structures of phosphine complexes of the arsenium ion (aR)-**40**, a number of structurally related complexes were prepared and characterised.



(a)

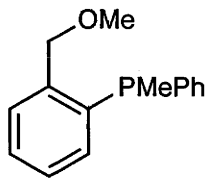


(b)

Figure 4.1: Selected region of ^{1}H NMR spectrum (a) and $^{31}P\{^{1}H\}$ NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**59** in CD_2Cl_2 at 25 °C.

4.2 Design of a *P*-chiral phosphine for deracemisation

Analyses of the interactions present within the solid state structures of the complexes of (a*R*)-**40** with achiral dimethylphenylphosphine and [2-(methoxymethyl)phenyl]dimethylphosphine (**56**) indicated that (±)-[2-(methoxymethyl)phenyl]methylphenylphosphine, (±)-**35**, would be a favourable chiral phosphine for attempted deracemisation by asymmetric transformation in the presence of an enantiomerically pure arsenium auxiliary.

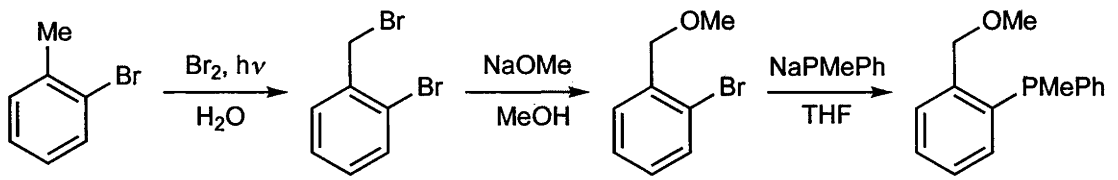


(±)-**35**

4.2.1 Synthesis of (±)-35

The phosphine (±)-**35** was prepared from 2-bromotoluene in three steps (Scheme 4.1).[12,117,118] First, 2-bromotoluene was reacted with 1 equiv of bromine under irradiation with a tungsten lamp to give 2-bromobenzyl bromide (**60**);[117] the subsequent reaction of **60** with sodium methoxide in methanol furnished the methyl ether **61** in 86% yield. The pure ether had bp 99 °C (15 mmHg) [Lit.[118] 106–107 °C (16 mmHg)]. The reaction of **61** with sodium methylphenylphosphide, which was generated in THF from (±)-methylphenylphosphine and excess sodium, gave the crude product as a cloudy orange oil that was distilled to give pure (±)-**35** in 70% yield, bp 146–148 °C (1.25 mmHg).

Scheme 4.1: Synthesis of (±)-**35**

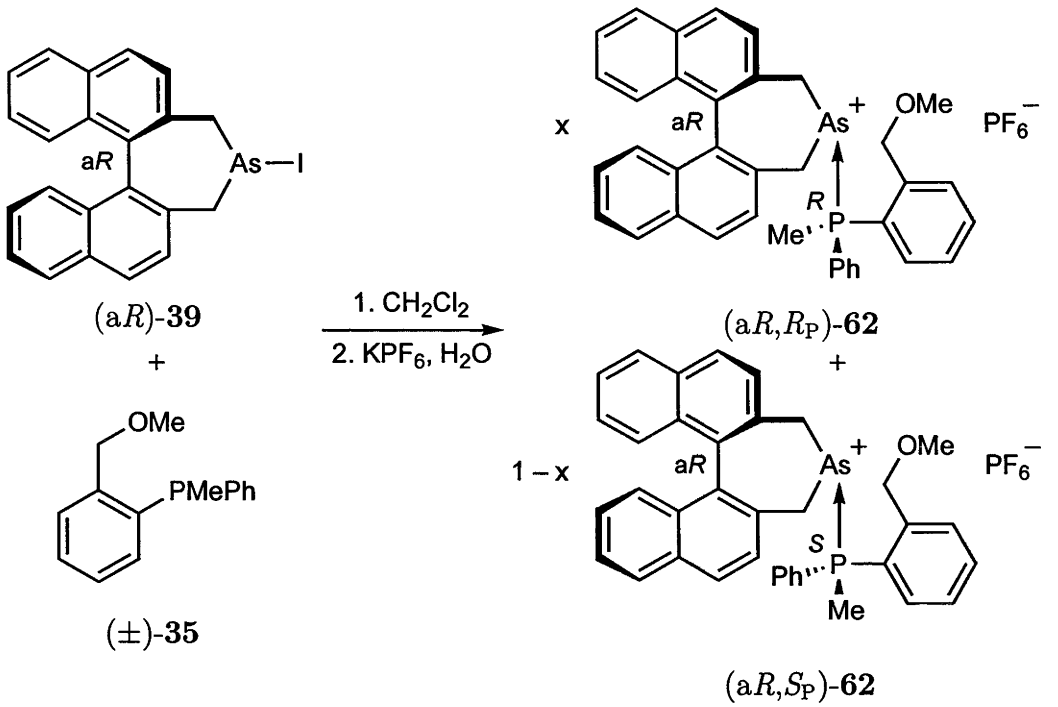


60 **61** (±)-**35**

4.2.2 Deracemisation of (±)-35

The possible deracemisation of (±)-**35** with (a*R*)-**39** (X = I) was investigated by allowing the two reagents to equilibrate for 3 h and then adding an aqueous solution of potassium hexafluorophosphate. After 1 h, the organic phase was separated from the aqueous phase, dried ($MgSO_4$) and filtered; removal of the solvent left an off-white powder. Attempted analysis of the reaction mixture by ^1H or $^{31}P\{^1H\}$ NMR spectroscopy failed to indicate the ratio of diastereomers due to rapid exchange of a small quantity of excess phosphine in the crude solution. The powder was dissolved in dichloromethane and a large quantity of diethyl ether was added to precipitate the phosphine-stabilised arsenium salt (a*R*,R_P)/(a*R*,S_P)-**62** in 38% yield.

Scheme 4.2: Synthesis of (a*R*,R_P)/(a*R*,S_P)-**62**



The ^{1}H and ^{31}P{^{1}H} NMR spectra of the precipitate in CD_2Cl_2 indicated an unequal mixture of the two diastereomers. Examination of the relative intensities of the P*Me* doublets for the mixture indicated a ratio of 74% (δ 1.86) to 26% (δ 2.28) (Figure 4.2(a)); integration of the phosphorus resonances for the compound in the ^{31}P{^{1}H} NMR spectrum gave the similar ratio of 73% (δ 9.58) to 27% (δ 12.30) (Figure 4.2(b)). The experiment was repeated four times, and in each case the same approximate ratio of the two diastereomers was obtained. Fractional crystallisation of the 74/26 mixture of (a*R*,R_P)/(a*R*,S_P)-**62** from dichloromethane–diethyl ether furnished the major diastereomer as colourless needles in spectroscopically pure form. Repeated attempts at determining the crystal structure of this compound were unsuccessful: even though the crystals appeared to be uniform and were mechanically strong, they showed no X-ray diffraction peaks. Extracting the crystals directly from the crystallising media and placing them in an inert mounting oil in an attempt to avoid the loss of possible solvent of crystallisation also proved fruitless. An attempted structural determination on a crystal at room temperature was also

undertaken to avoid the possibility of low temperature induced microcracking of the crystals, but without success. The crystals appeared to maintain their integrity (as analysed by optical microscopy) throughout these manipulations and could be cut cleanly with a scalpel blade. Attempted recrystallisations of the spectroscopically pure diastereomer from acetone or 2-butanone by the addition of diethyl ether were also unsuccessful.

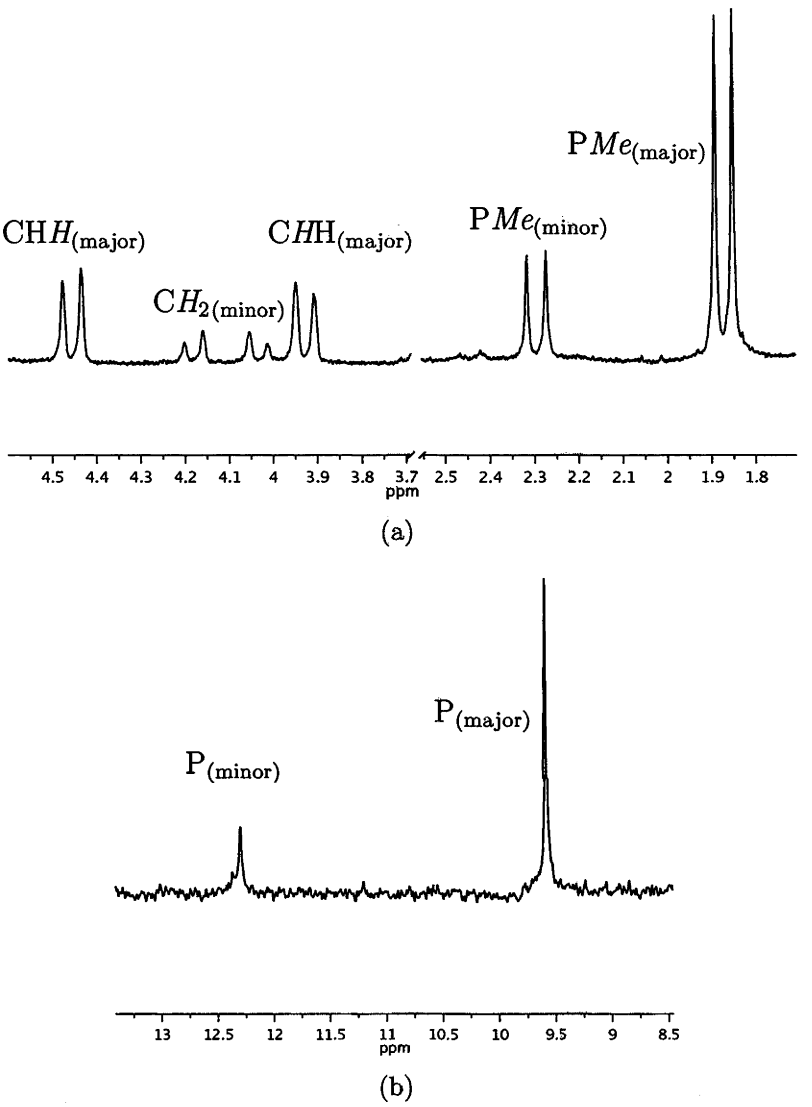
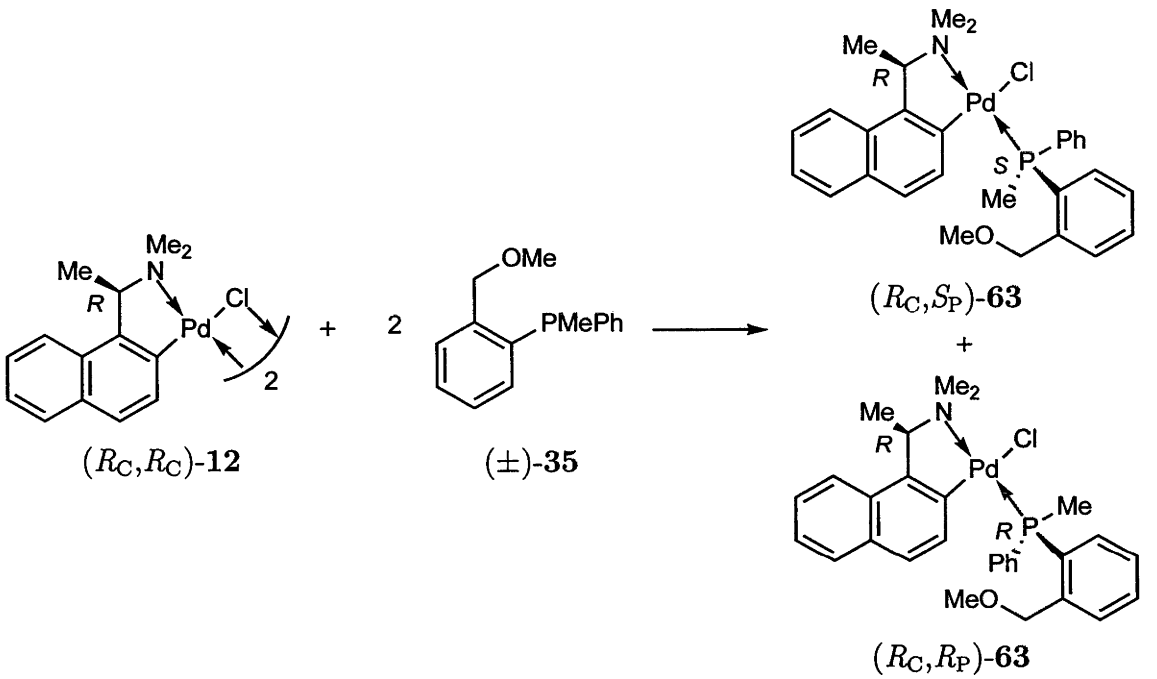


Figure 4.2: Aliphatic region of ^{1}H NMR spectrum (a) and ^{31}P{^{1}H} NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**62** in CD_2Cl_2 at 25 °C.

The absolute configuration of the coordinated phosphine in the crystalline diastereomer of (aR,R_P)/(aR,S_P)-**62** was subsequently determined by the resolution of (±)-**35** with (R_C,R_C)-**12** and the structural characterisation of the less soluble diastereomer of the mixture (R_C,R_P)/(R_C,S_P)-**63** (Scheme 4.3).

Scheme 4.3: Resolution of (±)-**35** with (R_C,R_C)-**12**



Thus, (±)-**35** and a small excess of (R_C,R_C)-**12** were dissolved in dichloromethane. After stirring overnight, the dichloromethane was removed in vacuo; methanol was added to dissolve the residue and the solution was filtered to remove the excess of the resolving complex. Evaporation of the solvent from the filtrate afforded a yellow foam. The ^{1}H and ^{31}P{^{1}H} NMR spectra of the foam in $CDCl_3$ indicated a 1/1 mixture of (R_C,R_P)/(R_C,S_P)-**63**. Fractional crystallisation of this mixture from acetone yielded a single diastereomer in poor yield (6.5%), which had ^{1}H and ^{31}P{^{1}H} NMR spectra consistent with the presence of a single diastereomer of the original 1/1 mixture. No attempt was made to increase the yield of this complex. An ORTEP diagram of the complex is shown in Figure 4.3. The absolute

configuration at phosphorus was assigned as R on the basis of the known configuration of (R_C,R_C)-**12** and refinement of the Flack parameter (0.020(16)). The resolved complex (R_C,R_P)-**63** crystallises in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell (Table 4.1). The palladium(II) centre in the molecule displays a significant tetrahedral distortion, most likely due to steric repulsion between the hydrogen attached to the chirotopic carbon C(51) and the hydrogen at C(48) of the naphthylenyl ring. Notable bond lengths and angles in the complex are given in Table 4.2

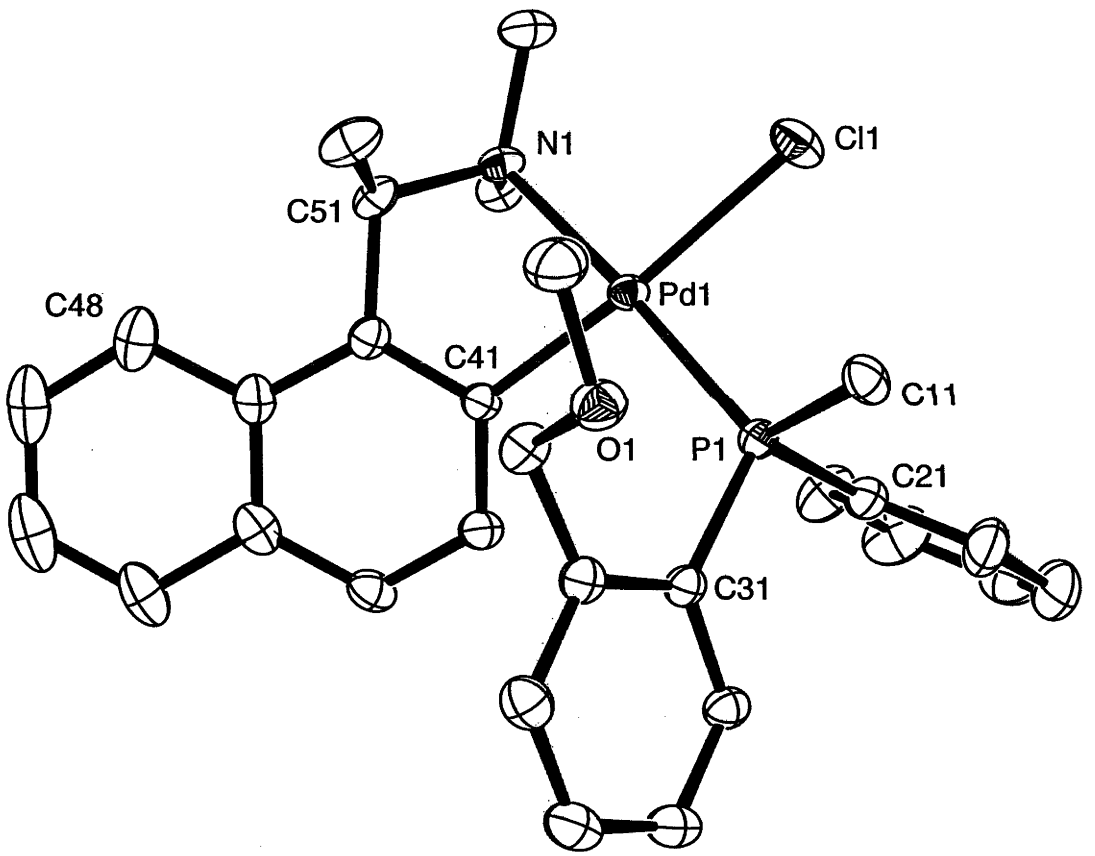


Figure 4.3: ORTEP diagram of (R_C,R_P)-**63** with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 4.1: Crystallographic data and experimental parameters for X-ray structural analysis of (R_C,R_P)-**63**

empirical formula	$C_{29}H_{33}ClNOPPd$
fw, (g mol^{-1})	584.41
cryst syst	orthorhombic
space group	$P2_12_12_1$
a, Å	9.7943(1)
b, Å	11.5628(2)
c, Å	24.0072(3)
V, Å^3	2718.80(6)
Z	4
D_{calcd}, (g cm^{-3})	1.428
cryst size, mm	0.30 × 0.24 × 0.23
μ, mm^{-1}	0.86
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique reflns	7935
no. of reflns obsd ($I > 3\sigma(I)$	6699
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0220, 0.0262
Flack parameter	0.020(16)

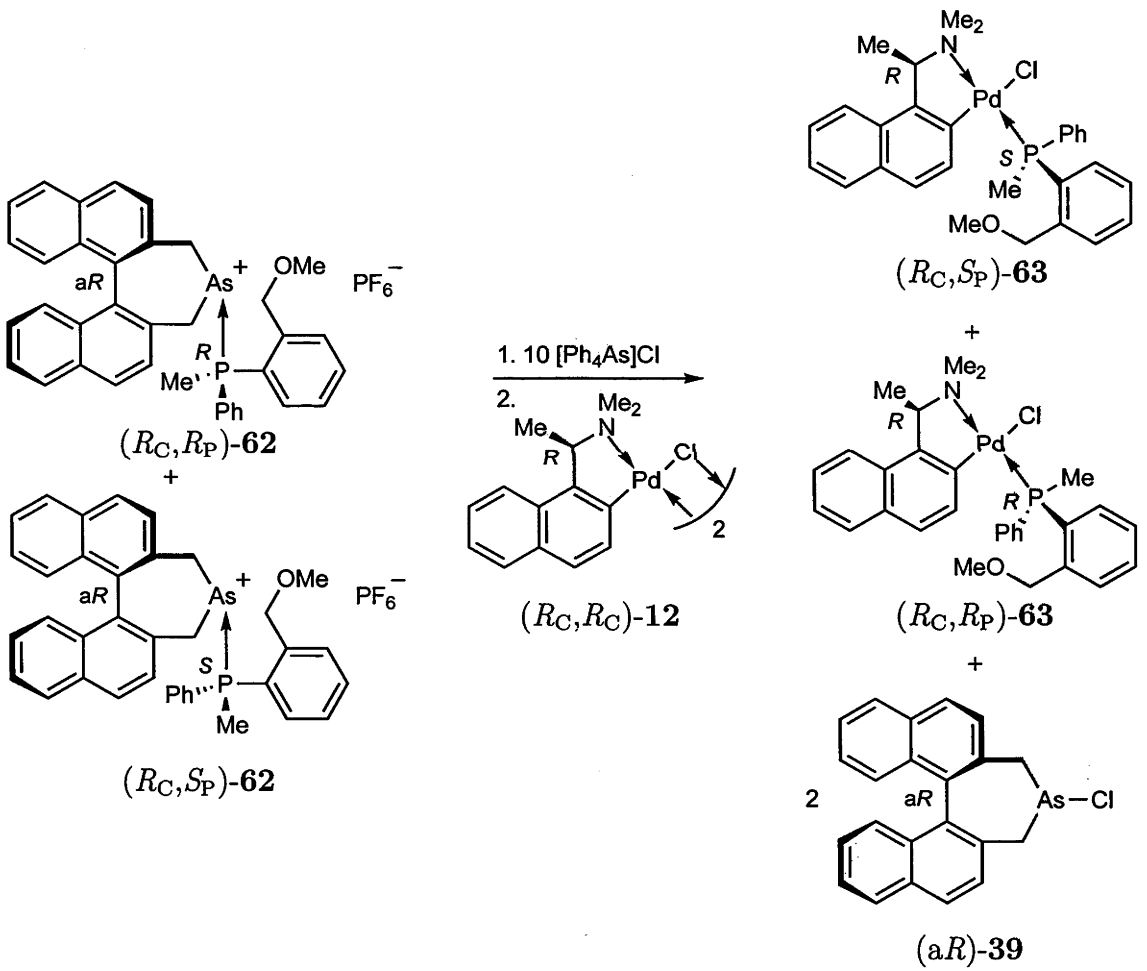
Table 4.2: Selected bond lengths (Å) and angles (°) in (R_C,R_P)-**63**

Pd(1)–Cl(1)	2.3856(5)	Cl(1)–Pd(1)–P(1)	88.17(2)
Pd(1)–P(1)	2.2647(5)	Cl(1)–Pd(1)–N(1)	95.27(5)
Pd(1)–N(1)	2.1453(16)	P(1)–Pd(1)–N(1)	175.59(5)
Pd(1)–C(41)	2.0080(18)	Cl(1)–Pd(1)–C(41)	175.06(5)
		P(1)–Pd(1)–C(41)	96.71(5)
		N(1)–Pd(1)–C(41)	79.82(7)

The structural determination of (R_C,R_P)-**63** enabled the configuration of the phosphine in the major diastereomer of the 74/26 mixture of (aR,R_P)/(aR,S_P)-**62** to be established. Thus, the tertiary phosphine was liberated from a diastereomerically enriched sample of phosphine–arsenium complex (aR,R_P)/(aR,S_P)-**62** by treatment with 5 equiv tetraphenylarsonium chloride and coordinated to (R_C,R_C)-**12** (Scheme

4.4). After 1 h, the solvent was removed from the solution and the residue was dissolved in CD_2Cl_2. The $^{31}P\{^1H\}$ NMR spectrum of the solution contained two peaks of unequal intensity corresponding to (R_C,S_P)/(R_C,R_P)-**63** in a ratio of ca. 32/68 (Figure 4.4). Thus, the major diastereomer of (aR,R_P)/(aR,S_P)-**62** in the original 74/26 precipitate has the (aR,R_P) configuration.

Scheme 4.4: Liberation and coordination of the tertiary phosphine from (aR,R_P)/(aR,S_P)-**62**



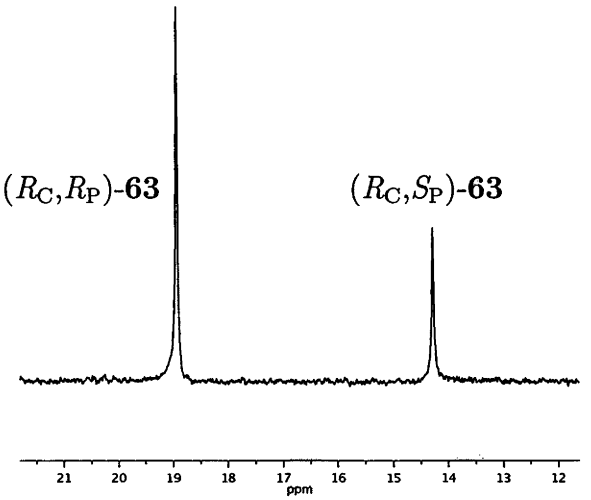
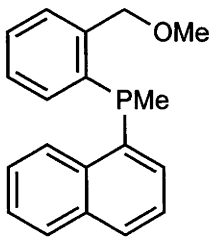


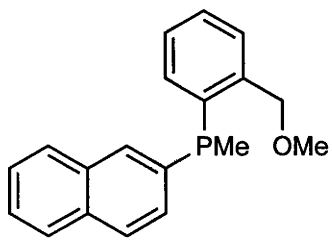
Figure 4.4: $^{31}P\{^1H\}$ NMR spectrum of the unequal mixture of (R_C,R_P)- and (R_C,S_P)-**63** in CD_2Cl_2.

From these data it is not clear if the original (aR,R_P)/(aR,S_P)-**62** = 74/26 mixture obtained by precipitation following the two-phase synthesis with the iodoarsepine (aR)-**39** (X = I) and (±)-**35** is the result of iodide-induced deracemisation of the phosphine, or selective precipitation of the (R_C,R_P)-**62** by the diethyl ether. It was not possible to recover a sample of (aR,R_P)/(aR,R_P)-**62** by use of other methods that was sufficiently pure for diagnostic ^1H or $^{31}P\{^1H\}$ NMR spectra to be recorded. In order to investigate steric effects of the phosphines on the diastereoselectivity of coordination to the arsenium ion, a pair of 1- and 2-naphthyl-substituted phosphines were prepared.

4.3 Synthesis of chiral (1- and 2-naphthyl) phosphines (±)-64 and (±)-65



(±)-**64**

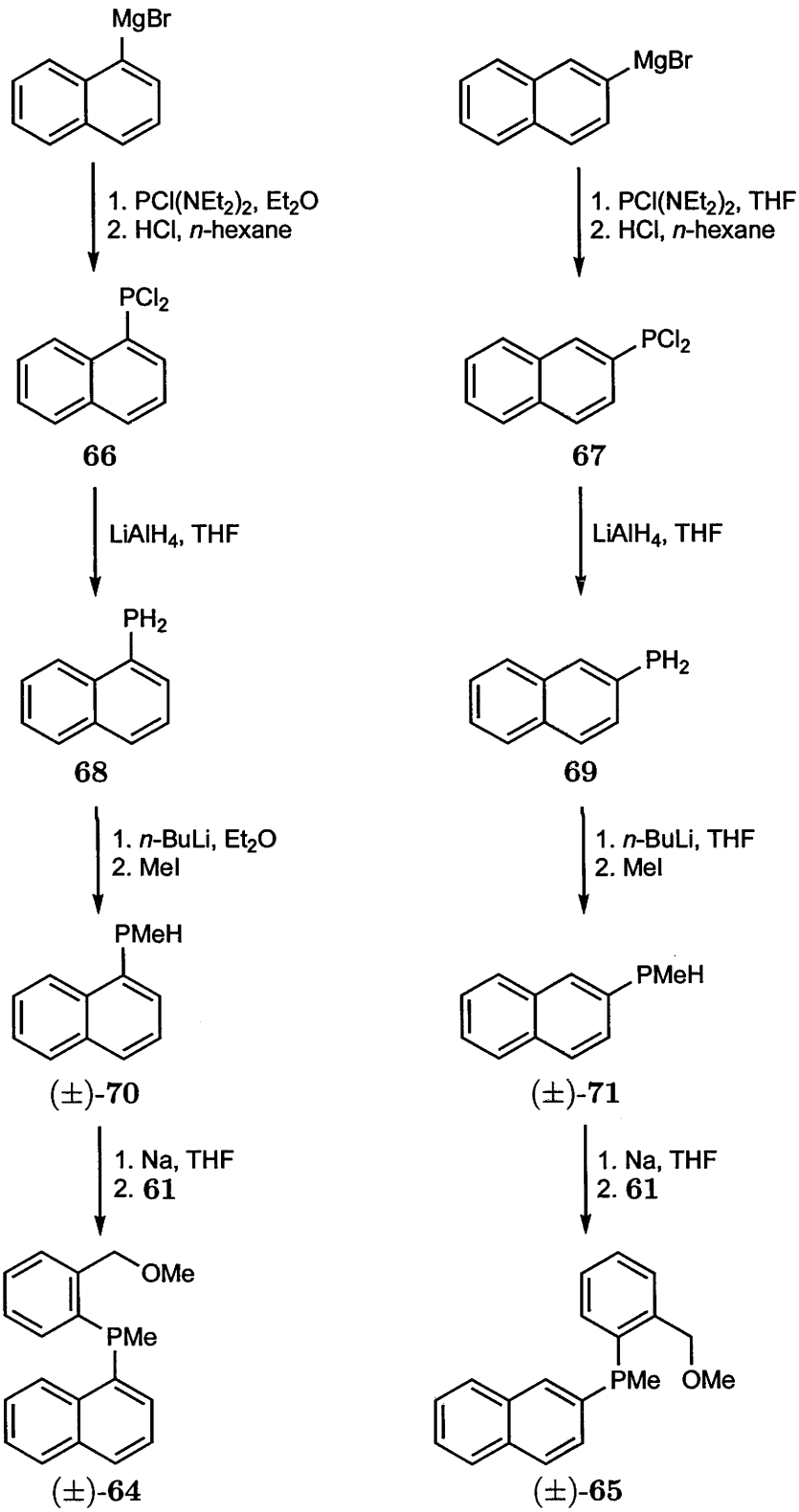


(±)-**65**

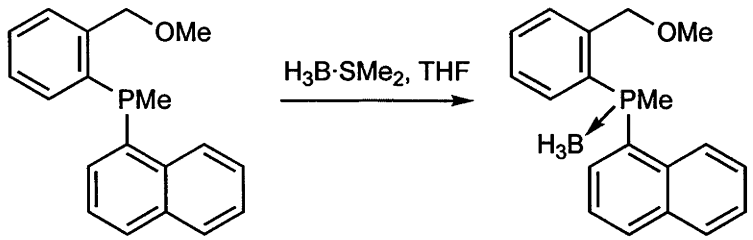
The routes to (±)-**64** and (±)-**65** are summarised in Scheme 4.5. The Grignard reagents derived from 1- or 2-bromonaphthalene and magnesium were reacted with chlorobis(diethylamino)phosphine; the resulting arylbis(diethylamino)phosphines were then treated in situ with hydrogen chloride to give the known dichloro(1-naphthyl)phosphine (**66**) in 86% yield[119,120] and dichloro-(2-naphthyl)phosphine (**67**) in 87% yield after distillation.[121] The dichlorophosphines were reduced with lithium aluminium hydride in THF to give the primary phosphines **68** and **69** after the usual work up procedures;[120] the phosphine **69** was isolated as an oil that crystallised over several days. The secondary phosphines (±)-methyl-1-naphthylphosphine, (±)-**70**, and (±)-methyl-2-naphthylphosphine, (±)-**71**, were prepared by a modification of the methods used for the synthesis of [2-(methoxymethyl)phenyl]methylphosphine.[122] Thus, *n*-butyllithium was added to a cooled solution of the primary phosphine in diethyl ether or THF, followed by the addition of iodomethane in the same solvent. The crude products were purified by vacuum distillation; (±)-**71** crystallised on standing, mp 54–55 °C. The tertiary phosphines, (±)-**64** and (±)-**65** were prepared by the addition of sodium to THF solutions of the appropriate secondary phosphines followed by the addition of 1-bromo-2-methoxymethylbenzene (**61**) to the cooled solutions of the resulting sodium methyl(1- and 2-naphthyl)phosphides. Extractions of the products into di-

ethyl ether and subsequent drying of the solutions ($MgSO_4$) gave the crude products as cloudy oils; distillation gave pure (±)-**65** in 45% yield as a viscous oil that crystallised on standing, mp 54–55 °C. Pure (±)-**64** could not be isolated by fractional distillation, but the phosphine–borane adduct was amenable to purification by column chromatography with use of toluene as the eluant. The adduct (±)-**64**·BH_3 was prepared by the mixing of the crude phosphine with borane–dimethylsulfide complex in THF (Scheme 4.6). The phosphine–borane adduct (±)-**64**·BH_3 was isolated as a colourless oil that crystallised on standing, mp 127–130 °C. Removal of the borane from (±)-**64**·BH_3 was effected by the addition of an excess of hot morpholine; the phosphine was isolated in 82% yield by removal of the excess morpholine in vacuo and extraction from the morpholine–borane adduct with dichloromethane/water; pure (±)-**64** crystallised on standing, mp 59–62 °C.

Scheme 4.5: Synthesis of (±)-**64** and (±)-**65**



Scheme 4.6: Synthesis of (±)-**64**·BH_3



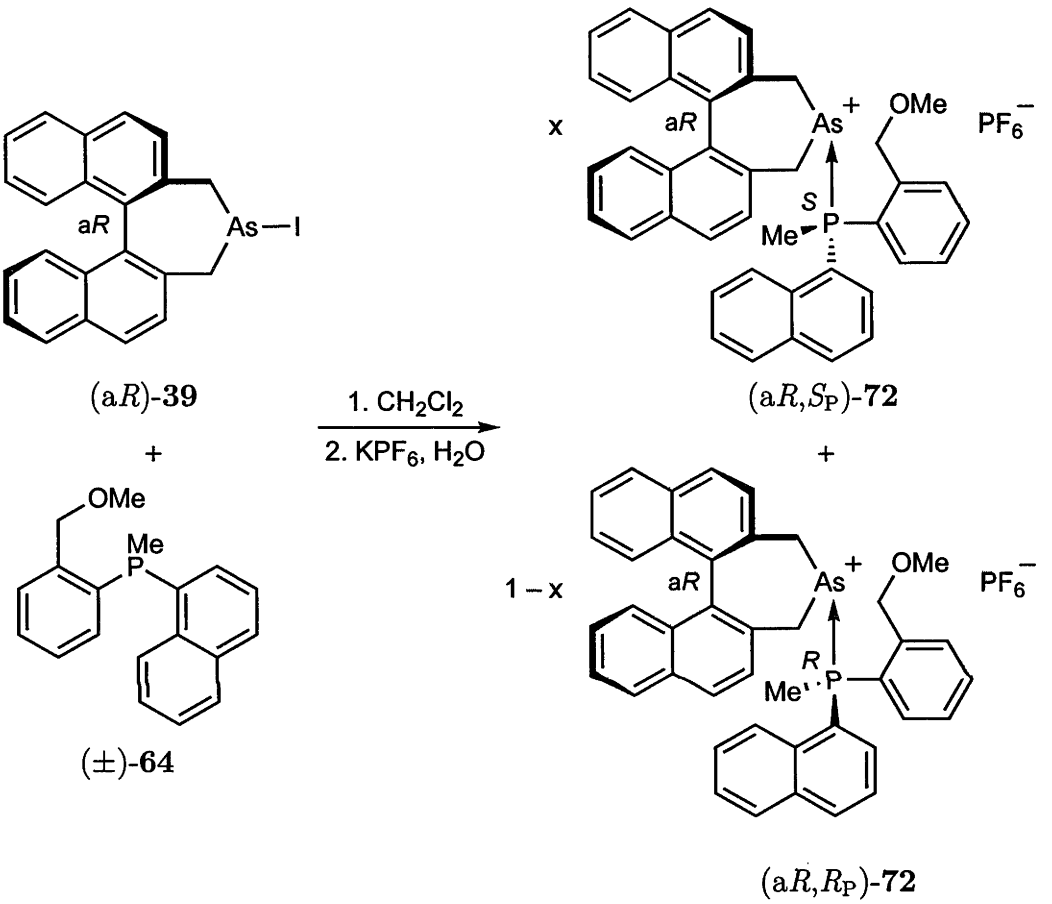
(±)-**64** (±)-**64**·BH_3

4.3.1 Deracemisation of (±)-64

The reaction of the phosphine (±)-**64** with (a*R*)-**39** (X = I) by the two-phase method gave the phosphine-stabilised arsenium salt (a*R*,R_P)/(a*R*,S_P)-**72**. Thus, a dichloromethane solution of (±)-**64** and (a*R*)-**39** (X = I) was stirred for 3 h and then treated with aq. potassium hexafluorophosphate. After 1 h, the organic phase was separated, dried ($MgSO_4$), filtered, and the solvent removed from the filtrate. The attempted analysis of the crude material by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy failed to indicate a ratio of diastereomers due to the rapidly exchanging phosphine. The off-white powder that remained was dissolved in a small amount of dichloromethane and a large quantity of diethyl ether was added to precipitate the phosphine-stabilised arsenium salt (a*R*,R_P)/(a*R*,S_P)-**72** in 15% yield (Scheme 4.7). The ^1H and $^{31}P\{^1H\}$ NMR spectra of the salt indicated an unequal mixture of the two diastereomers of the complex. Unlike (a*R*,R_P)/(a*R*,S_P)-**62**, the resonances for (a*R*,R_P)/(a*R*,S_P)-**72** overlapped in many regions. The resonances for the methylene protons of the [2-(methoxymethyl)phenyl] groups in (a*R*,R_P)/(a*R*,S_P)-**72**, however, appeared as distinct AB doublets (Figure 4.5(a)). Integration of the baseline-separated doublets in the spectrum gave the ratio 43% (δ 3.79 (d, $^2J(^1H^1H)$ = 12.30 Hz, C*H*H)), 4.14 (d, $^2J(^1H^1H)$ = 12.30 Hz, CH*H*)) to 57% (δ 3.88 (d, $^2J(^1H^1H)$ = 12.30 Hz, C*H*H))), 4.23 (d, $^2J(^1H^1H)$ = 12.30 Hz, CH*H*))) for the two diastereomers. Analysis of the phosphorus resonances in the $^{31}P\{^1H\}$ NMR spec-

trum of the mixture gave the identical ratio 43% (δ 7.89) to 57% (δ 9.39) (Figure 4.5(b)).

Scheme 4.7: Synthesis of (aR,R_P)/(aR,S_P)-**72**



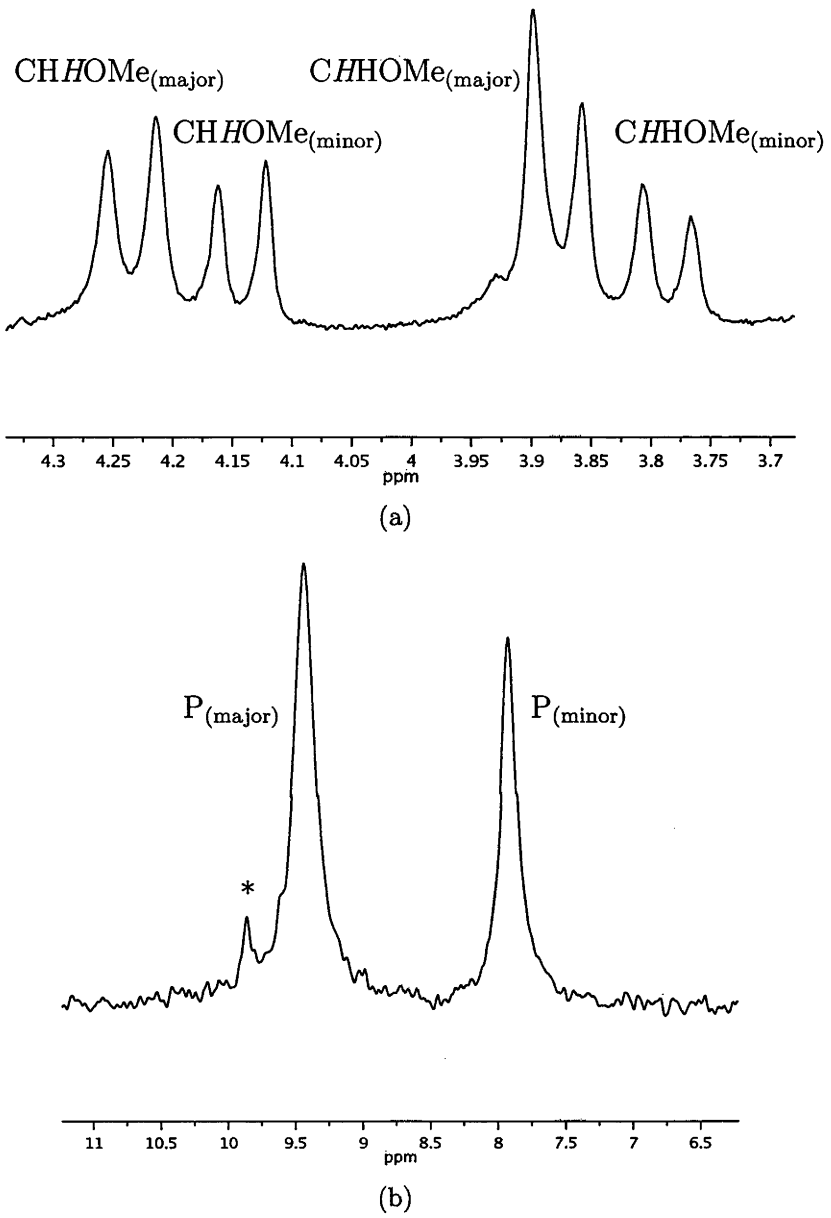


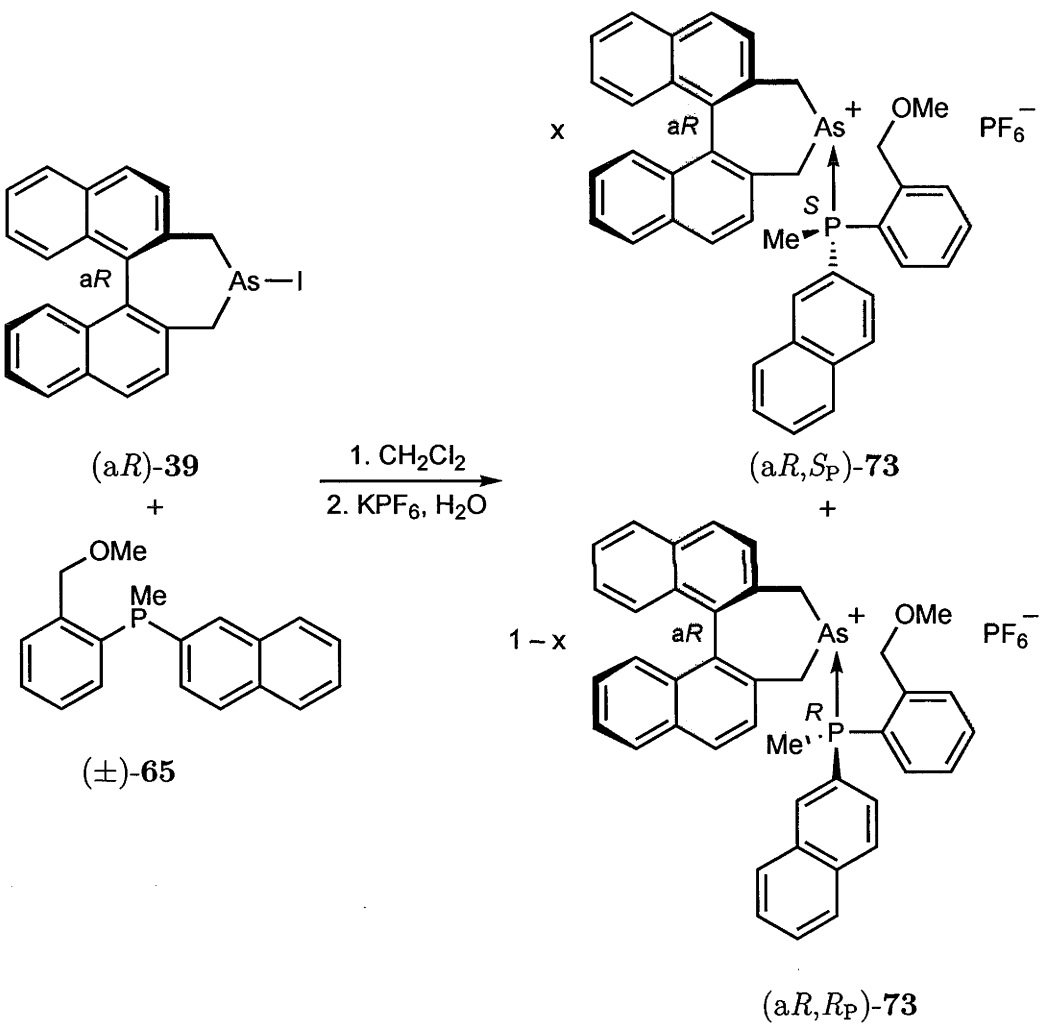
Figure 4.5: Methylene region of ^{1}H NMR spectrum (a) and ^{31}P{^{1}H} NMR spectrum (b) of (aR,R_P)/(aR,S_P)-**72** in CD_2Cl_2 at 25 °C. * Impurity.

4.3.2 Deracemisation of (±)-65

The reaction of the phosphine (±)-**65** with (a*R*)-**39** (X = I) to furnish the phosphine-stabilised arsenium salt (a*R*,R_P)/(a*R*,S_P)-**73** was performed in an identical manner to the earlier example (Scheme 4.8). Precipitation of the product was effected by the addition of a large quantity of diethyl ether to a concentrated dichloromethane solution of the initial solid that was isolated; the resulting white powder was collected and dried in vacuo. The ^{1}H and ^{31}P{^{1}H} NMR spectra of the powder indicated an unequal mixture of two diastereomers. Integration of the P*Me* resonances in the ^{1}H NMR spectrum of the complex gave the ratio of 79% (δ 1.96) to 21% (δ 2.37) (Figure 4.6(a)); integration of the phosphorus resonances gave the identical ratio of 79% (δ 10.14) to 21% (δ 12.73) (Figure 4.6(b)).

Recrystallisation of the 79/21 mixture of (a*R*,R_P)/(a*R*,S_P)-**73** from dichloromethane by the addition of diethyl ether afforded the major diastereomer as colourless needles, mp > 165 °C dec. The needles were too small for X-ray crystallography. A further recrystallisation of the pure diastereomer from 2-butanone by the addition of diethyl ether, however, provided crystals suitable for an X-ray crystal structure determination. The major diastereomer crystallises in the tetragonal space group $P4_32_12$, with eight units within the cell (Table 4.3). The asymmetric unit contains the cation of the (a*R*,R_P)-**73** and a hexafluorophosphate ion distributed over two sites of symmetry, as well as 0.5 molecules of 2-butanone. Attempted modelling of the disordered solvent molecule did not provide an adequate solution. Analysis through the plane of the peripheral atoms of the modelled solvent by a Slant Fourier in CRYSTALS indicated the presence of electron density, but no obvious atomic locations could be identified. When the data was analysed with Squeeze in PLATON, which indicated a solvent accessible void of 1404.6 Å^3 containing 64 electrons was indicated, which corresponded to 0.5 equiv 2-butanone per asymmetric unit. The absolute configuration of the cation was assigned on

Scheme 4.8: Synthesis of (aR,R_P)/(aR,S_P)-**73**



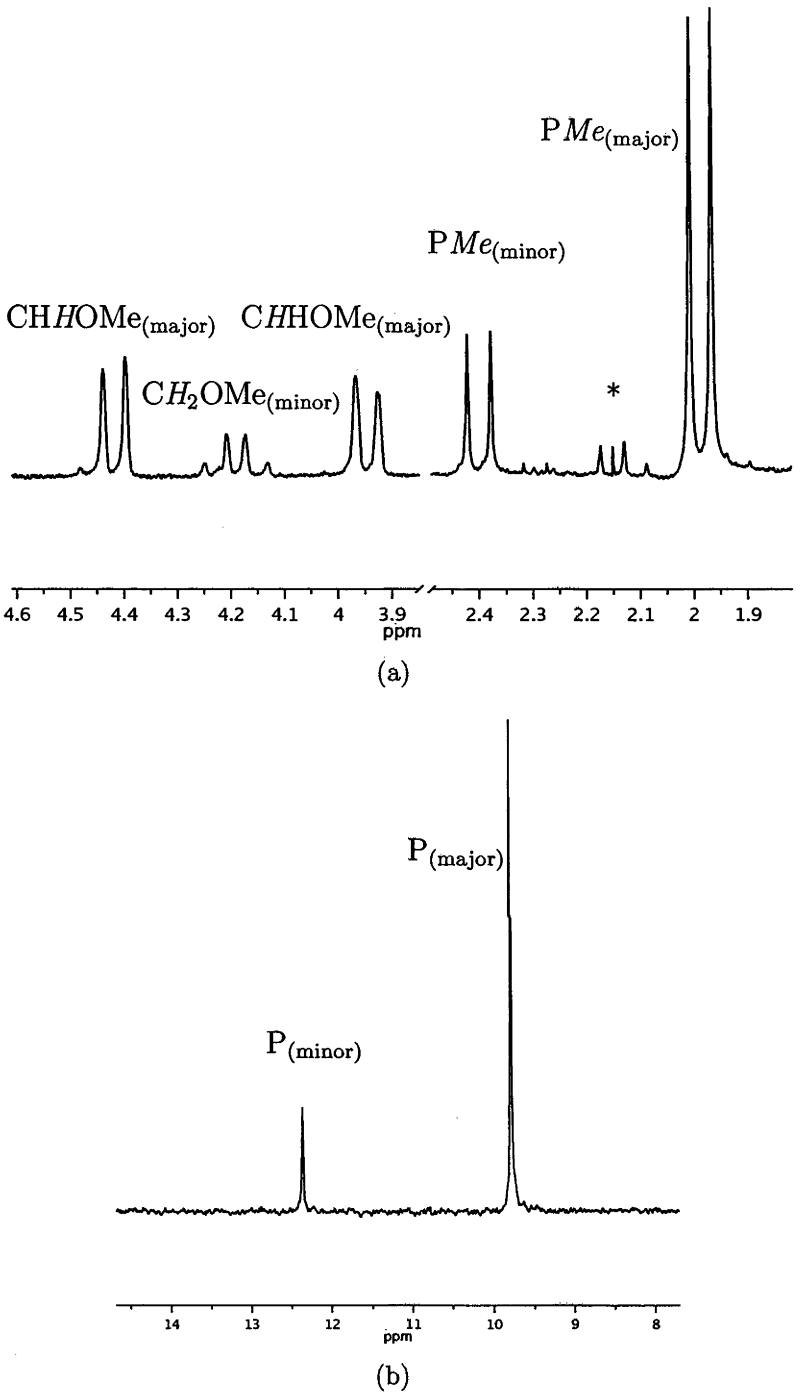


Figure 4.6: Methylene region of ^{1}H NMR spectrum (a) and ^{31}P{^{1}H} NMR spectrum (b) of (a*R*,*R*$_P$)/(a*R*,*S*$_P$)-**73** in CD_2Cl_2 at 25 °C. * Impurity.

the basis of the known configuration of the starting material (a*R*)-**47** and was confirmed by refinement of the Flack parameter, which was −0.012(11). The major diastereomer in the mixture has the (a*R*,R_P) configuration. The structure of the cation of the complex is shown in Figure 4.7.

The bond between As(1) and P(1) in (a*R*,R_P)-**73** of 2.3433 Å is similar to those observed in (a*R*)-**55**·C_4H_8O and (a*R*)-**58**. Orthogonal coordination of the phosphine to the planar arsenium ion is evident from the angles P(1)–As(1)–C(1) and P(1)–As(1)–C(2), which are 98.19(19) and 98.20(17), respectively. The oxygen atom of the methoxymethyl group interacts with the arsenic and phosphorus atoms at distances of 2.931(5) and 2.955(5) Å, respectively. Additional bond lengths and angles of note are given in Table 4.4. The naphthyl group of the phosphine does not interact with the binaphthyl group in an aryl–aryl embrace. The large size of the naphthyl group compared to the methyl group may prevent the approach of the other enantiomer of the phosphine towards the cavity beneath the binaphthyl. The similarity of the shifts of the $^{31}P\{^1H\}$ NMR resonances for (a*R*,R_P)-**73** with those of the phenyl analogue (a*R*,R_P)-**62** suggests a similar mode of binding of the enantiomers of (±)-**35** and (±)-**65** to the arsenium cation (a*R*)-**40**. This suggests that the phenyl group of the phosphine in (a*R*,R_P)-**62** is also located away from the region beneath the binaphthyl group of the arsenium ion.

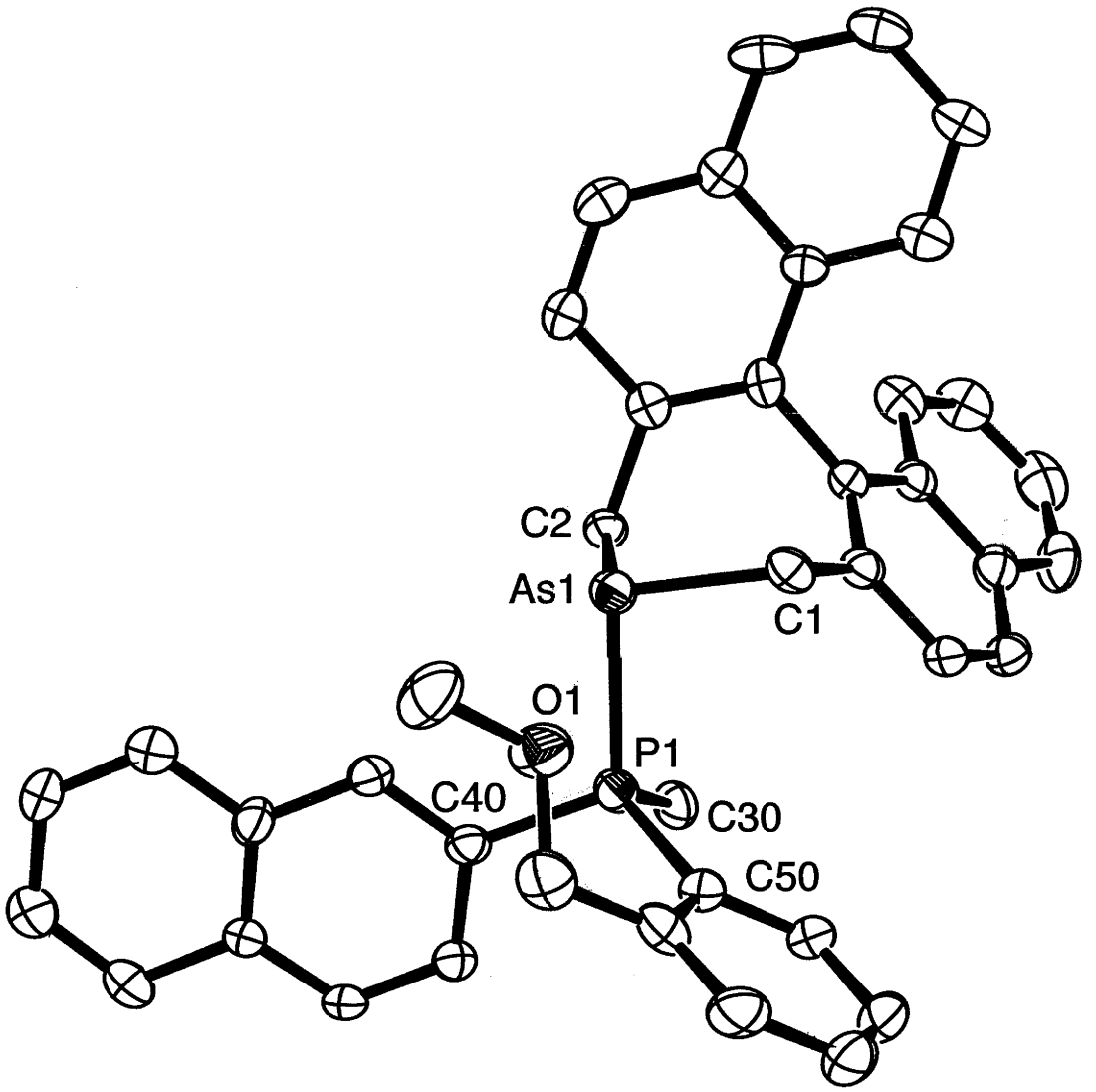


Figure 4.7: ORTEP diagram of the cation of (aR,R_P)-**73**·0.5C_4H_8O with selected atoms labelled (30% ellipsoid probability shown). Hydrogen atoms have been omitted for clarity.

Table 4.3: Crystallographic data and experimental parameters for X-ray structural analysis of (aR,R_P)-**73**·0.5C_4H_8O

empirical formula	$C_{43}H_{39}AsF_6O_{1.5}P_2$
fw, (g mol^{-1})	830.59
cryst syst	tetragonal
space group	$P4_32_12$
a, Å	18.7230(4)
b, Å	18.7230(4)
c, Å	23.0827(4)
V, Å^3	8091.7(3)
Z	8
D_{calcd}, (g cm^{-3})	1.36
cryst size, mm	0.22 × 0.08 × 0.07
μ, mm^{-1}	0.98
instrument	Nonius Kappa CCD
radiation	Mo Kα
no. of unique refins	9636
no. of refins obsd ($I > 2\sigma(I)$)	3553
temp, K	200
struct refinement	CRYSTALS[110]
final R_1, wR_2	0.0389, 0.0412
Flack parameter	−0.012(11)

Table 4.4: Selected bond lengths (Å) and angles (°) in (aR,R_P)-**73**·0.5C_4H_8O

As(1)–P(1)	2.3433(17)	P(1)–As(1)–C(1)	98.19(19)
As(1)–C(1)	2.003(6)	P(1)–As(1)–C(2)	98.20(17)
As(1)–C(2)	1.976(5)	C(1)–As(1)–C(2)	97.0(2)
P(1)–C(30)	1.808(6)	As(1)–P(1)–C(30)	110.5(2)
P(1)–C(40)	1.795(6)	As(1)–P(1)–C(40)	110.24(19)
P(1)–C(50)	1.798(7)	As(1)–P(1)–C(50)	115.2(2)
As(1)···O(1)	2.931(5)	C(19)–C(10)–C(20)–C(29)	−66.0(7)
P(1)···O(1)	2.955(5)		

Chapter 5

Conclusions

The first enantiomerically pure and configurationally stable chloro- and iodoarsines based on the 2,2'-bis(methylene)-1,1'-binaphthyl group have been synthesised in high yield. The seven-membered (a*R*)-iodoarsepine (a*R*)-**39** (X = I) was synthesised by disproportionation of triiodoarsine with the enantiomerically pure (a*R*)-phenylarsepine (a*R*)-**53** in boiling toluene; the (a*R*)-chloroarsepine (a*R*)-**39** (X = Cl) was prepared by halide metathesis of the iodoarsepine with silver chloride in dichloromethane.

Phosphine-stabilised arsenium salts of the enantiomerically pure arsenium ion were prepared by a two-phase method from the (a*R*)-iodoarsepine and dimethylphenylphosphine or [2-(methoxymethyl)phenyl]dimethylphosphine in dichloromethane and aq. potassium hexafluorophosphate. The resulting phosphine-stabilised arsepinenium hexafluorophosphates were characterised by X-ray crystallography and ^{1}H NMR spectroscopy.

Moderately fast dissociative exchange of the phosphine was indicated for the dimethylphenylphosphine complex, (a*R*)-**55**·CH_2Cl_2, as evidenced in the ^{1}H NMR spectrum of the complex in CD_2Cl_2 at 25 °C by the diastereotopic P*Me* resonances and a single, broad AB quartet corresponding to the averaging of the resonances for the two pairs of methylene protons of the arsenium group. The complex containing

[2-(methoxymethyl)phenyl]dimethylphosphine, (a*R*)-**58**, under these conditions had a ^{1}H NMR spectrum consistent with slow exchange of the phosphine compared to the NMR timescale, as indicated by two baseline separated diastereotopic P*Me* resonances in the ^{1}H NMR spectrum and a complex multiplet corresponding to the AB and A'B' spin systems for the four inequivalent methylene protons in the asymmetric molecule, with additional coupling to the ^{31}P nucleus of the phosphine.

A new method for the asymmetric synthesis of tertiary phosphines was investigated by the attempted asymmetric transformation of racemic *P*-chiral tertiary phosphines with the enantiomerically pure iodoarsine (a*R*)-**39** (X = I) in dichloromethane, followed by trapping of the diastereomerically enriched product by the addition of aq. potassium hexafluorophosphate. The reaction of (±)-[2-(methoxymethyl)phenyl]methylphenylphosphine with the (a*R*)-iodoarsepine under these conditions indicated a ratio of 74/26 for the (aR,R_{P})/(aR,S_{P}) diastereomers of the isolated phosphine-stabilised arsenium hexafluorophosphate. A further analysis of this effect was undertaken with (±)-[2-(methoxymethyl)phenyl]methyl-1-naphthylphosphine and (±)-[2-(methoxymethyl)phenyl]methyl-2-naphthylphosphine. The diastereomers of the phosphine-stabilised arsenium salt of the 1-naphthyl isomer were found to be in a very similar ratio, with minimal asymmetric induction (43/57). This was in contrast to the diastereomeric ratio of the phosphine-stabilised arsenium salt of the 2-naphthyl isomer, where the ratio of diastereomers (79/21) was similar to that obtained for the arsenium complex of (±)-[2-(methoxymethyl)phenyl]methylphenylphosphine. The major diastereomer of the (±)-[2-(methoxymethyl)phenyl]methyl-2-naphthylphosphine-stabilised arsenium hexafluorophosphate was isolated by fractional crystallisation, and was found to have the (aR,R_{P}) relative configuration by X-ray crystallography.

Chapter 6

Experimental

6.1 General

Reactions involving air sensitive compounds were performed under a positive pressure of nitrogen using Schlenk techniques. Dry, degassed solvents were obtained by distillation over appropriate drying agents and stored under nitrogen.[123] Dichlorophenylarsine,[124] (a*R*)-1,1'-binaphthol-2,2'-bis(trifluoromethanesulfonate),[125] (a*R*)-2,2'-dimethyl-1,1'-binaphthyl,[99] (±)-methylphenylphosphine,[89] dimethylphenylphosphine,[126] (±)-ethylmethylphenylphosphine,[127] triiodoarsine,[128] 2-bromonaphthalene,[129] chloro-bis(diethylamino)phosphine,[130] dichloro[2-(methoxymethyl)phenyl]phosphine,[12] (±)-1-naphthylphenylphosphine,[131] and (R_C,R_C)-**12**,[48,132] were synthesised by published methods. (a*R*)-BINOL, triflic anhydride, 2-bromotoluene, 1-bromonaphthalene, iodomethane, *n*-butyllithium in hexanes, and tetraphenylarsonium chloride were purchased from commercial sources. Routine NMR spectra were measured on a Varian Mercury spectrometer operating at 300 MHz (^{1}H), 75 MHz (^{13}C{^{1}H}) and 120 MHz (^{31}P{^{1}H}); routine and variable temperature NMR were measured on a Varian Inova spectrometer operating at 300 MHz (^{1}H), 75 MHz (^{13}C{^{1}H}) and 120 MHz (^{31}P{^{1}H}). Chemical shifts (δ) are reported in parts per

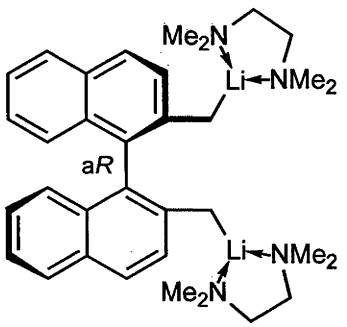
million (ppm) relative to the residual solvent peaks for ^{1}H and $^{13}C\{^{1}H\}$ spectra and external aq. H_3PO_4 (85%) for $^{31}P\{^{1}H\}$ spectra. The following abbreviations have been used to describe the multiplicity and shapes of the NMR resonances: s (singlet), d (doublet), t (triplet), q (quartet), sept (septuplet), m (multiplet), br (broad).

Melting points were measured with use of a Reichart hot stage melting point apparatus or a Stanford Research Systems OptiMelt melting point apparatus in sealed glass tubes. Melting and boiling points are uncorrected. Elemental analysis were performed by staff within the Microanalytical Unit of the Research School of Chemistry. EI mass spectra were recorded with a VG AutoSpec M series sector instrument, and ESI mass spectra with a VG Quattro II triple quadrupole instrument. For mass spectral data reported for salts, the notation [M] indicates the cation of the complex. Optical rotations were recorded with a Perkin–Elmer Model 241 MC polarimeter, using 1 dm quartz cells on solutions of c g of material in 100 mL of solvent.

X-ray diffraction data were recorded on a Nonius Kappa CCD diffractometer with the crystal under a stream of nitrogen gas at 200 K. Structures were solved by direct methods (SIR92)[133] and refined by full matrix on F with use of CRYSTALS.[110] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included at calculated positions and allowed to ride on the atoms to which they are attached. Molecular graphics were produced with ORTEP-3.[134]

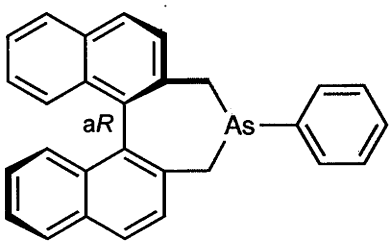
6.2 Preparations

(a*R*)-[{Li(TMEDA)}$_2${2,2'-bis(methylene)-1,1'-binaphthylyl}], (a*R*)-43



This compound was prepared by a modified literature procedure.[100] *n*-Butyllithium (47.0 mL, 1.6 M in hexanes, 75.2 mmol) was placed in a 250 mL Schlenk flask under nitrogen. The hexanes were then removed in vacuo with stirring to leave an oil. Diethyl ether (35 mL) was added to the oil and the solution was cooled to 0 °C. Solid (a*R*)-2,2'-dimethyl-1,1'-binaphthyl (a*R*)-**42**, (7.00 g, 24.79 mmol) was added and the mixture was stirred to dissolve the solid. TMEDA (11.30 mL, 75 mmol) was added slowly by syringe to the solution, which was then allowed to slowly come to RT. The flask was left to stand for at least 12 h before the solution was filtered to collect the air sensitive, deep red prisms of the product. Yield: 8.07 g, (62%).

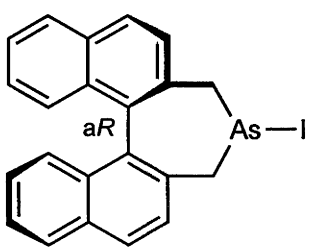
(a*R*)-4-Phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-c;1',2'-e]arsepine, (a*R*)-53



The dilithium complex (a*R*)-**43** (17.86 g, 33.91 mmol) was stirred under freshly distilled *n*-hexane (150 mL) with a magnetic stirrer bar. The suspension was cooled to 0 °C with an ice/water bath and dichlorophenylarsine (4.60 mL, 34.0 mmol) was

added. The temperature of the reaction mixture was maintained at 0 °C for 2 h and was left to stir overnight as it warmed to RT. The reaction vessel was then fitted with a reflux condenser and the suspension was refluxed for 2 h. The *n*-hexane was removed in vacuo and toluene (175 mL) and deoxygenated water (200 mL) were added. The organic layer was separated and the aqueous phase washed with toluene (2 × 25 mL). The combined organic fractions were dried ($MgSO_4$) and the solution filtered through a Schlenk frit. The collected solids were washed with toluene (2 × 50 mL) and the toluene was removed in vacuo. The resulting foam was dissolved in toluene and methanol was added; the product crystallised and was collected, washed with methanol, and dried in vacuo. Yield: 8.34 g (57%); mp > 150 °C dec; $[\alpha]_D^{19}$ = +233.8 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 2.65 (d, 1H, $^2J(^1H^1H)$ = 12.60 Hz, CH*H*), 2.69 (d, 1H, $^2J(^1H^1H)$ = 12.60 Hz, C*H*H), 2.78 (d, 1H, $^2J(^1H^1H)$ = 10.50 Hz, CH*H*), 2.96 (d, 1H, $^2J(^1H^1H)$ = 10.50 Hz, C*H*H), 6.85–7.94 (m, 17H, Ar*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.93, 30.62, 124.62, 124.87, 125.73, 125.93, 126.36, 126.40, 127.00, 127.06, 128.08, 128.12, 128.16, 128.24, 128.38, 132.08, 132.13, 132.49, 132.59, 132.84, 134.87, 135.67, 139.34. EI MS: *m*/*z* 432 ([M]$^+$, 100), 355 amu ([M−Ph]$^+$, 8). Anal. Calcd for $C_{28}H_{21}As$: C, 77.8; H, 4.9. Found: C, 77.5; H, 5.2.

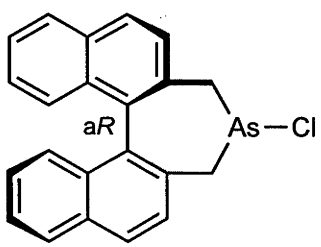
(a*R*)-4-Iodo-4,5-dihydro-3*H*-dinaphtho[2,1-c;1',2'-e]arsepine, (a*R*)-39 (X = I)



The phenylarsepine (a*R*)-**53** (3.47 g, 8.034 mmol) and triiodoarsine (3.70 g, 8.12 mmol) were placed in a Schlenk tube under nitrogen and toluene (15 mL) was

added. The solution was heated under reflux for 24 h. The toluene was removed in vacuo and the resulting oil was dissolved in dichloromethane. The solution was filtered and the filtrate was evaporated under a stream of nitrogen, which resulted in the crystallisation of the crude product. *n*-Hexane was added to cover this solid, and the vessel was sonicated for 1 h. The solid was collected by filtration and the procedure repeated until the product was free of orange diiodophenylarsine. The resulting solid was recrystallised from warm dichloromethane by the addition of methanol, giving yellow needles of the pure product. Yield: 2.90 g (75%); mp > 136 °C dec; $[\alpha]_D^{18} = -249.0$ (*c* 1.0, C_6H_6). ^{1}H NMR (C_6D_6): δ 2.38 (d, 1H, $^2J(^1H^1H)$= 13.20 Hz, CH*H*), 2.68 (d, 1H, $^2J(^1H^1H)$ = 13.20 Hz, C*H*H), 2.84 (d, 1H, $^2J(^1H^1H)$ = 10.95 Hz, CH*H*), 3.00 (d, 1H, $^2J(^1H^1H)$ = 10.95 Hz, C*H*H) 6.88–7.72 (m, 12H, Ar*H*). ^{13}C{^{1}H} NMR (C_6D_6): δ 30.86, 34.95, 125.42, 125.82, 126.06, 126.40, 126.65, 126.70, 127.08, 127.68, 128.54, 128.71, 128.74, 132.56, 133.01, 133.17, 133.46, 133.53, 133.68, 134.59, 134.11 (One resonance obscured by C_6D_6). EI MS: *m*/*z* 482 ([M]$^+$, 38), 355 amu ([M−I]$^+$, 100). Anal. Calcd for $C_{22}H_{16}AsI$: C, 54.8; H, 3.3. Found: C, 54.6; H, 3.6.

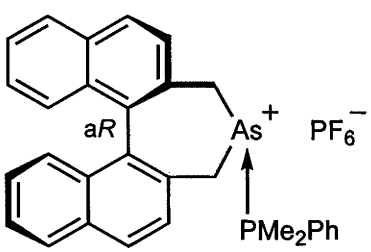
(a*R*)-4-Chloro-4,5-dihydro-3*H*-dinaphtho[2,1-c;1',2'-e]arsepine, (a*R*)-39 (X = Cl)



The iodoarsepine (a*R*)-**39** (X = I) (2.00 g, 4.15 mmol) and freshly prepared silver chloride (2.97 g, 20.74 mmol) were placed in a Schlenk tube under nitrogen and dichloromethane (150 mL) was added. Aluminium foil was used to cover the flask to reduce exposure of the suspension to light and the solution was stirred overnight at

RT. The suspension was filtered to remove silver iodide and unreacted silver chloride. The solvent was removed from the filtrate in vacuo and the residue was recrystallised from a small quantity of boiling ethyl acetate to give colourless prisms of the pure product. Yield: 1.23 g (76%); mp > 137 °C dec; $[\alpha]_D^{19} = -237.0$ (*c* 1.0, C_6H_6). ^1H NMR (CD_2Cl_2): δ 2.70 (d, 1H, $^2J(^1H^1H)$ = 13.5 Hz, CH*H*), 2.76 (d, 1H, $^2J(^1H^1H)$ = 11.0 Hz, C*H*H), 3.15 (d, 1H, $^2J(^1H^1H)$ = 13.5 Hz, C*H*H), 3.49 (d, 1H, $^2J(^1H^1H)$ = 11.0 Hz, CH*H*) 7.14–7.92 (m, 12H, Ar*H*). $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 37.13, 40.16, 125.50, 125.87, 126.31, 126.55, 126.63, 126.82, 126.95, 127.80, 128.58, 128.62, 128.77, 128.90, 132.41, 132.96, 133.04, 133.28, 133.50 (two signals superimposed), 133.87, 133.94. EI MS: *m/z* 390 ($[M]^+$, 88), 355 amu ($[M-Cl]^+$, 6). Anal. Calcd for $C_{22}H_{16}AsCl$: C, 67.6; H, 4.1. Found: C, 67.8; H, 4.4.

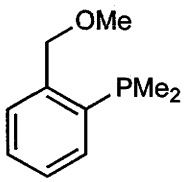
(a*R*)-(Dimethylphenylphosphine-*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] Hexafluorophosphate 1-Dichloromethane, (a*R*)-55·CH_2Cl_2



The iodoarsepine (a*R*)-**39** (X = I) (504 mg, 1.05 mmol) was dissolved in dichloromethane (75 mL) and dimethylphenylphosphine (156 μL, 1.10 mmol) was added via syringe. A solution of potassium hexafluorophosphate (0.97 g, 5.25 mmol) in water (50 mL) was deoxygenated with nitrogen and added to the dichloromethane solution and the two-phase mixture was vigorously stirred for 30 min. The organic phase was separated, dried ($MgSO_4$), and the solvent removed in vacuo. The resulting powder was recrystallised from dichloromethane/diethyl ether to furnish the pure complex. Yield: 0.615 g (92%); mp > 176 °C dec; $[\alpha]_D^{19} = -23.7$ (*c* 1.0,

CH_2Cl_2). ^1H NMR (CD_2Cl_2): δ 2.05 (d, 3H, $^2J(^1H^{31}P)$ = 11.10 Hz, PCH_3), 2.09 (d, 3H, $^2J(^1H^{31}P)$ = 11.10 Hz, PCH_3), 2.98 (d, 2H, $^2J(^1H^1H)$ = 11.70 Hz, CHH), 3.18 (d, 2H, $^2J(^1H^1H)$ = 11.70 Hz, CHH), 7.00–7.99 (m, 17H, ArH). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 5.16 (s), −143.27 (sept, $^1J(^{19}F^{31}P)$ = 711.52 Hz, PF_6^-). ES MS: m/z 493 ($[M]^+$, 69), 355 ($[M-PMe_2Ph]^+$, 67), 139 amu ($[PMe_2Ph]^+$, 100). Anal. Calcd for $C_{31}H_{29}AsCl_2F_6P_2$: C, 51.5; H, 4.0. Found: C, 52.0; H, 4.1. Crystals suitable for X-ray crystallographic analysis were grown from an 2-butanone solution of the complex by the addition of diethyl ether.

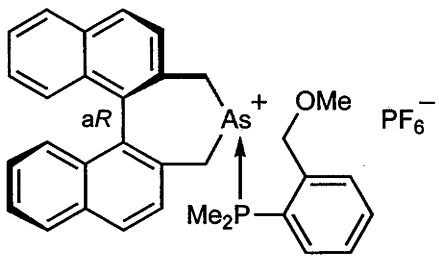
[2-(Methoxymethyl)phenyl]dimethylphosphine, 56



A solution of the Grignard reagent derived from iodomethane (1.90 mL, 30.2 mmol) and magnesium (0.81 g, 33.2 mmol) in diethyl ether (20 mL) at 0 °C was treated with dichloro[2-(methoxymethyl)phenyl]phosphine (**57**)[12] (3.06 g, 13.7 mmol) in diethyl ether (25 mL). After the addition was complete, the reaction mixture was refluxed for 30 min and then cooled to 0 °C. Saturated aq. ammonium chloride (25 mL) was slowly added to the reaction mixture with stirring. The two-phase mixture was left to warm to RT and then it was transferred to a Schlenk separating funnel via cannula. The reaction vessel was washed with diethyl ether (3 × 30 mL) and the organic fractions combined. The organic layer was separated and the aqueous phase extracted with diethyl ether (2 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent removed in vacuo from the filtrate to leave an oil. Distillation gave the colourless product; bp 78 °C (0.7 mmHg). Yield: 1.78 g (70%). ^1H NMR ($CDCl_3$): δ 1.18 (d, 6H, $^2J(^1H^{31}P)$ = 3.30 Hz, PCH_3), 3.32 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2), 7.21–7.40 (m, 4H, ArH).

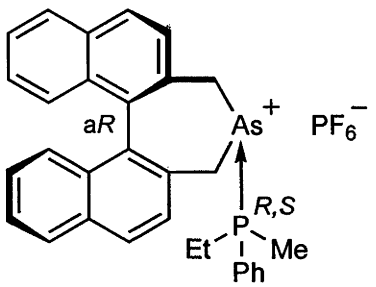
$^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −58.04 (s). EI MS: m/z 183 amu ($[M]^+$, 100). Anal. Calcd for $C_{10}H_{15}OP$: C, 65.9; H, 8.3. Found: C, 66.0; H, 8.4.

(a*R*)(Dimethyl[2-(methoxymethyl)phenyl]phosphine-*O*,*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] Hexafluorophosphate, (a*R*)-58



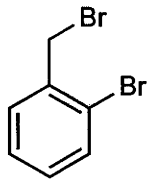
The iodoarsepine (a*R*)-**39** (X = I) (0.503 g, 1.04 mmol) was dissolved in dichloromethane (50 mL) and [2-(methoxymethyl)phenyl]dimethylphosphine (**56**) (0.210 g, 1.15 mmol) was added. A solution of potassium hexafluorophosphate (0.96 g, 5.20 mmol) in water (50 mL) was added to the dichloromethane solution and the two-phase mixture was vigorously stirred for 30 min. The organic phase was separated, dried ($MgSO_4$), and the solution evaporated to dryness. The resulting off-white solid crystallised as X-ray quality crystals from dichloromethane/diethyl ether. Yield: 0.524 g (74%); mp > 145 °C dec; $[\alpha]_D^{19}$ = +147.2 (*c* 1.0, CH_2Cl_2). ^1H NMR (CD_2Cl_2): δ 1.88 (d, 3H, $^2J(^1H^{31}P)$ = 12.50 Hz, PCH_3), 2.13 (d, 3H, $^2J(^1H^{31}P)$ = 12.50 Hz, PCH_3), 2.83–3.31 (m, 4H, CH_2), 3.51 (s, 3H, CH_2OCH_3), 4.73 (d, 1H, $^2J(^1H^1H)$ = 12.50 Hz, CHHOCH$_3$), 4.76 (d, 1H, $^2J(^1H^1H)$ = 13.00 Hz, CHHOCH$_3$), 6.29 (d, 1H, $^3J(^1H^1H)$ = 8.50 Hz, ArH) 6.96–7.99 (m, 15H, ArH). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 4.26 (s), −143.83 (sept, $^1J(^{19}F^{31}P)$ = 711.69 Hz, PF_6^-). ES MS: m/z 537 ($[M]^+$, 5), 355 ($[M-P(CH_3)_2(CH_3OCH_2C_6H_4)]^+$, 8), 183 amu ($[HPCH_3OCH_2C_6H_4))]^+$, 100). Anal. Calcd for $C_{32}H_{31}AsF_6OP_2$: C, 56.3; H, 4.6. Found: C, 56.0; H, 4.4.

(a*R*,*R*$_P$)/(a*R*,*S*$_P$)-(Ethylmethylphenylphosphine-*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] Hexafluorophosphate, (a*R*,*R*$_P$)/(a*R*,*S*$_P$)-59



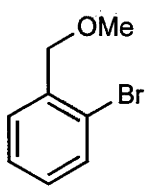
The iodoarsepine (a*R*)-**39** (X = I) (0.144 g, 299 μmol) was dissolved in dichloromethane (20 mL) and (±)-ethylmethylphenylphosphine (50 μL, 314 μmol) was added via syringe. The solution was stirred for 5 h and then a solution of potassium hexafluorophosphate (0.55 g, 2.99 mmol) in water (20 mL) was added; the two-phase mixture was vigorously stirred for 30 min. The organic phase was separated, dried ($MgSO_4$), and the filtrate evaporated to dryness. The resulting powder was recrystallised from dichloromethane/diethyl ether to afford the pure product as a 1/1 mixture of diastereomers. Yield: 0.092 g (47%). ^{1}H NMR (CD_2Cl_2): δ 1.14–1.31 (m, 6H, PCH_2CH_3), 1.81 (d, 3H, $^2J(^1H^{31}P)$ = 13.50 Hz, PCH_3), 2.02 (d, 3H, $^2J(^1H^{31}P)$ = 13.20 Hz, PCH_3), 2.43–2.59 (m, 4H, PCH_2CH_3), 2.84–3.42 (m, 8H, $As(CH_2)_2$), 6.94–8.08 (m, 34H, Ar*H*). ^{31}P{^{1}H} NMR (CD_2Cl_2): δ 12.57 (s), 14.52 (s), −143.27 (sept, $^1J(^{19}F^{31}P)$ = 711.47 Hz, PF_6^-). ES MS: m/z 507 ([M]$^+$, 57), 355 amu ([M−PEtMePh]$^+$, 38). Anal. Calcd for $C_{31}H_{29}AsF_6P_2$: C, 57.1; H, 4.5. Found: C, 56.8; H, 4.8.

2-Bromobenzyl bromide, 60



This compound was prepared by the literature procedure with the following modifications.[117] 2-Bromotoluene (183.6 g, 1.07 mol), water (3.5 L), and bromine (171.6 g, 1.07 mol) were placed in a 5 L round-bottomed flask fitted with a reflux condenser. The solution was irradiated with a tungsten lamp for 2 h with vigorous stirring, which resulted in decolourisation of the solution and warming of the solution by the lamp. Irradiation was continued for an additional 1.5 h to ensure reaction completion. The final solution was brought to RT and dichloromethane (2 × 100 mL) was added to extract the product from the aqueous layer. The aqueous layer was then separated from the organic phase; the latter was dried ($MgSO_4$) and the dichloromethane removed in vacuo. The crude product was distilled to give the pure product as a colourless oil after discarding an initial fraction; bp 120–124 °C (9.5 mmHg) [Lit.[135] 74 °C (0.3 mmHg)]. Yield: 207 g (77%). ^{1}H NMR ($CDCl_3$): δ 4.61 (s, 2H, CH_2Br), 7.15–7.59 (m, 4H, ArH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 33.44, 124.47, 127.93, 130.10, 131.25, 133.33, 136.99.

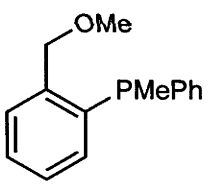
1-Bromo-2-(methoxymethyl)benzene, 61



This compound was prepared by the literature procedure with the following modifications.[118] Sodium (21.50 g, 0.935 mol, large chunks) was added cautiously to methanol (500 mL) under nitrogen in a 1 L, 2-necked flask fitted with a reflux

condenser. The reaction was controlled by cooling the flask in an ice bath. Upon complete reaction of the sodium, the sodium methoxide solution was cooled to 0 °C and 2-bromobenzyl bromide (**60**) (203.2 g, 0.813 mol) was added. The solution was left to warm to RT and then it was heated under reflux for 2 h. The resulting solution was filtered to remove precipitated sodium bromide and water (350 mL) was added to the filtrate. The methanol was removed in vacuo and diethyl ether (3 × 150 mL) was used to extract the product. The combined organic layers were washed with water (2 × 200 mL), brine (100 mL), dried ($MgSO_4$), and filtered. The diethyl ether was removed in vacuo from the filtrate and the crude product distilled; bp 99 °C (15 mmHg) [Lit.[118] 106–107 °C (16 mmHg)]. Yield: 141 g (86%). ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.13–7.55 (m, 4H, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 58.55, 73.81, 122.62, 127.33, 128.84, 128.86, 132.44, 137.46.

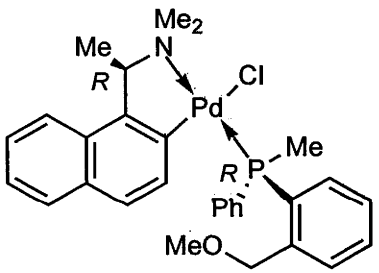
(±)-[2-(Methoxymethyl)phenyl]methylphenylphosphine, (±)-35



This compound was prepared according to a previously published procedure.[12] (±)-Methylphenylphosphine (9.08 g, 73.2 mmol) was dissolved in THF (100 mL), sodium (1.68 g, 73.1 mmol) was added, and the mixture left to stir overnight. Additional sodium (1.0 g, 43.5 mmol) was added and the mixture was stirred for a further 12 h. Excess sodium was removed and the solution was cooled to −78 °C. 1-Bromo-2-(methoxymethyl)benzene (**61**) (15.4 g, 76.82 mmol) in THF (50 mL) was added to the cooled solution of sodium methylphenylphosphide. The reaction mixture was allowed to warm to RT and then it was stirred for 2 h. Deoxygenated water (80 mL) was added, the THF was removed in vacuo, and diethyl ether (50 mL) was added. The two-phase mixture was transferred to a separating funnel, the organic layer

separated, and the aqueous phase extracted with diethyl ether (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and the filtrate evaporated to dryness. The resulting cloudy, orange liquid was distilled to give the pure product; bp 146–148 °C (1.25 mmHg). Yield: 12.5 g (70%). ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 3H, $^2J(^1H^{31}P)$ = 3.90 Hz, PC*H*$_3$), 3.39 (s, 3H, OC*H*$_3$), 4.54 (d, 1H, $^2J(^1H^1H)$ = 12.00 Hz, C*H*H), 4.84 (d, 1H, $^2J(^1H^1H)$ = 11.90 Hz, $^4J(^1H^{31}P)$ = 2.40 Hz, CH*H*), 7.30–7.52 (m, 9H, Ar*H*). ^{31}P{^{1}H} NMR ($CDCl_3$): δ −37.87 (s).

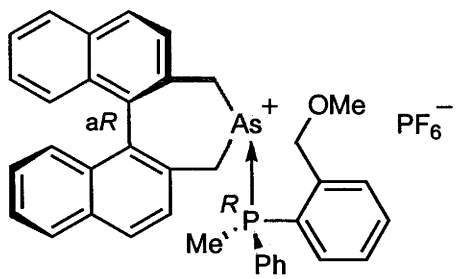
(R_C,R_P)-Chloro[1-[1-(dimethylamino)ethyl]naphthalenyl-*C*,*N*][(2-(methoxymethyl)phenyl)methylphenylphosphine-*P*]palladium(II), (R_C,R_P)-63



The phosphine (±)-**35** (7.12 g, 29.2 mmol) and di-μ-chlorobis[(*R*)-1-[1-dimethylamino)ethyl]-2-naphthalenyl-C^2,*N*]–dipalladium(II) (R_C,R_C)-**12** (12.27 g, 16.0 mmol) were combined in dichloromethane (150 mL) under nitrogen. The resulting solution was stood overnight and then the solvent was removed in vacuo. Methanol (100 mL) was added to dissolve the diastereomers of the complex and the solution was filtered to remove the small excess of palladium(II) dimer. The solution was evaporated to dryness to leave a yellow foam. The ^{31}P{^{1}H} NMR spectrum of a $CDCl_3$ solution of the foam indicated equimolar quantities of the diastereomers (δ_P 14.75 (s), 19.25 (s)). The mixture was recrystallised from acetone, giving the (R_C,R_P) diastereomer as yellow prisms. Yield: 1.10 g (6.5%); mp 200–203 °C dec; $[\alpha]_D^{19}$ = −133.73 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.99 (d,

3H, $^3J(^1H^1H)$ = 6.30 Hz, CHCH_3), 2.26 (d, 3H, $^3J(^1H^{31}P)$ = 10.50 Hz, PCH_3), 2.74 (d, 3H, $^4J(^1H^{31}P)$ = 1.80 Hz, NCH_3), 2.94 (d, 3H, $^4J(^1H^{31}P)$ = 3.60 Hz, NCH_3), 3.28 (s, 3H, CH_2OCH_3), 4.33 (q, 1H, $^3J(^1H^1H)$ = 6.30 Hz, C*H*CH_3), 4.52 (d, 1H, $^2J(^1H^1H)$ = 12.30 Hz, CH*H*), 5.42 (dd, 1H, $^2J(^1H^1H)$ = 12.00 Hz, $^2J(^1H^{31}P)$ = 2.10 Hz, CH*H*), 6.52–8.14 (m, 15H, Ar*H*). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 19.39 (s). EI MS: m/z 585 ($[M]^+$, 10), 229 amu ($[M-C_{15}H_{19}ClNPd]^+$, 100). Anal. Calcd for $C_{29}H_{33}NClOPPd$: C, 59.6; H, 5.7; N, 2.4. Found: C, 59.5; H, 6.0; N, 2.3. The identity of the diastereomer was established by X-ray crystallography.

(a*R*,*R*$_P$)-[(2-(Methoxymethyl)phenyl)methylphenylphosphine-*O*,*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] Hexafluorophosphate, (a*R*,*R*$_P$)-62



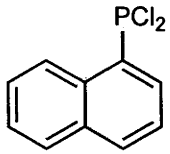
The iodoarsepine (a*R*)-**39** (X = I) (0.54 g, 1.12 mmol) was dissolved in dichloromethane (15 mL) and a solution of (±)-**35** (0.29 g, 1.18 mmol) in dichloromethane (10 mL) was added. The solution was stirred for 3 h and then a solution of potassium hexafluorophosphate (1.04 g, 5.6 mmol) in water (25 mL) was added. The two-phase mixture was vigorously stirred for 60 min and then the organic phase was separated, dried ($MgSO_4$), filtered, and the filtrate evaporated to dryness. The resulting powder was dissolved in a small quantity of dichloromethane and a large quantity of diethyl ether was added to precipitate all of the crude product as a solid. Yield: 0.316 g, (38%). ^1H and $^{31}P\{^1H\}$ NMR spectroscopy of the solid indicated an unequal mixture of the two possible diastereomers of the product,

(δ_H 1.86 (74%, $^2J(^1H^{31}P)$ = 12.00 Hz, PCH_3), δ_H 2.28 (26%, $^2J(^1H^{31}P)$ = 12.90 Hz, PCH_3), δ_P 9.58 (73%), δ_P 12.30 (27%)). The (aR,R_P) diastereomer was obtained pure by three fractional crystallisations of the mixture from dichloromethane by the slow addition of diethyl ether. Yield of the less soluble diastereomer: 0.120 g (14%); mp > 103 °C dec; $[\alpha]_D^{18}$ = +280.3 (c 1.0, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2): δ 1.86 (d, 3H, $^2J(^1H^{31}P)$ = 11.70 Hz, PCH_3), 2.91 (s, 3H, CH_2OCH_3), 2.98–3.36 (m, 4H, As(CH_2)$_2$), 3.93 (d, 1H, $^2J(^1H^1H)$ = 12.90 Hz, CHH), 4.18 (d, 1H, $^2J(^1H^1H)$ = 12.60 Hz, CHH), 6.04 (d, 1H, $^3J(^1H^1H)$ = 8.40 Hz, ArH) 7.01–8.05 (m, 20H, ArH). ^{31}P{^{1}H} NMR (CD_2Cl_2): δ 10.02 (s), −143.37 (sept, $^1J(^{19}F^{31}P)$ = 711.52 Hz, PF_6^-). ES MS: m/z 599 ([M]$^+$, 8), 355 ([M−P(2-CH_3OCH_2)C_6H_4)CH_3Ph]$^+$, 10), 213 amu ([P(2-$CH_2C_6H_4$)CH_3Ph]$^+$, 100). HRMS: Calcd. for $C_{37}H_{33}$AsOP 599.1485. Found: 599.1470.

Determination of Absolute Configuration of Major Diastereomer of (aR,R_P)/(aR,S_P)-62 by Liberation of Phosphine and Complexation with (R_C,R_C)-12

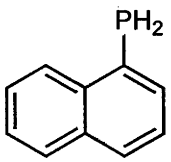
The 74/26 mixture of diastereomers (aR,R_P)/(aR,S_P)-**62** (0.0432 g, 58.8 μmol) was dissolved in dichloromethane (5 mL) and tetraphenylarsonium chloride (0.219 g, 294 μmol) was added. The solution was stirred for ca. 5 min and then (R_C,R_C)-**12** (0.0495 g, 64.7 μmol) was added and the solution left to stand for 1 h. The solvent was removed from the reaction mixture and the product was analysed by ^{31}P{^{1}H} spectroscopy, which indicated unequal quantities of (R_C,S_P)/(R_C,R_P)-**63** (δ_P 14.28 (s, 32%), δ_P 18.92 (s, 68%)).

Dichloro(1-naphthyl)phosphine, 66



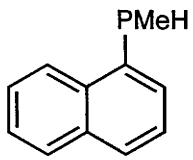
Chlorobis(diethylamino)phosphine (30.0 g, 142 mmol) was dissolved in diethyl ether (75 mL) and added dropwise to a solution of the Grignard reagent prepared from magnesium (4.20 g, 173 mmol) and 1-bromonaphthalene (22.0 mL, 32.5 g, 157 mmol) in diethyl ether (100 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then it was warmed to RT and heated under reflux for 60 min. The mixture was cooled and the solvents were removed in vacuo and *n*-hexane (250 mL) was added to extract the phosphine. The suspension was brought to reflux for 60 min to complete the extraction of the phosphine from the magnesium salts. The mixture was filtered and the solids were washed with *n*-hexane (3 × 50 mL) Anhydrous hydrogen chloride gas was bubbled through the filtrate for 45 min. The solution was filtered to remove $[Et_2NH_2]Cl$, which was washed with *n*-hexane (3 × 50 mL). The combined extracts were concentrated in vacuo to leave an off-white solid. Distillation gave the pure product as a colourless liquid, which crystallised on standing; bp 135–137 °C (0.5 mmHg). Yield: 28.0 g (86%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 164.1 (s). [Lit.[120] $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 164.2 (s)]

1-Naphthylphosphine, 68



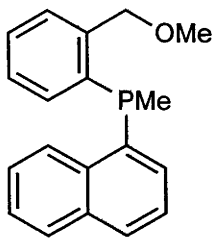
This compound was prepared by the reduction of dichloro(1-naphthyl)phosphine with lithium aluminium hydride, following the literature procedure.[120] Yield: 28.0 g (86%). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ −133.61 (s). [Lit.[120] $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ −133.5 (s)]

(±)-Methyl(1-naphthyl)phosphine, (±)-70



An *n*-butyllithium solution in hexanes (30.7 mL, 76.8 mmol, 2.5 M) was added slowly by syringe to a solution of **68** (11.72 g, 73.2 mmol) in diethyl ether (100 mL) at −78 °C. The solution was allowed to warm to RT whereupon it became a dark orange. This solution was cooled to −78 °C and a solution of iodomethane (4.78 mL, 10.90 g, 76.8 mmol) in diethyl ether (50 mL) was added dropwise with stirring over 5 min. Warming of the solution to RT and stirring overnight resulted in decolourisation of the phosphide. Water (100 mL) was added and the two-phase mixture was transferred to a separating funnel. The organic phase was separated and the aqueous phase was extracted with dichloromethane (5 × 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and the solvents removed in vacuo to leave a turbid oil. Distillation of this material gave the pure product as a colourless oil; bp 114 °C (1.6 mmHg). Yield: 11.9 g (93%); ^{1}H NMR (CD_2Cl_2): δ 1.49 (dd, 3H, $^3J(^1H^1H)$ = 3.30 Hz, $^2J(^1H^{31}P)$ = 7.50 Hz, PCH_3), 4.53 (dq, 1H, $^3J(^1H^1H)$ = 7.50 Hz, $^1J(^1H^{31}P)$ = 212.60 Hz, P*H*), 7.42–8.26 (m, 7H, Ar*H*); ^{31}P{^{1}H} NMR (CD_2Cl_2): δ −79.58 (s). EI MS: m/z 174 ([M]$^+$, 100), 159 ([M−CH_3]$^+$, 70), 128 amu ([M−$PHCH_3$]$^+$, 82). Anal. Calcd for $C_{11}H_{11}P$: C, 75.9; H, 6.4. Found: C, 75.6; H, 6.1.

(±)-[2-(Methoxymethyl)phenyl]methyl-1-naphthylphosphine, (±)-64

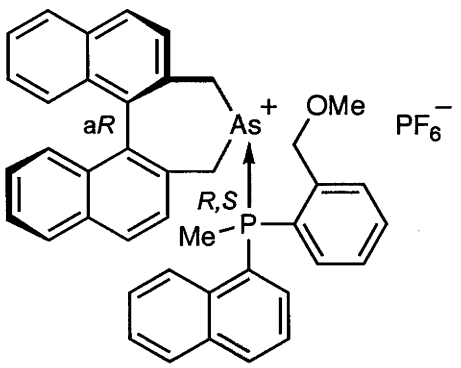


The secondary phosphine (±)-**70** (11.91 g, 68.4 mmol) was dissolved in THF (100 mL). Sodium (1.57 g, 68.4 mmol) was added and the mixture was stirred overnight. Additional sodium (1.29 g, 47.9 mmol) was added and the mixture was stirred for a further 2 h. Excess sodium was removed and the solution was cooled to −78 °C. 1-Bromo-2-(methoxymethyl)benzene (**61**) (14.44 g, 71.8 mmol) dissolved in THF (50 mL) was added to the cooled phosphide solution and the resulting solution was left to warm to RT and then stirred overnight. Deoxygenated water (50 mL) was added to destroy the remaining phosphide. The THF was removed in vacuo and diethyl ether (100 mL) and water (100 mL) were added. The two-phase mixture was transferred to a separating funnel, the organic layer separated, and the aqueous phase extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to dryness. The resulting cloudy liquid was distilled to give the impure product as an oil; bp 170 °C (0.05 mmHg). Repeated attempts at fractional distillations were unsuccessful in improving the purity of the product. The crude phosphine (6.99 g) was dissolved in THF (50 mL), the solution cooled to 0 °C, and borane dimethylsulfide (2.50 mL, 1.99 g, 26.12 mmol) was added dropwise with stirring. The solution was left to warm to RT and then it was stirred overnight. The THF was removed in vacuo to leave a viscous oil of the borane adduct of the phosphine. Purification of this mixture was accomplished by silica gel column chromatography of 5.30 g of the crude material with use of toluene as the eluant. The pure borane–phosphine adduct (±)-**64**·BH_3 was thus isolated as an oil, which crystallised as a colourless solid on standing. Yield: 2.32 g (45%); mp

127–130 °C; ^{1}H NMR (CD_2Cl_2): δ 1.14 (br q, 3H, $^1J(^1H^{11}B)$ = 109.82 Hz, BH_3) 2.07 (d, 3H, $^2J(^1H^{31}P)$ = 9.90 Hz, PCH_3), 2.94 (s, 3H, OCH_3), 3.96 (d, 1H, $^2J(^1H^1H)$ = 12.30 Hz, CHH), 4.26 (d, 1H, $^2J(^1H^1H)$ = 12.30 Hz, CHH), 7.29–7.35 (m, 1H, ArH), 7.43–7.55 (m, 4H, ArH), 7.59–7.65 (m, 1H, ArH), 7.80–7.93 (m, 3H, ArH), 8.05–8.20 (m, 2H, ArH). ^{31}P{^{1}H} NMR (CD_2Cl_2): δ 10.20 (br d, $^1J(^{11}B^{31}P)$ = 153.11 Hz). EI MS: m/z 308 ([M]$^+$, 20), 294 ([M−BH_3]$^+$, 55), 279 amu ([M−(CH_3BH_3)]$^+$, 100). Anal. Calcd for $C_{19}H_{22}BOP$: C, 74.1; H, 7.2. Found: C, 73.8; H, 7.2.

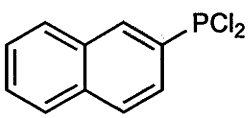
The borane adduct, (±)-**64**·BH_3, (2.32 g, 7.53 mmol) was dissolved in morpholine (25 mL) and the solution was heated at 100 °C for 3 h. The volatiles were removed in vacuo and water (25 mL) and dichloromethane (40 mL) were added and the two-phase mixture stirred for 15 min. The aqueous phase was extracted and the organic phase washed with water (2 × 25 mL), dried ($MgSO_4$), and filtered. The volatiles were removed in vacuo, leaving an oil that crystallised on standing. Yield: 1.83 g (82%); mp 59–62 °C; ^{1}H NMR (CD_2Cl_2): δ 1.65 (d, 3H, $^2J(^1H^{31}P)$ = 4.95 Hz, PCH_3), 3.37 (s, 3H, OCH_3), 4.58 (d, 1H, $^2J(^1H^1H)$ = 11.70 Hz, CHH), 4.90 (dd, 1H, $^2J(^1H^1H)$ = 11.70 Hz, $^4J(^1H^{31}P)$ = 2.40 Hz, CHH), 7.12–7.16 (m, 1H, ArH), 7.28–7.33 (m, 1H, ArH), 7.40–7.50 (m, 5H, ArH), 7.84–7.88 (m, H, ArH), 8.31–8.84 (m, 1H, ArH). ^{31}P{^{1}H} NMR (CD_2Cl_2): δ −47.64 (s). EI MS: m/z 294 ([M]$^+$, 55), 279 amu ([M−(CH_3)]$^+$, 100). Anal. Calcd for $C_{19}H_{29}OP$: C, 77.5; H, 6.5. Found: C, 77.2; H, 6.5.

(a*R*,*R*$_P$)/(a*R*,*S*$_P$)-[(2-(Methoxymethyl)phenyl)methyl-1-naphthylphosphine-*O*,*P*)[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] hexafluorophosphate, (a*R*,*R*$_P$)/(a*R*,*S*$_P$)-72



The iodoarsine (a*R*)-**39** (X = I) (521 mg, 1.08 mmol) was dissolved in dichloromethane (25 mL) and (±)-**64** (334 mg, 1.14 mmol) in dichloromethane (10 mL) was added. After stirring for 3 h, a solution of potassium hexafluorophosphate (1.00 g, 5.4 mmol) dissolved in distilled water (25 mL) was added to the dichloromethane solution and the two-phase mixture was vigorously stirred for 1 h. The organic phase was separated, dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting powder was dissolved in a small quantity of dichloromethane and re-precipitated with a large excess of diethyl ether. Yield: 0.130 g, (15%). ^{1}H and ^{31}P{^{1}H} NMR spectroscopy of the solid indicated an unequal mixture of diastereomers, δ_P 7.89 (s, 43%), δ_P 9.39 (s, 57%)). ES MS: m/z 649 ([M]$^+$, 21), 389 amu ([M−P(2-MeOCH$_2$C$_6$H$_4$)Me(C$_{10}$H$_7$)]$^+$, 13). HRMS: Calcd. for $C_{41}H_{35}AsOP$ 649.164150. Found: 649.161999.

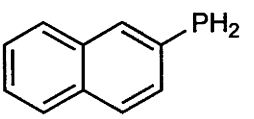
Dichloro(2-naphthyl)phosphine, 67



This compound was prepared by the literature procedure with the following modifications.[121] Chlorobis(diethylamino)phosphine (30.0 g, 142 mmol) in THF (75 mL)

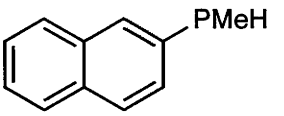
was added dropwise to a solution of the Grignard reagent prepared from magnesium turnings (4.20 g, 173 mmol) and 2-bromonaphthalene (32.5 g, 157 mmol) in diethyl ether (100 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, warmed to RT, and then heated under reflux for 60 min. The solvents were removed in vacuo and *n*-hexane (250 mL) was added to dissolve the phosphine. The suspension was brought to reflux for 60 min to complete extraction of the phosphine from the magnesium salts. The resulting solution was filtered and the collected solids were washed with *n*-hexane (3 × 50 mL). Anhydrous hydrogen chloride was bubbled through the filtrate for 45 min. The solution was filtered, the collected solids washed with *n*-hexane (3 × 50 mL), and the combined filtrates were concentrated in vacuo to leave an off-white solid. Distillation of this material gave a colourless liquid, which crystallised on standing; bp 138 °C (1.75 mmHg) [Lit.[121] bp 100 °C (0.2 mmHg)]; mp 70–71 °C. Yield: 28.2 g (86.5%); ^{1}H NMR (CD_2Cl_2): δ 7.58–8.36 (m, 7H, Ar*H*); $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 161.79. EI MS: m/z 228 ($[M]^+$, 5), 192 ($[M-Cl]^+$, 48), 128 amu ($[M-PCl_2]^+$, 100).

2-Naphthylphosphine, 69



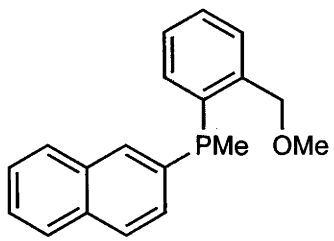
This compound was prepared by a procedure similar to the one used for 1-naphthylphosphine.[120] Yield: 11.9 g, (95%); $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ −122.53 (s). [Lit.[136] $^{31}P\{^1H\}$ NMR ($CDCl_3$) −122.0 (s)]

(±)-Methyl(2-naphthyl)phosphine, (±)-71



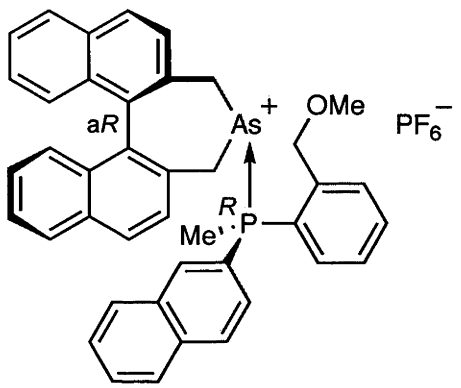
An *n*-butyllithium solution in hexanes (31.1 mL, 77.8 mmol, 2.5 M) was added slowly by syringe to a solution of **69** (11.86 g, 74.1 mmol) dissolved in THF (100 mL) at −78 °C. The solution was allowed to warm to RT and stirred for 30 min, resulting in a dark orange solution of the corresponding phosphide. This solution was cooled to −78 °C and a solution of iodomethane (4.61 mL, 10.51 g, 74.1.8 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 5 min and then it was warmed to RT and stirred overnight. The decolourised solution was treated with water (100 mL) and the THF was removed in vacuo. Diethyl ether (150 mL) was added and the two-phase mixture was transferred to a separating funnel. The organic phase was separated and the aqueous phase was extracted with dichloromethane (5 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo to leave a turbid oil. Distillation of this oil gave the colourless product, which crystallised on standing; bp 122 °C (2.5 mmHg); mp 33–34 °C. Yield: 10.35 g (80%); ^{1}H NMR (CD_2Cl_2): δ 1.49 (dd, 3H, $^3J(^1H^1H)$ = 3.00 Hz, $^2J(^1H^{31}P)$ = 7.80 Hz, PCH_3), 4.37 (dq, 1H, $^3J(^1H^1H)$ = 7.80 Hz, $^1J(^1H^{31}P)$ = 216.20 Hz, P*H*), 7.45–8.00 (m, 7H, Ar*H*); $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ −69.77 (s). EI MS: *m*/*z* 174 ($[M]^+$, 100), 159 ($[M-CH_3]^+$, 50), 128 amu ($[M-PHCH_3]^+$, 75). Anal. Calcd for $C_{11}H_{11}P$: C, 75.9; H, 6.4. Found: C, 76.0; H, 6.2.

(±)[2-(Methoxymethyl)phenyl]methyl(2-naphthyl)phosphine, (±)-65



The secondary phosphine (±)-**71** (10.03 g, 57.6 mmol) was dissolved in THF (100 mL), sodium (1.39 g, 60.5 mmol) was added, and the solution left to stir overnight. Additional sodium (1.10 g, 47.9 mmol) was added and the solution was stirred for a further 2 h. The excess sodium was then removed and the solution was cooled to −78 °C. 1-Bromo-2-(methoxymethyl)benzene (**61**) (12.16 g, 60.5 mmol) in THF (50 mL) was added to the cooled phosphide solution and the resulting solution was left to come to RT and stirred overnight. Deoxygenated water (50 mL) was added to destroy any remaining phosphide. All volatiles were removed in vacuo and diethyl ether (100 mL) and water (100 mL) were added. The two-phase mixture was transferred to a separating funnel, the organic layer separated, and the aqueous phase extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and the volatiles removed in vacuo. The resulting cloudy liquid was fractionally distilled to give the pure product as a colourless viscous oil, which crystallised on standing; bp 168 °C (0.05 mmHg); mp 54–55 °C. Yield: 7.63 g (45%); ^{1}H NMR (CD_2Cl_2): δ 1.67 (d, 3H, $^2J(^1H^{31}P)$ = 3.90 Hz, PCH_3), 3.35 (s, 3H, OCH_3), 4.56 (d, 1H, $^2J(^1H^1H)$ = 11.70 Hz, CHH), 4.82 (dd, 1H, $^2J(^1H^1H)$ = 11.70 Hz, $^4J(^1H^{31}P)$ = 2.10 Hz, CHH), 7.26–7.92 (m, 4H, ArH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −37.87. EI MS: m/z 294 ([M]$^+$, 55), 279 amu ([M−(CH_3)]$^+$, 100). Anal. Calcd for $C_{19}H_{29}OP$: C, 77.5; H, 6.5. Found: C, 77.5; H, 6.8.

(a*R*,*R*$_P$)-[(2-(Methoxymethyl)phenyl)methyl(2-naphthyl)phosphine-*O*,*P*)-[2,2'-bis(methylene)-1,1'-binaphthylarsepinenium] Hexafluorophosphate, (a*R*,*R*$_P$)-73



The iodoarsine (a*R*)-**39** (X = I) (0.523 g, 1.08 mmol) was dissolved in dichloromethane (25 mL) and (±)-**65** (0.335 g, 1.14 mmol) in dichloromethane (10 mL) was added and the solution stirred for 3 h. A solution of potassium hexafluorophosphate (1.00 g, 5.4 mmol) in water (25 mL) was added to the dichloromethane solution and the two-phase mixture was vigorously stirred for 60 min. The organic phase was separated, dried ($MgSO_4$), and the dichloromethane removed in vacuo. The resulting powder was dissolved in a small quantity of dichloromethane and diethyl ether was added to precipitate the solid. Yield: 0.40 g, (47%). ^{1}H and ^{31}P{^{1}H} NMR spectroscopy of the precipitated solid indicated an unequal mixture of diastereomers, (δ_H 1.96 (79%, $^2J(^1H^{31}P)$ = 12.00 Hz, PCH_3), δ_H 2.37 (21%, $^2J(^1H^{31}P)$ = 12.90 Hz, PCH_3), δ_P 10.14 (79%), δ_P 12.73 (21%)). Fractional crystallisation of the mixture was achieved by the addition of diethyl ether to a dichloromethane solution of the mixture. Yield of the less soluble diastereomer: 0.185 g (22%); mp > 165 °C dec; $[\alpha]_D^{18}$ = +221.0 (*c* 1.0, acetone). ^{1}H NMR (CD_2Cl_2): δ 1.95 (d, 3H, $^2J(^1H^{31}P)$ = 11.70 Hz, PCH_3), 2.89 (s, 3H, CH_2OCH_3), 3.02–3.42 (m, 4H, As(CH_2)$_2$), 3.90 (d, 1H, $^2J(^1H^1H)$ = 11.70 Hz, CH*H*), 4.39 (d, 1H, $^2J(^1H^1H)$ = 12.60 Hz, C*H*H), 6.07 (d, 1H, $^3J(^1H^1H)$ = 8.40 Hz, Ar*H*) 6.98–8.24 (m, 22H, Ar*H*). ^{31}P{^{1}H} NMR (CD_2Cl_2):

δ 9.61 (s), -143.88 (sept, $^1J(^{19}F^{31}P) = 711.08$ Hz, PF_6^-). ES MS: m/z 649 ($[M]^+$, 28), 389 ($[M-P(2\text{-}MeOCH_2C_6H_4)Me(C_{10}H_7)]^+$, 4), 213 amu ($[P(2\text{-}CH_2C_6H_4)Me_2Ph]^+$, 100). HRMS: Calcd. for $C_{41}H_{35}AsOP$ 649.16415. Found: 649.16160. Crystals suitable for X-ray crystallographic analysis were grown from a 2-butanone solution of the pure diastereomer by the addition of diethyl ether.

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