Synthesis of P-Stereogenic Bisphosphine Ligands: Application as Hemi-labile Ligands in the Asymmetric Pauson-Khand Reaction

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by

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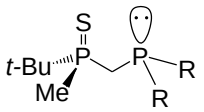
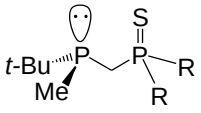
Abstract

The synthesis of new *P*-stereogenic ligands and investigation of their use in a Co-catalysed asymmetric Pauson-Khand reaction has been carried out. The ligands were synthesised by asymmetric lithiation of a phosphine sulfide or a phosphine borane using alkyllithium/(–)-sparteine complexes, trapping with Ph_2PCl or *t*-Bu_2PCl and treatment with BH_3•Me_2S or sulfur. This gave *P*-stereogenic bisphosphines. To afford highly enantioenriched ligands, the bisphosphines were recrystallised to increase the enantiomeric ratio up to 99:1 er.

After borane deprotection of the bisphosphines using DABCO, hemi-labile ligands **A** and **B** were obtained. These hemi-labile ligands contain a phosphorus lone pair as a strong coordinating group and a sulfur lone pair on the P=S group as a weak coordinating group. The sensitivity after deboronation to oxidation to the phosphine oxide was studied through ^{1}H and ^{31}P NMR spectra. To evaluate the new hemi-labile ligands, they were used as a coordinating ligand with $Co_2(CO)_8$ in a catalytic asymmetric intramolecular Pauson-Khand reaction of a 1,6-enyne to a cyclopentenone.



A



B

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Author’s Declaration

The research presented in this thesis is, to the best of my knowledge, original except where due reference has been made to other authors and / or co-workers.

Chehasnah Haji-Cheteh

Abbreviations

$[\alpha]_D$	optical rotation
aq	aqueous
Ar	aryl
atm	atmosphere
br	broad
BisP*	1,2-bis-(alkylmethylphosphino)ethanes
calcd	calculated
cm^{-1}	wavenumber
CSP	chiral stationary phase
d	doublet
dd	double doublet
ddd	double double doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DiPAMP	1,2-bis[(*o*-methoxyphenyl)phenylphosphino]ethane
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
L-DOPA	L-3,4-dihydroxyphenylalanine
dr	diastereomeric ratio
dt	doublet of triplets
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
eq.	equivalent
ee	enantiomeric excess

er	enantiomeric ratio
ESI	electrospray ionization
g	grams
h	hours
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IR	infrared spectroscopy
J	coupling constant
m	meta
M	molar (mol dm^{-3})
mg	milligrams
min	minutes
MiniPHOS	bis(alkylmethylphosphino)methanes
mL	millilitres
mmol	millimoles
mol%	percent by moles
MS	mass spectrometry
Mp	melting point
n	normal
NMR	nuclear magnetic resonance
o	ortho
p	para

ppm	parts per million
PMDETA	*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine
q	quartet
QuinoxP*	2,3-bis(*tert*-butylmethylphosphino)quinoxaline
rac	racemic
R_F	retention factor
rt	room temperature (18-25 ˚C)
s	*sec*, secondary
s	singlet
(–)-sp	(–)-sparteine
t	triplet
t-BuBisP*	1,2-bis-((*tert*-butyl)methylphosphino)ethane
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
p-TsCl	*para*-toluenesulfonyl chloride
tt	triplet of triplets

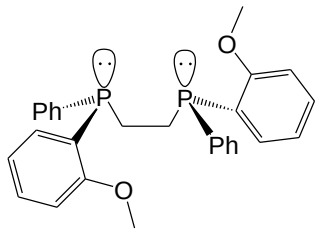
Contents

1. Introduction

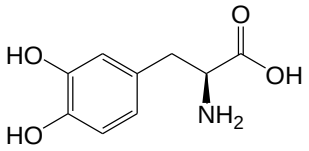
1.1 Introduction to *P*-Stereogenic Phosphine Ligands

In the past few decades, *P*-stereogenic compounds have become very important in organic synthesis because of their role as chiral ligands in asymmetric synthesis. In particular, *P*-stereogenic bisphosphines have been explored and applied as powerful ligands for many reactions.[1-6] For example, in 1968, Knowles reported the synthesis of the *P*-chiral bisphosphine DiPAMP (Figure 1.1) and its use as an effective ligand complexed with Rh for the asymmetric hydrogenation of alkenes.[7] The Rh complex of DiPAMP was then applied to synthesize L-DOPA (Figure 1.1), a medicine for the treatment of Parkinson's disease.[8]

Figure 1.1



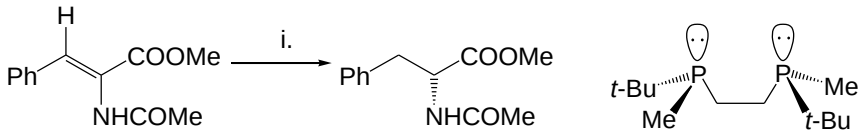
(*R*,*R*)-DiPAMP



L-DOPA

The development of other *P*-stereogenic ligands was slow because there were no good synthetic routes.[9] In 1998, BisP* ligands were prepared by Imamoto[10] and their Rh-complexes were utilized as catalysts in the enantioselective hydrogenation of α-(acylamino)acrylates **1**. Hydrogenation of alkene **1** using a (*S*,*S*)-*t*-BuBisP*/Rh complex gave (*R*)-**2** in 99.9% ee (Scheme 1.1).

Scheme 1.1



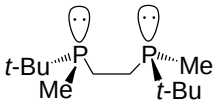
1 (*R*)-**2,** 99.9% ee (*S*,*S*)-*t*-BuBisP*

Reagents and conditions: i. *(S,S)-t*-BuBisP*-Rh (0.2 mol%), H_2 (2 atm), rt, 0.2-2 h, MeOH.

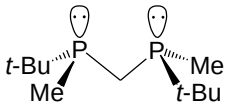
The successful application of BisP* led to increased interest in the synthesis and use of *P*-stereogenic ligands. Not only have *P*-stereogenic phosphines achieved high enantioselectivity but C_2-symmetric ligands were also one of the important structural features for potential new chiral ligands. A selection of the most useful and widely

used chiral bisphosphines are shown in Figure 1.2. Thus, Imamoto developed the C_2-symmetric bisphosphines *t*-BuBisP*,[10] *t*-BuMiniPHOS[11,12] and QuinoxP*.[13] Hoge explored the *P*-chiral trichickenfootphos.[14] Finally, Zhang developed several chiral ligands including TangPhos,[15] DuanPhos[16] and, most recently in 2010, ZhangPhos.[17]

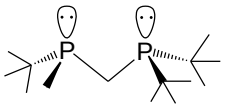
Figure 1.2



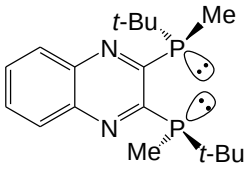
t-BuBisP*



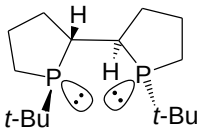
t-BuMiniPHOS



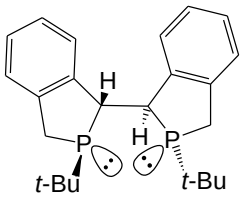
Trichickenfootphos



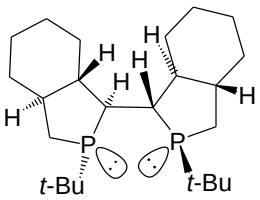
QuinoxP*



TangPhos



DuanPhos



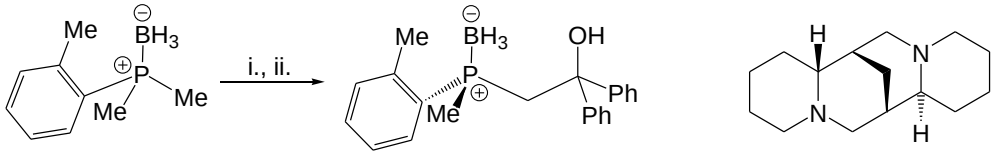
ZhangPhos

1.2 Synthesis of *P*-Stereogenic Phosphine Boranes using Organolithium Reagents and Chiral Diamines

1.2.1 Asymmetric Synthesis of Ethylene-bridged Phosphines

The difficulties of the asymmetric synthesis of *P*-stereogenic phosphines led Evans to develop a convenient method to acquire *P*-chiral diphosphines *via* enantioselective deprotonation using an alkyllithium/(−)-sparteine chiral base.[18] In this study, alkyllithium reagents and solvents were optimized to obtain the highest enantioselectivity. Thus, for the enantioselective deprotonation of phosphine boranes, a *s*-BuLi/(−)-sparteine complex was used as the preferred chiral base and Et_2O was the optimal solvent. An example is shown in Scheme 1.2. Asymmetric deprotonation of dimethyl-*o*-tolylphosphine borane **3** by *s*-BuLi in the presence of (−)-sparteine (Et_2O, −78 ˚C) and trapping with benzophenone gave hydroxy phosphine borane (*S*)-**4** in 84% yield and 87% ee after purification by chromatography.

Scheme 1.2



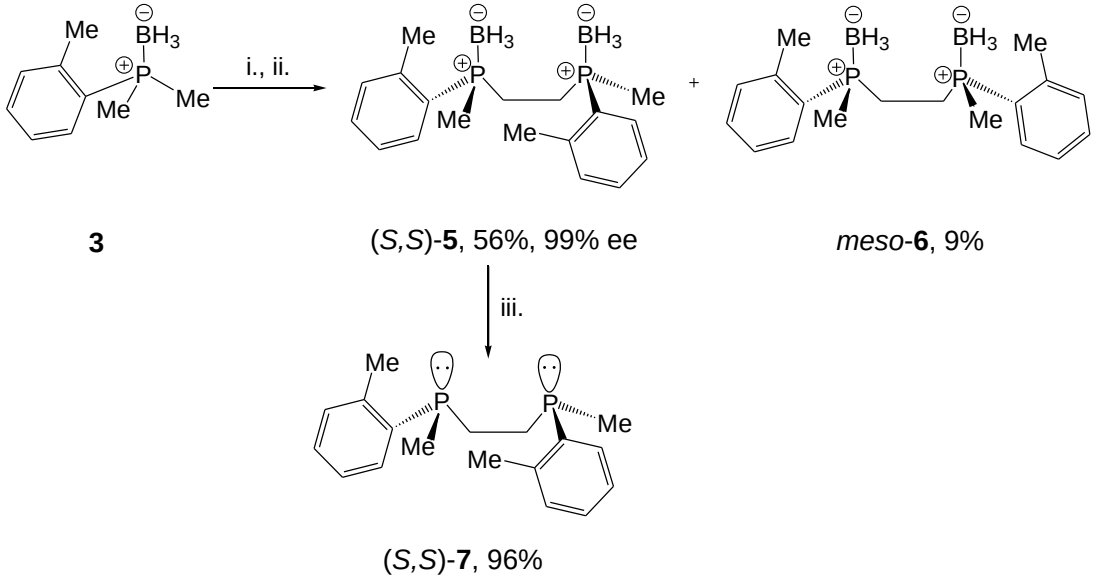
3 (*S*)-**4**, 84%, 87% ee (−)-sparteine

Reagents and conditions: i. *s*-BuLi (1.1 eq.), (−)-sparteine (1.1 eq.), −78 ˚C, 3 h, Et_2O; ii. Ph_2CO (1.1 eq.), −78 ˚C to −20 ˚C, 3 h, THF.

Having developed a convenient method for the asymmetric deprotonation of phosphines, Evans then applied it to the synthesis of C_2-symmetric bisphosphines. The synthesis of diphosphines depended upon the enantioselective deprotonation of aryldimethylphosphine boranes and subsequent oxidative coupling with copper(II) pivalate to afford the desired C_2-symmetric products (Scheme 1.3). The result of oxidative coupling provided the enantiomerically enriched diastereomer (*S*,*S*)-**5** in 56% yield with 99% ee and the *meso* diastereomer **6** as a minor product (9% yield). After separation by flash chromatography, the C_2-symmetric diastereomer (*S*,*S*)-**5**

had the borane protecting group removed by treatment with excess diethylamine to give diphosphine (*S,S*)-**7** in 96% yield (Scheme 1.3).

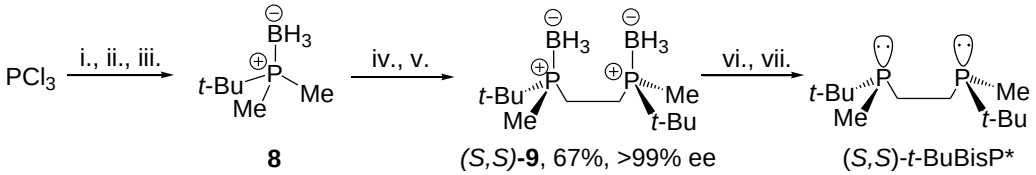
Scheme 1.3



Reagents and conditions: i. *s*-BuLi (1.1 eq.), (−)-sparteine (1.1 eq.), −78 ˚C, 3 h, Et_2O; ii. $Cu(OPiv)_2$ (3.0 eq.), −78 ˚C to −20 ˚C, 3 h, THF; iii. excess Et_3N, 55 ˚C, 8 h.

Based on Evans' work, Imamoto explored the preparation of *P*-chiral bis(trialkylphosphine) ligands. A main characteristic of Imamoto's ligands is that a bulky alkyl group and methyl group (the smallest group) are bonded to each phosphorus atom.[10] To synthesise *(S,S)-t*-BuBisP* (Scheme 1.4)[10,19] for instance, *t*-butyldimethylphosphine borane **8** was prepared from commercially available PCl_3 by reaction with *t*-butyl magnesium chloride, followed by a second reaction with methyl magnesium chloride and protection as the borane adduct. Phosphine borane **8** was then deprotonated by *s*-BuLi/(−)-sparteine and the lithiated intermediate was dimerised using copper(II) chloride to give bisphosphine borane (*S,S*)-**9** in 67% yield and 99% ee after recrystallisation. Deprotection using trifluoromethanesulfonic acid and KOH afforded (*S,S*)-*t*-BuBisP*. In comparison with other 1,2-bis(alkylmethylphosphino)ethanes (alkyl = 1-adamantyl, *t*-butyl, 1,1-diethylpropyl, cyclopentyl, cyclohexyl), (*S,S*)-*t*-BuBisP* was the most useful because not only could it be synthesised from inexpensive starting materials but it also gave high enantioselectivity in several catalytic asymmetric reactions when it was complexed to transition metals.[20,21]

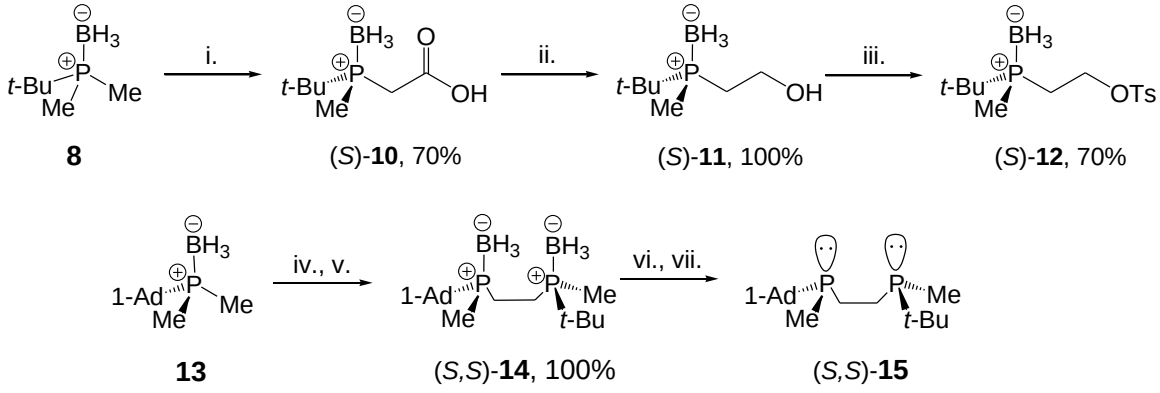
Scheme 1.4



Reagents and conditions: i. *t*-BuMgCl (1.1 eq.), −78 ˚C for 2 h, rt for 1 h, THF; ii. MeMgCl (2.4 eq.), 0 ˚C, 1 h; iii. BH_3-THF (1.5 eq.), 0 ˚C, 1 h; iv. *s*-BuLi (1.2 eq.), (−)-sparteine (1.2 eq.), −78 ˚C, 3 h, Et_2O; v. $CuCl_2$ (1.5 eq.) −78 ˚C to rt, 2 h; vi. excess TfOH, 0 ˚C for 30 min, rt; vii. aq. KOH, 50 ˚C for 1-2 h.

Three years later, unsymmetric *P*-stereogenic bisphosphines with alkyl groups attached to the two phosphorus atoms were reported by Imamoto and Ohashi.[22] 1-Ad-*t*-BuBisP* (*S,S*)-**15** was prepared from a convergent synthetic route (Scheme 1.5). Thus, *t*-butylphosphine borane **8** was enantioselectively deprotonated by *s*-BuLi/(−)-sparteine and then reacted with CO_2 to afford acid (*S*)-**10** in 70% yield. Reduction of the carboxylic acid (*S*)-**10** by BH_3-THF provided a quantitative yield of alcohol (*S*)-**11** which was then reacted with *p*-TsCl to give tosylate (*S*)-**12**. Compound (*S*)-**12** was then coupled with lithiated 1-adamantylmethylphosphine borane **13** to afford bisphosphine borane adduct (*S,S*)-**14** in quantitative yield. To deprotect the borane, trifluoromethanesulfonic acid and KOH in EtOH were added to obtain 1-Ad-*t*-BuBisP* (*S,S*)-**15** (Scheme 1.5).

Scheme 1.5

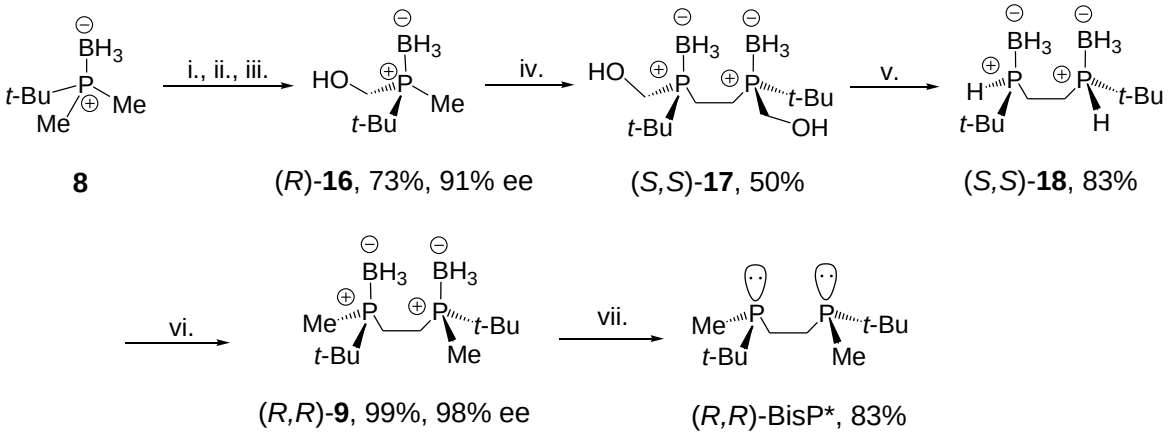


Reagents and conditions: i. (a) *s*-BuLi/(−)-sparteine, Et_2O, −78 ˚C, 3 h (b) CO_2; ii. BH_3-THF, THF, 0 ˚C, 1 h; iii. *p*-TsCl, Py, −15 ˚C, 1 h; iv. *n*-BuLi, THF, 0 ˚C, 20 min; v. Tosylate (*S*)-**12**, 55 ˚C, 10 min; vi. TfOH, toluene, rt, 20 min; vii. KOH/EtOH, 55 ˚C, 2 h.

On the other hand, in 2002 Mezzetti reported a synthesis of bisphosphines bearing bulky, highly symmetric substituents on the two phosphorus atoms but the % ee of the products was disappointingly low (18-37% ee).[24]

To develop a route to (*R,R*)-BisP*, Imamoto synthesised optically active secondary diphosphine (*S,S*)-**18**[25] by adopting Evans' procedure.[18] Thus, phosphine borane **8** was enantioselectively deprotonated by *s*-BuLi in the presence of (−)-sparteine and reacted with triethyl phosphite and O_2 at −78 ˚C for 1 hour to give hydroxymethyl phosphine borane (*R*)-**16** in 73% yield and 91% ee.[26] Hydroxy phosphine borane (*R*)-**16** was then deprotonated by *s*-BuLi and the lithiated intermediate was oxidatively coupled using $CuCl_2$ to give bisphosphine borane (*S,S*)-**18** in 50% yield. Hydrolysis in the presence of $K_2S_2O_8$ and $RuCl_3.3H_2O$ yielded secondary diphosphine (*S,S*)-**18** in 83% yield. Bisphosphine (*S,S*)-**18** was lithiated using *n*-BuLi and trapped with MeI to provide bisphosphine borane (*R,R*)-**9** in 99% yield with 98% ee. Finally, deboronation gave (*R,R*)-BisP* in 83% yield (Scheme 1.6).[25]

Scheme 1.6

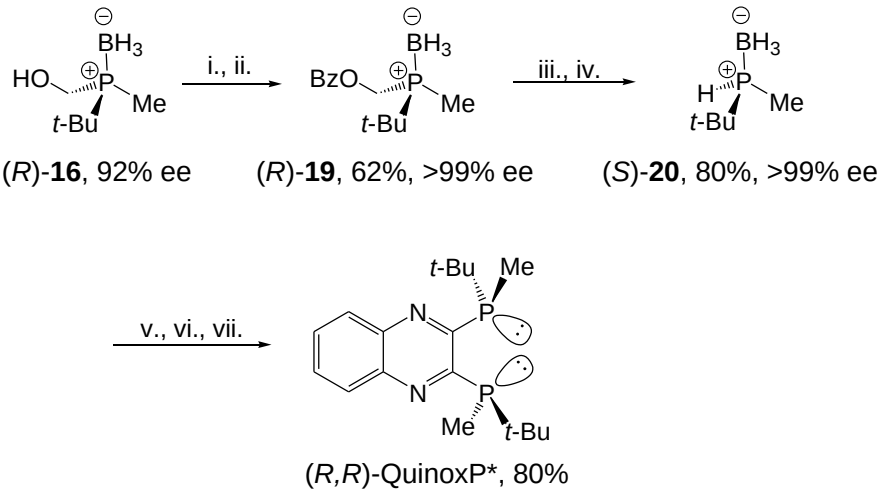


Reagents and conditions: i. *s*-BuLi/(−)-sparteine, Et_2O, −78 ˚C, 3 h; ii.,$(EtO)_3P$, −78 ˚C; iii. O_2, −78 ˚C, 1 h; iv. (a) *s*-BuLi, −78 ˚C, 1 h then −25 ˚C, 4 h, THF (b). $CuCl_2$, 2 h; v. $K_2S_2O_8$, KOH, H_2O, 0 ˚C, then $RuCl_3.3H_2O$; vi. (a) *n*-BuLi, −78 ˚C, 30 min, THF (b) MeI, 0 ˚C, CH_2Cl_2; vii. deboronation.

Although a number of *P*-stereogenic phosphines were developed and subsequently used in transition metal-catalyzed asymmetric reactions,[3,27] the ligands were typically air-sensitive due to the high electron density at the two phosphorus atoms.[10,11,13,19] Consequently, this problem prompted Imamoto to explore a novel and versatile ligand, (*R,R*)-QuinoxP*.[13] The synthesis of this ligand started with benzoylation of hydroxyl phosphine borane (*R*)-**16** (obtained in 92% ee by

asymmetric deprotonation using *s*-BuLi/(−)-sparteine). This was followed by recrystallisation (two times) to obtain enantiomerically pure benzoyl phosphine borane (*R*)-**19** in 62% yield and >99% ee. Then, phosphine borane (*R*)-**19** was hydrolysed under KOH/EtOH conditions and subsequent ruthenium-catalyzed oxidation to cleave one carbon in the presence of $K_2S_2O_8$ gave phosphine borane (*S*)-**20** in 80% yield with >99% ee. Next, *n*-BuLi was added to deprotonate phosphine borane (*S*)-**20** and the lithiated intermediate was reacted with 2,3-dichloroquinoxaline. Finally, treatment with TMEDA afforded ligand (*R,R*)-QuinoxP* in 80% yield (Scheme 1.7). This ligand was remarkably neither oxidized nor epimerized at the *P*-stereogenic position even when it was kept in the air at room temperature for more than 6 months.[13]

Scheme 1.7

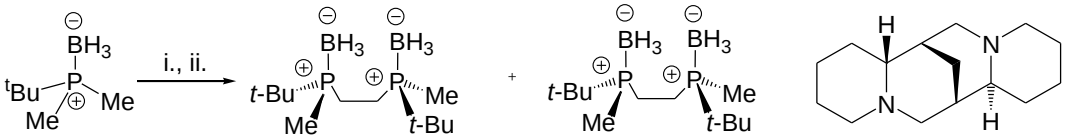


Reagents and conditions: i. BzCl, 0 ˚C to rt, pyridine; ii. recrystallisation, EtOAc; ii. KOH/EtOH; iv. $RuCl_3$ (5 mol %), $K_2S_2O_8$, 2 h; v. *n*-BuLi, −78 ˚C, THF; vi. 2,3-dichloroquinoxaline, −78 ˚C to rt, THF; vii. TMEDA, rt, 2 h.

Over the past 20 years, most of asymmetric methods that have been utilized to prepare bisphosphines use stoichiometric quantities of chiral auxiliaries or chiral ligands. Compared to stoichiometric conditions, the development of catalytic asymmetric synthesis of bisphosphine ligands is challenging. In 2006, O'Brien[28] introduced catalytic asymmetric lithiation-dimerization of phosphine borane **8** using (−)-sparteine and the (+)-sparteine surrogate.[29-32] To achieve a catalytic asymmetric synthesis of (*S,S*)-**9**, phosphine borane **8** was enantioselectively deprotonated using *s*-BuLi in the presence of 0.2 equivalents of (−)-sparteine. The lithiated intermediate

was then homocoupled using 1.6 equivalents of $CuCl_2$ to obtain (*S,S*)-**9** in 48% yield (≥99:1 er) and *meso*-**21** in 27% yield (Scheme 1.8).

Scheme 1.8

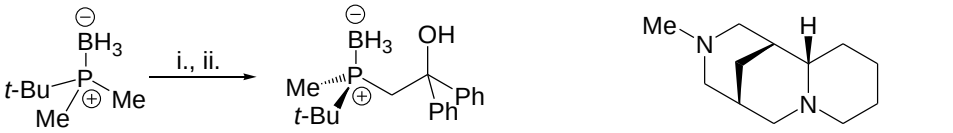


8 (*S,S*)-**9**, 48%, >99:1 er *meso*-**21**, 27% (–)-sparteine

Reagents and conditions: i. *s*-BuLi (1.1 eq.), (–)-sparteine (0.2 eq.), –78 ˚C, 3 h, Et_2O; ii. $CuCl_2$ (1.6 eq.).

In a similar way, (*R,R*)-BisP* precursor, (*R,R*)-**9** could be prepared *via* a catalytic desymmetrization using (+)-sparteine surrogate **23**. Kann was the first group that introduced a synthetic method using (+)-sparteine surrogate **23** as a chiral ligand to desymmetrise phosphine borane **8**. In Kann's work, Evans' procedure was adapted. Thus, phosphine substrate **8** was enantioselectively deprotonated by *s*-BuLi/(+)-sparteine surrogate **23** and trapping with benzophenone afforded hydroxy phosphine borane (*R*)-**22** in 78% yield and 92% ee (Scheme 1.9).[33,34]

Scheme 1.9

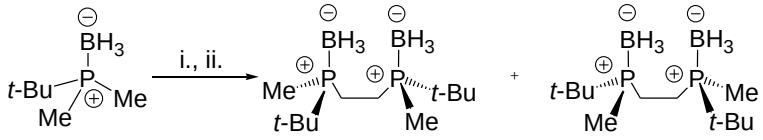


8 (*R*)-**22**, 78%, 92% ee (+)-sparteine surrogate **23**

Reagents and conditions: i. *s*-BuLi (1.1 eq.), (+)-sparteine surrogate **23** (1.1 eq.), –78 ˚C, 3 h, Et_2O; ii. Ph_2CO, –78 ˚C to –20 ˚C, 4 h, Et_2O.

To carry out a catalytic asymmetric synthesis of (*R,R*)-**9**, phosphine borane **8** was lithiated using *s*-BuLi in the presence of just 0.1 equivalents of (+)-sparteine surrogate **23**. Then, the lithiated intermediate was dimerized using $CuCl_2$ to afford (*R,R*)-**9** in 45% yield (≥99:1 er) and *meso*-**21** in 25% yield (Scheme 1.10).[28]

Scheme 1.10

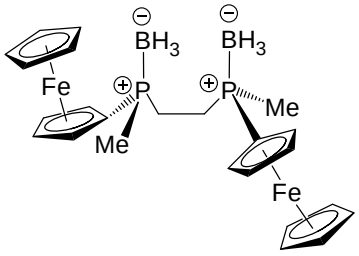


8 (*R*,*R*)-**9**, 45%, >99:1 er *meso*-**21**, 25%

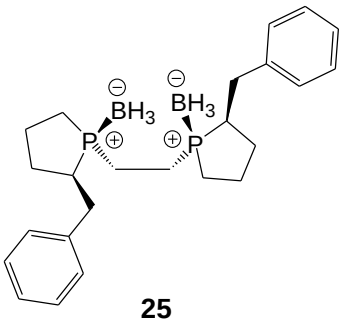
Reagents and conditions: i. *s*-BuLi (1.1 eq.), (+)-sparteine surrogate **23** (0.1 eq.), −78 ˚C, 3 h, Et_2O; ii. $CuCl_2$.

Not only were *P*-stereogenic (*S*,*S*)-1,2-bis(alkylmethylphosphino)ethane (BisP*) ligands successfully developed but 1,2-bis(arylmethylphosphino)ethanes were also prepared. For instance, in 2003 Imamoto reported an asymmetric synthesis of (*S*,*S*)-1,2-bis-[(ferrocenyl)methylphosphino]ethane **24** (Figure 1.3).[35] Moreover, due to the difficulty in preparing *P*-stereogenic ligands, *P*-chirogenic bisphospholanes were alternative ligands, For example, bisphospholane **25** was developed by Hoge (Figure 1.3).[36]

Figure 1.3



24



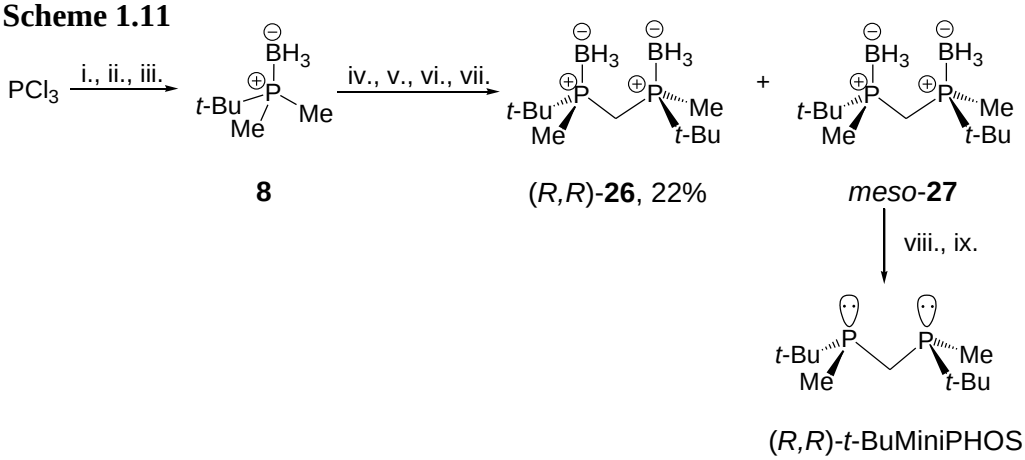
25

1.2.2 Asymmetric Synthesis of Methylene-bridged Phosphines

In 1999, Imamoto applied his procedure[10] to prepare methylene-bridged *P*-stereogenic diphosphines, known as MiniPHOS.[11,12] These ligands are characterized by having a methyl group which is the smallest group and a bulky alkyl group attached to the phosphorus atom. When these ligands complex to a metal, they form four-membered C_2-symmetric chelates with a rigid conformation and it was hoped that this might make these ligands give high enantioselectivity in transition metal-catalysed reactions.[5,11]

A synthetic route to (*R,R*)-*t*-BuMiniPHOS is shown in Scheme 1.11. Firstly, PCl_3 was reacted sequentially with *t*-butyl magnesium bromide and methyl magnesium bromide to give phosphine borane **8** as an intermediate compound. Next, *s*-BuLi and (−)-sparteine were used to deprotonate phosphine **8**. This was followed by reaction with *t*-BuPCl_2, methyl magnesium bromide and BH_3-THF to obtain optically active (*R,R*)-**26** in a low 22% yield after recrystallisation and *meso*-**27** (Scheme 1.11). After deboronation by treatment with trifluoromethanesulfonic acid and aqueous KOH to give (*R,R*)-*t*-BuMiniPHOS (Scheme 1.11), the bisphosphine was reacted with $[Rh(nbd)_2]^+X^-$ (X = BF_4 or PF_6) to obtain bischelate complexes $[Rh(MiniPHOS)_2]^+X^-$, without further purification, and used in the catalytic enantioselective hydrogenation of dehydroamino acids and asymmetric ring-opening reactions of azabenzonorbornadienes.[11]

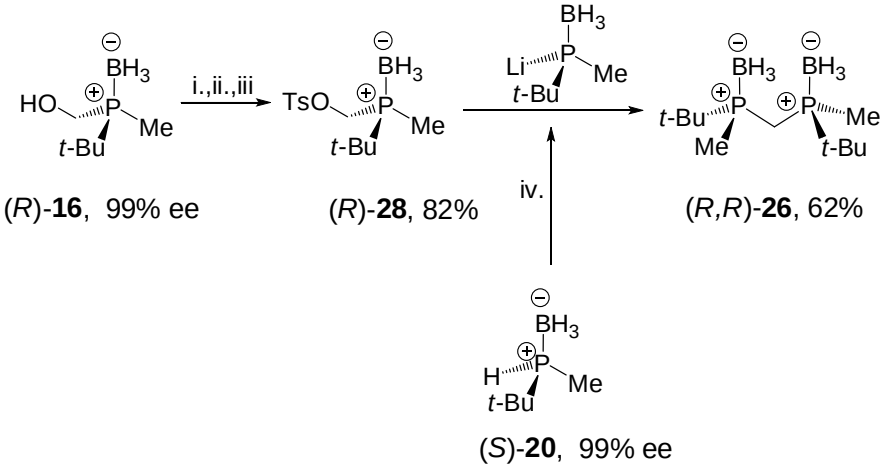
Scheme 1.11



Reagents and conditions: i. *t*-BuMgBr, −78 ˚C, 2 h, rt 1 h, THF; ii. MeMgBr, 0 ˚C, 30 min, rt 1 h; iii. BH_3-THF, 0 ˚C, 1 h; iv. *s*-BuLi (1.2 eq.), (−)-sparteine (1.2 eq.), −78 ˚C, 3 h, Et_2O; v. *t*-BuPCl_2, −78 ˚C to rt, Et_2O; vi. MeMgBr, 0 ˚C; vii. BH_3-THF, 0 ˚C; viii. TfOH, 0 ˚C, 30 min; ix. aq. KOH, 50 ˚C, 2 h.

Due to being the most useful chiral ligand compared to other derivatives, (*R,R*)-*t*-BuMiniPHOS was utilized in Rh-catalyzed asymmetric hydrogenation and catalytic asymmetric hydrosilylation of ketones.[11,19,37] Consequently, Imamoto developed a new synthetic route to MiniPHOS through the use of a secondary phosphine borane. To synthesise (*R,R*)-*t*-BuMiniPHOS precursor (*R,R*)-**26**,[40] hydroxy phosphine borane (*R*)-**16** (99% ee) and phosphine borane (*S*)-**20** (99% ee) were prepared as outlined previously in Scheme 1.7. Then, phosphine borane (*R*)-**16** was reacted with *p*-TsCl to give tosylated phosphine borane (*R*)-**28** in 82% yield. After lithiation of secondary phosphine borane (*S*)-**20** using *n*-BuLi, the lithiated intermediate was reacted with tosylate (*R*)-**28** to obtain (*R,R*)-**26** in 62% yield. In this result, no *meso*-**27** was observed due to the approach used (Scheme 1.12).[40]

Scheme 1.12



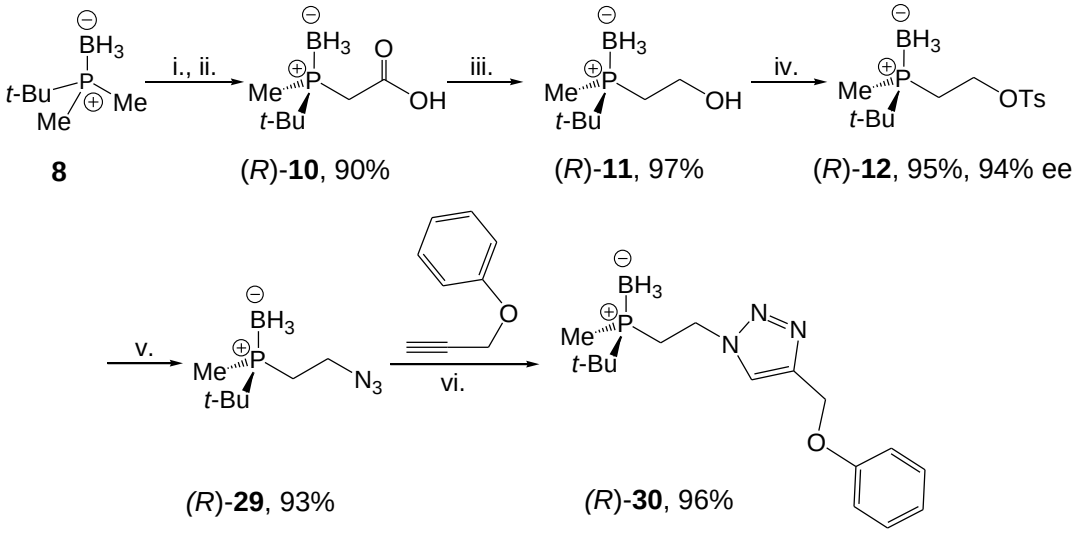
Reagents and conditions: i. BzCl, pyridine; ii. recrystallisation from Hexane/EtOAc (20:1) then KOH/aq. EtOH; iii. *p*-TsCl, Et_3N; iv. *n*-BuLi.

1.2.3 Asymmetric Synthesis of Phosphine-Heteroatom Ligands

As a variation, Kann was interested in developing mixed phosphine-heteroatom ligands, prepared by asymmetric deprotonation. For example, in 2007, Kann reported the synthesis of a library of novel *P*-stereogenic phosphine ligands having a triazole moiety, the so-called ChiraClick ligands.[41]

To synthesise 1,4-triazole phosphine (*R*)-**30** (Scheme 1.13), phosphine borane **8** was deprotonated in an asymmetric fashion using *s*-BuLi/(+)-sparteine surrogate **23** and the lithiated intermediate was then reacted with CO_2 to generate α-carboxyphosphine borane (*R*)-**10** in 90% yield. The carboxylic acid was reduced using BH_3•Me_2S to give hydroxy phosphine borane (*R*)-**11** in 97% yield and subsequent reaction with *p*-TsCl afforded tosylate (*R*)-**12** in 95% yield and 94% ee. Tosylate (*R*)-**12** was next reacted with NaN_3 to give azidophosphine borane (*R*)-**29** (93% yield). Finally, a "click" reaction of azidophosphine borane (*R*)-**29** with phenyl propargyl ether in the presence of copper(II) sulfate pentahydrate and sodium ascorbate gave 1,4-triazole phosphine borane (*R*)-**30** in 96% yield (Scheme 1.13).[41]

Scheme 1.13

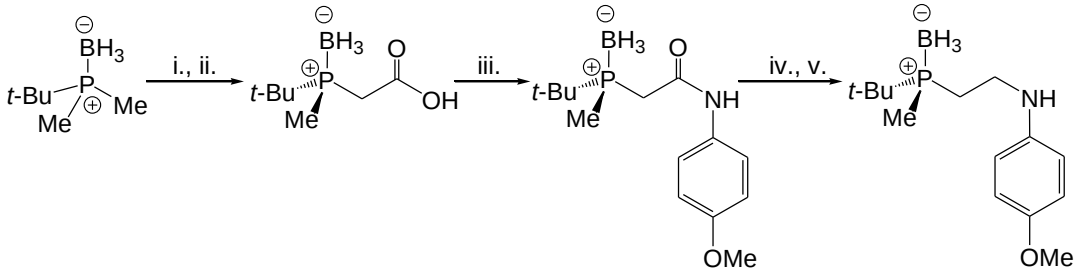


Reagents and conditions: i. *s*-BuLi/(+)-sparteine surrogate **23**, −78 ˚C, 1 h, Et_2O; ii. CO_2, −78 ˚C to rt, 1 h; iii. BH_3•Me_2S, THF, rt, 16 h; iv. *p*-TsCl, pyridine, CH_2Cl_2, rt, 16 h; v. NaN_3, DMF, 80 ˚C, 1 h; vi. $CuSO_4.5H_2O$, sodium ascorbate, H_2O/*t*-BuOH, rt, 16 h.

Kann has also developed *P*-stereogenic β-amino phosphine borane ligands for use in the asymmetric copper-catalyzed conjugate addition of diethylzinc to *trans*-β-

nitrostyrene.[42] To prepare the *P,N*-ligand (Scheme 1.14), phosphine borane **8** was desymmetrised using *s*-BuLi/(−)-sparteine and reacted with CO_2 to give α-carboxyphosphine borane (*S*)-**10** with 94% ee. Then, the carboxylic acid in (*S*)-**10** was reacted with 1-(3-dimethylaminpropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole hydrate (HOBt) and an amine to obtain amidophosphine borane (*S*)-**31** in 88% yield. The resulting amide was reduced with BH_3•Me_2S to give β-aminophosphine borane (*S*)-**32**. However, after the borane reduction, the product was also protected with BH_3 partially on the nitrogen. Consequently, a strong cationic ion exchange resin (SCX-2) was applied to selectively remove the borane on the nitrogen to afford β-aminophosphine borane (*S*)-**32** in 71% yield (Scheme 1.14). [42]

Scheme 1.14



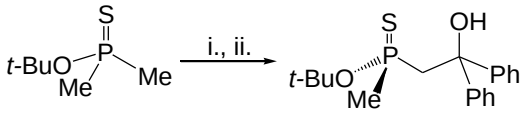
8 (*S*)-**10**, 94% ee (*S*)-**31**, 88% (*S*)-**32**, 71%

Reagents and conditions: i. *s*-BuLi/(−)-sparteine, −78 ˚C, 1 h, Et_2O; ii. CO_2, −78 ˚C to rt, 1 h, Et_2O; iii. EDCI, HOBt, *p*-$MeOC_6H_4NH_2$, CH_2Cl_2, rt; iv. BH_3•Me_2S, 50 ˚C, THF; v. cationic ion-exchange resin (SCX-2).

1.3 Synthesis of *P*-Stereogenic Phosphine Sulfides using Organolithium Reagents and Chiral Diamines

The first example of the asymmetric deprotonation of a phosphine sulfide using organolithium reagents and (−)-sparteine was reported by Evans in 1995.[18] A representative example is shown in Scheme 1.15. Thus, treatment of phosphine sulfide **33** with *n*-BuLi/(−)-sparteine and then trapping with benzophenone gave hydroxyl phosphine sulfide **34** in 80% yield and 81% ee. Moreover, the results in Evans' work showed that *n*-BuLi gave higher enantioselectivity than *s*-BuLi in the lithiation of phosphine sulfides.[18]

Scheme 1.15



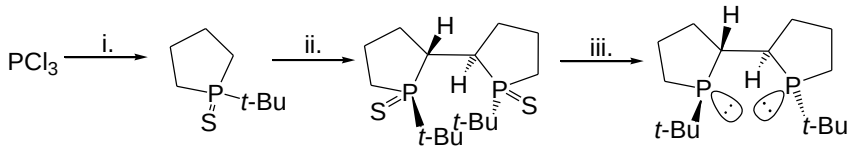
33 (*R*)-**34**, 80%, 81% ee

Reagents and conditions: i. *n*-BuLi (1.1 eq.), (−)-sparteine (1.1 eq.), −78 ˚C for 3 h, Et_2O; ii. Ph_2CO, −78 ˚C to −20 ˚C, 3 h, THF.

In 2002, Zhang reported the development of a rigid *P*-stereogenic bisphosphalane,[15] (*1S,1S',2R,2R'*)-TangPhos. The main feature of this ligand is the four stereogenic centres (two at phosphorus and two at carbon. The ligand has conformational flexibility of the two five-membered rings in the backbone and it was hypothesized that it could provide high enantioselectivity in subsequent transition metal-catalysed reactions.[15]

TangPhos was prepared from the reaction of PCl_3 with *t*-butyl magnesium chloride and $BrMg(CH_2)_4MgBr$ and protection with sulfur. This gave phosphine sulfide **35** in 45% yield. Then, *n*-BuLi/(−)-sparteine was used to deprotonate phosphine sulfide **35** and the lithiated intermediate was coupled using $CuCl_2$ to obtain C_2-symmetric bisphosphine sulfide **36** in 20% yield and ≥99% ee after recrystallisation. Desulfurisation of bisphospholane **36** using hexachlorodisilane afforded the air-sensitive (*1S,1S',2R,2R'*)-TangPhos in 88% yield (Scheme 1.16). TangPhos was applied to the Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acid[5,15] and β-amino acids[43] and these reactions gave products in up to >99% ee.

Scheme 1.16

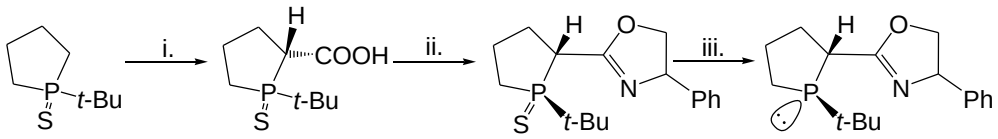


35, 45% **36**, 20%, >99% ee TangPhos, 88%

Reagents and conditions: i. (a) *t*-BuMgCl, (b) $BrMg(CH_2)_4MgBr$, (c) S_8; ii. *n*-BuLi/(–)-sparteine, $CuCl_2$, recrystallisation; iii. hexachlorodisilane, benzene.

In addition, new *P*-stereogenic, phospholane-oxazoline ligands were developed in the Zhang group.[44] The main feature of these ligands is a stereogenic centre in the oxazoline ring and at the phosphorus atom.[44,45] The synthesis of *P*,*N*-ligand **39** is shown in Scheme 1.17. Thus, phospholane sulfide **35** was deprotonated with *n*-BuLi/(–)-sparteine and reacted with CO_2 to give carboxyphospholane sulfide **37** in 72% ee. After recrystallisation, the % ee of acid **37** was improved to ≥99% ee (40% yield). Then, enantiopure carboxylic acid **37** was condensed using a chiral amino alcohol, EDC and HOBT to give a coupled product which was subsequently reacted with methanesulfonyl chloride to generate oxazoline **38** in 70-80% yield. Desulfurization of phosphine sulfide **38** using Raney Ni afforded phospholane-oxazoline **39** in 80-95% yield (Scheme 1.17).[45]

Scheme 1.17



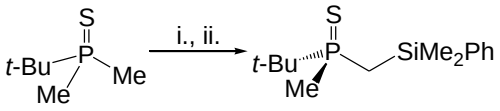
35 **37**, 40%, >99% ee **38**, 70-80% **39**, 80-95%

Reagents and conditions: i. (a) *n*-BuLi/(–)-sparteine, (b) CO_2, −78 ˚C, (c) recrystallisation; ii. (a) amino alcohol, EDC, HOBT, DMF, 70 ˚C (b) MsCl, CH_2Cl_2; iii. Raney Ni, CH_3CN.

O'Brien has also studied the catalytic asymmetric deprotonation of phosphine sulfide **40** using *n*-BuLi or *s*-BuLi in the presence of (–)-sparteine.[46] In this work, the use of *n*-BuLi under stoichiometric conditions (1.2 equivalents of (–)-sparteine) was compared with catalytic conditions (0.2 equivalents of (–)-sparteine) (Scheme 1.18 and Table 1.1). An enantioselective lithiation-silylation of phosphine sulfide **40** using stoichiometric conditions provided silyl product (*S*)-**41** in 74% yield with

84:16 er (entry 1). In contrast, under catalytic conditions, (*S*)-**41** was formed in 75% yield but with a significant drop in enantioselectivity (60:40 er, entry 2). In the case of using *n*-BuLi, when phosphine sulfide **40** was deprotonated under stoichiometric conditions product (*S*)-**41** was formed in 76% yield with 89:11 er (entry 3) but catalytic asymmetric lithiation-silylation gave (*S*)-**41** in 82% yield with 83:17 er (entry 4). These results clearly show that the optimum alkyllithium base for catalytic asymmetric deprotonation of phosphine sulfide **40** is *n*-BuLi.

Scheme 1.18



40 (*S*)-**41**

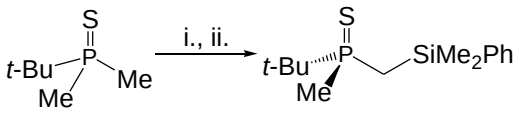
Table 1.1

Entry[a]	Alkyllithium	Equiv. (–)-sparteine	Yield (%)[b]	Er[c]
1	*s*-BuLi	1.2	74	84:16
2	*s*-BuLi	0.2	75	60:40
3	*n*-BuLi	1.2	88	88:12
4	*n*-BuLi	0.2	82	83:17

[a] *Reagents and conditions:* i. RLi (1.1 eq.), (–)-sparteine (0.2-1.2 eq.), –78 ˚C, 3 h, Et_2O; ii. $PhMe_2SiCl$, –78 ˚C to rt, 16 h. [b] Isolated yield after purification by chromatography. [c] Enantiomeric ratio determined by CSP-HPLC.

To optimize the reaction solvent, the results using *n*-BuLi in Et_2O and toluene were compared (Scheme 1.18 and Table 1.2). In Et_2O, silyl product (*S*)-**41** was obtained in 88% yield with 88:12 er under stoichiometric conditions (entry 1), while the catalytic result (0.05 equivalents of (–)-sparteine) gave (*S*)-**41** in 74:26 er (entry 2). However, in toluene, silyl adduct (*S*)-**41** was isolated in 90% yield with 89:11 er using a stoichiometric amount of (–)-sparteine (entry 3). The catalytic procedure in toluene gave product (*S*)-**41** in 88% yield while maintaining high enantioselectivity (85:15 er, entry 4). Thus, toluene was shown to be an efficient solvent for catalytic asymmetric lithiation.[46]

Scheme 1.19



40 (*S*)-**41**

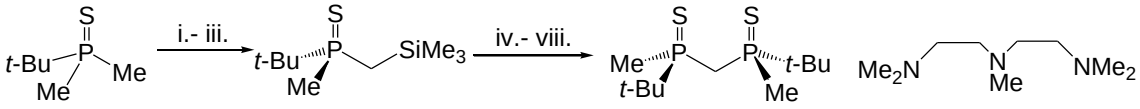
Table 1.2

Entry[a]	Solvent	Equiv. (–)-sparteine	Yield (%)[b]	Er[c]
1	Et_2O	1.2	88	88:12
2	Et_2O	0.05	88	74:26
3	Toluene	1.2	90	89:11
4	Toluene	0.05	88	85:15

[a] *Reagents and conditions:* i. *n*-BuLi (1.1 eq.), (–)-sparteine (0.05-1.2 eq.), −78 ˚C, 3 h, Et_2O or toluene; ii. $PhMe_2SiCl$, −78 ˚C to rt, 16 h. [b] Isolated yield after purification by chromatography. [c] Enantiomeric ratio determined by CSP-HPLC.

Having developed an efficient catalytic asymmetric synthesis of silyl phosphine (*S*)-**41**, O'Brien used this compound to develop a synthesis of MiniPHOS precursor (*R,R*)-**42** (Scheme 1.20). It was found that optimal conditions for the regioselective lithiation of silyl phosphine sulfide (*S*)-**41** involved the use of *s*-BuLi and PMDETA in THF.[47] The synthetic route employed as a first step catalytic asymmetric deprotonation of phosphine sulfide **40** using *n*-BuLi/(–)-sparteine to give silyl phosphine sulfide (*S*)-**41** in 56% yield and 99:1 er after purification by recrystallisation. The silyl adduct (*S*)-**41** was then regioselectively lithiated using *s*-BuLi in the presence of PMDETA and trapped with *t*-$BuPCl_2$. The resulting intermediate was subsequently reacted with methyl magnesium bromide, sulfur and finally TBAF to afford MiniPHOS precursor (*R,R*)-**42** in 46% yield with 99:1 er (Scheme 1.20).[47]

Scheme 1.20



40 (*S*)-**41**, 56%, 99:1 er (*R,R*)-**42**, 46%, 99:1 er PMDETA

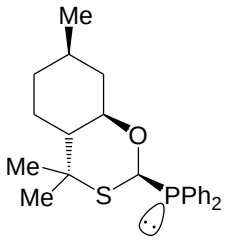
Reagents and conditions: i. *n*-BuLi (1.1 eq.), (–)-sparteine (0.05 eq.), –78 ˚C, 3 h, toluene; ii. Me_3SiCl, –78 ˚C to rt, 16 h; iii. recrystallisation; iv. *s*-BuLi (1.0 eq.), PMDETA (1.0 eq.), –78 ˚C, 1.5 h, THF; v. *t*-$BuPCl_2$; vi. MeMgBr; vii. S_8; viii. TBAF, THF.

In summary, use of organolithium reagents and (–)-sparteine or (+)-sparteine surrogate **23** is a very useful method for the synthesis of *P*-stereogenic bisphosphine ligands.

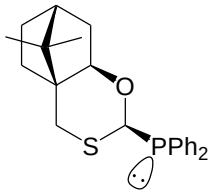
1.4 Project Outline

P-Stereogenic bisphosphines are generally used as ligands in Rh-catalysed asymmetric hydrogenation. These ligands possess two strongly coordinating phosphorus atoms. In contrast, Pericàs and Riera have found that hemi-labile ligands such as PuPHOS[48] and CamPHOS[49] (Figure 1.4) work well in Co-catalysed asymmetric Pauson-Khand reactions. PuPHOS and CamPHOS each contain a strongly coordinating phosphorus atom and a weakly coordinating sulfur atom.

Figure 1.4



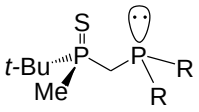
PuPHOS



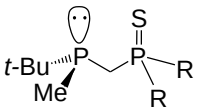
CamPHOS

Using CamPHOS and PuPHOS as a starting point, we designed phosphines (*S*)-**43**, (*S*)-**44**, (*R*)-**45** and (*R*)-**46** (Figure 1.5) as new ligands for application in catalytic asymmetric Pauson-Khand reactions. The new ligands are hemi-labile bisphosphines that contain a P=S group with a weak coordinating sulfur group and a phosphorus lone pair as a strong coordinating group. These ligands were selected mainly due to their ease of synthesis using organolithium bases and (−)-sparteine.

Figure 1.5



(*S*)-**43**, R = Ph
(*S*)-**44**, R = *t*-Bu

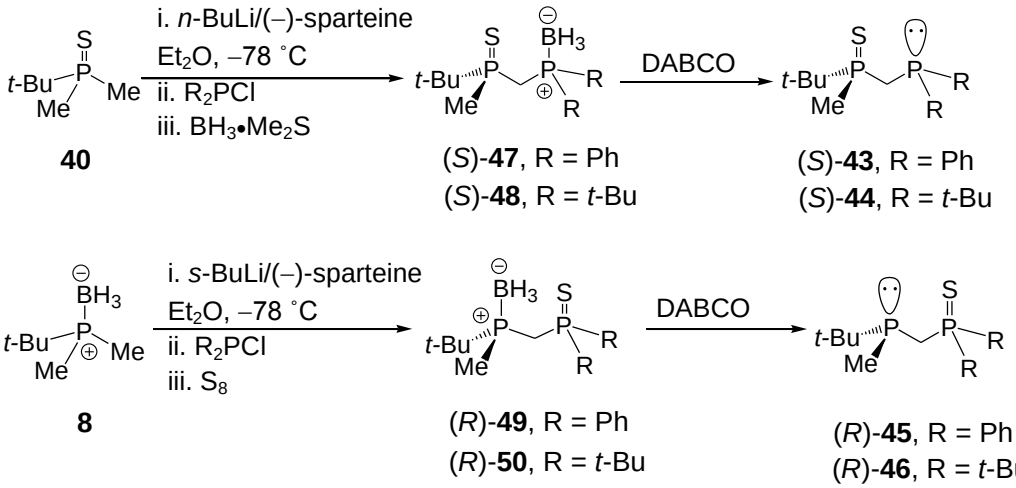


(*R*)-**45**, R = Ph
(*R*)-**46**, R = *t*-Bu

The proposed synthetic route to prepare the new hemi-labile ligands is shown in Scheme 1.21. To synthesise bisphosphine sulfides (*S*)-**43** and (*S*)-**44**, phosphine sulfide **40** will be deprotonated using *n*-BuLi/(−)-sparteine and the lithiated intermediate will be trapped with R_2PCl (R = Ph or *t*-Bu) as the electrophile. Finally, addition of $BH_3 \bullet Me_2S$ as a protecting group would give bisphosphine sulfide boranes

(*S*)-**47** and (*S*)-**48**. In a similar way, phosphine borane **8** will be lithiated using *s*-BuLi/(−)-sparteine, trapped with R_2PCl (R = Ph or *t*-Bu) and treated with sulfur to afford bisphosphine sulfide boranes (*R*)-**49** and (*R*)-**50**. To achieve >99:1 er, the bisphosphine sulfide boranes will be recrystallised. The borane protecting group will finally be removed using DABCO to produce the hemi-labile ligands.

Scheme 1.21

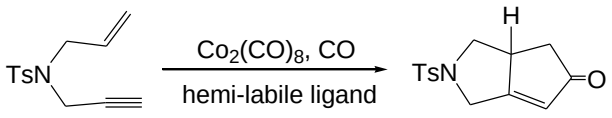


40 (*S*)-**47**, R = Ph; (*S*)-**48**, R = *t*-Bu; (*S*)-**43**, R = Ph; (*S*)-**44**, R = *t*-Bu

8 (*R*)-**49**, R = Ph; (*R*)-**50**, R = *t*-Bu; (*R*)-**45**, R = Ph; (*R*)-**46**, R = *t*-Bu

With the hemi-labile ligands (*S*)-**43**, (*S*)-**44**, (*R*)-**45** and (*R*)-**46** in hand, our plan is to determine whether they are suitable for use in the catalytic asymmetric intramolecular Pauson-Khand reaction of enyne sulfonamide **51** to give enone **52** (Scheme 1.22). The ligands will be investigated under different conditions in order to optimise the enantioselectivity.

Scheme 1.22



51 **52**

2. Synthesis of Bisphosphine Hemi-labile Ligands

2.1 Synthesis of Dimethylphosphines

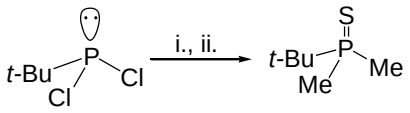
To investigate the synthesis of the new hemi-labile ligands, the dimethylphosphines, *t*-butyldimethylphosphine sulfide **40** and *t*-butyldimethylphosphine borane **8** (Figure 2.1), needed to be prepared from *t*-$BuPCl_2$ or PCl_3. The synthesis of phosphine sulfide **40** was reported by Kuchen in 1970.[51] In 2005, Imamoto reported a simple procedure for the synthesis of phosphine borane **8**.[21] Consequently, we used these methods to prepare phosphine sulfide **40** and phosphine borane **8** in multi-gram quantities.

Figure 2.1

40 **8**

Phosphine sulfide **40** was first prepared from *t*-$BuPCl_2$ (Scheme 2.1).[21] Thus, *t*-$BuPCl_2$ was reacted with 1.1 equivalents of methyl magnesium bromide at room temperature for 5 hours. Then, 1.5 equivalents of sulfur was added and the reaction mixture was heated at 80 ˚C for 5 minutes and then at room temperature for 5 hours. This procedure gave phosphine sulfide **40** in 57% yield after recrystallisation.

Scheme 2.1

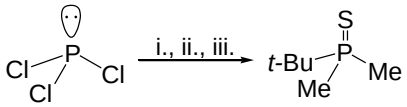


40, 57%

Reagents and conditions: i. MeMgBr (1.1 eq.), rt, 5 h, THF; ii. S_8 (1.5 eq.), 80 ˚C for 5 min then rt for 5 h.

Due to the high cost of *t*-$BuPCl_2$, we carried out the multi-gram synthesis using a cheaper reagent (PCl_3) *via* Evans' procedure (Scheme 2.2).[18] Thus, a solution of PCl_3 was reacted with 1.0 equivalent of *t*-butyl magnesium chloride to substitute one of the chlorines to form *t*-$BuPCl_2$ *in situ*. Then, 2.2 equivalents of methyl magnesium bromide were added to displace the remaining two chlorine atoms and give *t*-$BuPMe_2$. To avoid oxidation to the phosphine oxide, 1.5 equivalents of sulfur was then added to give 6.29 g of phosphine sulfide **40** in 77% yield after recrystallisation.

Scheme 2.2



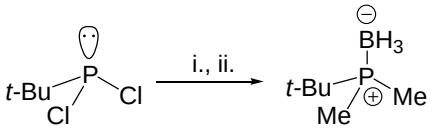
40, 77%

Reagents and conditions: i. *t*-BuMgCl (1.0 eq.), −78 ˚C for 1 h then rt for 3 h, THF; ii. MeMgBr (2.2 eq.), 0 ˚C to rt, 2 h, THF; iii. S_8 (1.5 eq.), 80 ˚C for 5 min then rt for 5 h.

The ^{1}H NMR spectrum of phosphine sulfide **40** contained a 6H doublet (J = 12.5 Hz) at δ_H 1.67 ppm assigned to the methyl protons which couple to the phosphorus. There was also a 9H doublet (J = 16.5 Hz) at δ_H 1.25 ppm due to the methyl protons of the *t*-butyl group which couple to the adjacent phosphorus. The ^{13}C NMR spectrum of phosphine sulfide **40** contained a doublet (J = 52.0 Hz) at δ_C 32.5 ppm corresponding to the quaternary carbon of the *t*-butyl group. There was also a doublet (J = 2.0 Hz) at δ_C 24.2 ppm due to the methyl carbons of the CMe_3 group and a doublet (J = 51.5 Hz) at δ_C 16.2 ppm corresponding to the PMe_2 group. In addition, the ^{31}P NMR spectrum of phosphine sulfide **40** contained a singlet at δ_P 54.3 ppm which confirmed that the sulfide protection was successful.

In a similar way, phosphine borane **8** was synthesized from *t*-$BuPCl_2$ except that BH_3•Me_2S was added instead of sulfur to give phosphine borane **8** in 67% yield after recrystallisation (Scheme 2.3).

Scheme 2.3



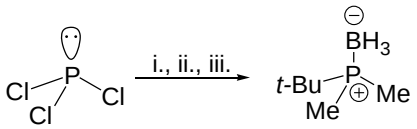
8, 67%

Reagents and conditions: i. MeMgBr (1.1 eq.), rt, 5 h, THF; ii. BH_3•Me_2S (1.3 eq.) 0 ˚C, rt 3 h.

For comparison, phosphine borane **8** was synthesized in a similar way according to Imamoto's procedure. A solution of PCl_3 was reacted with 1.0 equivalent of *t*-butyl magnesium bromide to substitute one chlorine atom. Then, 2.2 equivalents of methyl magnesium bromide were added to substitute two chlorine atoms and give *t*-$BuPMe_2$. The lone pair on the phosphorus was then protected using 1.3 equivalents of BH_3•Me_2S. This gave 5.8 g of phosphine borane **8** in 72% yield after recrystallisation (Scheme 2.4). Phosphine borane **8** is more moisture sensitive than

phosphine sulfide **40** and so it needed to be freshly recrystallised before setting up an asymmetric deprotonation reaction.

Scheme 2.4



8, 72%

Reagents and conditions: i. *t*-BuMgCl (1.0 eq.), –78 ˚C for 1 h then rt for 3 h, THF; ii. MeMgBr (2.2 eq.), 0 ˚C to rt, 2h, THF; iii. BH_3•Me_2S (1.3 eq.) 0 ˚C, rt 3 h.

The ^{1}H NMR spectrum of phosphine borane **8** contained a doublet (J = 10.0 Hz) at δ_H 1.22 ppm assigned to the methyl protons with coupling to the phosphorus nuclei. There was also a doublet (J = 13.5 Hz) at δ_H 1.15 ppm from the protons of the *t*-butyl group and a broad quartet of doublets (J = 94.0, 15.0 Hz) at δ_H 0.43 ppm from the BH_3 protons coupled to the boron (I = 3/2) and phosphorus. These signals confirmed that the free phosphine was successfully protected by BH_3. The ^{31}P NMR spectrum of phosphine borane **8** contained a singlet at δ_P 20.9 ppm confirming the borane protection. In the ^{13}C NMR spectrum of phosphine borane **8**, a doublet (J = 35.0 Hz) was observed at δ_C 26.6 ppm from the quaternary carbon of the *t*-butyl group. There were also a doublet (J = 2.0 Hz) at δ_C 24.7 ppm from the three *t*-butyl methyl carbons and a doublet (J = 35.5 Hz) at δ_C 7.3 ppm which was assigned to the PMe_2 group which couples to phosphorus.

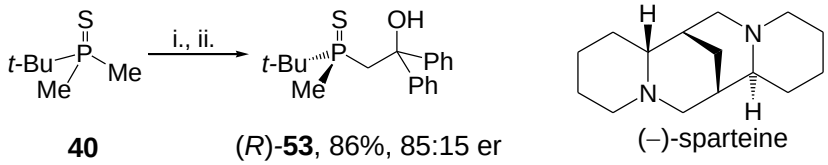
In conclusion, the best route to phosphine sulfide **40** and phosphine borane **8** is from PCl_3. In this way, the two dimethylphosphine substrates were readily prepared on a gram scale.

2.2 Asymmetric Deprotonation and Trapping with Benzophenone

To start with, benzophenone (Ph_2CO) was used as an electrophile to trap the phosphine sulfide **40** or phosphine borane **8** which were deprotonated with *n*-BuLi/(−)-sparteine or *s*-BuLi/(−)-sparteine respectively. This was to verify that the lithiation procedure could be carried out successfully.

Evans has shown that *n*-BuLi gives better enantioselectivity than *s*-BuLi for the asymmetric lithiation of phosphine sulfides.[18] Therefore, phosphine sulfide **40** was deprotonated with 1.1 equivalents of *n*-BuLi in the presence of 1.2 equivalents of (−)-sparteine in Et_2O at −78 ˚C for 3 hours. Then, the lithiated species was trapped with benzophenone to give hydroxy phosphine sulfide (*R*)-**53** in 86% yield and 85:15 er after purification by chromatography (Scheme 2.5).

Scheme 2.5



Reagents and conditions: i. *n*-BuLi (1.1 eq.), (−)-sparteine (1.2 eq.), −78 ˚C, 3 h, Et_2O; ii. Ph_2CO (1.2 eq.), −78 ˚C to rt, 18 h, THF.

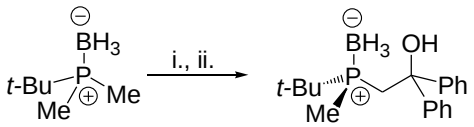
The ^1H NMR spectrum of hydroxy phosphine sulfide (*R*)-**53** contained a multiplet at δ_H 7.57-7.55 ppm assigned to two protons on the phenyl ring. A 1H doublet of doublets (J = 14.0, 8.0 Hz) at δ_H 2.97 ppm and a 1H doublet of doublets (J = 14.0, 10.5 Hz) at δ_H 2.84 ppm were assigned to the diastereotopic methylene protons which couple to each other and to phosphorus. There are two doublets at δ_H 1.23 and 1.00 ppm with J = 16.5 and 12.5 Hz respectively which are assigned to the methyl protons of the *t*-butyl group and the methyl group next to the phosphorus.

To determine the er of hydroxy phosphine sulfide **53**, the compound was analysed using CSP-HPLC on a Daicel Chiracel OD column with 95:5 hexane-*i*-PrOH as eluent. The minor enantiomer (*S*)-**53** eluted first at 7.2 minutes and was followed by the major enantiomer (*R*)-**53** at 17.0 minutes. The major enantiomer was assigned as having (*R*)-configuration which is consistent with the asymmetric lithiation of

phosphine sulfide **40** using *n*-BuLi/(–)-sparteine reported in the literature (87:13 er).[46]

A test reaction with phosphine borane **8** was also carried out. In this case, *s*-BuLi gives the highest enantioselectivity. Thus, phosphine borane **8** was lithiated using 1.1 equivalents of *s*-BuLi together with 1.2 equivalents of (–)-sparteine in Et_2O at –78 ˚C for 3 hours. Then, the lithiated species was trapped with benzophenone to give hydroxy phosphine borane (*S*)-**22** in 77% yield and 93:7 er after purification by chromatography (Scheme 2.6).

Scheme 2.6



8 (*S*)-**22**, 77%, 93:7 er

Reagents and conditions: i. *s*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), –78 ˚C for 3 h, Et_2O; ii. Ph_2CO (1.2 eq.), –78 ˚C to rt, 18 h, THF.

In the ^{1}H NMR spectrum of hydroxy phosphine borane (*S*)-**22**, two 4H multiplets at δ_H 7.52-7.47 and 7.34-7.30 ppm were assigned to the eight protons on the two phenyl rings. There was also a 2H multiplet at δ_H 7.27-7.21 ppm due to the phenyl protons. A 1H singlet at δ_H 4.59 ppm was assigned to the OH group. The methylene protons appeared as a 1H triplet (J = 14.5 Hz) at δ_H 2.88 ppm and a 1H doublet of doublets (J = 14.5, 6.0 Hz) at δ_H 2.68 ppm.

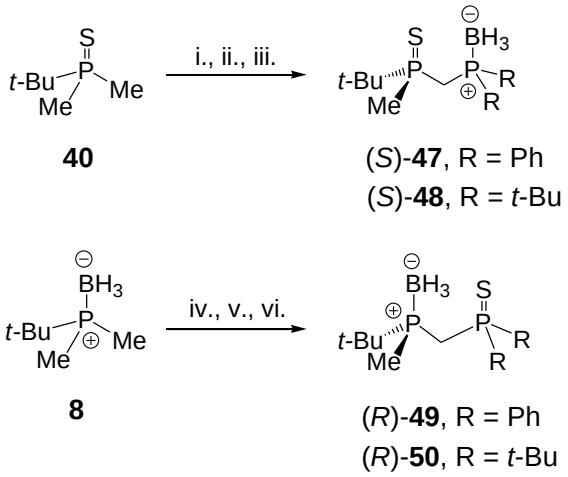
The er of hydroxy phosphine borane (*S*)-**22** was determined using CSP-HPLC on a Diacel Chiracel OD column eluting with 95:5 hexane-*i*-PrOH: the minor enantiomer (*R*)-**22** eluted at 11.0 minutes and the major enantiomer (*S*)-**22** eluted at 13.0 minutes. The major enantiomer was assigned as having (*S*)-configuration. This result is consistent with the asymmetric lithiation of phosphine borane **8** using *s*-BuLi/(–)-sparteine reported in Kann's work (96:4 er).[34]

In summary, we were successful in carrying out the two test reactions in high yield and high enantioselectivity. It should be noted that the products ((*R*)-**53** and (*S*)-**22**) are formed with the same sense of induction but have opposite stereochemistry labels according to the Cahn-Ingold-Prelog rules.

2.3 Synthesis of Methylene-bridged Bisphosphines

Having replicated the lithiation-trapping of phosphine sulfide **40** and phosphine borane **8** with benzophenone, these two substrates were used to synthesise mixed phosphine sulfide-phosphine boranes. An outline of our planned syntheses is shown in Scheme 2.7. Thus, starting with phosphine sulfide **40**, asymmetric lithiation-trapping with R_2PCl and subsequent reaction with BH_3•Me_2S should give (*S*)-**47** and (*S*)-**48**. In contrast, lithiation-trapping of phosphine borane **8** with R_2PCl and reaction with sulfur should produce (*R*)-**49** and (*R*)-**50** (Scheme 2.7).

Scheme 2.7

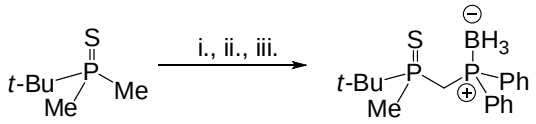


Reagents and conditions: i. *n*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), –78 ˚C, 3 h, Et_2O; ii. R_2PCl, –78 ˚C to rt, 18 h, THF; iii. BH_3•Me_2S, 0 ˚C to rt 3 h; iv. *s*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), –78 ˚C, 3 h, Et_2O; v. R_2PCl, –78 ˚C to rt, 18 h, THF; vi. S_8, 80 ˚C, 5 min, rt 5 h.

2.3.1 Lithiation-Trapping of Phosphine Sulfide 40 with Ph_2PCl

To evaluate the synthetic route, we started by synthesizing racemic bisphosphine sulfide *rac*-**47**. Phosphine sulfide **40** was deprotonated by 1.1 equivalents of *n*-BuLi in THF at –78 ˚C for 3 hours. The lithiated intermediate was trapped with Ph_2PCl and then reacted with BH_3•Me_2S. The reaction worked well and gave bisphosphine sulfide *rac*-**47** in 75% yield after purification by chromatography (Scheme 2.8).

Scheme 2.8



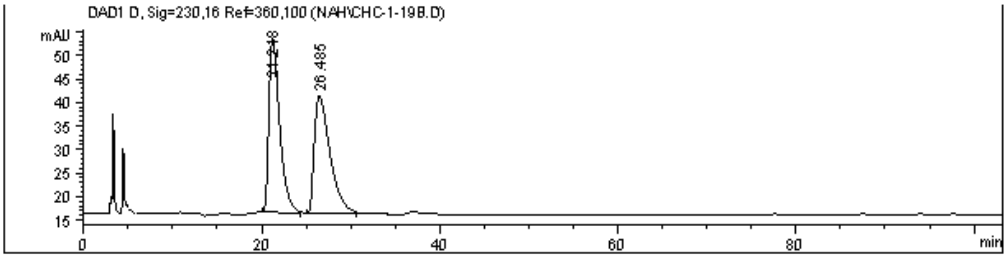
40 *rac*-**47**, 75%

Reagents and conditions: i. *n*-BuLi (1.1 eq.), −78 ˚C, 3 h, THF; ii. Ph_2PCl, −78 ˚C to rt, 18 h, THF; iii. $BH_3 \bullet Me_2S$, 0 ˚C to rt, 3 h.

The ^{1}H NMR spectrum of bisphosphine sulfide *rac*-**47** contained a 2H multiplet at δ_H 8.00-7.96 ppm and a 2H multiplet at δ_H 7.71-7.66 ppm due to the phenyl protons. In addition, a 1H quartet (J = 14.5 Hz) at δ_H 3.05 ppm and a 1H double double doublet (J = 14.5, 10.5, 9.0 Hz) at δ_H 2.77 ppm were assigned to the diastereotopic PCH_2 protons. In the ^{13}C NMR spectrum of bisphosphine sulfide borane *rac*-**47**, a double doublet (J = 51.0, 3.0 Hz) at δ_C 35.0 ppm was assigned to the quaternary carbon on the *t*-butyl group and a double doublet (J = 36.0, 24.5 Hz) at δ_C 26.0 ppm was assigned to the PCH_2 carbon. A doublet (J = 2.0 Hz) at δ_C 24.2 ppm from the methyl carbon on the *t*-butyl group and a doublet (J = 55.0 Hz) at δ_C 15.6 ppm from the methyl group were observed. The ^{31}P NMR spectrum of bisphosphine sulfide borane *rac*-**47** contained signals at δ_P 56.0 and 15.3 ppm which were assigned to the PS and PBH_3 groups respectively. The NMR spectroscopic data were consistent with those reported previously.[46]

With phosphine sulfide borane *rac*-**47** in hand, it was important to show that the enantiomers could be separated by CSP-HPLC. Thus, using a Daicel Chiracel AD column and eluting with 99:1 hexane-*i*-PrOH, the two enantiomers were well resolved with retention times of 21.2 minutes and 26.5 minutes (Figure 2.2).

Figure 2.2

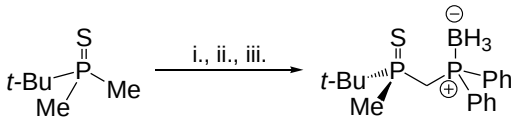


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.218	BB	1.2532	3105.01733	37.06918	50.4367
2	26.485	BB	1.7703	3051.25073	24.95873	49.5633

Next, to access the enantiomerically enriched compound, phosphine sulfide **40** was deprotonated using *n*-BuLi in the presence of (−)-sparteine at −78 ˚C for 3 hours. After trapping with Ph_2PCl, the free phosphine was protected with BH_3•Me_2S to give bisphosphine (*S*)-**47** in 49% yield and 83:17 er after purification by chromatography (Scheme 2.9 and Table 2.1, entry 1). This first reaction was carried out on a 100 mg scale. Then, the reaction was scaled up to 300 mg of phosphine sulfide **40** and the yield dropped slightly to 40% without a change in the enantiomeric ratio (entry 2). Similarly, the reaction worked well on a 1.0 g and 2.0 g scale (entries 3 and 4). The configuration of (*S*)-**47** was assigned by comparison of the sign of the $[\alpha]_D$ value (−22.0 (*c* 1.0 in $CHCl_3$)) with that reported in the literature (−26.3 (*c* 0.9 in $CHCl_3$)).[46]

Scheme 2.9



40 (*S*)-**47**

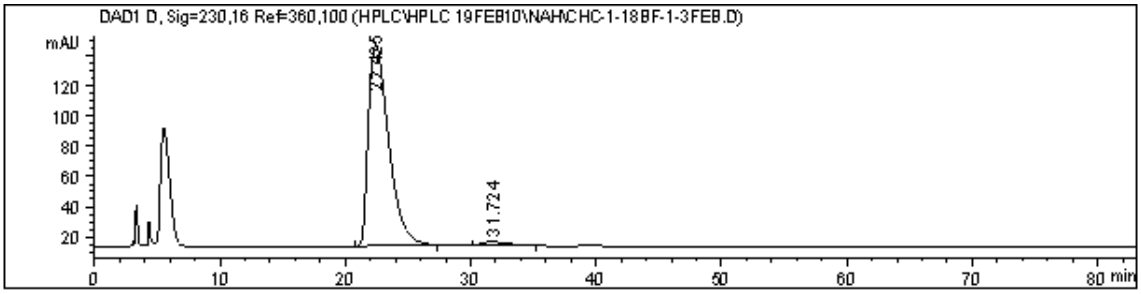
Table 2.1

Entry[a]	Scale of **40**	Yield, %[b]	Er (*S*:*R*)[c]
1	100 mg	49	83:17
2	300 mg	40	83:17
3	1.00 g	66 (47[d])	82:18 (97.5:2.5[d])
4	2.00 g	80 (67[d])	91:9 (95.5:4.5[d])

[a] *Reagents and conditions:* i. *n*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), –78 ˚C, 3 h, Et_2O; ii. Ph_2PCl (1.1 eq.), –78 ˚C to rt, 18 h, THF; iii. BH_3•Me_2S (1.5 eq.) 0 ˚C to rt 3 h. [b] Yield after purification by chromatography. [c] Er determined using CSP-HPLC. [d] Yield and er after recrystallisation.

Starting with 1.0 g of phosphine sulfide **40**, we isolated bisphosphine (*S*)-**47** in 66% yield and 82:18 er. Recrystallisation gave a solid in 15% yield and 68:32 er and the filtrate from which we isolated (*S*)-**47** in 47% yield and 97.5:2.5 er (entry 3). The CSP-HPLC on a Daicel Chiracel AD column is shown in Figure 2.3.

Figure 2.3



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

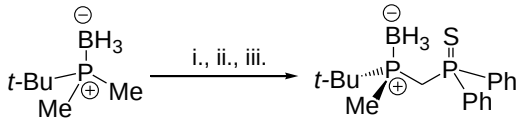
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.425	BB	1.7391	1.51501e4	133.58426	97.5499
2	31.724	BB	1.7137	380.52185	2.62116	2.4501

The reaction on a 2.0 g scale was also high yielding and we isolated (*S*)-**47** of 95.5:4.5 er in 67% yield after recrystallisation. Thus, we had successfully developed an efficient, multi-gram scale synthesis of bisphosphine (*S*)-**47** in high er (>95.5:4.5 er.

2.3.2 Lithiation-Trapping of Phosphine Borane 8 with Ph_2PCl

Next we synthesized bisphosphine sulfide *rac*-**49** starting from phosphine borane **8**. *s*-BuLi was added to phosphine borane **8** in THF at −78 ˚C and the lithiated species was trapped with Ph_2PCl. The free phosphine was then protected with sulfur to give bisphosphine *rac*-**49** in 70% yield after purification by chromatography (Scheme 2.10).

Scheme 2.10



8 *rac*-**49**, 70%

Reagents and conditions: i. *s*-BuLi (1.1 eq.), −78 ˚C for 3 h, THF; ii. Ph_2PCl (1.1 eq.), −78 ˚C to rt, 18 h, THF; iii. S_8 (1.3 eq.), 80 ˚C for 5 min, rt for 5 h.

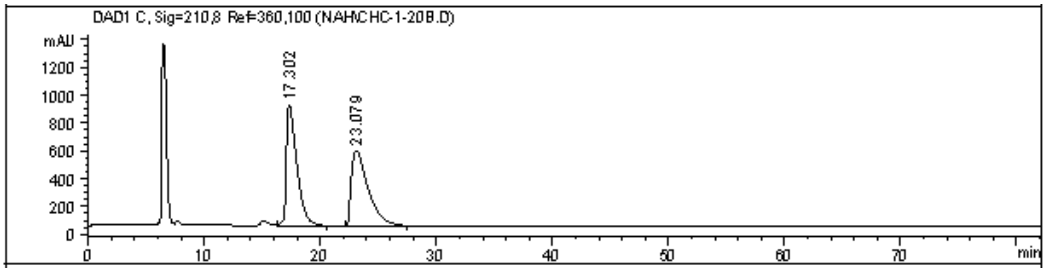
In the ^1H NMR spectrum of bisphosphine borane sulfide *rac*-**49**, two 2H double double doublets at δ_H 8.06 and 7.80 ppm (J = 9.5, 8.0, 1.5 Hz) were assigned to the four *ortho* protons on the phenyl rings. A 6H multiplet was observed at δ_H 7.59-7.50 ppm corresponding to the other six phenyl protons. The two double double doublets at δ_H 3.12 (J = 15.0, 13.0, 6.5 Hz) and 2.66 (J = 17.0, 15.0, 12.5 Hz) ppm were assigned to the methylene protons between the two phosphorus atoms.

The ^{13}C NMR spectrum of bisphosphine borane sulfide *rac*-**49** contained two doublets at δ_C 135.9 (J = 3.5 Hz) and δ_C 135.1 ppm (J = 3.5 Hz) which were assigned to the *ipso*-Ph carbons. A double doublet (J = 36.5, 7.5 Hz) was observed at δ_C 57.5 ppm due to the quarternary carbon on the *t*-butyl group, and there was also a double doublet (J = 32.5, 3.5 Hz) at δ_C 28.7 ppm corresponding to the methylene carbon. In addition, a doublet (J = 2.0 Hz) at δ_C 25.6 ppm due to the methyl carbon next to phosphorus and a doublet (J = 2.5 Hz) at δ_C 24.9 ppm corresponding to the

methyl carbons on the *t*-butyl group were observed. The ^{31}P NMR spectrum of bisphosphine borane sulfide *rac*-**49** contained two multiplets at δ_P 37.8 and 28.8 ppm which were assigned to PS and PBH_3 respectively.

With phosphine borane sulfide *rac*-**49** in hand, it was shown that the enantiomers could be separated by CSP-HPLC. Thus, using a Daicel Chiracel AD column with 95:5 hexane-*i*-PrOH as eluent, the two enantiomers were resolved with retention times of 17.3 minutes and 23.1 minutes (Figure 2.4).

Figure 2.4

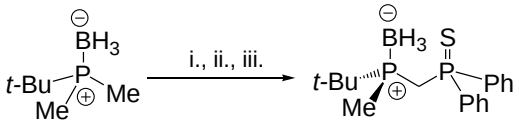


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.302	VB	0.8414	5.47073e4	867.90051	49.9246
2	23.079	BB	1.3843	5.48726e4	545.15039	50.0754

Next, in order to prepare the enantiomerically enriched bisphosphine borane sulfide (*R*)-**49**, phosphine borane **8** was used as a substrate for asymmetric deprotonation by 1.1 equivalents of *s*-BuLi and 1.2 equivalents of (−)-sparteine at −78 ˚C for 3 hours. Then, trapping with 1.1 equivalents of Ph_2PCl and protection of the free phosphine gave bisphosphine borane sulfide (*R*)-**49** in 57% yield and 90:10 er after purification by chromatography (Scheme 2.11 and Table 2.2, entry 1). The configuration of (*R*)-**49** was assigned based on the well-known preference for *s*-BuLi/(−)-sparteine lithiations.[10,18]

Scheme 2.11



8 (*R*)-**49**

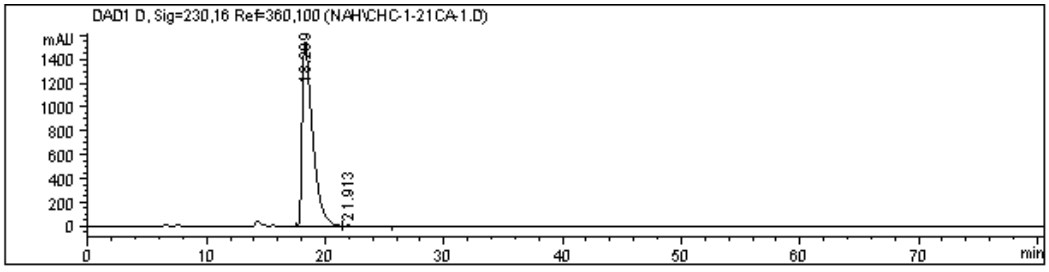
Table 2.2

Entry [a]	Scale of **8**	yield, % [b]	Er (*R*:*S*) [c]
1	102 mg	57	90:10
2	1.00 g	44 (20 [d])	93:7 (99:1 [d])
3	1.50 g	62 (33 [d])	88:12 (98.5:1.5 [d])

[a] *Reagents and conditions:* i. *s*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), –78 ˚C for 3 h, Et_2O; ii. Ph_2PCl (1.1 eq.), –78 ˚C to rt, 18 h, THF; iii. S_8 (1.3 eq.), 80 ˚C for 5 min, rt 5 h. [b] Yield after purification by chromatography. [c] Er determined using CSP-HPLC. [d] Yield and er after recrystallisation.

After scaling-up the reaction to 1.0 g of phosphine borane **8**, the yield dropped slightly to 44% whereas the enantiomeric ratio was slightly higher (93:7 er). Recrystallisation gave bisphosphine (*R*)-**49** of 99:1 er as a solid in 20% yield and a filtrate from which we isolated (*R*)-**49** in 20% yield and 89:11 er (entry 2). The CSP-HPLC on a Daicel Chiracel AD column is shown in Figure. 2.5.

Figure 2.5



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.299	BV	0.8841	9.55762e4	1557.11511	99.0944
2	21.913	VB	1.1573	873.46729	10.05696	0.9056

We also repeated the reaction on a 1.50 g scale. In this case, bisphosphine borane sulfide (*R*)-**49** was isolated in 62% yield and 88:12 er after purification by

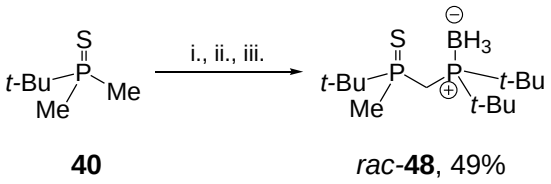
chromatography, which was slightly lower er than expected. Nonetheless, after recrystallisation, the enantiomeric ratio of bisphosphine borane sulfide (*R*)-**49** was increased to 98.5:1.5 er (33% yield, entry 3).

2.3.3 Lithiation–Trapping of Phosphine Sulfide 40 with *t*-Bu_2PCl

In order to synthesize other bisphosphines, *t*-Bu_2PCl was used as an electrophile. This was primarily because it would give bisphosphines with electron donating alkyl groups on both of the phosphorus atoms.

Thus, phosphine sulfide **40** was lithiated using 1.1 equivalents of *n*-BuLi at −78 ˚C in THF for 3 hours and then trapped with 1.0 equivalent of *t*-Bu_2PCl. Next, 1.5 equivalents of BH_3•Me_2S was added to protect the free phosphine. This afforded bisphosphine *rac*-**48** in 49% yield after purification by chromatography (Scheme 2.12).

Scheme 2.12



40 *rac*-**48**, 49%

Reagents and conditions: i. *n*-BuLi (1.1 eq.), −78 ˚C for 3 h, THF; ii. *t*-Bu_2PCl (1.1 eq.), −78 ˚C to rt, 18 h, THF; iii. BH_3•Me_2S (1.5 eq.) 0 ˚C to rt, 3 h.

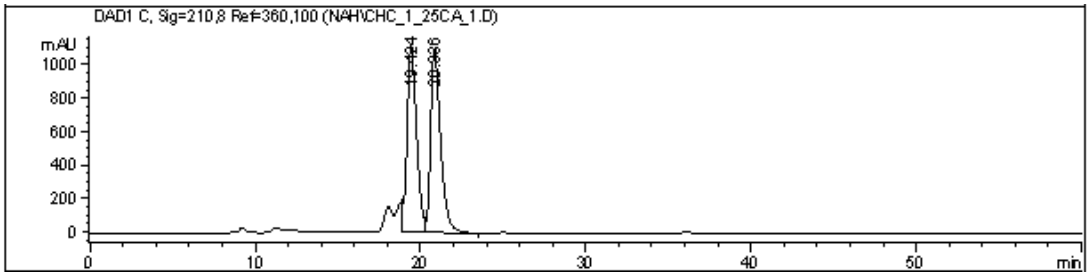
In the ^1H NMR spectrum of bisphosphine *rac*-**48**, a double double doublet (J = 15.0, 13.0, 10.5 Hz) was observed at δ_H 2.37 ppm and assigned to one of the methylene protons. The other methylene proton appeared as a doublet of triplets (J = 15.5, 14.5 Hz) at δ_H 2.22 ppm. A doublet (J = 12.2 Hz) at δ_H 1.98 ppm was assigned to the methyl protons. Three 9H doublets at at δ_H 1.45, 1.31 and 1.28 ppm were assigned to the protons of the three *t*-butyl groups.

The ^{13}C NMR spectrum of bisphosphine *rac*-**48** contained a doublet of doublets (J = 52.0, 4.0 Hz) at δ_C 35.8 ppm, assigned to a quaternary carbon of the *t*-butyl group attached to the P=S group. It is coupled with a large ^1J value to phosphorus and a small ^3J value to the other phosphorus. A doublet of doublets (J = 52.0, 4.0 Hz) and

a doublet (J = 25.0 Hz) at δ_C 34.3 and 33.2 ppm respectively were assigned to the quaternary carbons of the two other *t*-butyl groups. Three doublets at δ_C 28.5, 27.8 and 24.6 ppm with J = 2.5, 1.0 and 1.0 Hz respectively were assigned to the methyl carbons of the three *t*-butyl groups. Moreover, a doublet of doublets (J = 39.0, 12.0 Hz) at δ_C 18.2 ppm due to the methylene carbon between the two phosphorus atoms was observed. In the ^{31}P NMR spectrum of bisphosphine *rac*-**48**, two multiplets at δ_P 60.2 and 49.0 ppm corresponding to PS and PBH_3 respectively were observed.

Analysis of bisphosphine sulfide *rac*-**48**, using CSP-HPLC on a Daicel Chiracel OD column showed that the enantiomers could be separated. The two enantiomers appeared with retention times of 18.9 minutes and 20.4 minutes after eluting with 99:1 hexane-*i*-PrOH (Figure 2.6).

Figure 2.6

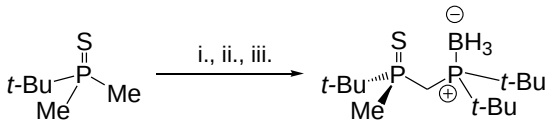


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.424	VV	0.6112	4.49220e4	1121.69849	49.1642
2	20.836	VB	0.6350	4.64494e4	1103.68628	50.8358

The asymmetric synthesis of bisphosphine (*S*)-**48** was then attempted. Phosphine sulfide **40** was deprotonated using 1.1 equivalents of *n*-BuLi in the presence of 1.2 equivalents of (–)-sparteine. The lithiated intermediate was trapped with *t*-Bu_2PCl and after warming to room temperature over 18 hours, it was protected with BH_3•Me_2S to give bisphosphine (*S*)-**48** in 45% yield and 61:39 er after purification by chromatography (Scheme 2.13 and Table 2.3, entry 1).

Scheme 2.13



40 (*S*)-**48**

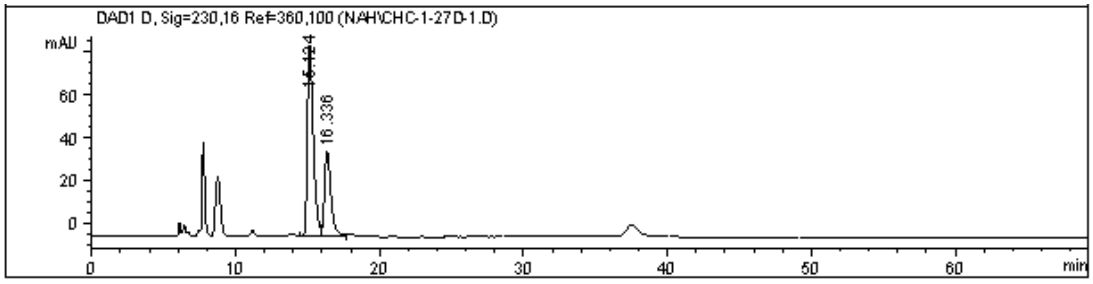
Table 2.3

[a] Entry	Scale of **40**	Yield, % [b]	Er (*S*:*R*) [c]
1	100 mg	45	61:39
2	1.00 g	38	68:32

[a] *Reagents and conditions:* i. *n*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), –78 ˚C for 3 h, Et_2O; ii. *t*-Bu_2PCl (1.1 eq.), –78 ˚C to rt, 18 h, THF; iii. BH_3•Me_2S (1.5 eq.), 0 ˚C to rt, 3 h. [b] Yield after chromatography. [c] Er determined using CSP-HPLC.

The formation of bisphosphine (*S*)-**48** in low enantioselectivity (61:39 er) was unexpected and disappointing. To ensure that it was a reproducible result, we repeated the reaction on a 1.00 g scale. In this case, bisphosphine (*S*)-**48** was formed in 38% yield and 68:32 er (entry 2). The CSP-HPLC of (*S*)-**48** of 68:32 er is shown in Figure 2.7. Despite repeated recrystallisation, it was not possible to improve the er of (*S*)-**48**. Bisphosphine (*S*)-**48** of 68:32 er was formed in the lowest er of all of the bisphosphines we have prepared.

Figure 2.7

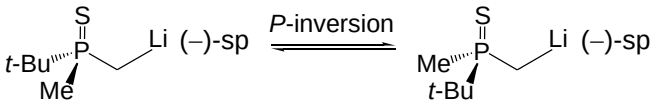


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.124	VV	0.4336	2558.58105	89.46915	67.8553
2	16.336	VB	0.4610	1212.05981	39.60909	32.1447

The following hypothesis is proposed which explains the low enantioselectivity observed for (*S*)-**48**. Recently, work in the O'Brien group shows that the (–)-sparteine-complexed lithiated intermediates (R_p)-**54** and (S_p)-**55** can interconvert at phosphorus at temperatures >0 ˚C (Scheme 2.14).[52]

Scheme 2.14



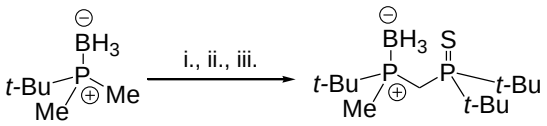
(R_p)-**54** (S_p)-**55**

The kinetic selectivity in the deprotection of phosphine sulfide **40** using *n*-BuLi/(–)-sparteine gives an 88:12 mixture of (R_p)-**54** and (S_p)-**55**. If (R_p)-**54** and (S_p)-**55** do not interconvert then we should obtain trapped products with 88:12 er. This is essentially what is observed with benzophenone (Scheme 2.5) and Ph_2PCl (Table 2.1). However, the reaction of lithiated intermediates (R_p)-**54** and (S_p)-**55** with the more sterically hindered *t*-$BuPCl_2$ could be slow, occurring only at higher temperatures such as 0 ˚C. At these higher temperatures (*e.g.* 0 ˚C), (R_p)-**54** and (S_p)-**55** can interconvert and so this could lead to an erosion in enantioselectivity. Hence, although bisphosphine (*S*)-**48** was successfully synthesized, we were not be able to obtain a highly enantioenriched sample.

2.3.4 Lithiation–Trapping of Phosphine Borane 8 with *t*-Bu_2PCl

We also investigated the trapping of lithiated phosphine borane **8** with *t*-Bu_2PCl. Phosphine borane **8** was lithiated by 1.1 equivalents of *s*-BuLi in the absence of (–)-sparteine at −78 ˚C for 3 hours. Then, 1.1 equivalents of *t*-Bu_2PCl was added and the reaction mixture was allowed to warm to room temperature over 18 hours. Finally, 1.5 equivalents of sulfur was added to the reaction to protect the free phosphine. This produced bisphosphine borane sulfide *rac*-**50** in 40% yield (Scheme 2.15).

Scheme 2.15



8 *rac*-**50,** 40%

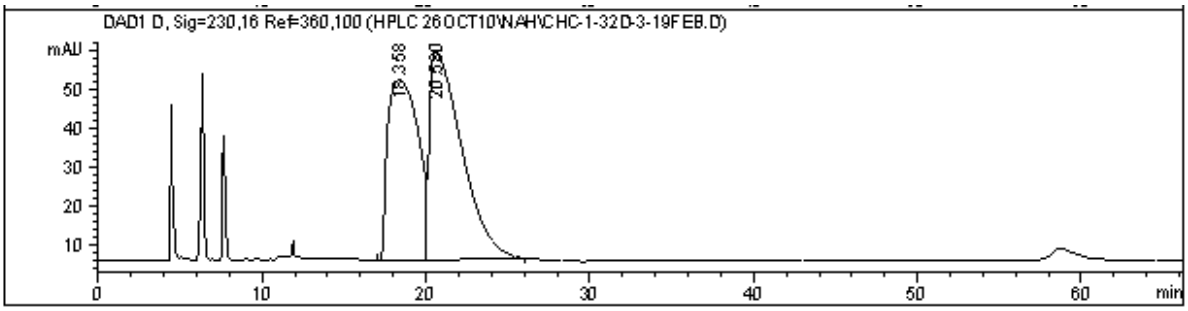
Reagents and conditions: i. *s*-BuLi (1.1 eq.), −78 ˚C for 3 h, THF; ii. *t*-Bu_2PCl (1.1 eq.), −78 ˚C to rt, 18 h, THF; iii. S_8 (1.3 eq.), 80 ˚C for 5 min, rt 5 h.

The ^{1}H NMR spectrum of bisphosphine *rac*-**50** contained a multiplet from δ_H 2.24-2.10 ppm corresponding to the methylene protons. It also showed a doublet (J = 10.0 Hz) at δ_H 1.75 ppm due to the methyl protons and three doublets with J = 16.0, 15.0, 13.5 δ_H 1.42, 1.36, 1.20 ppm respectively, which were assigned to the methyl protons of each *t*-butyl group.

In the ^{13}C NMR spectrum of bisphosphine borane sulfide *rac*-**50**, two doublets at δ_C 39.8 and 39.1 ppm, both with ^1J = 42.0 Hz were assigned to the quaternary carbons of the *t*-butyl groups attached to the P=S group. A doublet of doublets (J = 33.5, 4.0 Hz) at δ_C 29.6 ppm was assigned to the quaternary carbon of the *t*-butyl group attached to the P-BH_3 group. A doublet of doublets (J = 32.0, 21.0 Hz) at δ_C 12.6 ppm was assigned to the methylene carbon between the two phosphorus atoms. The ^{31}P NMR spectrum contained two multiplets at δ_P 76.3 and 32.0 ppm due to PS and PBH_3 groups, respectively.

With phosphine borane sulfide *rac*-**50** in hand, it was important to show that the enantiomers could be separated by CSP-HPLC. Thus, using a Daicel Chiracel OD column eluting with 99.7:0.3 hexane-*i*-PrOH, the two enatiomers were resolved with retention times of 18.4 minutes and 20.6 minutes (Figure 2.8).

Figure 2.8

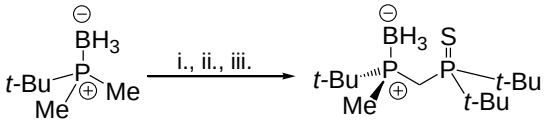


Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.358	BV	1.7892	5917.13818	46.23275	44.6789
2	20.580	VB	1.7915	7326.56396	53.44011	55.3211

Next, the asymmetric deprotonation of phosphine borane **8** was carried out using 1.1 equivalents of *s*-BuLi in the presence of 1.2 equivalents of (–)-sparteine at −78 °C. After trapping with 1.1 equivalents of *t*-Bu_2PCl and protection with 1.5 equivalents of sulfur bisphosphine borane sulfide (*R*)-**50** was formed in 53% yield and 93:7 er (Scheme 2.16).

Scheme 2.16



8 *(R)*-**50**

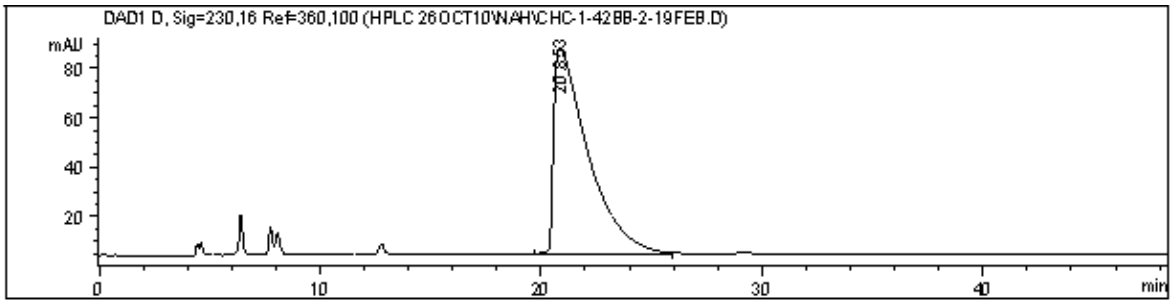
Before recrystallisation: 53%, 93:7 er

After recrystallisation: 40%, ≥99:1 er

Reagents and conditions: i. *s*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), −78 ˚C for 3 h, Et_2O; ii. *t*-Bu_2PCl (1.1 eq.), −78 ˚C to rt, 18 h, THF; iii. S_8 (1.3 eq.), 80 ˚C for 5 min, rt 5 h.

Analysis of bisphosphine borane (*R*)-**50** using CSP-HPLC on a Daicel Chiracel OD column with 99.7:0.3 hexane-*i*-PrOH as eluent indicated 93:7 er after purification by chromatography. After recrystallisation, the enantiomeric ratio of bisphosphine borane (*R*)-**50** was improved to ≥99:1 er and the product was isolated in 40% yield (Figure 2.9).

Figure 2.9



Signal 4: DAD1 D, Sig=230,16 Ref=360,100

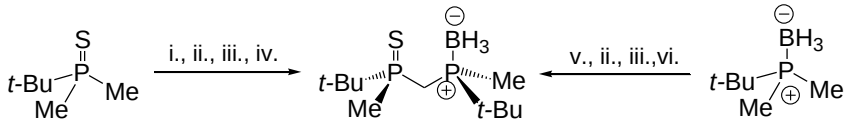
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.853	BB	1.5583	9042.52734	83.83839	100.0000

In this case, there was no loss of enantioselectivity. This is because, unlike phosphine sulfide **40**, the lithiated phosphine boranes do not interconvert even at 0 ˚C.

2.4 Synthesis of (*R*)-*t*-Butylmethylphosphinoborane-(*S*)-*t*-butylmethylphosphinesulfide 56

As an additional example of a precursor to a hemi-labile ligand, we decided to attempt the synthesis of bisphosphine sulfide borane (*S,R*)-**56**. Based on the features of MiniPHOS,[11] bisphosphine (*S,R*)-**56** with two stereogenic centres, one at each phosphorus, was designed as an analogue. We proposed two synthetic routes to bisphosphine (*S,R*)-**56** as outlined in Scheme 2.17, starting from either phosphine sulfide **40** or phosphine borane **8**. From phosphine sulfide **40**, deprotonation and trapping with *t*-$BuCl_2$ would be followed by a reaction with methyl magnesium bromide and BH_3•Me_2S to give bisphosphine (*S,R*)-**56**. A similar route from phosphine borane **8** but adding sulfur in this last step should also produce bisphosphine (*S,R*)-**56**.

Scheme 2.17

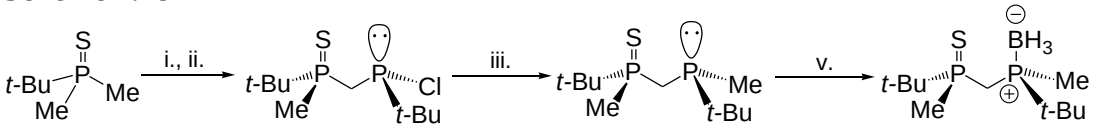


40 (*S,R*)-**56** **8**

Reagents and conditions: i. *n*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), −78 ˚C for 3 h, Et_2O; ii. *t*-$BuPCl_2$ (1.1 eq.), −78 ˚C to rt, 16 h, THF; iii. MeMgBr (1.3 eq.) −78 ˚C for 2 h then rt for 3 h; iv. BH_3•Me_2S (1.3 eq.), 0 ˚C to rt, 16 h; v. *s*-BuLi (1.1 eq.), (–)-sparteine (1.2 eq.), −78 ˚C for 3 h, Et_2O; vi. S_8 (1.3 eq.), 80 ˚C for 5 min, rt 16 h.

Thus, to start with, phosphine sulfide **40** was deprotonated by 1.1 equivalents of *n*-BuLi in the presence of 1.2 equivalents of (–)-sparteine in Et_2O at −78 ˚C for 3 hours lithiation time. Then, 1.1 equivalents of *t*-$BuPCl_2$ in THF was added and the resulting mixture was allowed to warm to room temperature over 16 hours to give bisphosphine sulfide intermediate (*S,R*)-**57**. The reaction was cooled to −78 ˚C and 1.3 equivalents of methyl magnesium bromide was then added to displace the remaining chlorine atom to give (*S,R*)-**58**. Then, the free phosphine in (*S,R*)-**58** was protected using BH_3•Me_2S to afford bisphosphine borane sulfide (*S,R*)-**56** in 12% yield and 89:11 er after purification by chromatography (Scheme 2.18).

Scheme 2.18



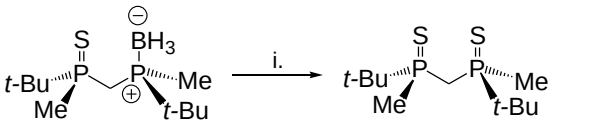
40 (*S*,*R*)-**57** (*S*,*R*)-**58** (*S*,*R*)-**56**, 12%

Reagents and conditions: i. *n*-BuLi (1.1 eq.), (−)-sparteine (1.2 eq.), −78 ˚C, 3 h, Et_2O; ii. *t*-$BuPCl_2$ (1.1 eq.), −78 ˚C to rt, 16 h, THF; iii. MeMgBr (1.3 eq.) −78 ˚C, 2 h then rt, 3 h; iv. BH_3•Me_2S (1.3 eq.), 0 ˚C to rt, 16 h.

In the ^{1}H NMR spectrum of bisphosphine borane sulfide (*S*,*R*)-**56**, a multiplet at δ_H 2.15-1.96 ppm was assigned to the methylene protons which couple to the two phosphorus nuclei. There were two 3H doublets at δ_H 1.93 (*J* = 12.4 Hz) and 1.69 (*J* =10.0 Hz) ppm due to the methyl groups. There were also two 9H doublets (*J* = 16.8 Hz and 14.0 Hz) at δ_H 1.23 and 1.15 ppm due to the methyl groups of the *t*-butyl groups which couple to the adjacent phosphorus. The ^{13}C NMR spectrum of bisphosphine borane sulfide (*S*,*R*)-**56** contained two double doublets at δ_C 35.0 (*J* = 51.5, 3.5 Hz) ppm and δ_C 29.0 (*J* = 33.5, 5.0 Hz) ppm due to the two quaternary carbons of the *t*-butyl groups. There was also a double doublet (*J* = 38.5, 20.0 Hz) at δ_C 18.9 ppm corresponding to the methylene carbon. Two doublets at δ_C 24.5 (*J* = 2.5 Hz) and δ_C 24.1 (*J* = 2.0 Hz) ppm were assigned to the methyl groups of the *t*-butyl groups. There were also two doublets at δ_C 15.9 (*J* = 51.5 Hz) ppm and δ_C 6.2 (*J* = 34.0 Hz) ppm corresponding to the two methyl groups. In addition, the ^{31}P NMR spectrum contained a singlet at δ_P 56.8 ppm due to the PS group and a multiplet δ_P 27.7 ppm due to the PBH_3 group.

The stereochemistry of bisphosphine borane sulfide (*S*,*R*)-**56** was proven by conversion into known bisphosphine sulfide (*S*,*S*)-**59**.[47] Therefore, deboronation of (*S*,*R*)-**56** was achieved using 1.2 equivalents of DABCO in the presence of 2.5 equivalents of sulfur. The reaction mixture was heated at 80 ˚C for 16 hours to give bisphosphine disulfide (*S*,*S*)-**59** in 77% yield and 83:17 er (Scheme 2.19).

Scheme 2.19



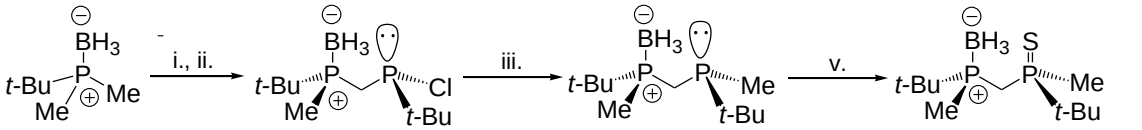
(*S,R*)-**56** (*S,S*)-**59**, 77%, 83:17 er

Reagents and conditions: i. DABCO (1.2 eq.), S_8 (2.5 eq.), 80 ˚C, 16 h, toluene.

In the ^{1}H NMR spectrum of bisphosphine (*S,S*)-**59**, a triplet at δ_H 2.40 (J = 13.0 Hz) ppm was assigned to the methylene protons between the two phosphorus atoms. A doublet at δ_H 2.13 (J = 13.0 Hz) ppm due to the two methyl groups was observed and a doublet at δ_H 1.25 (J = 17.2 Hz) ppm was assigned to the two *t*-butyl groups. The ^{31}P NMR spectrum of bisphosphine borane sulfide (*S,S*)-**59** contained a singlet at δ_P 56.4 ppm due to the PS group. The ^{1}H NMR spectrum of (*S,S*)-**59** was identical to that reported in the literature.[47]

For comparison, bisphosphine borane sulfide (*S,R*)-**56** was also prepared from phosphine borane **8** (Scheme 2.20). In this case, phosphine borane **8** was lithiated with 1.1 equivalents of *s*-BuLi and 1.2 equivalents of (−)-sparteine and trapped with 1.1 equivalents of *t*-BuPCl$_2$ in THF to give free phosphine (*S,R*)-**60**. Then, 1.3 equivalents of methyl magnesium bromide were added to give bisphosphine borane (*R,R*)-**61**. To avoid oxidation, the free phosphine in (*R,R*)-**61** was protected by adding 1.3 equivalents of sulfur. This gave bisphosphine sulfide borane (*S,R*)-**56** in 24% yield and 98:2 er (Scheme 2.20).

Scheme 2.20

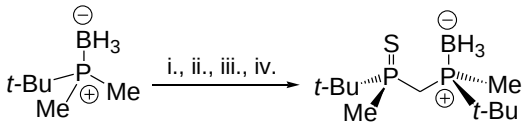


8 (*R,R*)-**60** (*R,R*)-**61** (*S,R*)-**56**, 24%, 98:2 er

Reagents and conditions: i. *s*-BuLi (1.1 eq.), (−)-sparteine (1.2 eq.), −78 ˚C for 3 h, Et_2O; ii. *t*-BuPCl$_2$ (1.1 eq.), −78 ˚C to rt, 16 h, THF; iii. MeMgBr (1.3 eq.) −78 ˚C for 2 h then rt for 3 h; v. S_8 (1.3 eq.), 80 ˚C for 5 min, rt 16 h.

In order to determine the enantiomeric ratio, bisphosphine borane sulfide *rac*-**56** was also synthesized in 19% yield (Scheme 2.21).

Scheme 2.21



8 *rac*-**56**, 19%

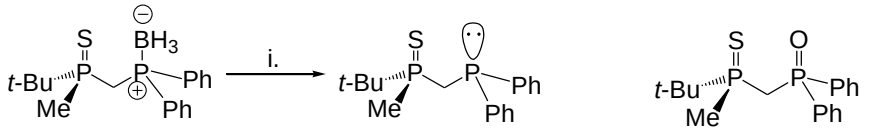
Reagents and conditions: i**.** *s*-BuLi (1.1 eq.), −78 ˚C for 3 h, THF; ii. *t*-BuPCl$_2$ (1.1 eq.), −78 ˚C to rt, 16 h, THF; iii. MeMgBr (1.3 eq.) −78 ˚C for 2 h then rt for 3 h; iv. S_8 (1.3 eq.), 80 ˚C for 5 min, rt 16 h.

In summary, the best route to bisphosphine borane sulfide (*R*,*S*)-**56** was that starting from phosphine borane **8**. The yield and er were both higher *via* this approach compared to that starting from phosphine sulfide **40**.

2.5 Investigation of the Borane Deprotection Step

To study the sensitivity of the free phosphine to oxidation, Hoge's protocol for removal of the borane protecting group was carried out.[14] The borane group on the bisphosphines was deprotected by treatment with DABCO. To avoid oxidation during the reaction, the toluene solvent was degassed before use. As shown in Scheme 2.22, the borane group of bisphosphine borane sulfide (*S*)-**47** was deprotected by treatment with 1.2 equivalents of DABCO at 80 ˚C for 4 hours. The organic solution was evaporated under reduced pressure to give the crude product. Hexane was added and the solid DABCO•BH_3 was removed by filtration. The filtrate was evaporated to give the crude product which contained free phosphine (*S*)-**43** and a small amount of DABCO•BH_3. There was no starting bisphosphine (*S*)-**47** and no phosphine oxide (*S*)-**62** present (by ^{1}H and ^{31}P NMR spectroscopy).

Scheme 2.22

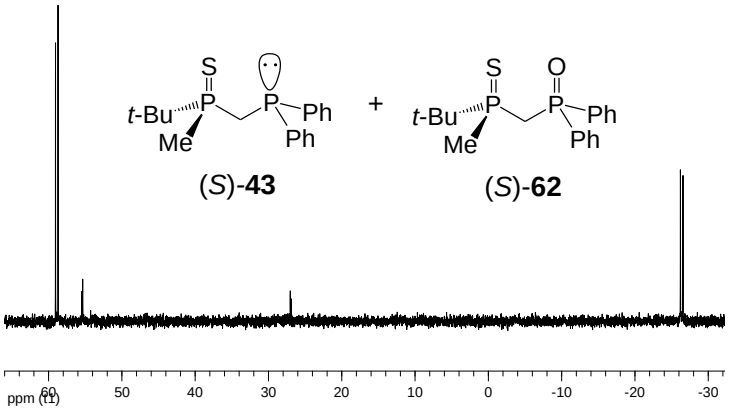


(*S*)-**47** (*S*)-**43**, 80% (*S*)-**62**

Reagents and conditions: i. DABCO, 80 ˚C for 4 h, toluene.

The crude product was then purified by flash chromatography to give free phosphine (*S*)-**43** in 80% yield. The ^{31}P NMR spectrum of the free phosphine (*S*)-**43** contained two signals: a doublet (J = 55.5 Hz) at δ_P 58.8 ppm due to the P=S group and a doublet (J = 55.5 Hz) at –26.3 ppm due to the PPh_2 group. In addition, there was also a small amount of phosphine oxide (*S*)-**62** now present. The ^{31}P NMR spectrum of phosphine oxide (*S*)-**62** showed a doublet (J = 16.5 Hz) at δ_P 55.4 ppm due to the P=S group and a doublet (J = 16.5 Hz) at δ_P 26.9 ppm due to the PO group (Figure 2.8). Thus, during chromatography, there was partial oxidation to the phosphine oxide. However, this reaction clearly showed that DABCO in refluxing, degassed toluene was an appropriate method for borane deprotection in bisphosphine borane sulfide (*S*)-**47**.

Figure 2.8

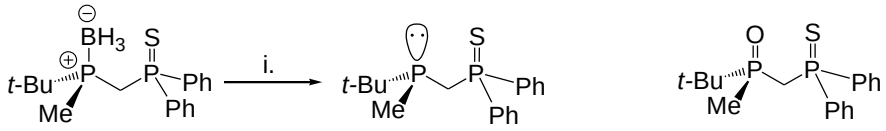


(*S*)-**43** (*S*)-**62**

Next, the deprotection of bisphosphine borane sulfide (*R*)-**49** was investigated. In this case, the free phosphine (*R*)-**45** is more electron rich (as it has alkyl groups attached). Consequently, it might be more likely to undergo oxidation to the phosphine oxide.

In a similar way, a solution of bisphosphine borane sulfide (*R*)-**49** and DABCO in toluene was stirred at 80 ˚C for 4 hours. The crude mixture was extracted with hexane and the solid DABCO•BH_3 was removed by filtration. The crude product contained free phosphine (*R*)-**45** and some DABCO•BH_3 but no phosphine oxide (*R*)-**63**. Purification by chromatography gave free phosphine (*R*)-**45** in 77% yield (Scheme 2.23).

Scheme 2.23



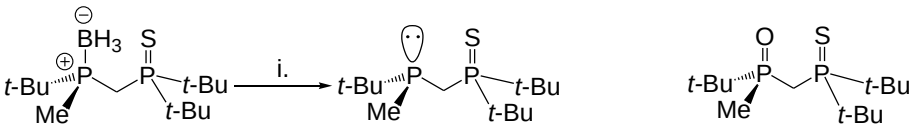
(*R*)-**49** (*R*)-**45**, 77% (*R*)-**63**

Reagents and conditions: i. DABCO, 80 ˚C for 4 h, toluene.

As shown in Scheme 2.23, after purification by flash chromatography, the ^{31}P NMR spectrum of free phosphine (*R*)-**45** contained a doublet (J = 63.5 Hz) at δ_P 41.1 ppm due to the PS group and a doublet (J = 63.5 Hz) at δ_P –22.6 ppm corresponding to the PMe group**.** Moreover, there was an evidence of partial oxidation to the phosphine oxide (*R*)-**63**. Thus, there was a doublet (J = 17.0 Hz) at δ_P 51.1 ppm corresponding to the PO group and a doublet (J = 16.5 Hz) at δ_P 37.8 ppm due to the PS group of phosphine oxide (*R*)-**63**.

Finally, the deprotection of bisphosphine borane sulfide (*R*)-**50** was also studied. Thus, a solution of bisphosphine borane sulfide (*R*)-**50** and DABCO in toluene was stirred at 80 ˚C for 4 hours (Scheme 2.24). After the usual work-up, the crude product was isolated. The ^{1}H and ^{31}P NMR spectra of crude free phosphine (*R*)-**46** showed that there was a slight oxidation to the phosphine oxide (*S*)-**64** even though the crude had not been purified by chromatography.

Scheme 2.24



(*R*)-**50** (*R*)-**46**, 73% (*S*)-**64**

Reagents and conditions: i. DABCO, 80 ˚C for 4 h, toluene.

The crude product was then purified by chromatography to give free phosphine (*R*)-**46** in 73% yield. The ^{31}P NMR spectrum of free phosphine (*R*)-**46** contained a doublet (J = 34.0 Hz) at δ_P −18.5 ppm corresponding to the PMe group and a doublet (J = 34.0 Hz) at δ_P 75.0 ppm due to the PS group. Moreover, there was a small amount of phosphine oxide (*S*)-**63**. The ^{31}P NMR spectrum of phosphine oxide (*S*)-**63** showed a doublet (J = 21.0 Hz) at δ_P 76.5 ppm corresponding to the PS group and a doublet (J = 34.0 Hz) at δ_P 52.4 ppm due to the PO group.

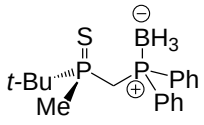
Thus, we found that free phosphines (*S*)-**43** and (*R*)-**45** were more stable to oxidation to the phosphine oxide than (*R*)-**46**. The stability of (*R*)-**45** is surprising since the phosphine has alkyl groups attached. However, with careful exclusion of oxygen, it has been shown that the borane groups can be deprotected successfully from three of the synthesized bisphosphine borane sulfides.

2.6 Synthetic Route to Bisphosphine Borane Sulfides – an Overview

To synthesize bisphosphine sulfide borane (*S*)-**47** or (*S*)-**48**, we started with an asymmetric lithiation of phosphine sulfide **8** using *n*-BuLi/(−)-sparteine and trapping with Ph_2PCl or *t*-Bu_2PCl as an electrophile. Treatment with BH_3•Me_2S led to bisphosphine sulfide borane (*S*)-**47** in 66% yield (82:18 er) or bisphosphine sulfide borane (*S*)-**48** in 38% yield (68:32 er) after purification by chromatography. In a similar way, phosphine borane **8** was deprotonated using *s*-BuLi/(−)-sparteine and trapped with Ph_2PCl or *t*-Bu_2PCl. Treatment with sulfur gave bisphosphine borane sulfide (*R*)-**49** in 62% yield (88:12 er) or bisphosphine borane sulfide (*R*)-**50** in 53% yield (93:7 er) after purification by chromatography. Based on Evans' protocol,[18] all bisphosphines were synthesized and obtained with the same sense of induction.

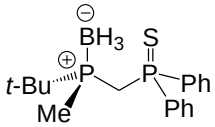
In the case of enantiomeric purity of the ligands, recrystallisation was used to increase the er of bisphosphine borane sulfide (*S*)-**47** to 97.5:2.5 er (47% yield). Both of bisphosphine sulfide borane (*R*)-**49** and bisphosphine (*R*)-**50** were recrystallised to afford 98.5:1.5 er (33% yield) and >99:1 er (40% yield) respectively (Figure 2.9). On the other hand, bisphosphine (*S*)-**48** was not recrystallised due to the low er. Thus, three ligands with >97.5:2.5 er were prepared in gram-quantities.

Figure 2.9



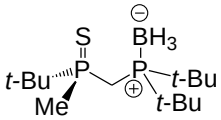
(*S*)-**47**

1.09 g, 47%
97.5:2.5 er



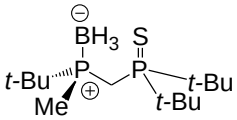
(*R*)-**49**

1.34 g, 33%
98.5:1.5 er



(*S*)-**48**

0.75 g, 38%
68:32 er



(R)-**50**

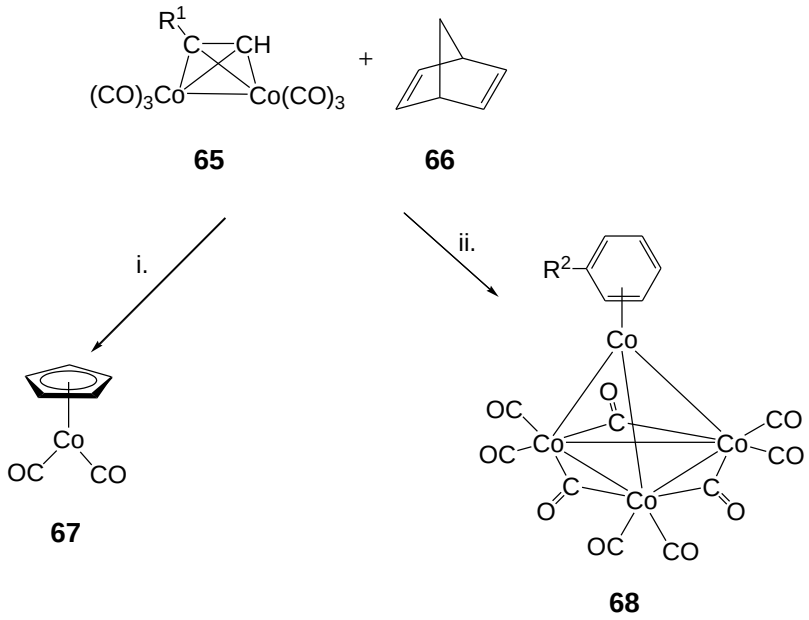
1.39 g, 40%
>99:1 er

3. Investigation of Asymmetric Pauson-Khand Reactions

3.1 Overview of Catalytic Asymmetric Pauson-Khand Reactions

In 1971, Pauson and Khand reported the complexation of alkyne complexes of hexacarbonyldicobalt **65** to norbornadiene **66**.[53] To study the behaviour of the complexes, the reactions were carried out in dimethoxyethane or iso-octane as solvent and dicarbonylcyclopentadienylcobalt **67** was a major product. In contrast, hexacarbonyl tetracobalt complexes **68** were successfully obtained as the major product when an aromatic hydrocarbon solvent was used (Scheme 3.1).

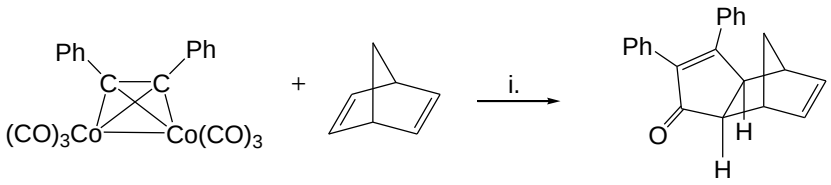
Scheme 3.1



Reagents and conditions: i. Dimethoxyethane or iso-octane; ii. Benzene or toluene

Two year laters in 1973, the same group presented a new synthesis of cyclopentenones. Reaction of acetylenehexacarbonyl dicobalt complex **69** with norbornadiene **66** in dimethoxyethane under nitrogen gave cyclopentenone **70** in 28% yield (Scheme 3.2).[54,55]

Scheme 3.2

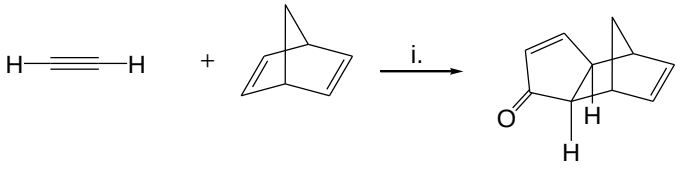


69 **66** **70**, 28%

Reagents and conditions: i. 60-70 ˚C for 4 h, DME.

In the initial study of intermolecular-type reactions, Pauson first reported, in 1973, examples of the catalytic cycloaddition of alkenes with $Co_2(CO)_8$ under a continuous supply of ethyne gas.[55] For example, reaction of acetylene, norbornadiene **66**, CO and $Co_2(CO)_8$ in iso-octane gave enone **71** in 74% yield (Scheme 3.3).[54]

Scheme 3.3

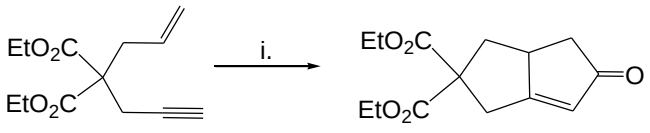


66 **71**, 74%

Reagents and conditions: i. $Co_2(CO)_8$ (0.1 eq.), acetylene:CO = 1:1, 60-70 ˚C until gas absorption ceased, iso-octane.

In this example, the amount of $Co_2(CO)_8$ was reduced to 0.1 equivalents. However, the 1:1 mixture of CO and alkyne gas had to be used under very high pressure. Consequently, various types of promoters were introduced to give higher reaction efficiency. In 1994, Jeong and coworkers presented intramolecular Pauson-Khand reactions in the presence of triphenyl phosphate as a promoter. The key point of their work was that the CO pressure could be reduced to 3 atmospheres and reaction of enyne **72** gave cyclopentenone **73** in 82% yield (Scheme 3.4).[57]

Scheme 3.4



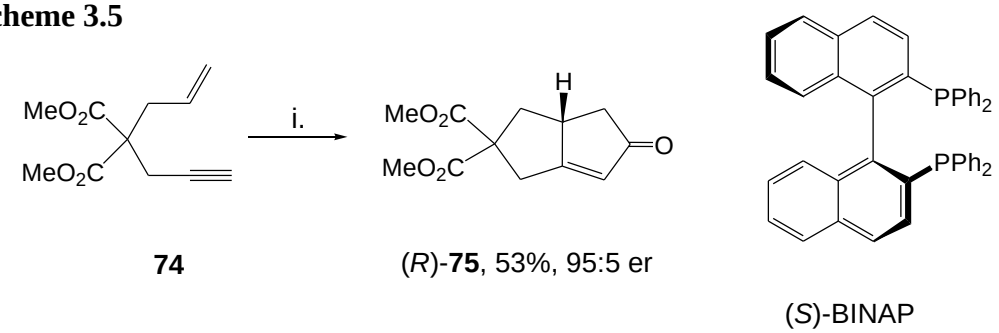
72 **73**, 82%

Reagents and conditions: i. $Co_2(CO)_8$ (3 mol%), $(PhO)_3P$ (10 mol%), CO (3 atm), 120 ˚C for 24 h, DME.

Under a low CO pressure, Gibson and coworkers reported that $Co_2(CO)_7PPh_3$ could also be utilized in a classical Pauson-Khand reaction.[58] Arias also showed that $Co_2(CO)_6(PPh_3)_2$ could be used with the same catalytic efficiency.[59]

In the case of asymmetric synthesis, Hiroi *et al*. had successfully developed Co-catalysed asymmetric Pauson-Khand reactions.[50,60] The reactions were carried out in the presence of commercially available chiral phosphine ligands, such as (*S*)-BINAP. Many solvents were employed to optimise the methodology. As an example, 1,6-enyne **74** was reacted with $Co_2(CO)_8$ and (*S*)-BINAP in refluxing DME for 14 hours under a CO atmosphere to give cyclopentenone (*R*)-**75** in 53% yield and 95:5 er (Scheme 3.5). It was shown that 0.2 equivalents of (*S*)-BINAP was the most effective amount for enantiocontrol. In contrast, use of (*R*,*R*)-DIOP provided products in low enantioselectivity (47:52-79:21 er).[60]

Scheme 3.5

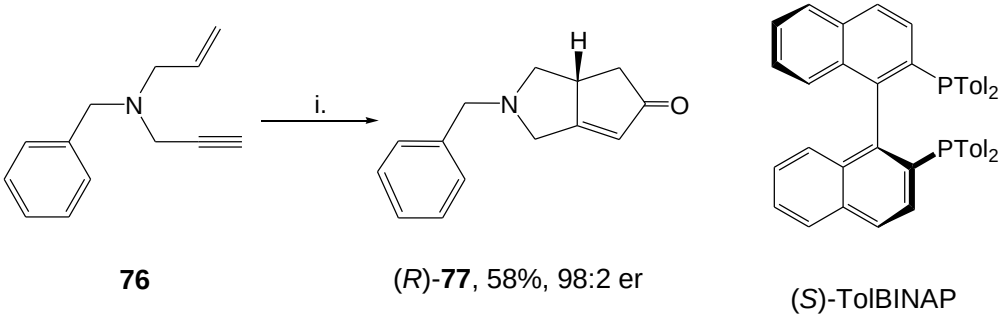


74 (*R*)-**75**, 53%, 95:5 er (*S*)-BINAP

Reagents and conditions: i. $Co_2(CO)_8$ (0.2 eq.), (*S*)-BINAP (0.2 eq.), reflux for 14 h, CO, DME.

In a similar way, intramolecular catalytic asymmetric Pauson-Khand reaction of 1,6-enyne **76** using 3.75 mol% of $Co_4(CO)_{12}$ and 7.5 mol% of (*S*)-TolBINAP in CO-saturated DME at 75 ˚C for 5 hours gave cyclopentenone **77** in 58% yield and 98:2 er (Scheme 3.6).[61]

Scheme 3.6

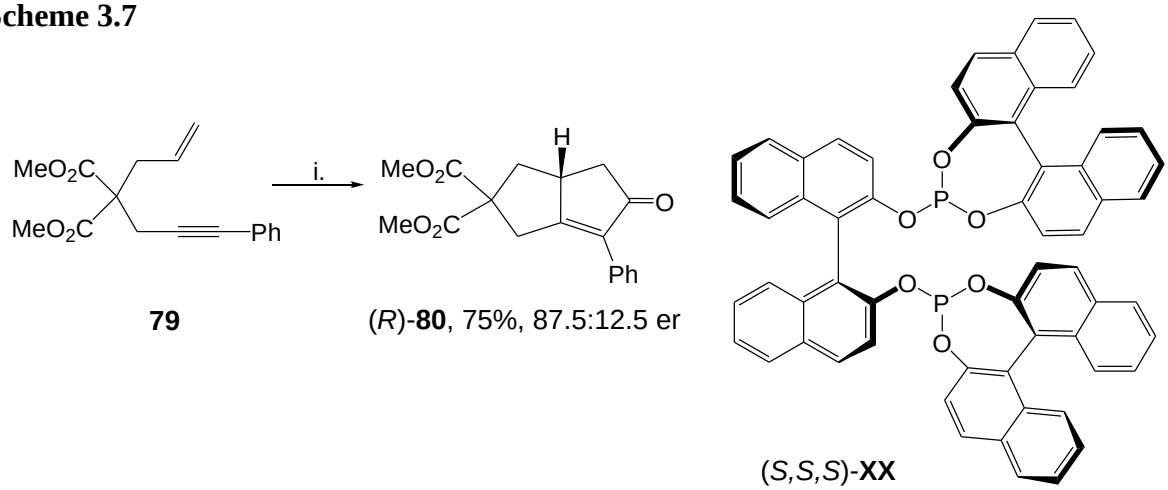


76 (*R*)-**77**, 58%, 98:2 er (*S*)-TolBINAP

Reagents and conditions: i. $Co_4(CO)_{12}$ (3.75 mol%), (*S*)-TolBINAP (7.5 mol%), 75 ˚C for 5 h, CO (1.05 atm), DME.

In 2002, Buchwald and Sturla utilized chiral aryl diphosphite (*S,S,S*)-**78**[62] as a chiral ligand in a catalytic asymmetric Pauson-Khand reaction of 1,6-enyne **79**. Using 6 mol% of $Co_2(CO)_8$ and 10 mol% of diphosphite (*S,S,S*)-**78** in toluene, heated at 95 ˚C for 24 hours, cyclopentenone (*R*)-**80** was obtained in high enantioselectivity (Scheme 3.7).[63]

Scheme 3.7

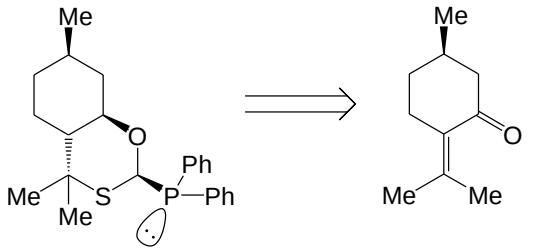


79 (*R*)-**80**, 75%, 87.5:12.5 er (*S,S,S*)-**XX**

Reagents and conditions: i. $Co_2(CO)_8$ (6 mol%), (*S,S,S*)-**78** (10 mol%), CO (1 atm), 95 ˚C for 24 h, toluene.

In the case of chiral promoter development, new chiral bidentate P,S-type ligand, PuPHOS which was directly prepared from (+)-pulegone was reported by the Pericàs and Riera group in 2000 (Scheme 3.8).[48]

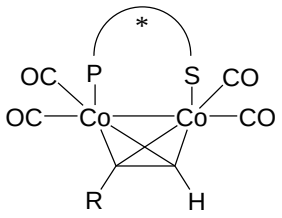
Scheme 3.8



PuPHOS (+)-Pulegone

The PuPHOS chiral auxiliary was designed with the idea that a sulfide arm can coordinate to the cobalt atom in the dicobalt-alkyne complex **81** (Figure 3.1). To drive the coordination effectively, a methylene group between the sulfur and phosphorus atom gave the optimum distance to support this purpose.

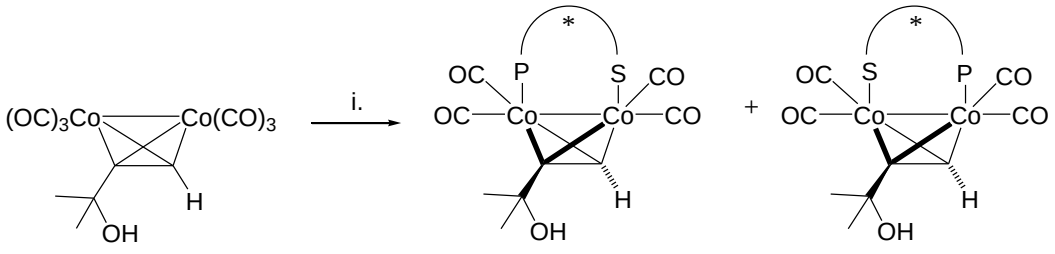
Figure 3.1



81

To study the complexation of PuPHOS to the cobalt, PuPHOS•BH_3 and alkyne-dicobalt hexacarbonyl complex **82** were heated at 60 ˚C in the presence of DABCO in toluene for 17 hours. The DABCO deprotected the borane and the PuPHOS coordinated to the cobalt to give a diastereoisomeric mixture of Co-complexes **83** and **84** in 84% yield (Scheme 3.9).[48]

Scheme 3.9



82 **83** **84**

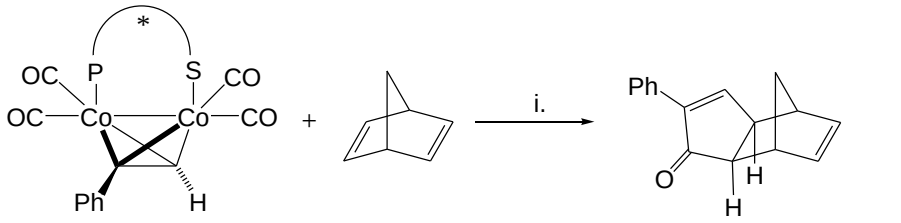
84%, **83**:**84** = 4.5:1

Reagents and conditions: i. PuPHOS-BH_3 (1.0 eq.), DABCO (2.0 eq.), 60 ˚C, N_2, toluene.

The stereochemistry of the diphenylphosphino substituent in the major product, Co-complex **83**, was confirmed by X-ray crystallography. To avoid steric interactions, the phosphorus atom occupied the *anti*-position relative to the dimethylcarbinol group.[48] Next, crystallized Co-complex **83** was to afford a high yield of the major product.

In a similar approach, diastereomerically pure Co-complex **85** was obtained after separation from the minor diastereoisomeric complex. Complex **85** was then exploited in the asymmetric intermolecular Pauson-Khand reaction with norbonadiene **66**. After heating in toluene at 50 ˚C for 30 minutes, cyclopentenone (*R,R*)-**86** was afforded in an excellent 99% yield and 99.5:0.5 er (Scheme 3.10).[48] Thus, the transfer of stereochemistry from Co-complex **85** to enone (*R,R*)-**86** was complete.

Scheme 3.10

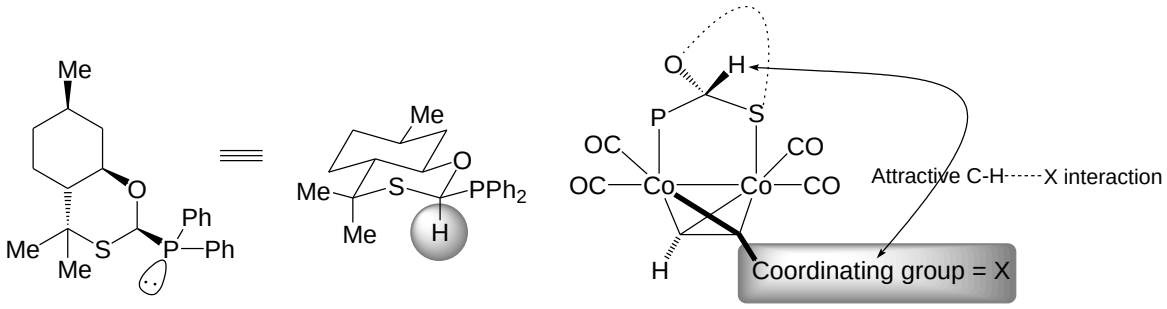


85 **66** (*R,R*)-**86**, 99%, 99.5:0.5 er

Reagents and conditions: i. 50 ˚C for 30 min, N_2, toluene.

As part of the study, the coordination of PuPHOS in Co-complex **87** was investigated using ^{1}H NMR, X-ray crystallography and quantum mechanical calculations by Riera, Verdaguer and coworkers.[64] The results showed that a non-classical hydrogen bond existed between the methine proton on the carbon attached to the three heteroatoms (O, P, S) in PuPHOS and the coordinating group on the alkyne substrate (Figure 3.2).

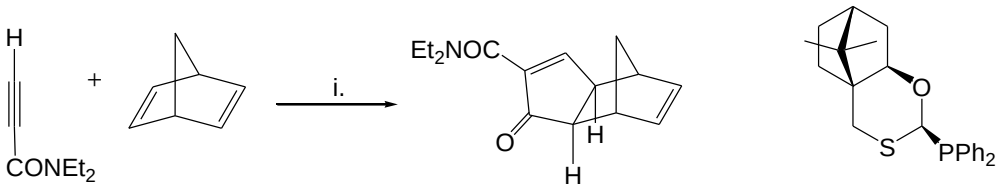
Figure 3.2



PuPHOS **87**

Recently, a related ligand, CamPHOS, has been developed by the same research group. As an example, the catalytic intermolecular asymmetric Pauson-Khand reaction of alkyne **88** and norbornadiene **66** was studied. In the presence of 5 mol% of the Co-CamPHOS complex under a low pressure of CO in toluene at 90 ˚C for 24 hours, a low 12% yield of the desired cyclopentenone **89** in 70:30 er was obtained (Scheme 3.11).[49,65]

Scheme 3.11



88 **66** **89**, 12%, 70:30 er CamPHOS

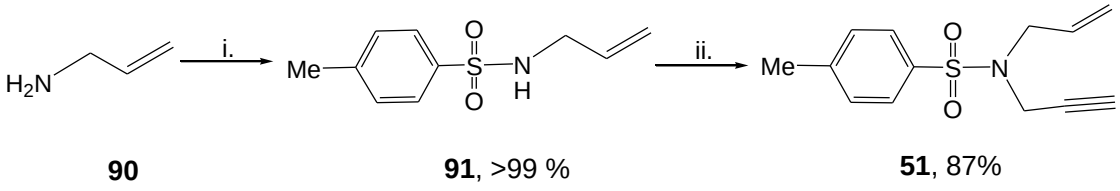
Reagents and conditions: i. Co-CamPHOS (5 mol%), 90 ˚C for 24 h, CO (0.5 bar), toluene.

In summary, there are a few examples of catalytic asymmetric Pauson-Khand reactions using $Co_2(CO)_8$ and chiral phosphines. The best results for intramolecular examples have been obtained using (*S*)-BINAP and (*S*)-tolBINAP (see Schemes 3.5 and 3.6). In addition, some success has been obtained with hemi-ligands such as PuPHOS and CamPHOS.[66]

3.2 Investigation of a Catalytic Asymmetric Pauson-Khand Reaction Using New Hemi-labile Ligands

To investigate a Pauson-Khand reaction, we selected 1,6-enyne sulfonamide **51** as a starting material as its Pauson-Khand reaction is well-known.[50,60] 1,6-Enyne sulfonamide **51** was prepared from allylamine **90** according to Dai and Shi's procedure.[67] The synthesis started with reaction of allylamine with *p*-toluenesulfonyl chloride to give crude sulfonamide **91**. Then, crude sulfonamide **91** was reacted with propargyl bromide and potassium carbonate in refluxing acetone for 8 hours. This gave enyne **51** in 87% yield over two steps after purification by flash chromatography (Scheme 3.12).

Scheme 3.12

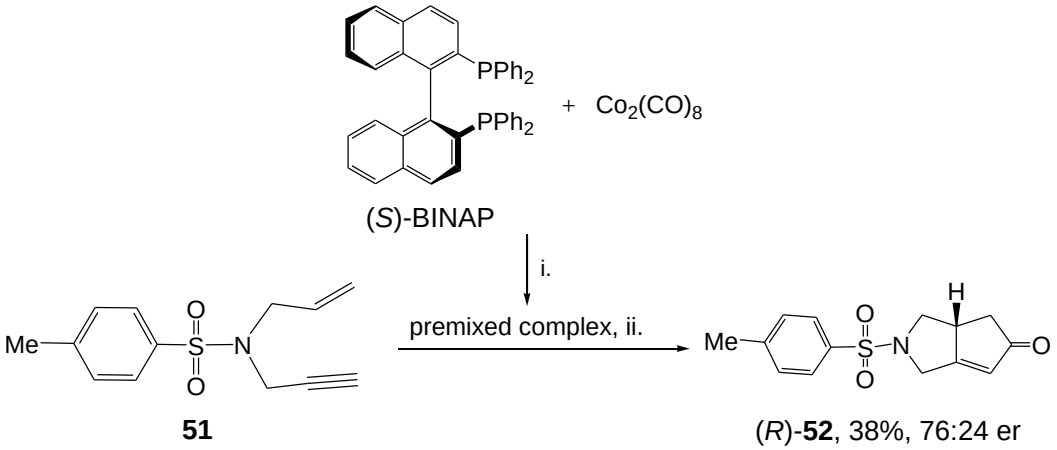


90 **91**, >99 % **51**, 87%

Reagents and conditions: i. Et_3N (1.1 eq.), *p*-toluenesulfonyl chloride (1.1 eq.), rt for 1 h, CH_2Cl_2; ii. propargyl bromide (1.5 eq.), K_2CO_3 (1.5 eq.), 65 ˚C for 8 h, acetone.

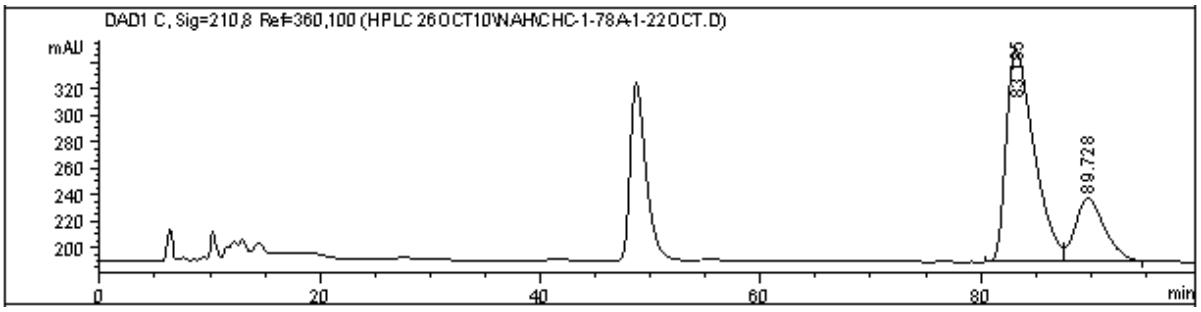
To start with, we decided to repeat a literature example of the intramolecular Pauson-Khand reaction of 1,6-enyne **51** to give cyclopentenone (*R*)-**52**. The method followed was based on that reported by Hiroi *et al*.[60] Thus, a solution of 40 mol% of (*S*)-BINAP and 40 mol% of $Co_2(CO)_8$ in degassed DME was stirred and heated at 65 ˚C under CO for 2 hours to allow complexation to occur. Then, 1,6-enyne **51** was added and the resulting mixture was refluxed for 17 hours under a CO atmosphere. This gave enone (*R*)-**52** in 38% yield and 76:24 er after purification by chromatography (Scheme 3.13). The enantiomeric ratio was determined using CSP-HPLC on a Daicel Chiracel OD column with 80:20 hexane-*i*-PrOH as eluent. The two enantiomers were resolved with retention times of 83.1 minutes and 89.7 minutes (Figure 3.3). The enantiomeric ratio we obtained was lower than that reported by Hiroi (95:5 er using 20 mol% of (*S*)-BINAP).[60] However, it provided a point of comparison for the results obtained using the new hemi-labile ligands.

Scheme 3.13



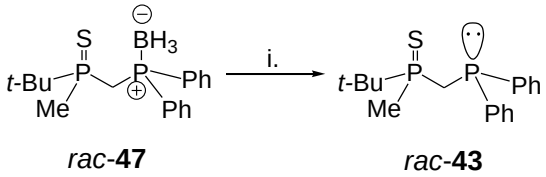
Reagents and conditions: i. 65 ˚C for 2 h, CO, DME; ii. reflux for 17 h, CO, DME.

Figure 3.3



Next, we investigated the use of hemi-labile ligand *rac*-**43** in the same Pauson-Khand reaction. In this case, the procedure needed to be modified since DABCO was needed to deprotect the borane in bisphosphine borane sulfide *rac*-**47** to give the hemi-labile ligand *rac*-**43** (Scheme 3.14).

Scheme 3.14



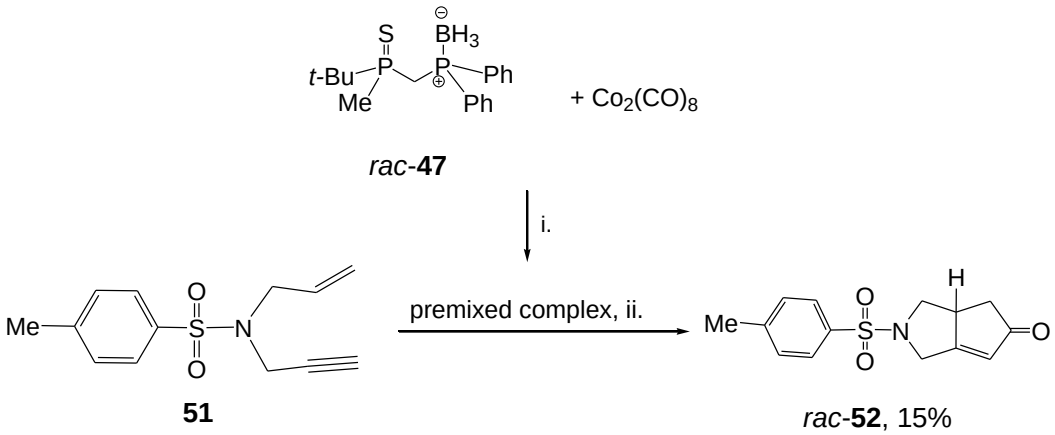
rac-**47** *rac*-**43**

Reagents and conditions: i. DABCO (1.1 eq.), 65 ˚C for 2 h, CO, DME.

A solution of 40 mol% of bisphosphine sulfide borane *rac*-**47**, 40 mol% of $Co_2(CO)_8$ and 44 mol% of DABCO in DME was heated at 65 ˚C under CO for 2 hours. Presumably, the borane group would be deprotected and a premixed Co-phosphine complex would be formed. This is similar to the method adopted with PuPHOS (see

Scheme 3.9). Then, a solution of 1,6-enyne **51** in DME was added and refluxed under CO for 17 hours to give cyclopentenone *rac*-**52** in 15% yield after purification by chromatography (Scheme 3.15). Although the yield was not high, this result showed that the hemi-labile ligand was able to promote the Pauson-Khand reaction.

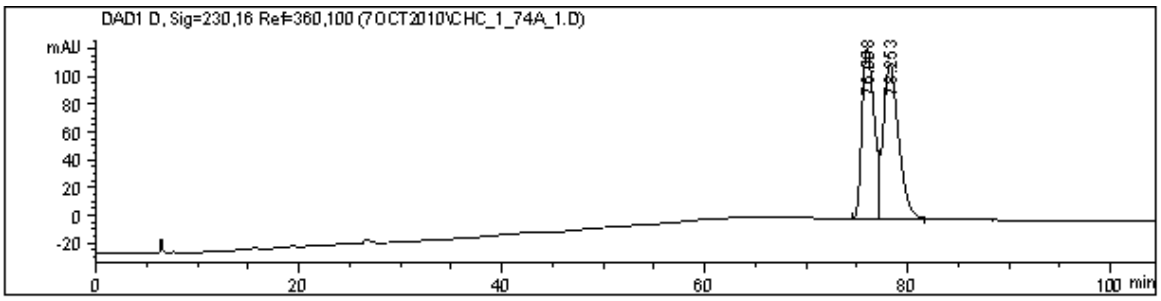
Scheme 3.15



Reagents and conditions: i. DABCO (44 mol%), 65 ˚C for 2 h, CO, DME; ii. reflux for 17 h, CO, DME.

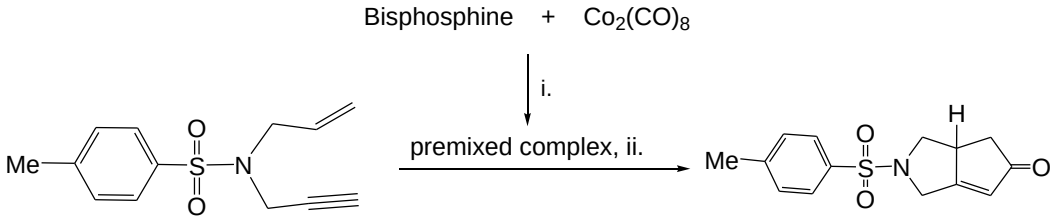
Analysis of cyclopentenone *rac*-**52** using CSP-HPLC on a Daicel Chiracel OD column eluting with 80:20 hexane-*i*-PrOH showed that the enantiomers were just separable. The two enantiomers appeared with retention times of 76.0 minutes and 78.2 minutes (Figure 3.4).

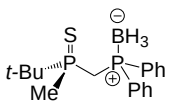
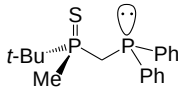
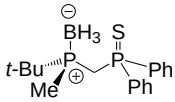
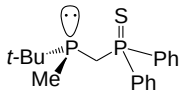
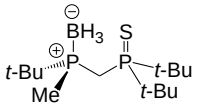
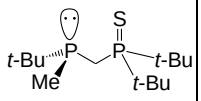
Figure 3.4



The next stage involved use of the same Pauson-Khand procedure with the enantioenriched phosphine borane sulfides (*S*)-**47** (97.5:2.5 er), (*R*)-**49** (99:1 er) and (*R*)-**50** (>99:1 er). The results are summaried in Table 3.1.

Table 3.1



Entry	Bisphosphine Borane sulfide	Hemi-labile ligand	Er of ligand	Yield, %[a]	Er[b] *R*:*S*
1	 (*S*)-**47**	 (*S*)-**43**	97.5:2.5	20	49:51
2	 (*R*)-**49**	 (*R*)-**45**	99:1	14	47:53
3			99:1	35[c]	48:52
4	 (*R*)-**50**	 (*R*)-**46**	>99:1	34	53:47

Reagents and conditions: i. DABCO (44 mol%), 65 ˚C for 2 h, CO, DME; ii. reflux for 17 h, CO, DME. [a] Yield after chromatography. [b] Er determined using CSP-HPLC. [c]. Reaction carried out in a Schlenk tube.

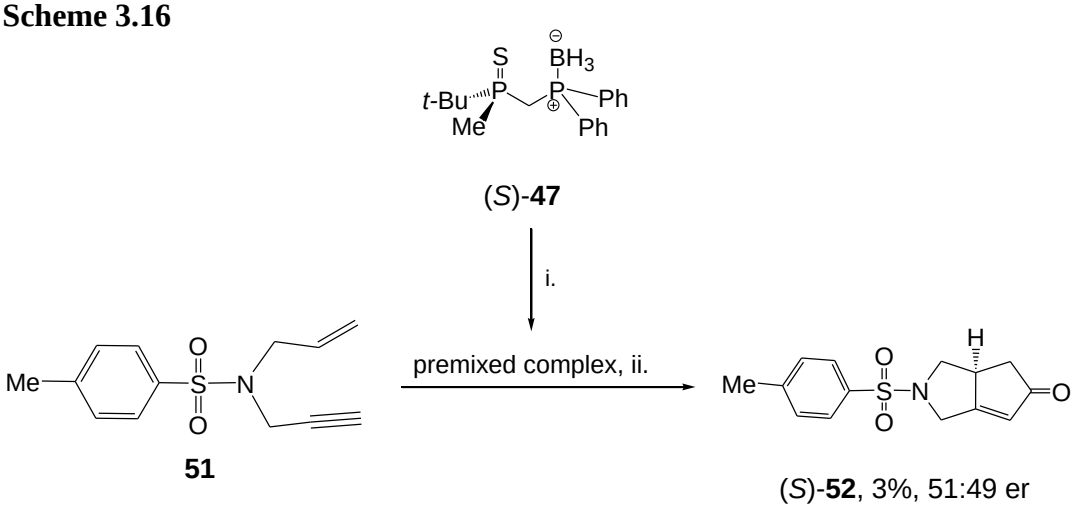
As shown in Table 3.1, use of bisphosphine borane sulfide (*S*)-**47** (97.5:2.5 er) as a precursor to hemi-labile (*S*)-**43** gave enone (*S*)-**52** in 20% yield and 51:49 er (entry 1). Unfortunately, there was no enantioselectivity with this ligand. In a similar way, using bisphosphine (*R*)-**49** (entry 2), a low 14% yield of enone (*S*)-**52** of 53:47 er was obtained (entry 2). However, when the same reaction was carried out under a higher pressure of CO in a Schlenk tube, use of bisphosphine (*R*)-**49** gave a higher

yield (35%) of enone (*S*)-**52**. Unfortunately, the enantioselectivity was poor (52:48 er) (entry 3). Finally, enone (*R*)-**52** of 53:47 er was afforded in 34% yield using bisphosphine sulfide borane (*R*)-**50** (entry 4). Hence, from the overall results, it appears that the new hemi-labile ligans are poor ligands in the case of the catalytic asymmetric Pauson-Khand reaction of 1,6-enzyne **51** to enone **52**. In all cases, there was a trace amount of starting enyne **51** in the ^{1}H NMR spectra of the crude products and no other products could be isolated after chromatography

Based on these initial results, we considered that the DABCO in the procedure could be responsible for the low enantioselectivity in the Pauson-Khand reaction. Thus, by adding DABCO in the presence of $Co_2(CO)_8$ and bisphosphine, it could be possible that a DABCO-Co complex would form and be more reactive than a hemi-labile ligand-Co complex. Then, instead of a phosphine-catalysed Pauson-Khand reaction, it could be possible to have a DABCO-catalysed Pauson-Khand reaction which would induce no enantioselectivity.

To reduce the likelihood of this result, we modified the procedure. Thus, 40 mol% of enantioenriched bisphophosphine (*S*)-**47** was deboronated by treatment with DABCO. The reaction mixture was refluxed in toluene for 2 hours under argon. Then, the solvent was removed. Hexane was added and the solid DABCO•BH_3 was removed by filtration. The filtrate was evaporated under reduced pressure and DME was added, followed by a solution of 40 mol% of $Co_2(CO)_8$ in DME. The resulting mixture was stirred at room temperature for 15 minutes under CO for complexation. A solution of 1,6-enyne **51** in DME was then added and the reaction was stirred and refluxed under CO for 17 hours to give cyclopentenone (*S*)-**52** in 3% yield and 51:49 er after purification by chromatography (Scheme 3.16). There was a significant amount of starting material, enyne **51**, in the ^{1}H NMR spectrum of the crude product. However, enyne **51** could not be recovered after chromatography.

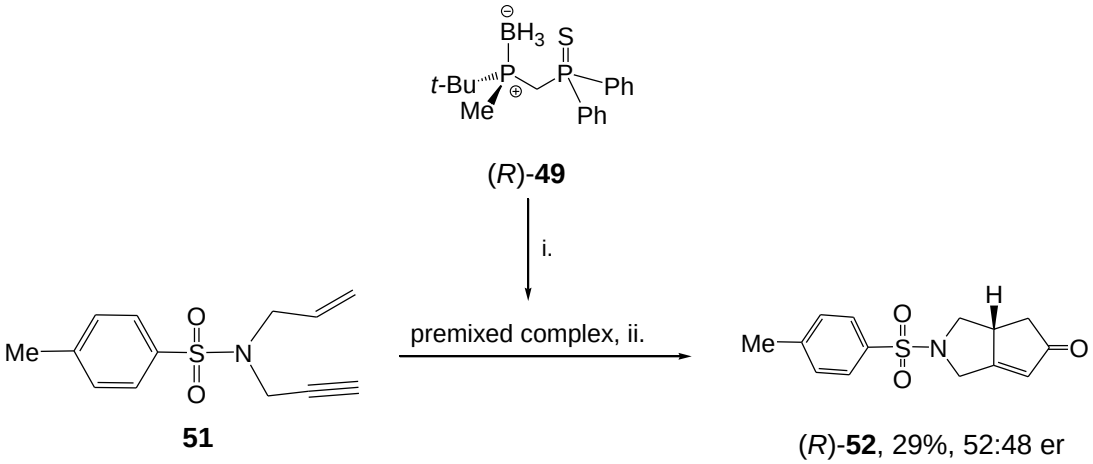
Scheme 3.16



Reagents and conditions: i. DABCO (40 mol%), reflux for 2 h, toluene; ii. $Co_2(CO)_8$ (40 mol%), rt for 15 min, CO, DME; iii. reflux for 17 h, CO, DME.

Unfortunately, enone **52** was still formed with no enantioselectivity. This suggested that hemi-labile ligand such as (*S*)-**43** are not suitable for Co-catalysed Pauson-Khand reactions. To verify this, the modified procedure was attempted starting from bisphosphine borane sulfide (*R*)-**49**. In this case, enone (*R*)-**52** was formed in 29% yield and 52:48 er (Scheme 3.17).

Scheme 3.17



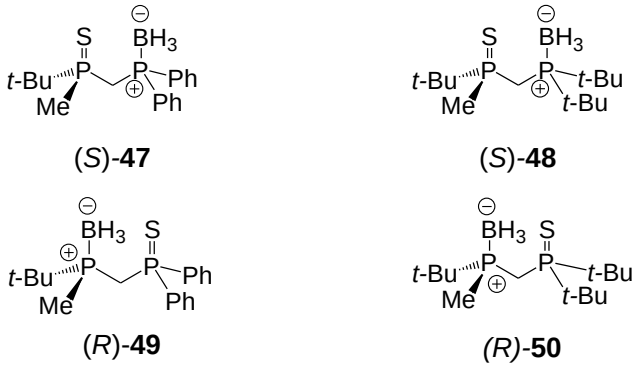
Reagents and conditions: i. DABCO (40 mol%), reflux for 2 h, toluene; ii. $Co_2(CO)_8$ (40 mol%), rt for 15 min, CO, DME; iii. reflux for 17 h, CO, DME.

In summary, under all conditions investigated, the yield and enantioselectivity of cyclopentenone **52** using the new hemi-labile ligands were very low. Hence, we conclude that such hemi-labile ligands are not suitable for catalytic asymmetric Pauson-Khand reactions.

4. Conclusions and Future Work

In summary, novel *P*-stereogenic bisphosphines were synthesized from either phosphine sulfide **40** or phosphine borane **8** which were prepared from PCl_3 or *t*-$BuPCl_2$ respectively. Thus, according to Evans' synthetic route,[18] an asymmetric lithiation of phosphine sulfide **40** using *n*-BuLi/(–)-sparteine, trapping with Ph_2PCl or *t*-Bu_2PCl and treatment with BH_3•Me_2S afforded bisphosphine sulfide borane (*S*)-**47** or (*S*)-**48**. In a similar way, deprotonation of phosphine borane **8** using *s*-BuLi/(–)-sparteine, trapping with Ph_2PCl or *t*-Bu_2PCl and treatment with sulfur gave bisphosphine borane sulfide (*R*)-**49** or (*R*)-**50** (Figure 4.1).

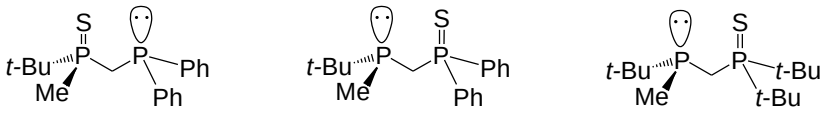
Figure 4.1



In this way, bisphosphine borane sulfide (*S*)-**47** was prepared in 80% yield and 91:9 er after purification by chromatography. To increase the er, bisphosphine (*S*)-**47** was then recrystallised to give 95.5:4.5 er. Bisphosphine borane sulfide (*R*)-**49** and (*R*)-**50** were obtained in 44% yield (93:7 er) and 53% yield (93:7 er) after purification by chromatography. However, the er of both bisphosphines was successfully improved up to 99:1 er after recrystallisation. Unfortunately, bisphosphine borane sulfide (*S*)-**48** was generated in 38% yield and 68:32 er and recrystallisation did not lead to an improvement in the er of this bisphosphine.

The three bisphosphines that were prepared in >97.5:2.5 er were then subjected to borane deprotection. Thus, treatment with DABCO gave hemi-labile ligands (*S*)-**43**, (*R*)-**45** and (*R*)-**46**. After deboronation, the ease of oxidation to the phosphine oxide was studied. The oxidation study showed that free phosphines (*S*)-**43** and (*R*)-**45** were more stable towards oxidation than free phosphine (*R*)-**46** (Figure 4.2).

Figure 4.2

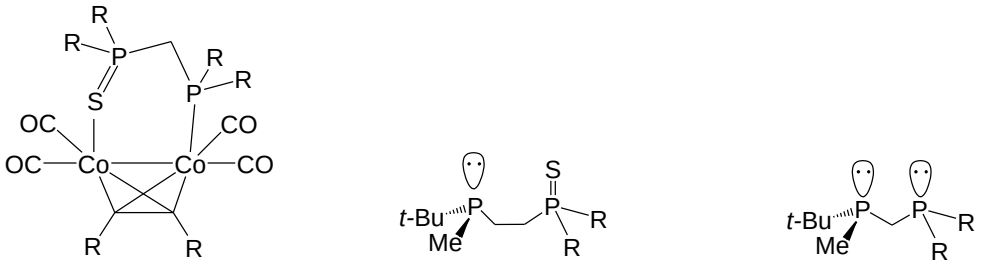


(*S*)-**43** (*R*)-**45** (*R*)-**46**

With three enantioenriched bisphosphines in hand, we used them in the Co-catalysed asymmetric Pauson-Khand reaction of 1,6-enyne **51**. However, enone **52** was obtained in low yield (7-35%) and low enantioselectivity (51:49 er-53:47 er). Hence, these results proved that our new bisphosphines are not suitable as ligands for the catalytic asymmetric Pauson-Khand reaction of 1,6-enyne **51**.

Based on the results of the Pauson-Khand reactions, it is questionable whether the ligands bind to the cobalt. As with PuPHOS,[48] the lone pair of electrons on the phosphorus and the sulfur can coordinate to the two cobalt atoms and the coordinated complex could be isolated. Thus, future work should focus on proving that the hemi-labile ligands do in fact bind to the cobalt. This could be investigated using *in situ* React IR spectroscopy and monitoring the ν_{CO} stretch in the IR spectra. In addition, in a similar way to PuPHOS, isolation of the ligand-Co complex **53** (Figure 4.3) should be attempted and then used in an intermolecular Pauson-Khand reaction. Other ideas for future work would involve synthesis and evaluation of an ethylene-bridged hemi-labile ligand **54** (Figure 4.3). If hemi-labile ligands are not successful then bisphosphine ligands **55** (Figure 4.3) could be investigated.

Figure 4.3



53 **54** **55**

5. Experimental

5.1 General

H_2O is distilled water. Brine refers to a saturated aqueous solution of NaCl. Et_2O, THF, hexane and toluene were freshly distilled from benzophenone ketyl or dispensed from a Pure Solv MD-7 solvent purification system under a N_2 atmosphere. (–)-Sparteine was distilled over CaH_2 by Kügelrohr distillation before use. Petrol refers to the fraction of petroleum ether boiling in the range of 40-60 ˚C. *s*-BuLi and *n*-BuLi were titrated against *N*-benzylbenzamide before use.[68] All reactions were carried out under O_2-free Ar using oven-dried and/or flame-dried glassware. Flash column chromatography was carried out using Fluka Silica gel 60 (0.035-0.070 mm particle size). Thin layer chromatography was carried out using Merck F_{254} aluminium-backed silica plates.

^1H (400 MHz), ^{13}C (100.6 MHz), ^{31}P (161 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H: 7.27) and $CDCl_3$ (δ_C: 77.0, centre line of triplet). ^{13}C and ^{31}P NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants *(J)* are quoted in Hertz. IR spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using the sodium D line; 259 nm) and $[\alpha]_D$ measurements are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Gallenkamp melting point apparatus. MS and HRMS were obtained using ESI or EI methods and recorded using a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase (CSP) HPLC was performed on an Agilent 1200 series instrument.

5.2 General Procedures

General Procedure A: Lithiation of phosphine sulfide 40 in the presence of (–)-sparteine

n-BuLi (2.5 M solution in hexane, 1.1 eq.) was added dropwise to a stirred solution of (–)-sparteine (1.2 eq.) in Et_2O (2 mL) in a flame-dried round bottomed flask at –78 ˚C under Ar. After stirring for 15 min, a solution of phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in Et_2O (7 mL) was added dropwise over 10 min *via* a syringe. The resulting mixture was stirred at –78 ˚C for 3 h. Then, a solution of Ph_2PCl or *t*-Bu_2PCl (1.1 eq.) in THF (2 mL) was added dropwise *via* a syringe and the mixture was allowed to warm to rt over 16 h. The solution was cooled to 0 ˚C and BH_3•Me_2S (1.5 eq.) was added dropwise and the reaction mixture was stirred at rt for 3 h. Then, 1 M $HCl_{(aq)}$ (6 mL) was added dropwise over 10 min (Caution – vigorous effervescence) and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure B: Lithiation of phosphine sulfide 40 in the absence of (–)-sparteine

n-BuLi (2.5 M solution in hexane, 1.1 eq.) was added dropwise to a stirred solution of phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in THF (6 mL) in a flame-dried round bottomed flask at –78 ˚C under Ar. The resulting mixture was stirred at –78 ˚C for 3 h. Then Ph_2PCl or *t*-Bu_2PCl (1.1 eq.) was added dropwise *via* a syringe and the mixture was allowed to warm to rt over 16 h. The solution was cooled to 0 ˚C and BH_3•Me_2S (1.5 eq.) was added dropwise and the reaction mixture was stirred at rt for 3 h. Then, 1 M $HCl_{(aq)}$ (6 mL) was added dropwise over 10 min (Caution – vigorous effervescence) and the resulting mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed

with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure C: Lithiation of phosphine borane 8 in the presence of (–)-sparteine

s-BuLi (1.3 M solution in cyclohexane, 1.1 eq.) was added dropwise to a stirred solution of (–)-sparteine (1.2 eq.) in Et_2O (2 mL) in a flame-dried round bottomed flask at −78 ˚C under Ar. After stirring for 15 min, a solution of phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in Et_2O (7 mL) was added dropwise over 10 min *via* a syringe. The resulting mixture was stirred at −78 ˚C for 3 h. Then, a solution of Ph_2PCl or *t*-Bu_2PCl (1.1 eq.) in THF (2 mL) was added dropwise *via* a syringe and the mixture was allowed to warm to rt over 16 h. Sulfur (1.3 eq.) was added and the reaction mixture was heated at 80 ˚C for 5 min and stirred at rt for 5 h. Then, the mixture was poured onto ice/H_2O (12 mL) and 1 M $HCl_{(aq)}$ (5 mL) and stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure D: Lithiation of phosphine borane 8 in the absence of (–)-sparteine

s-BuLi (1.3 M solution in cyclohexane, 1.1 eq.) was added dropwise to a stirred solution of phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in THF (6 mL) in a flame-dried round bottomed flask at −78 ˚C under Ar. The resulting mixture was stirred at −78 ˚C for 3 h. Then, Ph_2PCl or *t*-Bu_2PCl (1.1 eq.) was added dropwise *via* a syringe and the mixture was allowed to warm to rt over 16 h. Sulfur (1.3 eq.) was added and the reaction mixture was heated at 80 ˚C for 5 min and stirred at rt for 5 h. Then, the mixture was poured onto ice/H_2O (12 mL) and 1 M $HCl_{(aq)}$ (5 mL) and stirred for 15 min to give a homogeneous biphasic solution. Then, 1 M $HCl_{(aq)}$ (6 mL) was added dropwise over 10 min and the resulting mixture was stirred for 15

min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Procedure E: Deboronation of bisphosphine borane sulfides using DABCO

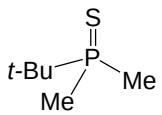
A solution of the bisphosphine borane sulfide (0.29 mmol, 1.0 eq.) and DABCO (1.2 eq.) in degassed toluene (5 mL) was stirred and heated at 80 ˚C for 4 h under Ar. Then, the reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure to give a solid. Hexane (5 mL) was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product.

General Procedure F: Catalytic asymmetric Pauson-Khand reaction

A solution of the bisphosphine borane sulfide (0.48 mmol, 0.40 eq.), DABCO (0.53 mmol, 0.44 eq.) and $Co_2(CO)_8$ (0.48 mmol, 0.40 eq.) in degassed DME (20 mL) was stirred at rt under CO. The resulting mixture was stirred and heated at 65 ˚C for 2 h. Then, a solution of sulfonamide **51** (1.20 mmol, 1.0 eq.) in degassed DME (15 mL) was added and the resulting mixture was stirred and heated at reflux under CO for 17 h. The reaction mixture was allowed to cool to rt. The solids were removed by filtration through a plug of silica and washed with EtOAc (40 mL). The filtrate was evaporated under reduced pressure to give the crude product.

5.3 Experimental for Chapter 2

tert-Butyldimethylphosphine sulfide 40

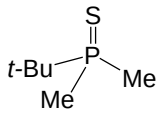


40

t-BuMgCl (30 mL of a 2.0 M solution in Et_2O, 60.0 mmol, 1.1 eq.) was added dropwise over 30 min to a stirred solution of PCl_3 (8.1 g, 58.9 mmol, 1.0 eq.) in THF (85 mL) at −78 °C under Ar. The resulting heterogeneous mixture was stirred at −78 ˚C for 1 h and allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to 0 ˚C and MeMgBr (40 mL of a 3.0 M solution in Et_2O, 120.1 mmol, 2.2 eq.) was added dropwise over 20 min. The resulting mixture was allowed to warm to rt over 2 h. Then, sulfur (2.8 g, 89.5 mmol, 1.5 eq.) was added and the mixture was heated at 80 °C for 5 min, cooled to rt and stirred for 16 h. Then, the mixture was poured onto ice/H_2O (130 mL) and conc. $HCl_{(aq)}$ (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (50 mL), H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow solid. Purification by recrystallisation from hot hexane (40 mL) gave phosphine sulfide **40** (6.29 g, 77%) as a white solid, mp 174–176 °C (lit.,[47] 206-207 °C); R_F (9:1 petrol-EtOAc) 0.1; IR (NaCl) 3020, 2970, 2401, 1470, 1419, 1366, 1297, 1215, 1015, 938, 912, 847, 755, 668, 629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.67 (d, J = 12.5 Hz, 6H, PMe), 1.25 (d, J = 16.5 Hz, 9H, $PCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 32.5 (d, J = 52.0 Hz, P*C*Me_3), 24.2 (d, J = 2.0 Hz, PC*Me*$_3$), 16.2 (d, J = 51.5 Hz, PMe); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ: 54.3; MS (ESI) *m/z* 151 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_6H_{15}PS$ $(M + H)^+$ 151.0705, found 151.0706. Spectroscopic data consistent with those reported in the literature.[46,51]

Lab book reference: chc/1/34

***tert*-Butyldimethylphosphine sulfide 40**

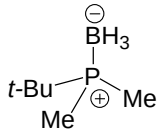


40

A solution of MeMgBr (16.5 mL of a 3.0 M solution in Et_2O, 49.5 mmol, 2.6 eq.) in THF (16.5 mL) was added dropwise to a stirred solution of *t*-$BuPCl_2$ (3.0 g, 18.9 mmol, 1.0 eq.) in THF (30 mL) at −10 °C under Ar. The resulting heterogeneous mixture was stirred at rt for 5 h. Sulfur (780 mg, 24.6 mmol, 1.3 eq.) was added and the mixture was heated at 80 °C for 5 min, cooled to rt and stirred for 5 h. Then, the mixture was poured onto ice/H_2O (36 mL) and conc. $HCl_{(aq)}$ (9 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (9 mL), H_2O (9 mL) and brine (9 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow solid. Purification by recrystallisation from hot hexane (15 mL) gave phosphine sulfide **40** (1.61 g, 57%) as a yellow solid.

Lab book reference: chc/1/2

***tert*-Butyldimethylphosphine borane 8**



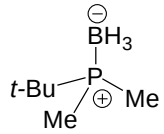
8

t-BuMgCl (33.2 mL of a 2.0 M solution in Et_2O, 66.6 mmol, 1.1 eq.) was added dropwise over 30 min to a stirred solution of PCl_3 (8.3 g, 60.6 mmol, 1.0 eq.) in THF (85 mL) at −78 ˚C under Ar. The resulting heterogeneous mixture was stirred at −78 ˚C for 1 h and allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to 0 ˚C and MeMgBr (44.3 mL of a 3.0 M solution in Et_2O, 133.2 mmol, 2.2 eq.) was added dropwise over 20 min. The resulting mixture was allowed to warm to rt over 2 h. Then, the resulting heterogeneous mixture was cooled to 0 °C and BH_3•Me_2S (36.3 mL of a 2.0 M solution in Et_2O, 72.6 mmol, 1.5 eq.) was added dropwise and the mixture was allowed to warm to rt and stirred for 16 h. Then, the

mixture was poured onto ice/H_2O (130 mL) and conc. $HCl_{(aq)}$ (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (50 mL), H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane (40 mL) gave phosphine borane **8** (5.77 g, 72%) as a white solid, mp 161-162 °C (lit.,[21] 164-165 ˚C); R_F (9:1 petrol-EtOAc) 0.3; IR (NaCl) 3018, 2731, 1423, 1215, 1070, 920, 755, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 10.0 Hz, 6H, PMe), 1.15 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.43 (qd, *J* = 94.0, 15.0 Hz, PBH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.6 (d, *J* = 35.0 Hz, P*C*Me_3), 24.7 (d, *J* = 2.0 Hz, PC*Me*$_3$), 7.3 (d, *J* = 35.5 Hz, PMe); $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$) δ: 20.9 (q, *J* = 42.0 Hz, PBH_3). Spectroscopic data consistent with those reported in the literature.[21]

Lab book reference: chc/1/36

***tert*-Butyldimethylphosphine borane 8**

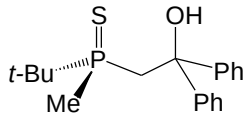


8

A solution of MeMgBr (7.5 mL of a 3.0 M solution in Et_2O, 22.5 mmol, 2.6 eq.) in THF (8 mL) was added dropwise to a stirred solution of *t*-$BuPCl_2$ (1.38 g, 8.7 mmol, 1.0 eq.) in THF (12 mL) at −10 °C under Ar. The resulting heterogeneous mixture was stirred at rt for 5 h. BH_3•Me_2S (5.2 mL of a 2.0 M solution in Et_2O, 10.4 mmol, 1.2 eq.) was added dropwise and the mixture was stirred for 1 h. Then, the mixture was poured onto ice/H_2O (20 mL) and conc. $HCl_{(aq)}$ (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane (10 mL) gave phosphine borane **8** (779 mg, 67%) as a white solid.

Lab book reference: chc/1/4

(*R*)-2-(*t*-Butylmethylphosphinothioyl)-1,1-diphenylethanol (*R*)-53

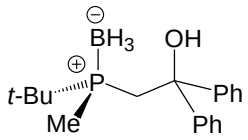


(*R*)-**53**

n-BuLi (0.29 mL of a 2.5 M solution in hexane, 0.74 mmol, 1.1 eq.) was added dropwise to a stirred solution of (–)-sparteine (188 mg, 0.80 mmol, 1.2 eq.) in Et_2O (4 mL) at –78 °C under Ar. After stirring for 15 min, a solution of phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in Et_2O (4 mL) was added dropwise over 10 min. After stirring at –78 °C for 3 h, a solution of Ph_2CO (135 mg, 0.74 mmol, 1.1 eq.) in THF (2 mL) was added dropwise and the reaction mixture was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (6 mL) was added and the resulting mixture was stirred for 10 min to give a homogeneous biphasic solution. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (15 mL), H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave hydroxy phosphine sulfide (*R*)-**53** (191 mg, 86%, 85:15 er) as a white solid, mp 162-166 °C (lit.,[52] 162-166 ˚C); R_F (9:1 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.55 (m, 2H, Ph), 7.47-7.44 (m, 2H, Ph), 7.38-7.31 (m, 4H, Ph), 7.26-7.22 (m, 2H, Ph), 2.97 (dd, *J* = 14.0, 8.0 Hz, 1H, PCH_AH$_B$), 2.84 (dd, *J* = 14.0, 10.5 Hz, 1H, PCH$_A$$H_B$), 1.23 (d, *J* = 16.5 Hz, 9H, $PCMe_3$), 1.00 (d, *J* = 12.5 Hz, 3H, PMe); HPLC: Daicel Chiracel OD, 95:5 hexane-*i*-PrOH, 1.0 mL min^{-1}, 7.2 min (*S*)-**53**, 17.0 min (*R*)-**53**. Spectroscopic data consistent with those reported in the literature.[52]

Lab book reference: chc/1/5

(*S*)-*P*-(2,2-Diphenyl-2-hydroxyethyl)-*P*-methyl-*t*-butylphosphine borane (*S*)-22

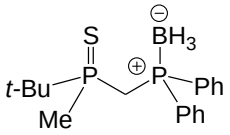


(*S*)-**22**

s-BuLi (0.65 mL of a 1.3 M solution in cyclohexane, 0.84 mmol, 1.1 eq.) was added dropwise to a stirred solution of (−)-sparteine (214 mg, 0.91 mmol, 1.2 eq.) in Et_2O (4 mL) at −78 ˚C under Ar. After stirring for 15 min, a solution of phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in Et_2O (4 mL) was added dropwise over 10 min. After stirring at −78 ˚C for 3 h, a solution of Ph_2CO (153 mg, 0.84 mmol, 1.1 eq.) in THF (2 mL) was added and the reaction mixture was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (6 mL) was added and the resulting mixture was stirred for 10 min to give a homogeneous biphasic solution. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (15 mL), H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc as eluent gave hydroxy phosphine borane (*S*)-**22** (185 mg, 77%, 93:7 er) as a white solid, mp 116-118 °C (lit.,[34] 116.5-117.5 ˚C); R_F (4:1 petrol-EtOAc) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52-7.47 (m, 4H, Ph), 7.34-7.30 (m, 4H, Ph), 7.27-7.21 (m, 2H, Ph), 4.59 (s, 1H, OH), 2.88 (t, *J* = 14.5 Hz, 1H, PCH_AH_B), 2.68 (dd, *J* = 14.5, 6.0 Hz, 1H, PCH_AH_B), 1.18 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 0.75 (d, *J* = 10.0 Hz, 3H, PMe); HPLC: Daicel Chiracel OD, 95:5 hexane-*i*-PrOH, 0.5 mL min^{-1}, 11.0 min (*R*)-**22**, 13.0 min (*S*)-**22**. Spectroscopic data consistent with those reported in the literature.

Lab book reference: chc/1/13

***rac*-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethaneborane *rac*-47**

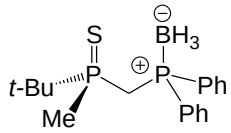


rac-**47**

Using general procedure B, *n*-BuLi (0.29 mL of a 2.5 M solution in hexane, 0.74 mmol, 1.1 eq.) and phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in THF (6 mL), Ph_2PCl (0.13 mL, 163 mg, 0.74 mmol, 1.1 eq.) and BH_3•Me_2S (0.50 mL of a 2.0 M solution in Et_2O, 1.0 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with toluene then 9:1 toluene-EtOAc as eluent gave bisphosphine *rac*-**47** (175 mg, 75%) as a white solid.

Lab book reference: chc/1/19

(*S*)-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethaneborane (*S*)-47



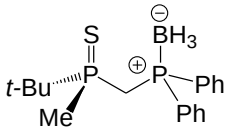
(*S*)-**47**

Using general procedure A, *n*-BuLi (5.92 mL of a 2.5 M solution in hexane, 14.8 mmol, 1.1 eq.) and (–)-sparteine (3.76 g, 16.0 mmol, 1.2 eq.) in Et_2O (40 mL), phosphine sulfide **40** (2.00 g, 13.4 mmol, 1.0 eq.) in Et_2O (140 mL), Ph_2PCl (3.26 g, 14.8 mmol, 1.1 eq.) in THF (40 mL) and BH_3•Me_2S (10.1 mL of a 2.0 M solution in Et_2O, 20.2 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with toluene then 9:1 toluene-EtOAc as eluent gave bisphosphine (*S*)-**47** (3.74 g, 80%, 91:9 er) as a white solid, R_F (9:1 petrol-EtOAc) 0.5; $[\alpha]_D$ −18.2 (*c* 1.0 in $CHCl_3$) (lit.,[47] $[\alpha]_D$ −26.3 (*c* 0.9 in $CHCl_3$)). Purification by recrystallisation from 3:4 $CHCl_3$-petrol (70 mL) gave bisphosphine (*S*)-**47** (569 mg, 12%, 86:14 er) as a white crystalline solid. The filtrate was evaporated under reduced pressure to give bisphosphine (*S*)-**47** (3.14 g, 67%, 95.5:4.5 er) as a white solid, mp 156-157 ˚C (lit.,[47] 176-177 ˚C); $[\alpha]_D$ −22.0 (*c* 1.0 in $CHCl_3$) (lit.,[47] $[\alpha]_D$ −26.3 (*c* 0.9 in $CHCl_3$)); IR (NaCl) 3019, 2977, 2400, 1730, 1437, 1216, 1060, 929, 892, 774, 744, 669, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.00-7.96 (m, 2H, Ph),

7.71-7.66 (m, 2H, Ph), 7.57-7.44 (m, 6H, Ph), 3.05 (q, J = 14.5 Hz, 1H, PCH_AH_B), 2.77 (ddd, J = 14.5, 10.5, 9.0 Hz, 1H, PCH_AH_B), 1.68 (d, J = 12.5 Hz, 3H, PMe), 1.26 (d, J = 17.0 Hz, 9H, PCMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 133.5 (d, J = 10.0 Hz, Ph), 132.1 (d, J =2.5 Hz, Ph), 131.6 (d, J = 9.5 Hz, Ph), 131.5 (d, J = 6.0 Hz, Ph), 131.3 (d, J = 2.5 Hz, Ph), 130.9 (d, J = 6.0 Hz, Ph), 128.9 (d, J = 10.0 Hz, Ph), 128.7 (d, J = 10.5 Hz, Ph), 35.0 (dd, J = 51.0, 3.0 Hz, PCMe$_3$), 26.0 (dd, J = 36.0, 24.5 Hz, PCH_2), 24.2 (d, J = 2.0 Hz, PCMe_3), 15.6 (d, J = 55.0 Hz, PMe); ^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$) δ: 56.0 (PS), 15.3 (PBH_3); MS (ESI) *m/z* 347 [(M − H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{27}BP_2S$ (M − H)$^+$ 347.1321, found 347.1313; HPLC: Daicel Chiracel AD, 99:1 v/v hexane-*i*-PrOH, 1.0 mL min^{-1}, 23.2 min (*S*)-**47**, 33.3 min (*R*)-**47**. Spectroscopic data consistent with those reported in the literature.[47]

Lab book reference: chc/1/39

(*S*)-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethaneborane (*S*)-47

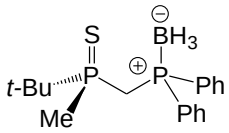


(*S*)-**47**

Using general procedure A, *n*-BuLi (0.30 mL of a 2.5 M solution in hexane, 0.74 mmol, 1.1 eq.) and (–)-sparteine (188 mg, 0.80 mmol, 1.2 eq.) in Et_2O (4 mL), phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in Et_2O (4 mL), Ph_2PCl (163 mg, 0.74 mmol, 1.1 eq.) in THF (2 mL) and BH_3•Me_2S (0.50 mL of a 2.0 M solution in Et_2O, 1.0 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with toluene then 9:1 toluene-EtOAc as eluent gave bisphosphine (*S*)-**47** (114 mg, 49%, 83:17 er) as a white solid.

Lab book reference: chc/1/7

(*S*)-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethaneborane (*S*)-47

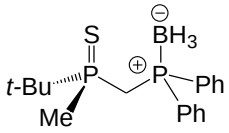


(*S*)-**47**

Using general procedure A, *n*-BuLi (0.88 mL of a 2.5 M solution in hexane, 2.22 mmol, 1.1 eq.) and (–)-sparteine (564 mg, 2.40 mmol, 1.2 eq.) in Et_2O (12 mL), phosphine sulfide **40** (300 mg, 2.01 mmol, 1.0 eq.) in Et_2O (12 mL), Ph_2PCl (490 mg, 2.22 mmol, 1.1 eq.) in THF (6 mL) and BH_3•Me_2S (1.50 mL of a 2.0 M solution in Et_2O, 3.0 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with toluene then 9:1 toluene-EtOAc as eluent gave bisphosphine (*S*)-**47** (280 mg, 40%, 83:17 er) as a white solid.

Lab book reference: chc/1/11

(*S*)-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethaneborane (*S*)-47

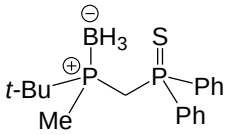


(*S*)-**47**

Using general procedure A, *n*-BuLi (2.96 mL of a 2.5 M solution in hexane, 7.40 mmol, 1.1 eq.) and (–)-sparteine (1.88 g, 8.00 mmol, 1.2 eq.) in Et_2O (20 mL), phosphine sulfide **40** (1.00 g, 6.70 mmol, 1.0 eq.) in Et_2O (70 mL), Ph_2PCl (1.63 g, 7.40 mmol, 1.1 eq.) in THF (20 mL) and BH_3•Me_2S (5.03 mL of a 2.0 M solution in Et_2O, 10.10 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with toluene then 9:1 toluene-EtOAc as eluent gave bisphosphine (*S*)-**47** (1.55 g, 66%, 82:18 er) as a white solid. Purification by recrystallisation from 1:2 $CHCl_3$-petrol (15 mL) gave bisphosphine (*S*)-**47** (343 mg, 15%, 68:32 er) as a white crystalline solid. The filtrate was evaporated under reduced pressure to give bisphosphine (*S*)-**47** (1.09 g, 47%, 97.5:2.5 er) as a white solid.

Lab book reference: chc/1/18

rac-_t_-Butylmethylphosphinoborane-diphenylphosphinomethanesulfide _rac_-49

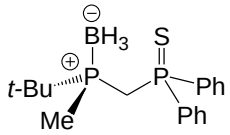


rac-**49**

Use general procedure D, *s*-BuLi (0.65 mL of a 1.3 M solution in cyclohexane, 0.84 mmol, 1.1 eq.) and phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in THF (6 mL), Ph_2PCl (0.15 mL, 184 mg, 0.84 mmol, 1.1 eq.) and sulfur (32 mg, 0.99 mmol, 1.3 eq.) gave the crude product. Purification by flash chromatography on silica with 4:1 petrol-EtOAc as eluent gave bisphosphine *rac*-**49** (184 mg, 70%) as a white solid.

Lab book reference: chc/1/20

(_R_)-_t_-Butylmethylphosphinoborane-diphenylphosphinomethanesulfide (_R_)-49



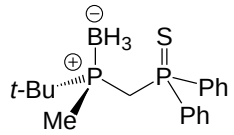
(*R*)-**49**

Using general prodecure C, *s*-BuLi (9.62 mL of a 1.3 M solution in cyclohexane, 12.5 mmol, 1.1 eq.) and (–)-sparteine (3.20 g, 12.5 mmol, 1.2 eq.) in Et_2O (30 mL), phosphine borane **8** (1.50 g, 11.3 mmol, 1.0 eq.) in Et_2O (120 mL), Ph_2PCl (2.76 g, 12.5 mmol, 1.1 eq.) in THF (40 mL) and sulfur (474 mg, 14.7 mmol, 1.3 eq.) gave the crude product. Purification by flash chromatography with 95:5 petrol-EtOAc as eluent gave bisphosphine (*R*)-**49** (2.47 g, 62%, 88:12 er) as a white solid, R_F (9:1 petrol-EtOAc) 0.2; $[\alpha]_D$ +12.2 (*c* 1.0 in $CHCl_3$). Purification by recrystallisation from 2:3 $CHCl_3$-petrol (25 mL) gave bisphosphine (*R*)-**49** (1.34 g, 33%, 98.5:1.5 er) as a white crystalline solid, mp 150-152 ˚C; $[\alpha]_D$ +20.5 (*c* 1.0 in $CHCl_3$); IR (NaCl) 2973, 2383, 1437, 1161, 1103, 1067, 892, 804, 692, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.06 (ddd, *J* = 9.5, 8.0, 1.5 Hz, 2H, Ph), 7.80 (ddd, *J* = 9.5, 8.0, 1.5 Hz, 2H, Ph), 7.59–7.50 (m, 6H, Ph), 3.12 (ddd, *J* = 15.0, 13.0, 6.5 Hz, 1H, PCH_AH_B), 2.66 (ddd, *J* = 17.0, 15.0, 12.5 Hz, 1H, PCH_AH_B), 1.41 (d, *J* = 10.0 Hz, 3H, PMe), 1.21 (d, *J* = 14.5 Hz, 9H, $PCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 135.9 (d, *J* = 3.5 Hz, *ipso*-Ph), 135.1 (d, *J* = 3.5 Hz, *ipso*-Ph), 132.2 (d, *J* = 3.0 Hz, Ph), 132.0 (d,

J = 11.0 Hz, Ph), 131.5 (d, *J* = 3.0 Hz, Ph),130.2 (d, *J* = 10.5 Hz, Ph), 128.8 (d, *J* = 12.0 Hz, Ph), 128.6 (d, *J* = 12.0 Hz, Ph), 57.5 (dd, *J* = 36.5, 7.5 Hz, P*C*Me$_3$), 25.6 (d, *J* = 2.0 Hz, PMe), 24.9 (d, *J* = 2.5 Hz, PC*Me$_3$*), 24.8 (dd, *J* = 47.5, 19.0 Hz,); ^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$) δ: 37.8 (PS), 28.8 (PBH_3); MS (ESI) *m/z* 347 [(M − H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{27}BP_2S$ (M − H)$^+$ 347.1321, found 347.1320; HPLC: Daicel Chiracel AD, 95:5 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 18.8 min (*R*)-**49**, 22.0 min (*S*)-**49**. The filtrate was evaporated under reduced pressure to give adduct (*R*)-**49** (982 mg, 25%, 84:16 er) as a white solid.

Lab book reference: chc/1/40

(*R*)-*t*-Butylmethylphosphinoborane-diphenylphosphinomethanesulfide (*R*)-49

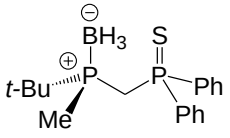


(*R*)-**49**

Using general prodecure C, *s*-BuLi (0.65 mL of a 1.3 M solution in cyclohexane, 0.84 mmol, 1.1 eq.) and (–)-sparteine (214 mg, 0.96 mmol, 1.2 eq.) in Et_2O (4 mL), phosphine borane **8** (102 mg, 0.76 mmol, 1.0 eq.) in Et_2O (4 mL), Ph_2PCl (184 mg, 0.84 mmol, 1.1 eq.) in THF (2 mL) and sulfur (32 mg, 0.99 mmol, 1.3 eq.) gave the crude product. Purification by flash chromatography with 95:5 petrol-EtOAc as eluent gave bisphosphine (*R*)-**49** (150 mg, 57%, 90:10 er) as a white solid.

Lab book reference: chc/1/17

(*R*)-*t*-Butylmethylphosphinoborane-diphenylphosphinomethanesulfide (*R*)-49



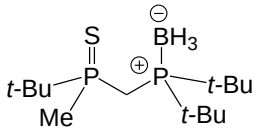
(*R*)-**49**

Using general prodecure C, *s*-BuLi (6.46 mL of a 1.3 M solution in cyclohexane, 8.40 mmol, 1.1 eq.) and (–)-sparteine (2.14 g, 9.12 mmol, 1.2 eq.) in Et_2O (20 mL),

phosphine borane **8** (1.00 g, 7.60 mmol, 1.0 eq.) in Et_2O (70 mL), Ph_2PCl (1.84 g, 8.36 mmol, 1.1 eq.) in THF (20 mL) and sulfur (320 mg, 9.88 mmol, 1.3 eq.) gave the crude product. Purification by flash chromatography with 95:5 petrol-EtOAc as eluent gave bisphosphine (*R*)-**49** (1.16 g, 44%, 93:7 er) as a white solid. Purification by recrystallisation from 1:2 $CHCl_3$-petrol (15 mL) gave bisphosphine (*R*)-**49** (525 mg, 20%, 99:1 er) as a white crystalline solid. The filtrate was evaporated under reduced pressure to give adduct (*R*)-**49** (542 mg, 20%, 89:11 er) as a white solid

Lab book reference: chc/1/21

rac-*t*-Butylmethylphosphinothioyl-di-*t*-butylphosphinomethaneborane _rac_-48

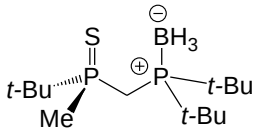


rac-**48**

Using general procedure B, *n*-BuLi (0.29 mL of a 2.5 M solution in Et_2O, 0.74 mmol, 1.1 eq.) and phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in THF (6 mL), *t*-Bu_2PCl (0.14 mL, 134 mg, 0.74 mmol, 1.1 eq.) and BH_3•Me_2S (0.50 mL, 1.0 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave bisphosphine *rac*-**48** (101 mg, 49%) as a white solid.

Lab book reference: chc/1/25

(*S*)-*t*-Butylmethylphosphinothioyl-di-*t*-butylphosphinomethaneborane (*S*)-48



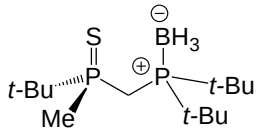
(*S*)-**48**

Using general procedure A, *n*-BuLi (2.96 mL of a 2.5 M solution in hexane, 7.4 mmol, 1.1 eq.) and (–)-sparteine (1.88 g, 8.0 mmol, 1.2 eq.) in Et_2O (20 mL), phosphine sulfide **40** (1.00 g, 6.7 mmol, 1.0 eq.) in Et_2O (70 mL), *t*-Bu_2PCl (1.34 g, 7.4 mmol, 1.1 eq.) in THF (20 mL) and BH_3•Me_2S (5.03 mL of a 2.0 M solution in

Et_2O, 10.1 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave biphosphine (*S*)-**48** (787 mg, 38%, 68:32 er) as a white solid, mp 109-111 ˚C; $[\alpha]_D$ +13.2 (*c* 1.0 in $CHCl_3$); R_F (95:5 petrol-EtOAc) 0.3; IR (NaCl) 3019, 2963, 2399, 1474, 1395, 1370, 1215, 1072, 1020, 929, 892, 756, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.37 (ddd, *J* = 15.5, 13.0, 10.5 Hz, 1H, PC$H_A$$H_B$), 2.22 (dt, *J* = 15.5, 14.5 Hz, 1H, PC$H_A$$H_B$), 1.98 (d, *J* = 12.5 Hz, 3H, PMe), 1.45 (d, *J* = 13.5 Hz, 9H, $PCMe_3$), 1.31 (d, *J* = 2.5 Hz, 9H, $PCMe_3$), 1.28 (d, *J* = 5.5 Hz, 9H, $PCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 35.8 (dd, *J* = 52.0, 4.0 Hz, P*C*Me_3), 34.3 (dd, *J* = 25.0, 5.0 Hz, P*C*Me_3), 33.2 (d, *J* = 25.0 Hz, P*C*Me_3), 28.5 (d, *J* = 2.5 Hz, PC*Me*$_3$), 27.8 (d, *J* = 1.0 Hz, PC*Me*$_3$), 24.6 (d, *J* = 1.0 Hz, PC*Me*$_3$), 18.2 (dd, *J* = 39.0, 12.0 Hz, PCH_2), 15.9 (d, *J* = 51.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 60.2 (PS), 49.0 (PBH_3); MS (ESI) m/z 331 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{35}BP_2S$ $(M + Na)^+$ 331.1922, found 331.1914; HPLC: Daicel Chiracel OD, 99:1 v/v hexane-*i*PrOH, 0.5 mL min^{-1}, 15.2 min (*S*)-**48**, 16.5 min (*R*)-**48**.

Lab book reference: chc/1/27

(*S*)-*t*-Butylmethylphosphinothioyl-di-*t*-butylphosphinomethaneborane (*S*)-48

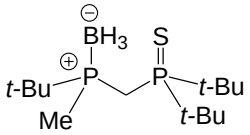


(*S*)-**48**

Using general procedure A, *n*-BuLi (0.30 mL of a 2.5 M solution in hexane, 0.74 mmol, 1.1 eq.) and (–)-sparteine (188 mg, 0.80 mmol, 1.2 eq.) in Et_2O (2 mL), phosphine sulfide **40** (100 mg, 0.67 mmol, 1.0 eq.) in Et_2O (7 mL), *t*-Bu_2PCl (134 mg, 0.74 mmol, 1.1 eq.) in THF (2 mL) and BH_3•Me_2S (0.50 mL of a 2.0 M solution in Et_2O, 1.01 mmol, 1.5 eq.) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave biphosphine (*S*)-**48** (92 mg, 45%, 61:39 er) as a white solid.

Lab book reference: chc/1/26

***rac*-*t*-Butylmethylphosphinoborane-di-*t*-butylphosphinomethanesulfide *rac*-50**

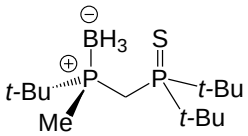


rac-**50**

Using general procedure D, *s*-BuLi (0.64 mL of a 1.3 M solution in cyclohexane, 0.84 mmol, 1.1 eq.) and phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in THF (7 mL), *t*-Bu_2PCl (0.13 mL, 152 mg, 0.84 mmol, 1.1 eq.) and sulfur (32 mg, 0.99 mmol, 1.3 eq.) gave the crude product. Purification by flash chromatography on silica with 9:1 petrol-EtOAc gave bisphosphine *rac*-**50** (94 mg, 40%) as a white solid.

Lab book reference: chc/1/32

(*R*)-*t*-Butylmethylphosphinoborane-di-*t*-butylphosphinomethanesulfide (*R*)-50



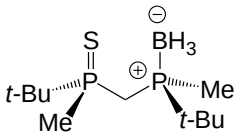
(*R*)-**50**

Using general procedure C, *s*-BuLi (9.69 mL of a 1.3 M solution in hexane, 12.5 mmol, 1.1 eq.) and (–)-sparteine (3.21 g, 13.6 mmol, 1.2 eq.) in Et_2O (30 mL), phosphine borane **8** (1.50 g, 11.4 mmol, 1.0 eq.) in Et_2O (105 mL), *t*-Bu_2PCl (2.28 g, 12.5 mmol, 1.1 eq) in THF (30 mL) and sulfur (480 mg, 14.8 mmol, 1.3 eq) gave the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc as eluent gave bisphosphine (*R*)-**50** (1.85 g, 53%, 93:7 er) as a white solid, $[\alpha]_D$ +8.8 (*c* 1.0 in $CHCl_3$); R_F (95:5 petrol-EtOAc) 0.3. Purification by recrystallisation from 2:3 $CHCl_3$-petrol (25 mL) gave bisphosphine (*R*)-**50** (397 mg, 37%, 84:16 er) as a white crystalline solid. The filtrate was evaporated under reduced pressure to give bisphosphine (*R*)-**50** (1.39 g, 40%, ≥99:1 er) as a white solid, mp 118-120 ˚C; $[\alpha]_D$ +14.4 (*c* 1.0 in $CHCl_3$); IR (NaCl) 2963, 2383, 1470, 1170, 1103, 1068, 1017, 891, 809, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.24-2.10 (m, 2H, PCH_2), 1.75 (d, *J* = 10.0 Hz, 3H, PMe), 1.42 (d, *J* = 16.0 Hz, 9H, $PCMe_3$), 1.36 (d, *J* = 15.0 Hz, 9H, $PCMe_3$), 1.20 (d, *J* = 13.5 Hz, 9H, $PCMe_3$); ^{13}C

NMR (100.6 MHz, $CDCl_3$) δ: 39.8 (d, *J* = 42.0 Hz, P*C*Me$_3$), 39.1 (d, *J* = 42.0 Hz, P*C*Me$_3$), 29.6 (dd, *J* = 33.5, 4.0 Hz, P*C*Me$_3$), 27.8 (d, *J* = 2.0 Hz, PC*Me$_3$*), 27.3 (s, PC*Me$_3$*), 25.0 (d, *J* = 2.0 Hz, PC*Me$_3$*), 12.6 (dd, *J* = 32.0, 21.0 Hz, PCH_2), 5.6 (d, *J* = 34.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 76.3 (PS), 32.0 (PBH_3); MS (ESI) *m/z* 307 [$(M - H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{35}BP_2S$ $(M - H)^+$ 307.1947, found 307.1946; HPLC: Chiracel OD, 99.7:0.3 v/v hexane-*i*-PrOH, 0.7 mL min^{-1}, 15.4 min (*S*)-**50**, 16.5 min (*R*)-**50**.

Lab book reference: chc/1/42

_t_-Butylmethylphosphinoborane-_t_-butylmethylphosphinesulfide (_S,R_)-56



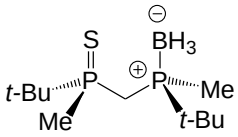
(*S,R*)-**56**

s-BuLi (0.65 mL of a 1.3 M solution in cyclohexane, 0.84 mmol, 1.1 eq.) was added dropwise to a stirred solution of (–)-sparteine (214 mg, 0.91 mmol, 1.2 eq.) in Et_2O (2 mL) at –78 °C under Ar. After stirring for 15 min, a solution of phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in Et_2O (7 mL) was added dropwise over 10 min. The resulting mixture was stirred at –78 ˚C for 3 h. Then, a solution of *t*-BuPCl_2 (134 mg, 0.84 mmol, 1.1 eq.) in THF (2 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. The mixture was cooled to –78 ˚C and MeMgBr (0.330 mL, 0.99 mmol, 1.3 eq.) was added dropwise over 10 min. The mixture was stirred at –78 ˚C for 2 h and then at rt for 3 h. Sulfur (32 mg, 0.99 mmol, 1.3 eq.) was added and the reaction mixture was heated at 80 °C for 15 min and stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc gave bisphosphine (*S,R*)-**56** (49 mg, 24%, 98:2 er) as a white solid, mp 135-

137 °C; $[\alpha]_D$ +46.7 (*c* 1.0 in $CHCl_3$); R_F(95:5 toluene-EtOAc) 0.25; IR (NaCl) 3006, 2969, 2871, 2389, 1468, 1367, 1217, 1162, 1067, 903, 812, 764, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.15-1.96 (m, 2H, PCH_2), 1.93 (d, *J* = 12.5 Hz, 3H, PMe), 1.69 (d, *J* = 10.0 Hz, 3H, PMe), 1.23 (d, *J* = 16.5 Hz, 9H, PC*Me*$_3$), 1.15 (d, *J* = 14.0 Hz, 9H, PC*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 35.0 (dd, *J* = 51.5, 3.5 Hz, P*C*Me_3), 29.0 (dd, *J* = 33.5, 5.0 Hz, P*C*Me_3), 24.5 (d, *J* = 2.5 Hz, PC*Me*$_3$), 24.1 (d, *J* = 2.0 Hz, PC*Me*$_3$), 18.9 (dd, *J* = 38.5, 20.0 Hz, PCH_2), 15.9 (d, *J* = 51.5 Hz, PMe), 6.2 (d, *J* = 34.0 Hz, PMe); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 56.8 (PS), 27.7 (PBH_3); MS (ESI) *m/z* 266 [$(M - H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{29}BP_2S$ $(M - H)^+$ 265.1477, found 265.1486; HPLC: Daicel Chiracel OD, 95:5 v/v hexane-*i*-PrOH, 1.0 mL min^{-1}, 6.6 min (*S*,*R*)-**56**, 7.5 min (*R*,*S*)-**56**.

Lab book reference: chc/1/44

_t_-Butylmethylphosphinoborane-_t_-butylmethylphosphinesulfide (*S*,*R*)-56



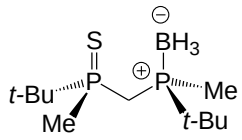
(*S*,*R*)-**56**

n-BuLi (1.48 mL of a 2.5 M solution in hexane, 3.70 mmol, 1.1 eq.) was added dropwise to a stirred solution of (–)-sparteine (940 mg, 4.00 mmol, 1.2 eq.) in Et_2O (10 mL) at −78 ˚C under Ar. After stirring for 15 min, a solution of phosphine sulfide **40** (500 mg, 3.35 mmol, 1.0 eq.) in Et_2O (35 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 ˚C for 3 h. Then, a solution of *t*-$BuPCl_2$ (590 mg, 3.70 mmol, 1.1 eq.) in THF (10 mL) was added dropwise and the resulting mixture was allowed to warm to rt over 16 h. The reaction mixture was cooled to −78 ˚C and MeMgBr (1.45 mL, 4.36 mmol, 1.3 eq.) was added dropwise over 10 min and the resulting solution was stirred at −78 ˚C for 2 h and then at rt for 3 h. The solution was cooled to 0 ˚C and BH_3•Me_2S (2.52 mL, 5.05 mmol, 1.5 eq.) was added dropwise and the reaction mixture was allowed to warm to rt over 16 h. Then, 1 M $HCl_{(aq)}$ (30 mL) was added and the mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer

was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (30 mL), H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 85:15 petrol-EtOAc as eluent gave bisphosphine (*S,R*)-**56** (103 mg, 12%, 89:11 er) as a white solid, mp 135-137 ˚C; $[\alpha]_D$ +28.1 (*c* 1.0 in $CHCl_3$).

Lab book reference: chc/1/51

_t_-Butylmethylphosphinoborane-_t_-butylmethylphosphinesulfide _rac_-56

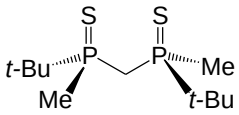


rac-**56**

s-BuLi (0.65 mL of a 1.3 M solution in cyclohexane, 0.84 mmol, 1.1 eq.) was added dropwise to a stirred solution of phosphine borane **8** (100 mg, 0.76 mmol, 1.0 eq.) in THF (7 mL) at −78 ˚C under Ar. The resulting mixture was stirred at −78 ˚C for 3 h. Then, a solution of *t*-$BuPCl_2$ (134 mg, 0.84 mmol, 1.1 eq.) in THF (2 mL) was added dropwise and the mixture was allowed to warm to rt over 16 h. The mixture was cooled to −78 ˚C and MeMgBr (0.330 mL, 0.99 mmol, 1.3 eq.) was added dropwise over 10 min. The mixture was stirred at −78 ˚C for 2 h and then at rt for 3 h. Sulfur (32 mg, 0.99 mmol, 1.3 eq.) was added and the reaction mixture was heated at 80 °C for 15 min and stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the mixture was stirred for 15 min to give a homogeneous biphasic solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 95:5 petrol-EtOAc gave bisphosphine *rac*-**56** (38 mg, 19%) as a white solid.

Lab book reference: chc/1/50

Bis(*t*-butylmethylphosphinothionyl)methane (*S*,*S*)-59

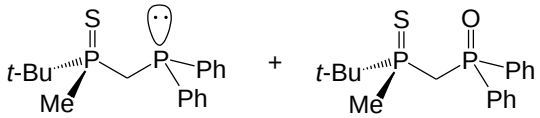


(*S*,*S*)-**59**

A mixture of bisphosphine (*S*,*R*)-**56** (50 mg, 0.19 mmol, 1.0 eq., 89:11 er), DABCO (26 mg, 0.23 mmol, 1.2 eq.) and sulfur (18 mg, 0.57 mmol, 2.5 eq.) in dry, degassed toluene (5 mL) was stirred and heated at 80 °C for 16 h under Ar. The reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica with 95:5 Et_2O-CH_2Cl_2 as eluent gave diphosphine disulfide (*S*,*S*)-**59** (33 mg, 77%, 83:17 er) as a white solid, mp 160-162 °C (lit.,[48]160-164 °C); $[\alpha]_D$ +33.9 (*c* 1.0 in $CHCl_3$) (lit.,[48] $[\alpha]_D$ +73.5 (*c* 1.5 in $CHCl_3$)); R_F (4:1 petrol-EtOAc) 0.3; IR (NaCl) 2950, 2373, 1588, 1408, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.40 (t, *J* = 13.0 Hz, 2H, PCH_2), 2.13 (d, *J* = 13.0 Hz, 6H, PMe), 1.25 (d, *J* = 17.0 Hz, 18H, $PCMe_3$); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 56.4; HPLC: Daicel Chiracel AD, 97:3 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 16.6 min (*S*,*S*)-**59**, 33.9 min (*R*,*R*)-**59**. Spectroscopic data consistent with those reported in the literature.

Lab book reference: chc/1/54

(*S*)-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethane (*S*)-43 and (*S*)-*t*-Butylmethylphosphinothionyl-diphenylphosphinomethane oxide (*S*)-62



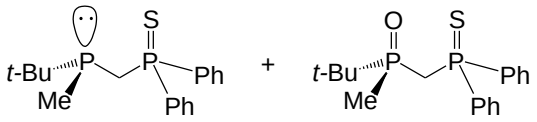
(*S*)-**43** (*S*)-**62**

Using general procedure E, bisphosphine sulfide borane (*S*)-**47** (100 mg, 0.29 mmol, 1.0 eq., 86:14 er) and DABCO (40 mg, 0.35 mmol, 1.2 eq.) in toluene (5 mL) gave the crude product (85 mg, 88%) as a colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.58-7.47 (m, 4H, Ph), 7.38-7.30 (m, 6H, Ph), 2.68-2.64 (m, 2H, PCH_2), 1.43 (d, *J* = 11.5 Hz, 3H, PMe), 1.25 (d, *J* = 16.5 Hz, 9H, $PCMe_3$); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 58.8 (d, *J* = 56.0 Hz, PS), –26.3 (d, *J* = 56.0, PPh_2). The ^1H NMR

spectrum of the crude product also contained signals due to the DABCO•BH_3 complex. Purification by flash chromatography on silica with 1:1 petrol-EtOAc as eluent gave phosphine (*S*)-**43** (77 mg, 80%) as a colorless oil, R_F (1:1 petrol-EtOAc) 0.5, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58-7.48 (m, 4H, Ph), 7.39-7.34 (m, 6H, Ph), 2.67 (d, *J* = 11.0 Hz, 2H, PCH_2), 1.45 (d, *J* = 12.0 Hz, 3H, PMe), 1.27 (d, *J* = 16.5 Hz, 9H, $PCMe_3$); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 58.8 (d, *J* = 55.5 Hz, PS), –26.3 (d, *J* = 55.5, PPh_2). There was evidence of formation of phosphine oxide (*S*)-**62** after chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) 7.98-7.92 (m, 2H, Ph), 7.78-7.72 (m, 2H, Ph); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 55.4 (d, *J* = 16.5 Hz, PS), 26.9 (d, *J* = 16.5 Hz, PO).

Lab book ref: chc/1/53

(*R*)-*t*-Butylmethylphosphine-diphenylphosphinomethane sulfide (*R*)-45 and (*S*)-*t*-Butylmethylphosphinoxide-diphenylphosphinomethane sulfide (*S*)-63



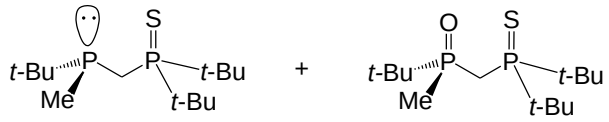
(*R*)-**45** (*S*)-**63**

Using general procedure E, bisphosphine sulfide boraine (*R*)-**49** (100 mg, 0.29 mmol, 1.0 eq., 89:11 er) and DABCO (40 mg, 0.35 mmol, 1.2 eq.) in toluene (5 mL) gave the crude product (121 mg, > 100%) as a colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92-7.85 (m, 4H, Ph), 7.50-7.45 (m, 6H, Ph), 2.67 (dd, *J* = 15.0, 14.5 Hz, 1H, PCH_AH_B), 2.36-2.29 (m, 1H, PCH_AH_B), 1.18 (d, *J* = 14.5 Hz, 3H, PMe), 1.98 (d, *J* = 12.0 Hz, 9H, $PCMe_3$); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 41.1 (d, *J* = 63.5 Hz, PS), –22.6 (d, *J* = 63.5, PMe). The ^{1}H NMR spectrum of the crude product also contained signals due to the DABCO•BH_3 complex. Purification by flash chromatography on silica with 1:1 petrol-EtOAc as eluent gave phosphine (*R*)-**45** (75 mg, 77%) as a colorless oil, R_F (1:1 petrol-EtOAc) 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92-7.85 (m, 4H, Ph), 7.50-7.46 (m, 6H, Ph), 2.70 (dd, *J* = 15.0, 14.5 Hz, 1H, PCH_AH_B), 2.36-2.29 (m, 1H, PCH_AH_B), 1.18 (d, *J* = 15.0 Hz, 3H, PMe), 1.98 (d, *J* = 12.5 Hz, 9H, $PCMe_3$); $^{31}P\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ: 41.1 (d, *J* = 63.5 Hz,

PS), –22.6 (d, *J* = 63.5, PMe). There was evidence of formation of phosphine oxide (*S*)-**62** after chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18-8.01 (m, 2H, Ph); $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: 51.1 (d, *J* = 17.0 Hz, PO), 37.8 (d, *J* = 16.5 Hz, PS).

Lab book ref: chc/1/55

(*R*)-*t*-Butylmethylphosphine-di-*t*-butylphosphinomethane sulfide (*R*)-46 and (*S*)-*t*-Butylmethylphosphinoxide-di-*t*-butylphosphinomethane sulfide (*S*)-64



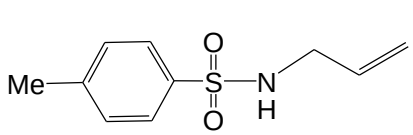
(*R*)-**46** (*S*)-**64**

Using general procedure E, bisphosphine borane sulfide (*R*)-**50** (100 mg, 0.32 mmol, 1.0 eq., 84:16 er) and DABCO (40 mg, 0.39 mmol, 1.2 eq.) in toluene (5 mL) gave the crude product (124 mg, >100%) as a colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97-1.90 (m, 1H, PCH_AH_B), 1.55 (dd, *J* = 14.0, 8.5 Hz,1H, PCH_AH_B), 1.34 (d, *J* = 14.5 Hz, 9H, $PCMe_3$), 1.26 (d, *J* = 14.5 Hz, 9H, $PCMe_3$), 1.18 (d, *J* = 3.5 Hz, 3H, PMe), 0.98 (d, *J* = 11.0 Hz, 9H, $PCMe_3$); $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: 75.4 (d, *J* = 34.0 Hz, PS), –18.5 (d, *J* = 34.0, PMe). The ^{1}H NMR spectrum of the crude product also contained signals due to the DABCO•BH_3 complex. Purification by flash chromatography on silica with 1:1 petrol-EtOAc as eluent gave free phosphine (*R*)-**46** (69 mg, 73%) as a colorless oil, R_F (1:1 petrol-EtOAc) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.01-1.94 (m, 1H, PCH_AH_B), 1.58 (dd, *J* = 14.0, 8.5 Hz,1H, PCH_AH_B), 1.38 (d, *J* = 14.5 Hz, 9H, $PCMe_3$), 1.31 (d, *J* = 14.5 Hz, 9H, $PCMe_3$), 1.22 (d, *J* = 3.5 Hz, 3H, PMe), 1.03 (d, *J* = 11.0 Hz, 9H, $PCMe_3$); $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: 75.5 (d, *J* = 34.0 Hz, PS), –18.5 (d, *J* = 34.0 Hz, PMe). There was evidence of formation of phosphine oxide (*S*)-**64** before and after chromatography: $^{31}P\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ: 76.5 (d, *J* = 21.0 Hz, PS), 52.4 (d, *J* = 21.0 Hz, PO).

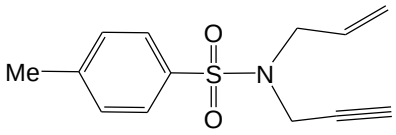
Lab book ref: chc/1/56

5.4 Experimental for Chapter 3

N-Allyl-4-methylbenzenesulfonamide 90 and *N*-(Prop-2-enyl)-*N*-(prop-2-ynyl)-*p*-toluenesulfonamide 51



90



51

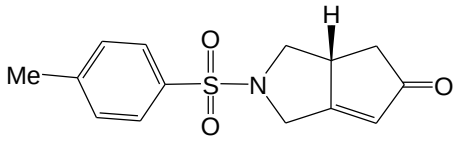
A solution of allylamine (2.18 g, 38.1 mmol, 1.0 eq.) and Et_3N (5.4 mL, 38.5 mmol, 1.1 eq.) in CH_2Cl_2 (30 mL) was added dropwise over 10 min to a stirred solution of *p*-toluenesulfonyl chloride (7.57 g, 38.5 mmol, 1.1 eq.) in CH_2Cl_2 (30 mL) at rt under Ar. After stirring for 1 h, H_2O (30 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give crude allyl sulfonamide **90** as a solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 8.0 Hz, 2H, *o*-$C_6H_4SO_2$), 7.41 (d, *J* = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 5.73 (ddt, *J* = 16.0, 10.5, 6.0 Hz, 1H, $NCH_2CH{=}CH_2$), 5.18 (dd, *J* = 16.0, 1.0 Hz, 1H, CH=CH_2*(trans)*), 5.11 (dd, *J* = 10.5, 1.0 Hz, 1H, CH=CH_2*(cis)*), 4.48-4.46 (br m, 1H, NH), 3.60 (tt, *J* = 6.0, 1.5 Hz, 2H, $NCH_2CH{=}CH_2$), 2.44 (s, 3H, Me).

Propargyl bromide (6.37 mL, 57.0 mmol, 1.5 eq.) was added dropwise over 10 min to a solution of crude sulfonamide **90** and K_2CO_3 (7.88 g, 57.0 mmol, 1.5 eq.) in acetone (100 mL) at rt under Ar. The resulting mixture was stirred and heated at 65 ˚C for 8 h. Then, H_2O (30 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a brown solid. Purification by flash chromatography with 5:1 hexane-Et_2O as eluent gave sulfonamide **51** (8.28 g, 87% over 2 steps) as a pale yellow solid, mp 60-63 ˚C (lit.,[69] 63–65 ˚C); R_F (5:1 hexane-Et_2O) 0.35; IR (NaCl) 3020, 2384, 1763, 1215, 1161, 758, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 8.5 Hz, 2H, *o*-$C_6H_4SO_2$), 7.31 (d, *J* = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 5.74 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, $NCH_2CH{=}CH_2$), 5.30 (dd, *J* = 16.5, 1.0 Hz, 1H, CH=CH_2*(trans)*), 5.25 (dd, *J* = 10.0, 1.0 Hz, 1H, CH=CH_2*(cis)*), 4.10 (d, *J* = 2.5 Hz, 2H, NCH_2C≡CH), 3.84 (d, *J* = 6.5 Hz, 2H , $NCH_2CH{=}CH_2$), 2.44 (s, 3H,

Me), 2.01 (t, *J* = 2.5 Hz, 1H, $NCH_2C{=}CH$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 143.5 (*ipso*-Ar), 135.8 (Ar), 131.8 ($CH{=}CH_2$), 129.4 (Ar), 127.6 (Ar), 120.0 ($CH{=}CH_2$), 76.4 ($C{\equiv}CH$), 73.7 ($C{\equiv}CH$), 48.9 (NCH_2), 35.7 (NCH_2), 21.5 (Me); MS (ESI) *m/z* 250 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}NO_2S$ $(M + H)^+$ 250.0896, found 250.0898. Spectroscopic data consistent with those reported in the literature.[69]

Lab book reference: chc/1/57 and chc/1/60

(*R*)-3-*p*-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (*R*)-52



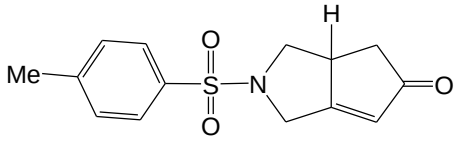
(R)-**52**

A solution of (*S)*-BINAP (200 mg, 0.32 mmol, 0.40 eq.) and $Co_2(CO)_8$ (110 mg, 0.32 mmol, 0.40 eq., >99:1 er) were added in a degassed DME (20 mL) was stirred at rt under CO. The resulting mixture was stirred and heated at 65 ˚C for 2 h. Then, a solution of sulfonamide **51** (200 mg, 0.80 mmol, 1.00 eq.) in degassed DME (15 mL) was added and the resulting mixture was stirred and heated at reflux under CO for 17 h. The reaction mixture was allowed to cool to rt. The solids were removed by filtration through a plug of silica and washed with EtOAc (40 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*R*)-**52** (86 mg, 38%, 76:24 er) as a brown solid, mp 111-114 ˚C (lit.,[70] 154 ˚C); R_F (3:2 hexane-EtOAc) 0.1; $[\alpha]_D$ +52.7 (*c* 1.0 in $CHCl_3$) (lit.,[50] $[\alpha]_D$ +133 (*c* 1.36 in $CHCl_3$); IR (NaCl) 3019, 1741, 1714, 1650, 1598, 1348, 1162, 783, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 8.5 Hz, 2H, *o*-$C_6H_4SO_2$), 7.36 (d, *J* = 8.0 Hz, 2H, *m*-$C_6H_4SO_2$), 5.99 (s, 1H, C=CH), 4.34 (d, *J* = 16.5 Hz, 1H), 4.03 (t, *J* = 8.5 Hz, 2H), 3.17-3.15 (m, 1H), 2.65-2.58 (m, 2H), 2.45 (s, 3H, Me), 2.06 (dd, *J* = 17.5, 3.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 207.4 (C=O), 178.7 (*C*=CH), 144.1 (*ipso*-Ar), 133.7 (*ipso*-Ar), 130.0 (CH), 127.4 (CH), 126.1 (CH), 52.4 (CH_2), 47.6 (CH_2), 43.9 (CH), 39.8 (CH_2), 21.5 (Me); MS (ESI) m/z calcd for $C_{14}H_{15}NO_3S$ $(M + H)^+$ 278.0847, found

278.0845; HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 83.2 min (*R*)-**52**, 89.7 min (*S*)-**52**.

Lab book reference: chc/1/78

rac-3-_p_-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one _rac_-52

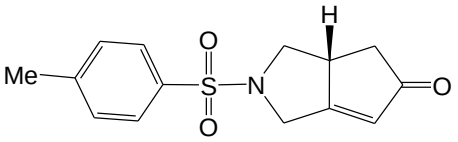


rac-**52**

Using general procedure F, bisphosphine sulfide borane *rac*-**47** (150 mg, 0.43 mmol, 0.40 eq.), DABCO (53 mg, 0.47 mmol, 0.44 eq.) and $Co_2(CO)_8$ (147 mg, 0.43 mmol, 0.40 eq.) in DME (20 mL) and sulfonamide **51** (268 mg, 1.07 mmol, 1.00 eq.) in DME (15 mL) gave the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone *rac*-**52** (46 mg, 15%) as a brown solid, R_F (3:2 hexane-EtOAc) 0.1.

Lab book reference: chc/1/74

(_R_)-3-_p_-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (_R_)-52



(*R*)-**52**

Using general procedure F, bisphosphine sulfide borane (*R)*-**50** (147 mg, 0.48 mmol, 0.40 eq., 99:1 er), DABCO (59 mg, 0.53 mmol, 0.44 eq.) and $Co_2(CO)_8$ (165 mg, 0.48 mmol, 0.40 eq.) in DME (20 mL) and sulfonamide **51** (300 mg, 1.20 mmol, 1.00 eq.) in DME (15 mL) gave the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*S*)-**52** (114 mg, 34%,

53:47 er) as a brown solid, mp 122-125 ˚C (lit.,[70] 154 ˚C); R_F (3:2 hexane-EtOAc); HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 77.5 min (*R*)-**52**, 81.9 min (*S*)-**52**.

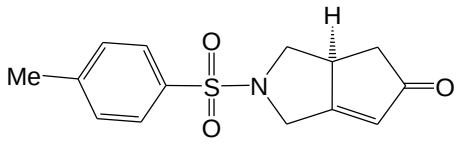
Lab book reference: chc/1/75

(*R*)-3-*p*-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (*R*)-52

A solution of bisphosphine borane sulfide (*R)*-**49** (110 mg, 0.32 mmol, 0.40 eq., 99:1 er) and DABCO (37 mg, 0.33 mmol, 0.40 eq.) in degassed toluene (15 mL) was stirred and heated at 80 ˚C for 2 h under Ar. Then, the reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure to give a colorless oil. Hexane (5 mL) was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a colorless oil and degassed DME (7 mL) was added**.** Then, a solution of $Co_2(CO)_8$ (110 mg, 0.32 mmol, 0.40 eq.) in degassed DME (5 mL) was added and the mixture was placed under a CO atmosphere. A solution of sulfonamide **51** (200 mg, 0.80 mmol, 1.0 eq.) in degassed DME (5 mL) was added and the resulting mixture was stirred and heated at reflux under CO for 17 h. Then, the reaction mixture was allowed to cool to rt. The solids was removed by filtration through a plug of silica and washed with EtOAc (40 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*R*)-**52** (64 mg, 29%, 52:48 er) as a brown solid, R_F (3:2 hexane-EtOAc); HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 85.8 min (*R*)-**52**, 91.3 min (*S*)-**52**.

Lab book reference: chc/1/81

(*S*)-3-*p*-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (*S*)-52



(*S*)-**52**

Using general procedure F, bisphosphine sulfide borane (*S*)-**47** (165 mg, 0.48 mmol, 0.40 eq., 97.5:2.5 er), DABCO (60 mg, 0.53 mmol, 0.44 eq.) and $Co_2(CO)_8$ (165 mg, 0.48 mmol, 0.40 eq.) in DME (20 mL) and sulfonamide **51** (300 mg, 1.20 mmol, 1.00 eq.) in DME (15 mL) gave the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*R*)-**52** (68 mg, 20%, 49:51 er) as a brown solid, R_F (3:2 hexane-EtOAc); HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 80.2 min (*R*)-**52**, 84.6 min (*S*)-**52**.

Lab book reference: chc/1/76

(*S*)-3-*p*-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (*S*)-52

Using general procedure F, bisphosphine sulfide borane (*S*)-**49** (55 mg, 0.16 mmol, 0.40 eq., 98.5:1.5 er), DABCO (20 mg, 0.18 mmol, 0.44 eq.) and $Co_2(CO)_8$ (55 mg, 0.48 mmol, 0.40 eq.) in DME (7 mL) and sulfonamide **51** (100 mg, 0.40 mmol, 1.00 eq.) in DME (5 mL) in a Schlenk tube under CO pressure gave the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*R*)-**52** (38 mg, 35%, 52:48 er) as a brown solid, R_F (3:2 hexane-EtOAc); HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 86.1 min (*R*)-**52**, 92.1 min (*S*)-**52**.

Lab book reference: chc/1/71

(*S*)-3-*p*-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (*S*)-52

Using general procedure F, bisphosphine sulfide borane (*S*)-**49** (165 mg, 0.48 mmol, 0.40 eq., 99:1 er), DABCO (60 mg, 0.53 mmol, 0.44 eq.) and $Co_2(CO)_8$ (165 mg,

0.48 mmol, 0.40 eq.) in DME (20 mL) and sulfonamide **51** (300 mg, 1.20 mmol, 1.00 eq.) in DME (15 mL) gave the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*R*)-**52** (47 mg, 14%, 53:47 er) as a brown solid, R_F (3:2 hexane-EtOAc); HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 83.8 min (*R*)-**52**, 89.8 min (*S*)-**52**.

Lab book reference: chc/1/79

(*S*)-3-*p*-Toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (*S*)-52

A solution of bisphosphine borane sulfide (*R)*-**47** (110 mg, 0.32 mmol, 0.40 eq., 99:1 er) and DABCO (37 mg, 0.33 mmol, 0.40 eq.) in degassed toluene (15 mL) was stirred and heated at 80 ˚C for 2 h under Ar. Then, the reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure to give a colorless oil. Hexane (5 mL) was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give a colorless oil and degassed DME (7 mL) was added**.** Then, a solution of $Co_2(CO)_8$ (110 mg, 0.32 mmol, 0.40 eq.) in degassed DME (5 mL) was added and the mixture was placed under a CO atmosphere. A solution of sulfonamide **51** (200 mg, 0.80 mmol, 1.0 eq.) in degassed DME (5 mL) was added and the resulting mixture was stirred and heated at reflux under CO for 17 h. Then, the reaction mixture was allowed to cool to rt. The solids was removed by filtration through a plug of silica and washed with EtOAc (40 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash chromatography with 3:2 hexane-EtOAc as eluent gave enone (*R*)-**52** (7 mg, 3%, 51:49 er) as a brown solid, R_F (3:2 hexane-EtOAc); HPLC: Daicel Chiracel OD, 80:20 v/v hexane-*i*-PrOH, 0.5 mL min^{-1}, 85.4 min (*R*)-**52**, 90.8 min (*S*)-**52**.

Lab book reference: chc/1/80

6. References

1. Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res*. **2007**, *40*, 1278.

2. Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev*. **2007**, *251*, 25.

3. Tang, W.; Zhang, X. *Chem. Rev*. **2003**, *103*, 3029.

4. Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem*. **2003**, *229*, 10.

5. Crépy, K. V. L.; Imamoto, T. *Adv. Synth. Catal*. **2003**, *103*, 3029.

6. Izod, K. *Coord. Chem. Rev*. **2002**, *227*, 153.

7. Knowles, W. S.; Sabacky, M. J. *Chemical Communications, (London)*, **1968**, 1445.

8. Knowles, W. S. *Acc. Chem. Res.*, **1983**, *16*, 106.

9. Pietrusiewicz, K. M.; Zabloka, M. *Chem. Rev*. **1994**, *94*, 1375

10. Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc*. **1998**, *120*, 1635.

11. Yamanoi, Y.; Imamoto, T. *J. Org. Chem*. **1999**, *64*, 2988.

12. Ogura, T.; Yoshida, K.; Yanagisawa, A.; Imamoto, T. *Org. Lett*. **2009**, *11*, 2245.

13. Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc*. **2005**, *127*, 11934.

14. Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc*. **2004**, *126*, 5966.

15. Tang, W.; Zhang, X. *Angew. Chem. Int. Ed*. **2002**, *41*, 1612.

16. Liu, D.; Zhang, X. *Eur. J. Org. Chem*. **2005**, 646.

17. Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem. Int. Ed*. **2010**, *49*, 6421.

18. Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc*. **1995**, *117*, 9075.

19. Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.*, **2001**, *343*, 118.

20. Imamoto, T. *Pure Appl. Chem.* **2001**, *73*, 373.

21. Crépy, K. V. L.; Imamoto, T. *Org. Synth*. **2005**, *82*, 22.

22. Ohashi, A.; Imamoto, T. *Org. Lett*. **2001**, *3*, 373.

23. Ohashi, A.; Imamoto, T. *Tetrahedron Lett.* **2001**, *42*, 1099.

24. Maienza, F.; Spindler, F.; Thommen, M.; Pugin, B.; Malan, C.; Mezzetti, A. *J. Org. Chem.* **2002**, *67*, 5239.

25. Crépy, K. V. L.; Imamoto, T. *Tetrahedron Lett*. **2002**, 43, 7735.

26. Nagata, K.; Matsukawa, S.; Imamoto, T. *J. Org. Chem*. **2000**, *65*, 4185.

27. Guiry, P. J.; Saunder, C. P. *Adv. Synth. Catal*. **2004**, *346*, 497.

28. Genet, C.; Canipa, S. J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc*. **2006**, *128*, 9336.

29. Dearden, M. J.; Firkin,C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc*. **2002**, *124*, 11870.

30. Hermet, J.-P. R.; Potter, D. W.; Dearden, M. J.; Harrison, J. R.; Kopin, T., O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977.

31. Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789.

32. O'Brien, P. *Chem. Commun*. **2008**, 655.

33. Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. *Eur. J. Org. Chem*. **2004**, 1894.

34. Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531.

35. Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2171.

36. Hoge, G. *J. Am. Chem. Soc*. **2003**, *125*, 10219.

37. Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268.

38. Gridnev, I. D.; Imamoto, T. *Organometallics* **2001**, *20*, 545.

39. Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett*. **2001**, *3*, 1701.

40. Imamoto, T.; Tamura, K.; Ogura, T.; Ikematsu, Y.; Mayama, D.; Sugiya, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1522.

41. Dolhem, F.; Johansson, J. M.; Antonsson, T.; Kann, N. *J. Comb. Chem*. **2007**, *9*, 477.

42. Johansson, J. M.; Andersson, H. O. K.; Kann, N. *J. Org. Chem*. **2008**, *73*, 4458.

43. Tang, W.; Zhang, X. *Org Lett*. **2002**, *4*, 4159.

44. Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed*. **2003**, *42*, 943.

45. Kudis, S.; Helmchen. G. *Angew. Chem. Int. Ed*. **1998**, *37*, 3047.

46. Gammon, J. G.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750.

47. Gammon, J. G.; O'Brien, P.; Kelly, B. *Org. Lett*. **2009**, *11*, 5022.

48. Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Maestro, M. A.; Mahía, J. *J. Am. Chem. Soc*. **2000**, *122*, 10242.

49. Solà, J.; Revés, M.; Riera, A.; Verdaguer, X. *Angew. Chem. Int. Ed*. **2007**, *46*, 5020.

50. Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron: Asymmetry* **2000**, *11*, 797

51. Hägele, G.; Kuchen, W. *Chem. Ber*. **1970**, *103*, 2885.

52. Gammon, J. J.; Gessner, V. H.; Barker, G. R.; Granander, J.; Whitwood, A. C.; Strohmann, C.; O'Brien, P.; Kelly, B. *J. Am. Chem. Soc.* **2010**, *132*, 13922.

53. Khand, I. U.; Knox, G. R.; Pauson. P. L.; Watts, W. E. *Chem. Commun.***1971**, *1*, 36.

54. Khand, I. U.; Knox, G. R.; Pauson. P. L.; Watts, W. E. *J. Chem. Soc. Perkin. Trans. I* **1973**, 977.

55. Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: United States of America, 2005.

56. Rautenstrauch, V.; Mégard, P.; Conesa, J.; Küster, W. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1413.

57. Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159.

58. Comely, A. C.; Gibson, S.E.; Stevenazzi, A.; Hales, N. J. *Tetrahedron Lett.* **2001**, *42*, 1183.

59. Arias, J. L.; Cabrera, A.; Sharma, P.; Rosas, N.; Sampere, R. *J. Mol. Catal. A* **2006**, *246*, 237.

60. Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron Lett.* **2000**, *41*, 891.

61. Gibson, S. E.; Lewis, S. E.; Loch, J. A.; Steed, J. W.; Tozer, M. T. *Organometallics* **2003**, *22*, 5382.

62. Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645.

63. Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 3398.

64. Solà, J.; Riera, A.; Verdaguer, X.; Maestro, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 13629.

65. Lledó, A.; Solà, J.; Verdaguer, X.; Riera, A.; Maestro, M. A. *Adv. Syn. Catal.* **2007**, *349*, 2121.

66. Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, 789.

67. Dai. L.-Z.; Shi. M. *Chem. Eur. J*. **2008**. *14*, 7011.

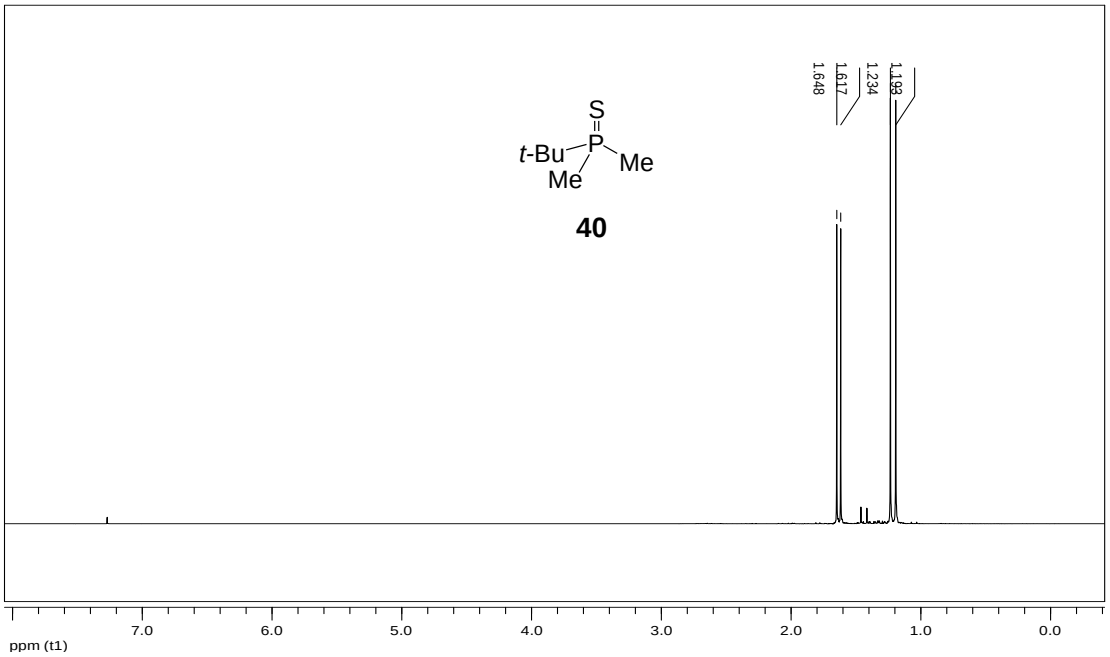
68. Burchat, A. F.; Chong, J. M.; Nielsen, N. *Organomet. Chem*. **1997**, 281.

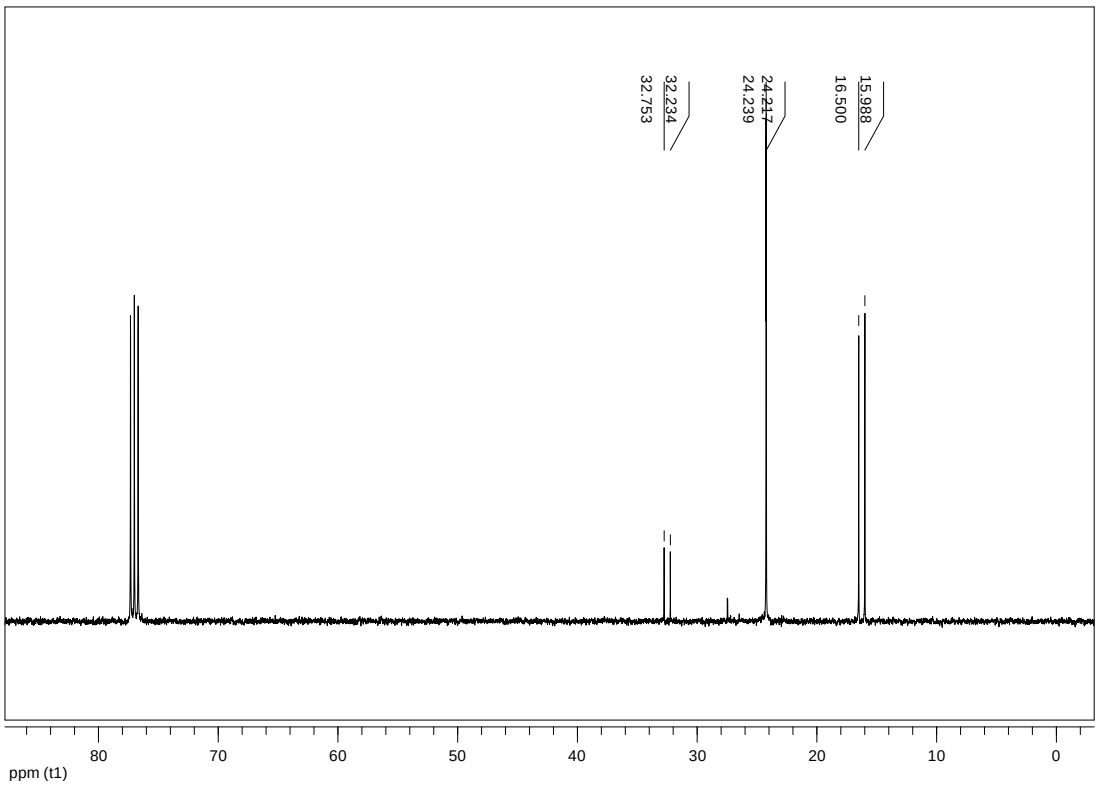
69. Gibson, S. E.; Hardick, D. J.; Haycock, P. R.; Kaufmann, K. A. C.; Miyazaki, A.; Tozer, M. J.; White, A. J. P. *Chem. Eur. J*. **2007**, *13*, 7099.

70. Jeong, K. S.; Kim, D. E.; Lee, E.; Jhon, Y. H.; Han, H.; Kim, J.; Jeong, N. *Tetrahedron: Asymmetry* **2009**, *20*, 1736.

6. Appendix: ^{1}H and ^{13}C NMR spectra

^{1}H and ^{13}C NMR spectra of phosphine sulfide 40 in $CDCl_3$





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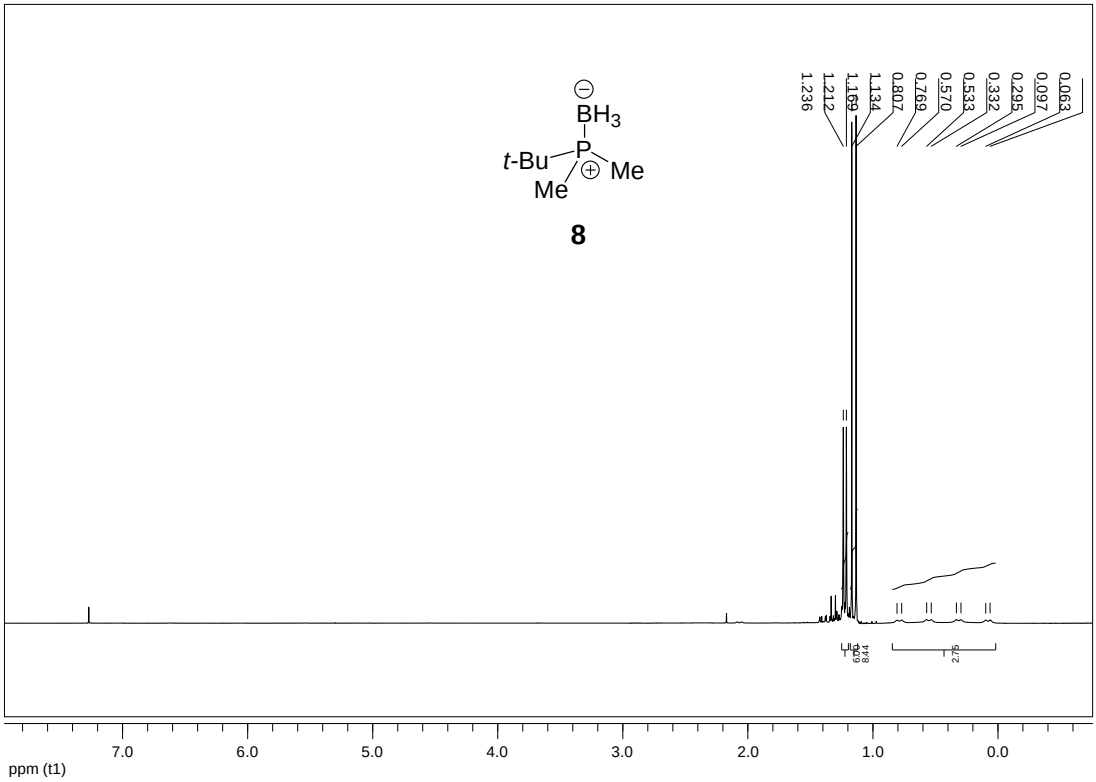
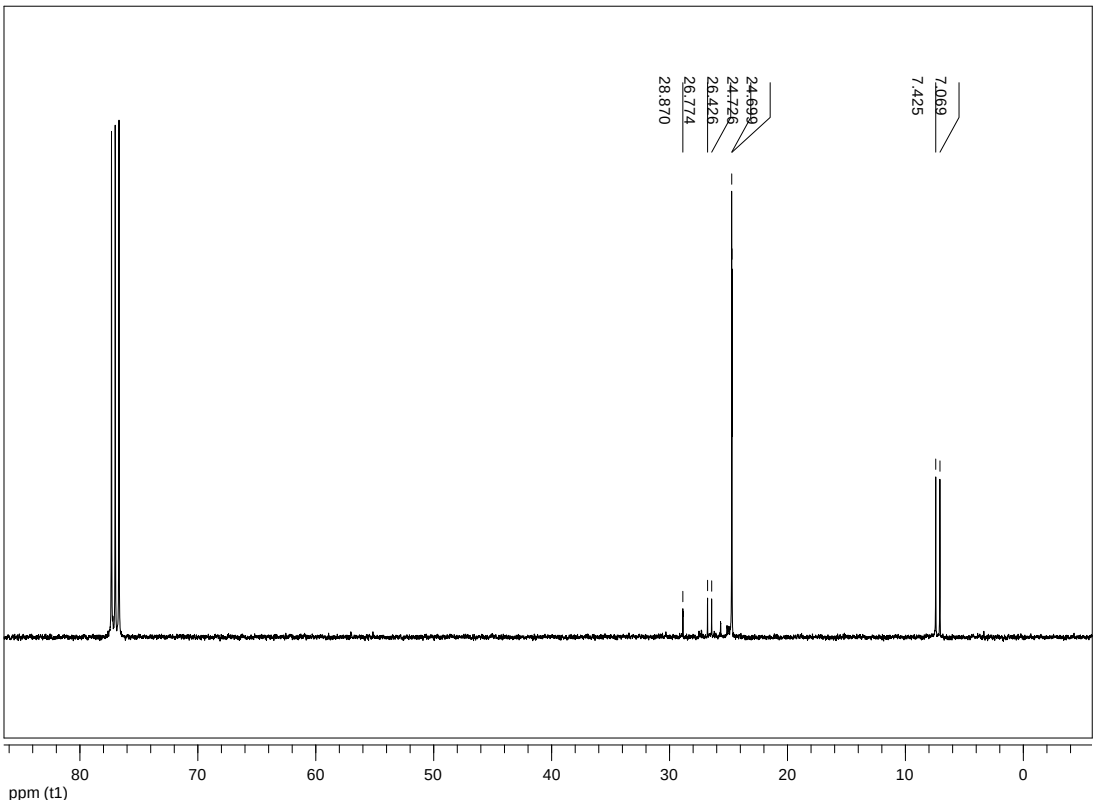
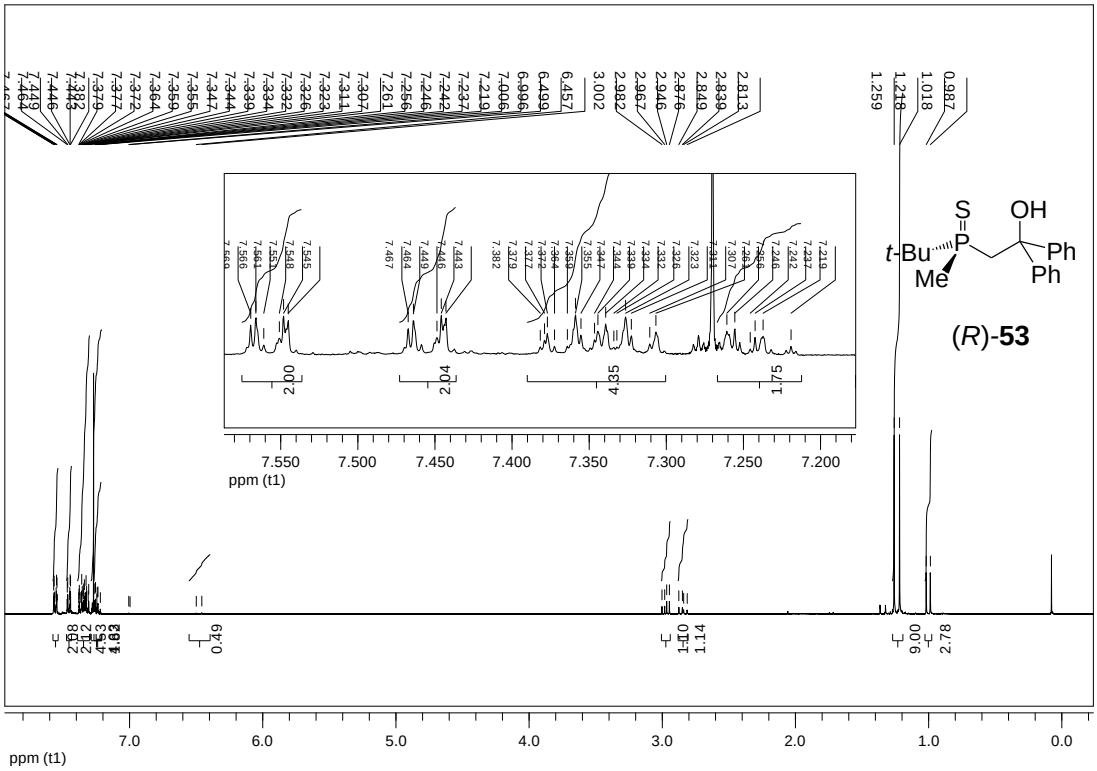
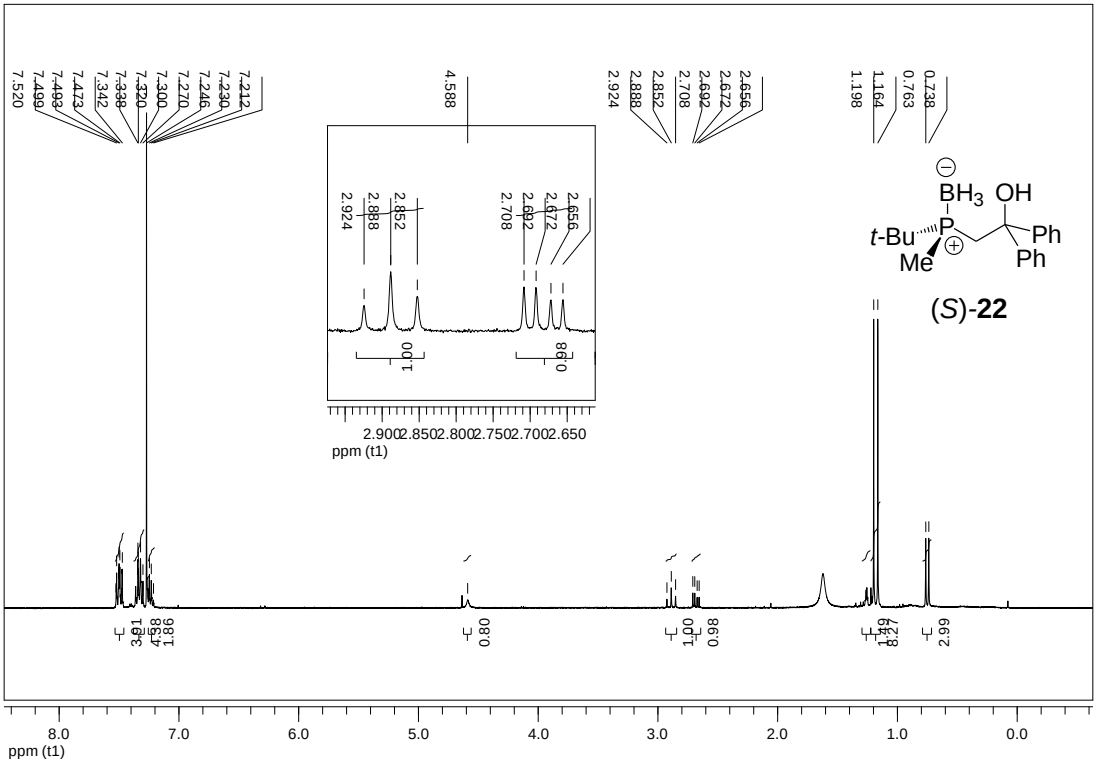




^{1}H NMR spectrum of hydroxy phosphine sulfide (*R*)-53 in $CDCl_3$



^{1}H NMR spectrum of hydroxy phosphine borane (*S*)-22 in $CDCl_3$



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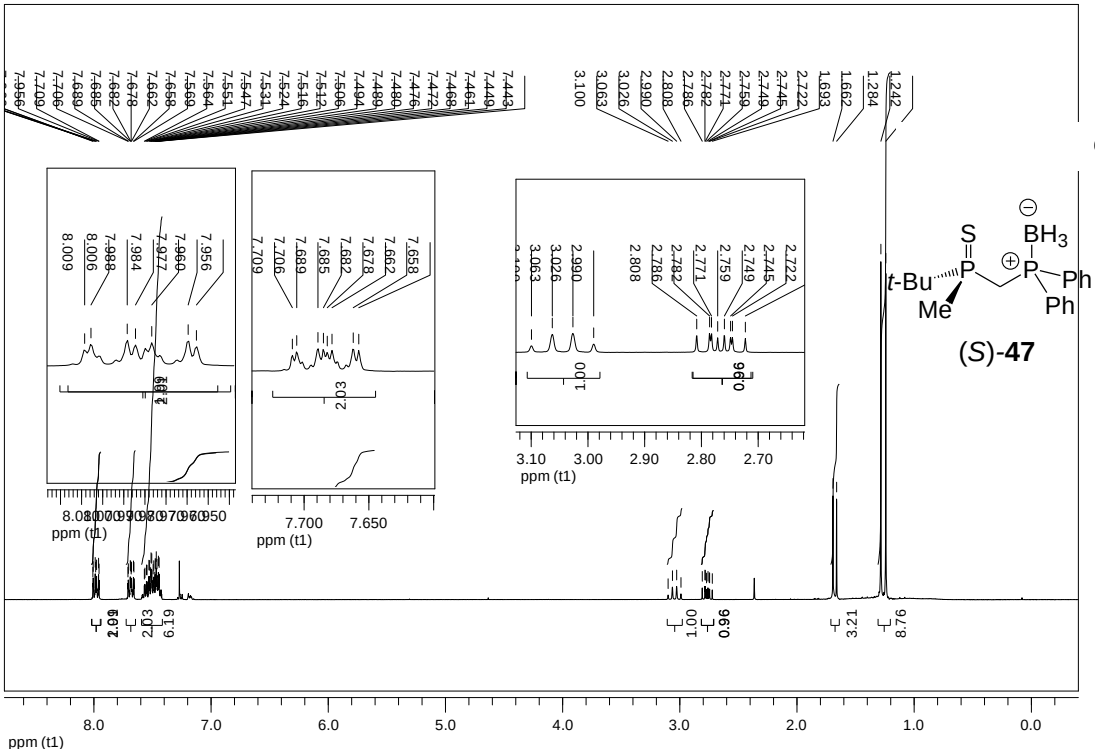

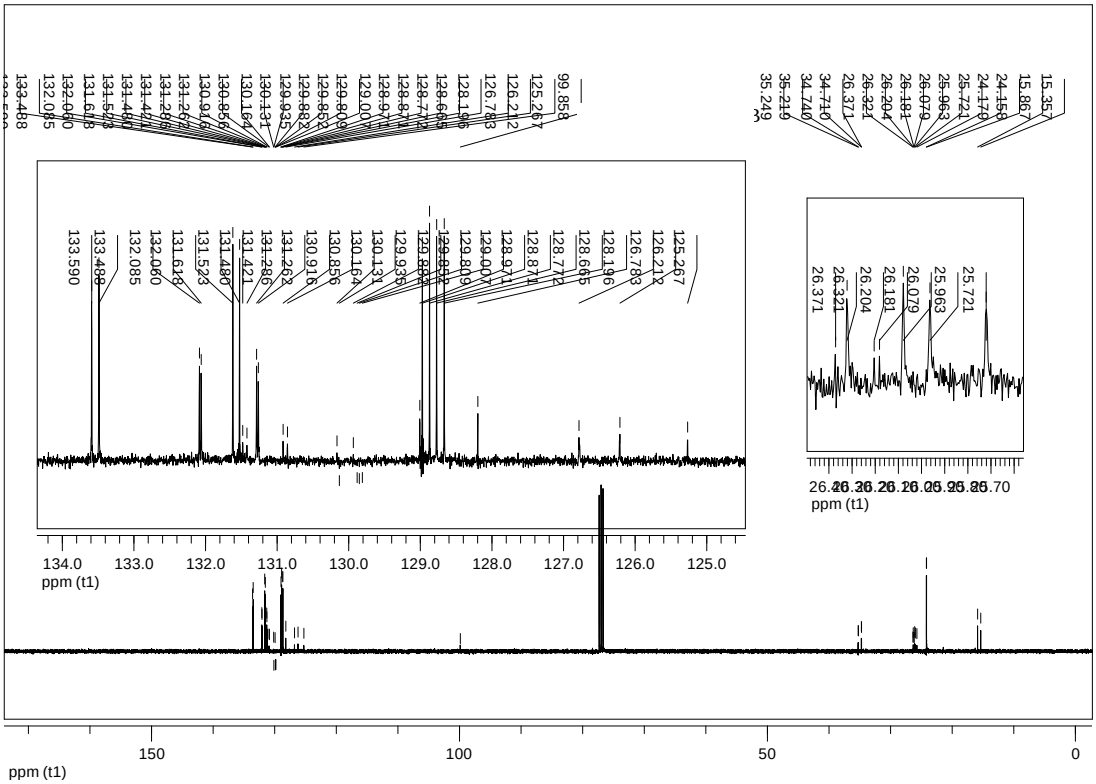

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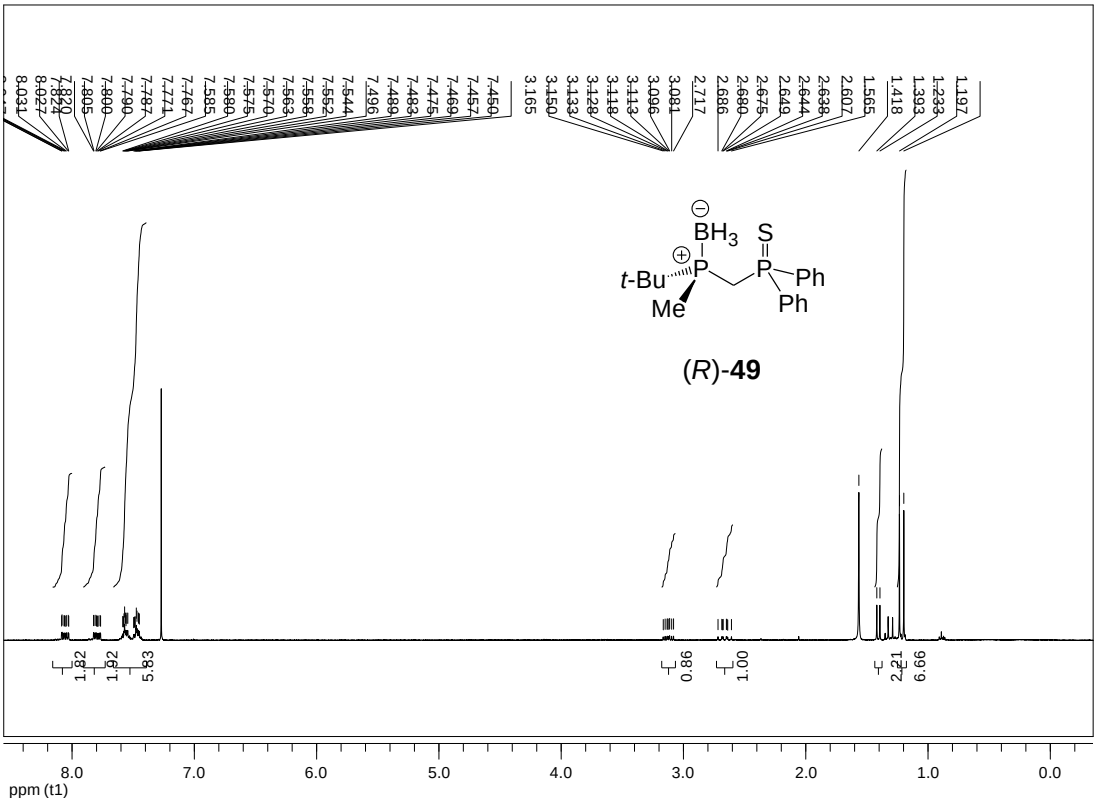

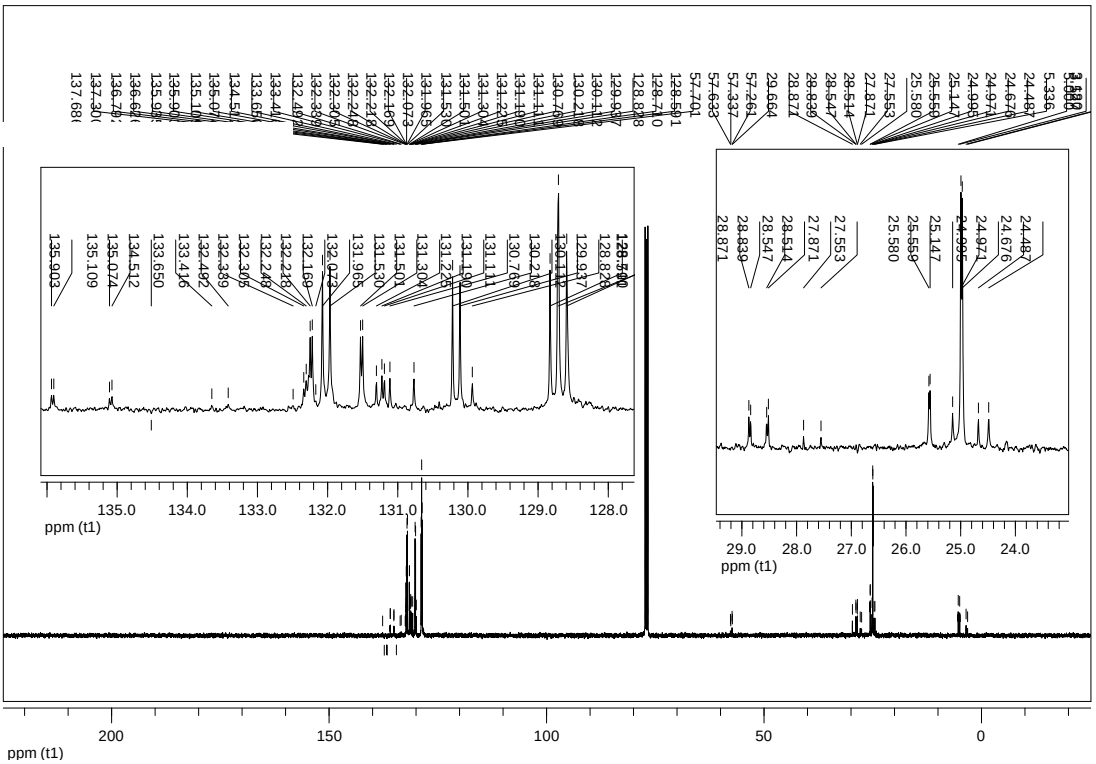

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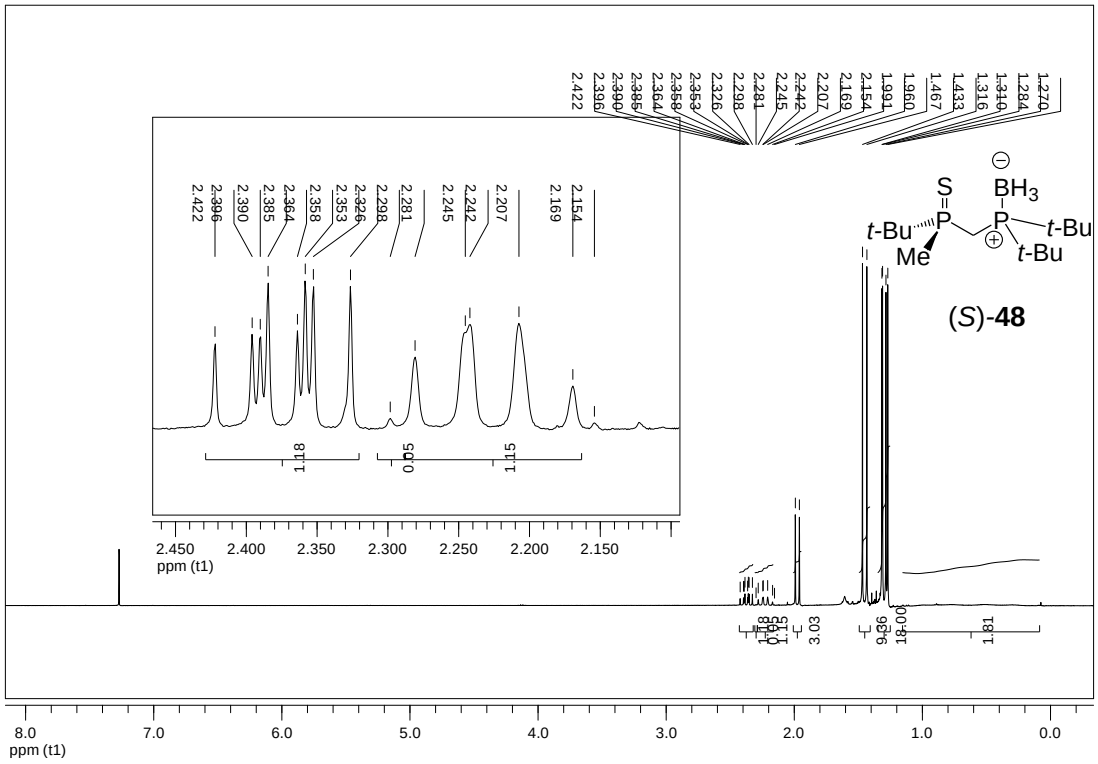

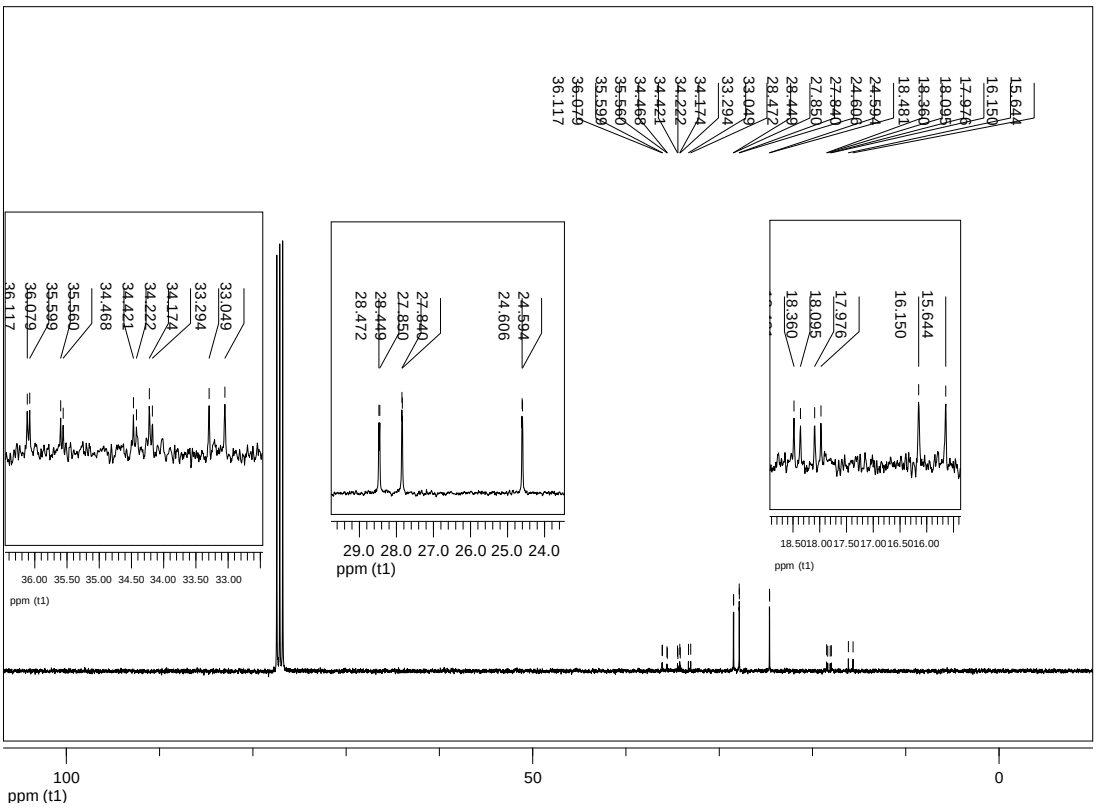

^{1}H and ^{13}C NMR spectra of phosphine borane sulfide (*R*)-50 in $CDCl_3$