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Preparation of Intermediates in the Synthesis of *P*-Chiral Bi- and Tridentate Amido- and Aminophosphine Ligands

Master's Thesis in Chemistry and Bioscience

Karin Lundberg

Department of Chemical & Biological Engineering
Division of Organic Chemistry
Chalmers University of Technology
Göteborg, Sweden 2011

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Supervisors: Kristian Andersson and Professor Nina Kann
Examiner: Professor Jerker Mårtensson

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Chalmers University of Technology
SE-412 96 Göteborg Sweden

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Abstract

Several key intermediates on the route to *P*-chiral amino- and amidophosphine ligands were prepared. Diarylmethylphosphines with phenyl, 2-biphenylyl, 1-naphthyl and 2-naphthyl substituents, were prepared using (–)-ephedrine as a chiral auxiliary. These precursors were then carboxylated on the methyl group and the acids were coupled to (1*S*,2*S*)- or (1*R*,2*R*)-cyclohexyldiamine, employing *N,N'*-dicyclohexylcarbodiimide and *N*-hydroxysuccinimide as coupling agents. The monoamide precursors for tridentate aminophosphine ligands were primarily formed. Moderate to good yields were achieved in the steps leading up to the diarylmethylphosphines, while lower yields were achieved in the synthesis of the acids and amides.

Keywords: P-chiral ligands, amidophosphine boranes, aminophosphine boranes, transition metal catalysis.

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Karin Lundberg, Gothenburg, March 2011.

Contents

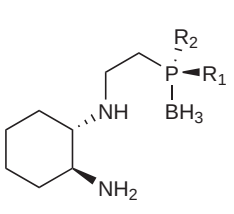
1

Introduction

The demand for routes to synthesize chiral and often complex molecules is ever increasing, particularly in the pharmaceutical industry. Different enantiomers of a drug molecule will most likely interact differently with the target, even though their chemical properties are the same. The difference might only be that between an active and an inactive substance, but it could also be that between a positive and a negative effect. Therefore it is important to be able to separate enantiomers, to resolve them, or to use an asymmetric reaction that will form only one enantiomer in large excess. For this purpose, transition metal catalyzed reactions have become very popular [1].

Transition metal complexes in solution can catalyze many different reactions, where among others the coupling of organic fragments and the reduction of carbonyl compounds can give rise to different stereoisomers. The structure and reactivity of the catalyst is determined by the ligands that coordinate to the metal. Consequently, the use of chiral ligands will give a chiral catalyst that can catalyze asymmetric reactions. The most common coordinating atoms are phosphorous, nitrogen and oxygen. Phosphorous has the advantage over the other two that it can be made persistently chiral, thus situating the chirality in the ligand closer to the reaction centre [2, 3].

Multidentate ligands which use phosphorous and nitrogen or oxygen as coordinating atoms have received some attention due to the combination of different binding properties of the different atoms. They have been used for many different purposes, especially within asymmetric synthesis. [4]. The chirality is then usually placed in the carbon backbone of the ligand, though *P*-chiral ligands are getting more popular. There, however, still exist many possibilities to use multidentate ligands that are chiral at phosphorous to enhance the yields and enantioselectivities of known catalysts.



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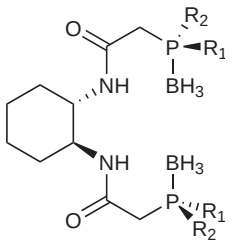

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The aim of this project was to synthesize two series of ligands based on a *P*-chiral diarylphosphine and a chiral cyclohexyldiamine. Thus, four possible stereoisomers of each ligand exist as two diasteromeric pairs of enantiomers. Only two diastereomers were prepared in the project, however. The configuration of the phosphine was kept the same, while that of the diamine was altered. Either one or both of the amino groups can be functionalized, giving rise to two types of ligands. The first ligand type, (**1**), contains one phosphine and two amino groups. In the second type (**2**), both amino groups are transformed into amides and connected to the phosphines. Both ligand types were intended for use in asymmetric transition metal catalyzed reactions, **1** in the hydrogenation of bulky ketones and **2** in the hydrovinylation of styrene ethene.

Due to the limited amount of time available to the project, the focus was placed on ligands of type **1** with phenyl and different bulky aryl groups as substituents. Also due to time limits, the prepared ligands were not tested in their designated reactions as a part of the project. They will however be tested within a few months.

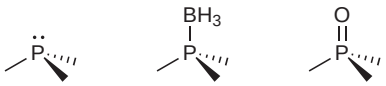
2

Theory

There are some topics within organic chemistry, with which some familiarity is needed to understand the work presented in this report. The chemistry of organophosphorous compounds is important for understanding some properties of the compounds that were synthesized in this project and the transition metal catalyzed reactions presented later are potential applications for the ligands.

2.1 Organophosphorous chemistry

The field of organophosphorous chemistry is very wide and includes many types of compounds which have carbon bound to phosphorous or are organic phosphorous acids. The coordination number on phosphorous can vary between 2 and 6, but in this project the focus is on 3-coordinate and 4-coordinate compounds, such as phosphines (**3**) and phosphine boranes (**4**). The carbon-phosphorous bond is quite stable towards most reaction conditions, especially in 4-coordinate structures [5].



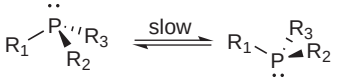
3 **4** **5**

Phosphines and other 3-coordinate compounds with three bonds to phosphorous have a pyramidal structure and a lone pair of electrons. This lone pair accounts for much of the reactivity of phosphines, especially towards electrophiles. It also reacts readily with many different oxidizing agents, in some cases even oxygen from air, forming phosphine oxides (**5**). The PO-double bond is very stable with a dissociation energy of around 130 kcal/mol and also quite resistant to reduction, requiring strong reducing agents e.g. lithium aluminum hydride or silicon hydrides. The orbital structure of the bond is not the same as in a carbon-carbon or a carbon-oxygen double bond and the bond does not react in a similar way to these [5]. To avoid oxidation of phosphines during synthesis, different protecting groups can be used. Borane complexed to phosphorous is probably the most common, since the complex is easy to form, stable under many reaction conditions and can be selectively broken up [6].

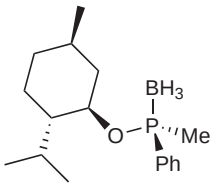
As expected, tetrahedral phosphorous groups with four different substituents are stereogenic

centres. More interestingly, phosphines can also be chiral, even though they are 3-coordinate. This property arises from the high energy of activation for the inversion of the pyramidal structure. The energy is around 30 kcal/mol, which makes the inversion close to non-existant at room temperature and very slow at higher temperatures. As can be seen in Scheme 2.1 the enantiomers would interconvert and not be observed if the inversion of phosphines were faster [5].

Scheme 2.1: Inversion of phosphines



Several methods for the enantioselective synthesis of phosphines exist, most of which employ 4-coordinate compounds such as phosphine-boranes or phosphine oxides. The earliest developed method uses resolution of a racemic mixture of the phosphine or a derivative with chiral auxiliaries [7, 8]. This method, however, gives low yields and is thus not so commonly used nowadays. Later, methods that make use of chiral auxiliaries during the synthesis were developed. The first auxiliary to be used was menthol, which results in a mixture of diastereomeric menthylphosphinites (**6**) [9]. The mixture then has to be separated before transformation into phosphines. A more widely used chiral auxiliary is ephedrine, which forms chiral oxazaphospholidines (**7**) [10]. Ephedrine is then removed by stepwise addition of organolithium reagents. Another popular method is to deprotonate dimethylphosphines (**8**) enantioselectively using lithium reagents and a chiral base, such as (–)-sparteine (**9**) [11]. This method is, however, not useful for the synthesis of di- or triarylphosphines, due to the need for two methyl groups. A more recently developed method is the palladium catalyzed cross-coupling of secondary phosphines with aryl or vinyl halides [12]. To make the reaction asymmetric, chiral ligands are used.



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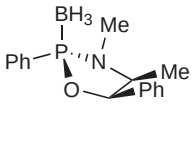

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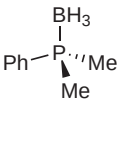

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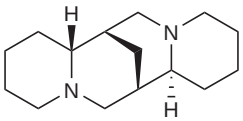

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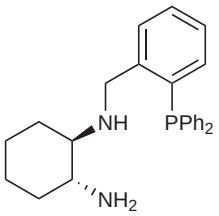
2.2 Transition metal catalysis

A number of different reaction types can be catalyzed by transition metal complexes in solution. The formation of carbon-carbon bonds is perhaps the most useful, since coupling of many kinds of organic molecules would not be possible without this methodology. Other reactions which are almost impossible to perform using classic methods, but which have been achieved by transition metal catalysis, are the couplings between heteroatoms and carbon. Cross-couplings are not the only reactions that can be catalyzed using transition metals and other examples are hydrogenation of different substrates as well as hydroformylation, where a carbonyl group is incorporated in the molecule [2].

An essential part of transition metal catalysts are the ligands that bind to the metal center. In addition to keeping the metal in solution, the ligands also lend new properties to the catalysts. The most common ligand type are phosphines, where phosphorous coordinates to the metal,

but amines with nitrogen as coordinating atom are also used. Ligands with different properties promote different reactions or even different steps of the catalytic cycle. Some properties that can be important are the electronic properties of the coordinating atom, which are induced by the groups bound to it, the size of the ligands and how rigid its structure is [2]. Multidentate ligands, which have more than one coordinating atom, have other properties than monodentate ligands, e.g. they often form a stronger bond to the metal. The angle between the coordinating atoms can also be very important for the reactivity of the catalyst [13]. To induce asymmetry into a reaction, chiral ligands are needed [3]. The chirality often resides in the carbon backbone of the ligand, which is due to previous difficulties in the synthesis of chiral phosphines. Since the development of the methods mentioned in section 2.1 P-chiral ligands have emerged as an important alternative .

2.2.1 Hydrogenation of ketones



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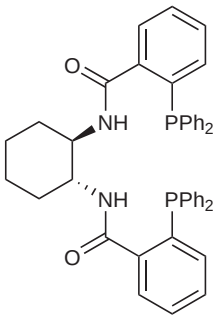

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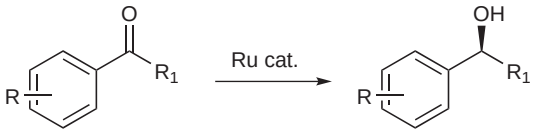
Chemoselective hydrogenation of ketones using homogeneous catalysts is efficiently performed with Noyori's methods [14]. The catalyst is a ruthenium complex bearing both a diphosphine and a diamine ligand, and it is proposed that the substrate hydrogen bonds to the nitrogen of the diamine instead of coordinating to the ruthenium metal centre. If the ligands are chiral, high enantioselectivities can be reached with many substrates. These catalysts are, however, not as effective when it comes to reducing bulky or heterocyclic ketones. A new ruthenium catalyst employing a tridentate aminophosphine ligand (**10**) has been developed to deal with substrates of the type shown in Scheme 2.2. The reaction has proven to give high yields and enantiomeric excesses between 45 and 90% for different substrates [15].

Scheme 2.2: Hydrogenation of ketones, R_1=bulky

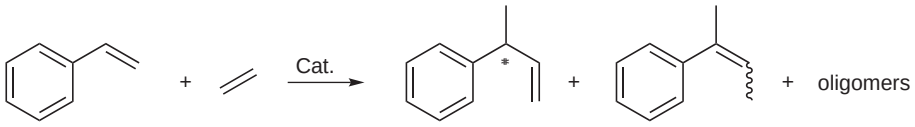


2.2.2 Hydrovinylation of styrene

The general hydrovinylation reaction is the coupling of ethene and alkenes, by addition of ethene across the double bond of the alkene. When using styrene as the alkene, the reaction can be catalyzed by nickel or palladium complexes [16]. These catalysts, however, also produce isomers of the desired product, as well as oligomers of the starting materials (Scheme 2.3). This

problem has been overcome by using a catalyst which only starts the isomerization after all starting material has been consumed. The catalyst is based on $CoCl_2$ and phosphine ligands and is activated by diethylaluminum chloride. High conversion of starting material and high selectivity for the desired isomer of the product were achieved using bidentate phosphine ligands and bidentate ligands employing both phosphorous and nitrogen or oxygen as coordinating atoms. As can be seen in Scheme 2.3 a stereocentre forms during the reaction and to control its configuration, chiral ligands have been tried. Using Trost's bis(phosphine-amide) ligand (**11**) and related amidophosphines, enantiomeric excesses of up to 50 % and high selectivity for the desired isomer was achieved [17]. It is theorized that the amide nitrogens do not coordinate to the cobalt centre, since the catalyst loses activity if related ligands with amine or imine nitrogens, which have been found to coordinate, are used [18].

Scheme 2.3: Hydrovinylation of styrene with ethene



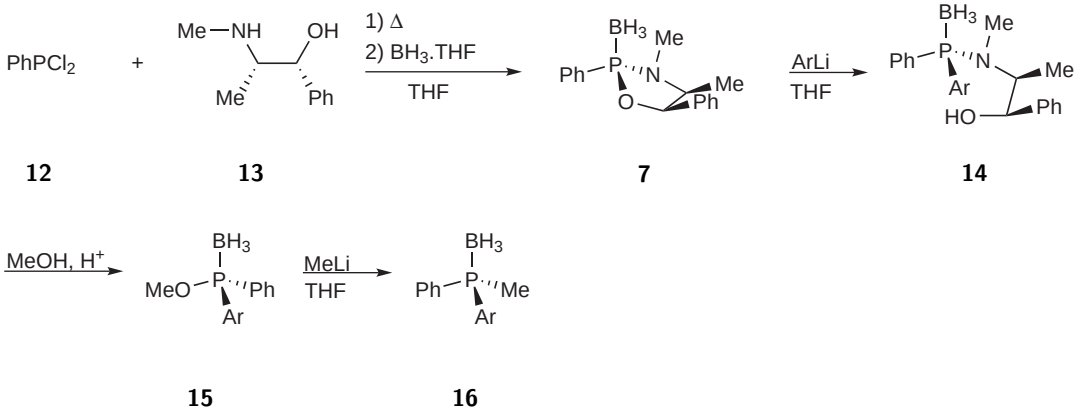
3

Methods

The main methods that were used for the preparation of the ligands were the ephedrine based method for the synthesis of P-chiral phosphines and a method to prepare amides and amines from the phosphines. All steps were performed using oven dried glass under a nitrogen atmosphere. If needed, the products were purified using flash chromatography. For the characterization of the ligands and the intermediates, well known methods, such as NMR, mass spectrometry, IR-spectrometry and measurement of optical rotation, were used.

3.1 Preparation of P-chiral phosphines

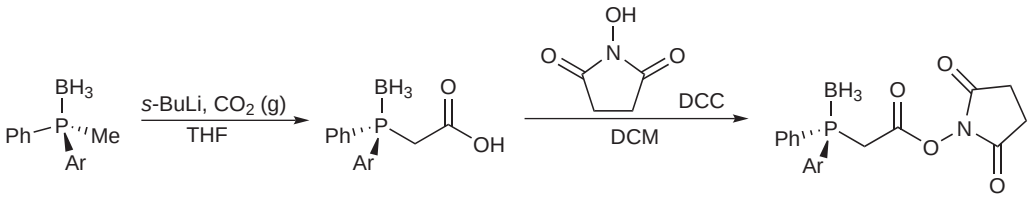
Scheme 3.1: The ephedrine based method for synthesizing P-chiral phosphines



The ephedrine based method was developed by Juge [10, 19] in the 1980's and has since then become very popular, especially for the preparation of di- and triarylphosphines [20, 21]. At the start of the route, an oxazaphospholidine borane (**7**) is formed from dichlorophenylphosphine (**12**), (–)-ephedrine (**13**) and borane. In this project the oxygen of ephedrine is displaced by an aryllithium reagent to form **14** and then an acidic methanolysis displaces the nitrogen forming **15**. Finally, the methoxy group is removed by methyllithium, forming the phosphine (**16**). By changing the order of the lithium reagents the chirality of the phosphine can be reversed, thus making both enantiomers of the phosphine available.

3.2 Preparation of amino- and amidophosphines

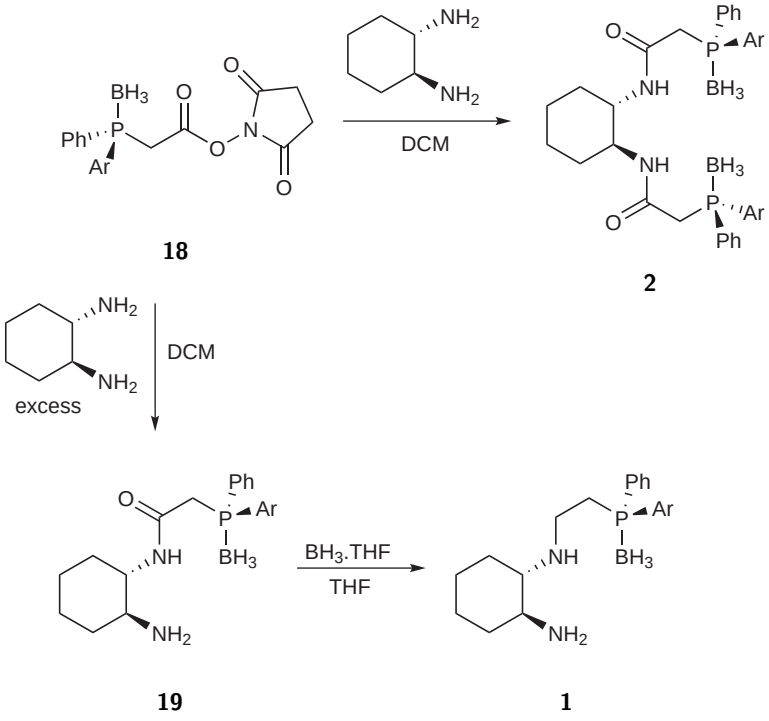
Scheme 3.2: Formation of carboxylic acid and active ester



16 **17** **18**

Several previously published methods were used with some modifications on the route from the phosphines to the finished ligands. In the first step the carboxylic acid (**17**) is formed by deprotonating the methyl group of **16** using *s*-BuLi and then letting CO_2 bubble through the reaction mixture [22]. The active ester (**18**) is then formed from the acid and *N*-hydroxysuccinimide, with assistance of the coupling agent dicyclohexylcarbodiimide (DCC). From **18** both the amino- and the amidophosphines can be formed [23], the only difference in the procedure being the amount of the cyclohexyldiamine used. By keeping the diamine in excess through slow addition of **18**, mainly the monoamide (**19**) is formed, as preferred in this project. To form the aminophosphine (**1**) the amide in **19** is finally reduced with borane at elevated temperatures [24].

Scheme 3.3: Formation of amido- and aminophosphines



18 **2**

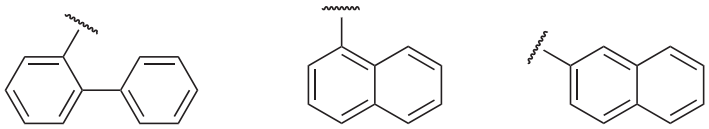
19 **1**

4

Results and Discussion

The three different aryl groups shown in Scheme 4.1 were selected as substituents to be tried in the potential ligands. Since they are all aromatic, the electronic properties of phosphorous will be similar to the Trost ligands, but the larger bulk of these substituents are thought to give a greater asymmetric induction power to the catalyst. It should thus be possible to increase the enantioselectivity of the catalyst and maybe alter other properties too.

Scheme 4.1: The aryl substituents used. **20**=2-biphenylyl, **21**=1-naphthyl, **22**=2-naphthyl



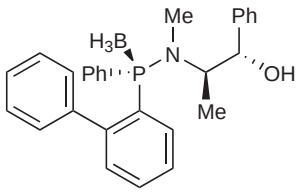
20 **21** **22**

The oxazaphospholidine borane (**7**) was prepared in two large batches according to the established procedure. The results were good and both batches were divided into halves for the continued synthesis.

All the substituents afforded relatively high yields in the first two steps of the preparation of the *P*-chiral phosphines. In the addition of the aryllithium reagent (Table 4.1) the yields were lower than reported in the literature, except for the addition of 2-naphthyllithium, which was performed under slightly different conditions by the supervisor. For the same reaction with the same substituents the yields range between 80 and 90% in the literature [20, 21]. The lower yields can probably be accounted for by the low solubility of the aryllithiums at -78 °C, which formed solid precipitates that hindered the stirring. More effective stirring during this step might therefore increase the yields. The methanolysis (Table 4.2), on the other hand, performed well for all the substituents, with yields close to the values from the literature.

In the last step of the phosphine synthesis, the addition of methyllithium (Table 4.3), the difference between the substituents could clearly be seen. The yield of the biphenylylphosphine (**29**) were significantly lower than that of the two naphthyl isomers. The difference is likely due to the greater freedom of movement of the biphenyl group. The reaction is a standard nucleophilic substitution [25] and the bulk of the biphenyl could hinder the methyl anion from attacking at the phosphorous. The lower reactivity of the biphenylyl derivative can be seen in the two proceeding reactions too, but the differences in yields are smaller.

Table 4.1: Addition of aryllithium



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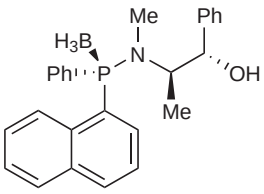

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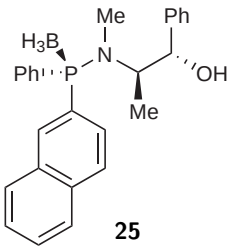
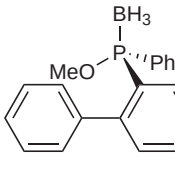


25

compound	yield (%)
23	60
24	72
25	96[a]

[a]Performed at slightly different conditions by supervisor.

Table 4.2: Methanolysis



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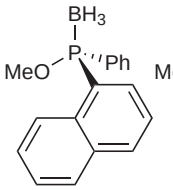

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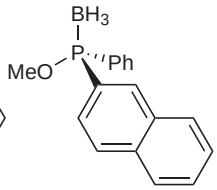


28

compound	yield (%)
26	75
27	85
28	88[a]

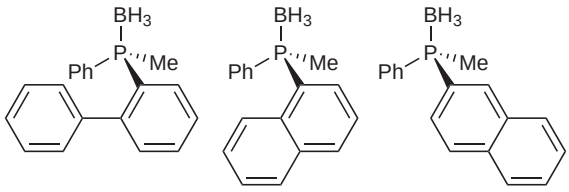
[a]Performed by supervisor.

The two naphthylphosphines (**30**, **31**) were achieved in moderate yields, which might be expected from the relatively bulky aryl substituents. It has been found that the yield for related substrates bearing an *o*-methoxyphenyl substituent was much higher than for other substituents [26]. The reason for this is thought to be that the lithium reagent coordinates to the methoxy group, which places the reagent closer to the phosphorous and accelerates the reaction. Thus longer reaction times might increase the yields for substituents that lithium cannot coordinate to.

The carboxylation of the phosphines (Table 4.4) was another step where the extra bulk of the large aryl substituents hindered the reaction. One advantage of the reaction procedure is that any unreacted starting material is easily recovered in an acid-base extraction and can be reused without purification. The extraction, however, did not afford the pure acid as anticipated, but a contaminated product and also left much product in the starting material phase. Especially the 2-naphthyl derivative (**34**, entries 6-8) behaved in this way. Thus the acid-base extraction was eventually discarded in favour of purification by flash chromatography (entry 5), which gave a moderate yield, though much higher than when extraction was used.

The biphenylylphosphine (entries 1-2) reacted very poorly and almost no product could be identified on NMR. Better results were achieved with the 1-naphthyl substituent (entry 3), but since the product was contaminated with starting material, it had to be purified and some material was lost in the process. To improve the yield, longer reaction times were tried. No

Table 4.3: Addition of methyllithium

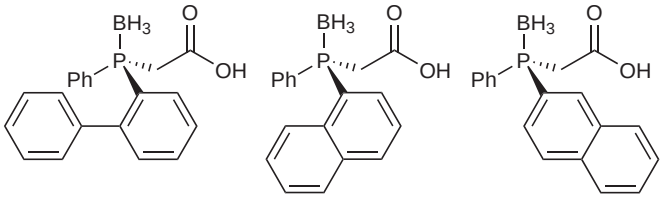


29 **30** **31**

compound	yield (%)
29	30
30	53
31	58

improvement could, however, be seen when the reaction was run with the recovered starting material (entry 4). The next measure to be taken was to change the carbon dioxide source from dry ice to a gas tube, to ensure the dryness of the gas. The higher yield for the 2-naphthyl derivative (**34**, entry 8) might be due to this change, but it might also be a result of the reaction being run twice before isolating the product.

Table 4.4: Carboxylation



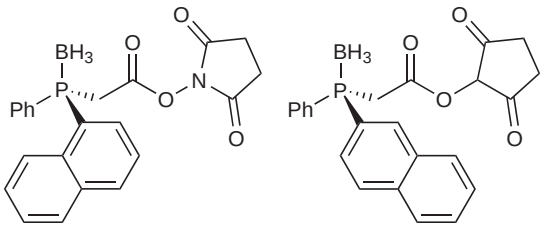
32 **33** **34**

entry	compound	reaction conditions and comments	yield (%)
1	**32**	1) 1.3 eq *s*-BuLi 3 h at -78 °C 2) CO_2(g) 2 h at 0 °C. CO_2 from dry ice.	10[a]
2	**32**	Recovered starting material. 1) 1.3 eq *s*-BuLi 3 h at -78 °C 2) CO_2(g) 2 h at RT. CO_2 from dry ice.	-
3	**33**	1) 1.3 eq *s*-BuLi 3 h at -78 °C 2) CO_2(g) 2 h at RT. CO_2 from dry ice.	9.7
4	**33**	Recovered starting material. 1) 1.3 eq *s*-BuLi 4 h at -78 °C 2) CO_2(g) 3 h at RT. CO_2 from dry ice.	13[a]
5	**33**	1) 1.3 eq *s*-BuLi 3.5 h at -78 °C 2) CO_2(g) 2.5 h at RT. CO_2 from gas tube. No acid-base extraction.	41
6	**34**	1) 1.3 eq *s*-BuLi 4 h at -78 °C 2) CO_2(g) 3 h at RT. CO_2 from gas tube.	8[a]
7	**34**	Recovered starting material. 1) 1.3 eq *s*-BuLi 3 h at -78 °C 2) CO_2(g) 2 h at RT. CO_2 from gas tube.	6[a]
8	**34**	Isolated as the sodium salt after purification of recovered starting material.	40[b]

[a]Crude yield.
[b]Yield over two runs.

The formation of the active ester (Table 4.5) gave a quite low yield for the 1-naphthyl derivative (**35**, entry 1) the first times the reaction was run. The cause might be that product was adsorbed to the pad of celite through which the reaction mixture was filtered. It seems to be a probable explanation since the yield was much higher for the third run of the 1-naphthyl ester (entry 2) and for the 2-naphthyl ester (**36**, entry 3), which were filtered through smaller pads of celite. Despite purification by flash chromatography, the active ester was contaminated with dicyclohexylcarbodiimide, which was used as coupling reagent during the reaction. No additional purifications were performed, since it was not thought probable that the contaminant would hinder the next reaction step.

Table 4.5: Formation of the active ester

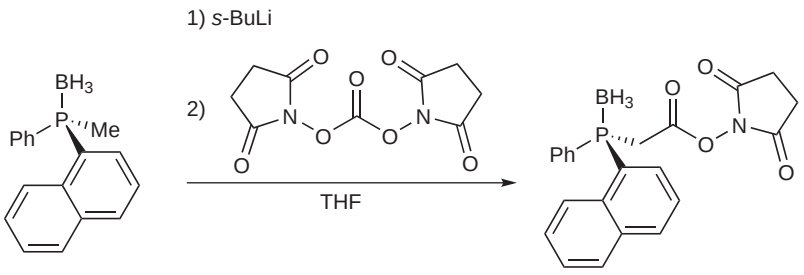


35 **36**

entry	compound	yield (%)
1	**35**	21
2	**35**	60
3	**36**	66

An alternative procedure for the synthesis of the active ester (Table 4.6) was tried with negative results. It was thought that the deprotonated methyl group of the phosphine (**30**) would be able to attack the electrophilic carbon in *N,N'*-discuccinimidyl carbonate and form the active ester in that way. No product could be isolated in either of the performed experiments, although in the second experiment (entry 2) it could be identified on TLC. One limiting factor in the experiments was that the carbonate was not soluble in tetrahydrofuran, which was the solvent used in the reaction. Due to shortage of time no further experiments were performed, but the reagent is still considered to be of interest since it would remove one step from the route to the ligands.

Table 4.6: Alternative synthesis of the active ester



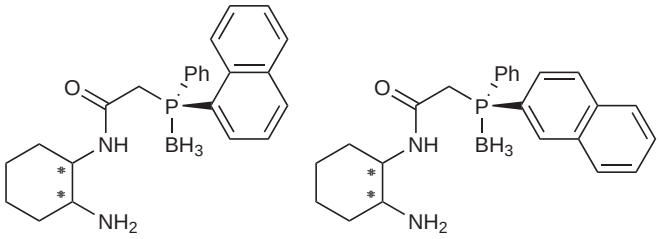
entry	reaction conditions
1	1) 1.3 eq *s*-BuLi 3 h at -78 °C 2) 2 eq *N,N'*-disuccinimidyl carbonate 1.5 h at RT
2	1) 1.3 eq *s*-BuLi 3 h at -78 °C 2) 2 eq *N,N'*-disuccinimidyl carbonate 1.5 h at 0 °C

Overall, the amide coupling (Table 4.7) gave quite low yields for both the naphthyl substituents. Since the active ester contained impurities in unknown quantities, the yield was calculated over

two steps from the acids. The extraordinary low yield of the (*R,R*)-1-naphthyl derivative ((*R,R*)-**37**) is probably due to a much shorter reaction time than for the other experiments (3.5 h as opposed to 20 h). The progress of the reaction was monitored on TLC and even though the starting material was considered to have been consumed, the reaction might not have been complete.

In all experiments, the diamide of type **2** could be isolated as a byproduct, though only in low yields which ranged between 2.5 and 7.5% for the three best yielding amides. To minimize the side reaction, the diamine was kept in large excess. This was achieved by adding the active ester slowly to the reaction mixture. The largest amount of diamide was found for (*S,S*)-**37**, where the addition was accidently made too fast over a period of time.

Table 4.7: Formation of amidophosphine



37 **38**

compound	yield (%)[a]	compound	yield (%)[a]
(*R,R*)-**37**	1.6	(*R,R*)-**38**	39
(*S,S*)-**37**	33	(*S,S*)-**38**	31

[a]Yield over two steps.

5

Conclusions

In this project, three new *P*-chiral diarylmethylphosphines with bulky aryl substituents were prepared and characterized. Two of them were transformed into carboxylic acids and then amides with (1*S*,2*S*)- and (1*R*,2*R*)-cyclohexyldiamine. Due to problems with the reduction of the amides, none of the desired aminophosphine ligands were prepared.

Future work includes the development of a method for the reduction of the amidophosphines into the aminophosphines that will allow for the characterization of the ligands. Screening of the ligands in the designated hydrogenation reaction could then be performed. If the attempts are successful, an optimization of the synthetic route would also be worthwhile, so as to enable preparation of larger quantities of the ligands.

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A

Experimental procedures

Chemicals were obtained from commercial suppliers and used without further purification unless otherwise noted. All reactions were performed under a nitrogen atmosphere with magnetic stirring and oven dried glassware. Commercially available anhydrous solvents were used. Low reaction temperatures were reached using cooling baths (ice–water mixture for 0 °C and acetone–dry ice for -78 °C).

Flash chromatography was performed using a Biotage Flash Chromatography System (Isolera One) with SNAP cartridges (340 g, 100 g, 25 g, 10 g HP-SIL). NMR spectra were recorded on a JEOL Eclipse 400 MHz spectrometer using $CDCl_3$ and CD_3OD. Measurements of optical rotation was carried out on a Perkin Elmer Polarimeter 341 LC using $CHCl_3$ as solvent. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer using NaCl plates. LC-MS analysis was performed using a Perkin Elmer Sciex API 150EX instrument, equipped with a Genesis C8 reversed phase column from Grace.

Abbreviations for NMR are the following: s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; app, apparent. Chemical shifts (δ) are given in ppm relative to the solvent residual peak ($CHCl_3$: 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR; and methanol: 3.31 ppm for ^{1}H NMR and 49.00 ppm for ^{13}C NMR) or an internal standard (TMS: 0.00 ppm for 1H NMR).

(2S_p,4R,5S)-(−)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine Borane (7) [10]: (−)-Ephedrine (13.2 g, 80 mmol) was dissolved in tetrahydrofuran (400 ml) and DIPEA (28 ml, 160 mmol) was added. The solution was cooled to 0 °C and dichlorophenylphosphine (10.8 ml, 80 mmol) was added. A white precipitate formed, which dissolved upon heating. The solution was heated at reflux for 22 h, during which a precipitate formed. When the solution had cooled to ambient temperature, $BH_3 \cdot THF$ (80 ml, 80 mmol, 1.0 M) was added and the precipitate partly dissolved. The mixture was stirred another 21 h ambient temperature. Then 200 ml H_2O was added and the phases separated. The aqueous phase was extracted with 3×100 ml diethyl ether. The combined organic layers were then washed with 200 ml brine and dried with Na_2SO_4, before concentrating under vacuum to yield a pale yellow solid. Purification by flash chromatography (10-26% ethyl acetate in petroleum ether, silica gel) yielded **7** as a white solid (7.53 g, 26.4 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.77 (m, 2H), 7.62 - 7.46 (m, 3H), 7.45 - 7.27 (m, 5H), 5.58 (dd, J=6.0, 3.0 Hz, 1H), 3.72 - 3.61 (m, 1H), 2.67 (d, J_{HP}=11.0 Hz, 3H), 1.41 - 0.48 (m, 6H), 0.82 (d, J=6.5 Hz, 3H).

(S_p,1*S*,2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(2-biphenylyl)-*P*-(phenyl)-phosphinamide Borane (23): A 1.0 M solution of 2-bromobiphenyl (17.8 mmol) in diethyl ether was cooled to -78 °C and a solution of *tert*-butyllithium (23.3 ml, 35.6 mmol) was added dropwise. The opaque, cream coloured mixture was stirred 15 min at -78 °C, warmed to 0 °C and stirred for an additional 30 min. A pale pink, opaque mixture of *o*-biphenylyllithium was produced. The lithium reagent was added dropwise via syringe to a solution of **39** (2.54 g, 8.9 mmol) in 9 ml tetrahydrofuran and a yellow precipitate formed. The mixture was stirred 30 min at -78 °C, then warmed to 0 °C and stirred for an additional 2 h. The precipitate dissolved upon warming and the solution turned red. 70 ml H_2O and 50 ml diethyl ether were added and the phases separated. The aqueous phase was extracted with 3×30 ml diethyl ether. The combined organic layers were washed with 2×50 ml brine and dried with Na_2SO_4, before concentrating under vacuum to yield a yellow oil. Purification by flash chromatography (5-40% ethyl acetate in petroleum ether, silica gel) yielded **23** as a white solid (2.351 g, 5.35 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.63 (m, 2H), 7.62 - 7.12 (m, 17H), 4.86 (s, 1H), 3.94 (dd, J=11.2, 4.9 Hz, 1H), 2.56 (dd, J_{HP}=7.2, 0.8 Hz, 3H), 1.48 (s, 1H), 1.37 - 0.73 (m, 3H), 0.67 (d, J=6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.54 (s), 142.59 (s), 141.48 (d, J_{CP}=3.0 Hz), 134.21 (d, J_{CP}=10.1 Hz), 133.80 (s), 133.22 (s), 132.80 (d, J_{CP}=8.2 Hz), 132.29 (d, J_{CP}=9.8 Hz), 130.62 (s), 129.76 (s), 129.31 (d, J_{CP}=11.9 Hz), 128.59 (s), 128.29 (s), 128.21 (d, J_{CP}=3.2 Hz), 127.45 (d, J_{CP}=4.8 Hz), 127.23 (s), 126.88 (d, J_{CP}=9.8 Hz), 125.74 (s), 78.91 (s), 58.15 (d, J_{CP}=10.2 Hz), 31.84 (s), 14.31 (s), 9.98 (d, J_{CP}=6.5 Hz).

(S_p,1*S*,2*R*)-*N*-Methyl-*N*-(1-hydroxy-1-phenyl)prop-2-yl-*P*-(1-naphtyl)-*P*-(phenyl)-phosphinamide Borane (24): A 1.0 M solution of 1-bromonaphthyl (23.4 mmol) in diethyl ether was cooled to -78 °C and a solution of *tert*-butyllithium (31 ml, 46.8 mmol) was added dropwise. The opaque mixture was stirred 15 min at -78 °C, warmed to 0 °C and stirred for an additional 35 min. An orange, opaque mixture of *o*-naphthyllithium was produced. The lithium reagent was added dropwise via syringe to a solution of **39** (3.81 g, 13.4 mmol) in 9 ml tetrahydrofuran and a brown precipitate formed. The mixture was stirred 30 min at -78 °C, then warmed to 0 °C and stirred for an additional 2 h. The precipitate dissolved upon warming. 100 ml H_2O and 50 ml diethyl ether were added and the phases separated. The aqueous phase was extracted with 3×40 ml diethyl ether. The combined organic layers were washed with 2×120 ml brine and dried with Na_2SO_4, before concentrating under vacuum to yield a yellow oil. Purification by flash chromatography (5-40% ethyl acetate in petroleum ether, silica gel) yielded **24** as a white solid (3.98 g, 9.6 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.63 - 7.26 (m, 14H), 5.01 (t, J = 3.7 Hz, 1H), 4.60 - 4.35 (m, 1H), 2.62 (t, J_{HP}= 8.1 Hz, 3H), 1.79 (s, 1H), 1.72 - 0.83 (m, 3H), 1.29 (d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.66 (s), 134.16 (d, J_{CP} = 8.0 Hz), 133.48 (d, J_{CP} = 11.3 Hz), 132.85 (d, J_{CP}= 7.5 Hz), 132.50 (d, J_{CP} = 2.4 Hz), 132.32 (d, J_{CP} = 10.1 Hz), 131.01 (d, J_{CP} = 2.3 Hz), 128.96 (d, J_{CP} = 1.4 Hz), 128.66 (s), 128.56 (s), 128.47 (s), 127.61 (s), 127.37 (d, J_{CP}= 5.6 Hz), 126.88 (s), 126.45 (s), 126.33 (s), 126.17 (s), 124.75 (d, J_{CP}= 10.5 Hz), 79.27 (d, J_{CP} = 2.6 Hz), 58.24 (d, J_{CP}= 10.4 Hz), 31.59 (d, J_{CP}= 3.4 Hz), 11.69 (d, J_{CP}= 4.3 Hz).

(*R*)-Methyl-[(2-biphenylyl)phenyl]phosphinite Borane (26) To a solution of **23** (2.27 g, 5.17 mmol) in methanol (52.5 ml), concentrated H_2SO_4 (0.35 ml) was added. The solution was

stirred at ambient temperature for 18 h. Then 20 ml H_2O and 47 ml dichloromethane was added and the phases separated. The aqueous phase was extracted with 3×25 ml dichloromethane. The combined organic layers were washed with 2×60 ml brine and dried with Na_2SO_4 before concentrating under vacuum to yield **26** as a white solid (1.189 g, 3.88 mmol, yield 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddd, J=12.6, 7.6, 1.4 Hz, 1H), 7.60 - 7.05 (m, 11H), 6.96 - 6.86 (m, 2H), 3.56 (dd, J_{HP}=12.0 Hz, 0.5, 3H), 1.32 - 0.47 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.75 (d, J_{CP}=7.4 Hz), 140.45 (d, J_{CP}=3.3 Hz), 133.62 (d, J_{CP}=14.9 Hz), 131.76 (d, J_{CP}=7.7 Hz), 131.63 (d, J_{CP}=2.3 Hz), 131.19 (d, J_{CP}=2.6 Hz), 131.01 (d, J_{CP}=11.4 Hz), 130.00 (s), 129.66 (s), 129.37 (s), 128.18 (d, J_{CP}=10.8 Hz), 127.33 (s), 127.27 (s), 127.14 (d, J_{CP}=11.3 Hz), 53.73 (d, J_{CP}=2.3 Hz).

(*R*)-Methyl-[(1-naphthyl)phenyl]phosphinite Borane (27) Concentrated H_2SO_4 (0.35 ml) was added to a solution of **24** (3.88 g, 9.4 mmol) in methanol (100 ml). The solution was stirred at ambient temperature for 17 h. Then 60 ml H_2O and 100 ml dichloromethane was added and the phases separated. The aqueous phase was extracted with 3×50 ml dichloromethane. The combined organic layers were washed with 2×120 ml saturated Na_2CO_3(aq) and dried with Na_2SO_4 before concentrating under vacuum to yield **27** as a pale yellow solid (2.22 g, 7.94 mmol, yield 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, J=15.1, 7.1 Hz, 1H), 8.19 - 7.85 (m, 3H), 7.85 - 7.26 (m, 8H), 3.78 (d, J_{HP}=12.2 Hz, 3H), 1.62 - 0.79 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.42 (d, J_{CP}=17.1 Hz), 133.92 (d, J_{CP}=2.4 Hz), 133.86 (s), 132.77 (d, J_{CP}=5.1 Hz), 132.66 (s), 131.99 (s), 131.77 (d, J_{CP}=2.4 Hz), 131.03 (d, J_{CP}=11.2 Hz), 129.25 (d, J_{CP}=0.9 Hz), 128.77 (d, J_{CP}=10.6 Hz), 127.29 (s), 126.97 (s), 126.46 (d, J_{CP}=6.2 Hz), 124.91 (d, J_{CP}=13.7 Hz), 54.16 (d, J_{CP}=2.6 Hz).

(*S*)-Methyl(2-biphenylyl)phenylphosphine Borane (29) A solution of **26** (1.122 g, 3.66 mmol) in tetrahydrofuran (3.8 ml) was cooled to -78 °C. Methyllithium (3.66 ml, 7.32 mmol) was added dropwise. The solution was stirred at -78 °C for 30 min, then warmed to 0 °C and stirred for another 50 min. Then 20 ml H_2O and 20 ml diethyl ether were added and the phases separated. The aqueous phase was extracted with 3×8 ml diethyl ether. The combined organic layers were washed with 2×50 ml brine and dried with Na_2SO_4 before concentrating under vacuum. Purification by flash chromatography (5-40% ethyl acetate in petroleum ether, silica gel) yielded **29** as a white solid (0.317 g, 1.09 mmol, 30% yield).

LC-MS (ES+) m/z = 287.2, 328,6 299.6, 277.4.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, J=13.4, 7.6, 1.5 Hz, 1H), 7.56 - 7.42 (m, 2H), 7.42 - 7.34 (m, 1H), 7.34 - 7.18 (m, 5H), 7.14 (t, J=7.7 Hz, 2H), 6.90 (d, J=7.1 Hz, 2H), 1.43 (d, J_{HP}=10.1 Hz, 3H), 1.34 - 0.45 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.02 (d, J_{CP}=3.8 Hz), 140.69 (d, J_{CP}=3.1 Hz), 134.49 (d, J_{CP}=15.3 Hz), 132.77 (s), 132.19 (s), 131.67 (d, J_{CP}=6.8 Hz), 131.30 (d, J_{CP}=9.5 Hz), 131.02 (d, J_{CP}=2.5 Hz), 130.53 (d, J_{CP}=2.4 Hz), 129.64 (s), 128.68 (d, J_{CP}=52.2 Hz), 128.56 (d, J_{CP}=10.1 Hz), 127.70 (d, J_{CP}=1.6 Hz), 127.47 (d, J_{CP}=11.6 Hz), 12.02 (d, J_{CP}=41.1 Hz).

(*S*)-Methyl(1-naphthyl)phenylphosphine Borane (30) A solution of **27** (2.15 g, 7.71 mmol) in tetrahydrofuran (8 ml) was cooled to -78 °C. Methyllithium (11.2 ml, 15.4 mmol)

was added dropwise. The solution was stirred at -78 °C for 30 min, then warmed to 0 °C and stirred for another 45 min. Then 35 ml H_2O and 40 ml diethyl ether were added and the phases separated. The aqueous phase was extracted with 3×15 ml diethyl ether. The combined organic layers were washed with 2×40 ml brine and dried with Na_2SO_4 before concentrating under vacuum. Purification by flash chromatography (5-40% ethyl acetate in petroleum ether, silica gel) yielded **30** as a white solid (1.39 g, 5.26 mmol, 53% yield).

LC-MS (ES+) m/z = 261.3, 302.5, 251.4.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 - 7.98 (m, 2H), 7.92 (dd, J=20.8, 8.4 Hz, 2H), 7.72 - 7.54 (m, 3H), 7.54 - 7.32 (m, 5H), 2.01 (d, J_{HP}=9.9 Hz, 3H), 1.45 - 0.68 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.06 (d, J_{CP}=6.9 Hz), 133.52 (d, J_{CP}=11.0 Hz), 133.01 (d, J_{CP}=2.7 Hz), 131.73 (s), 131.40 (d, J_{CP}=9.6 Hz), 131.18 (s), 131.03 (d, J_{CP}=2.5 Hz), 129.39 (d, J_{CP}=1.0 Hz), 129.05 (d, J_{CP}=10.1 Hz), 126.92 (s), 126.63 (d, J_{CP}=6.7 Hz), 126.40 (s), 125.61 (s), 125.05 (d, J_{CP}=11.9 Hz), 13.01 (d, J_{CP}=40.8 Hz).

(*S*)-Methyl(2-naphthyl)phenylphosphine Borane (31) A solution of **28** (1.65 g, 5.9 mmol) in tetrahydrofuran (6 ml) was cooled to -78 °C. Methyllithium (9.4 ml, 11.8 mmol) was added dropwise. The solution was stirred at -78 °C for 30 min, then warmed to 0 °C and stirred for another 60 min. Then 20 ml H_2O and 10 ml diethyl ether were added and the phases separated. The aqueous phase was extracted with 3×10 ml diethyl ether. The combined organic layers were washed with 2×25 ml brine and dried with Na_2SO_4 before concentrating under vacuum. Purification by flash chromatography (5-40% ethyl acetate in petroleum ether, silica gel) yielded **31** as a white solid (0.911 g, 3.45 mmol, 58% yield).

LC-MS (ES+) m/z = 261.3, 264.4, 251,5, 260.3, 304,4.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J=13.0 Hz, 1H), 8.05 - 7.79 (m, 3H), 7.78 - 7.63 (m, 2H), 7.63 - 7.50 (m, 3H), 7.50 - 7.33 (m, 3H), 1.92 (d, J_{HP}=10.0 Hz, 3H), 1.49 - 0.65 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.37 (d, J_{CP} = 2.0 Hz), 133.50 (d, J_{CP} = 10.9 Hz), 132.79 (d, J_{CP} = 11.6 Hz), 131.90 (s), 131.80 (s), 131.27 (d, J_{CP} = 2.5 Hz), 129.03 (s), 128.93 (s), 128.86 (s), 128.75 (d, J_{CP} = 4.2 Hz), 128.14 (s), 127.92 (d, J_{CP} = 1.0 Hz), 127.11 (d, J_{CP} = 0.7 Hz), 126.87 (d, J_{CP} = 8.6 Hz), 11.98 (d, J_{CP} = 40.2 Hz).

(*S*)-2-[2-Biphenylyl(phenyl)phosphino]acetic acid Borane (32) A solution of **40** (0.296 g, 1.02 mmol) in tetrahydrofuran (12 ml) was cooled to -78 °C. *sec*-Buthyllithium (0.90 ml, 1.12 mmol) was added dropwise and the solution was then stirred at -78 °C for 3 h. CO_2 gas from dry ice was bubbled through the solution while stirring at 0 °C for 2 h. The reaction mixture was transferred to 11 ml HCl (1 M), 10 ml ethyl acetate was added and the phases separated. The aqueous phase was extracted with 2×10 ml ethyl acetate after which the combined organic layers were washed with 4×15 ml saturated Na_2CO_3. Then the pH of the basic phase was lowered to 1 by adding 20 ml concentrated HCl and this aqueous phase was extracted with 4×25 ml ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated under vacuum (0.017 g crude product). The desired product could be identified on crude NMR, though it could not be isolated. From the first organic phase crude starting material (0.216 g) was recovered.

Alternative procedure: Same proportions of reagents, but let CO_2 bubble through reaction mixture at ambient temperature. No product could be identified.

(*S*)-2-[1-Naphthyl(phenyl)phosphino]acetic acid Borane (33) A solution of **30** (1.3 g, 4.94 mmol) in tetrahydrofuran (50 ml) was cooled to -78 °C. *sec*-Buthyllithium (5.5 ml, 6.42 mmol) was added dropwise and the solution was then stirred at -78 °C for 3 h. CO_2 gas from dry ice was bubbled through the solution while stirring at ambient temperature for 2 h. The reaction mixture was transferred to 50 ml HCl (1 M), 50 ml ethyl acetate was added and the phases separated. The aqueous phase was extracted with 3×25 ml ethyl acetate after which the combined organic layers were washed with 5×50 ml saturated Na_2CO_3. Then the pH of the basic phase was lowered to 1 by adding 80 ml concentrated HCl and this aqueous phase was extracted with 5×100 ml ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated under vacuum (0.373 g crude product). Purification by flash chromatography (5-50% ethyl acetate in petroleum ether followed by 0-25% methanol in dichloromethane, silica gel) yielded **33** as a white solid (0.149 g, 0.48 mmol, 9.7% yield). From the first organic phase crude starting material (0.711 g) was recovered.

Alternative procedure 1: Same proportions of reagents but 4 h stirring at -78 °C and 3 h at ambient temperature. From 0.711 g crude starting material 0.111 g crude product was achieved.

Alternative procedure 2: Same proportions of reagents and same procedure as originally, except 3.5 and 2.5 h reaction times and that the acid-base extraction was no performed. Instead 30 ml HCl and 25 ml ethyl acatete was added to the reaction mixture and the phases separated. The aqueous phase was extracted with 3×15 ml ethyl acetate. The combined organic layers were washed with 2×35 ml brine and dried with Na_2SO_4 before concentrating under vacuum. Purifation by gradient flash chromatography yielded **33** as a white solid (0.216 g, 0.70 mmol, 40.5% yield) and **30** (0.110 g).

LC-MS (ES+) m/z = 305.3, 263.2, 235.0, 317.1, 331.3, 277.4.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.38 - 7.78 (m, 4H), 7.78 - 7.24 (m, 8H), 3.55 - 3.35 (m, 2H), 1.56 - 0.80 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.25 (d, J_{CP} = 2.7 Hz), 134.73 (d, J_{CP} = 11.3 Hz), 134.06 (d, J_{CP} = 7.3 Hz), 133.52 (d, J_{CP} = 2.6 Hz), 132.87 (d, J_{CP} = 7.1 Hz), 131.99 (d, J_{CP} = 9.9 Hz), 131.58 (d, J_{CP} = 2.5 Hz), 129.56 (d, J_{CP} = 1.0 Hz), 129.32 (s), 129.11 (d, J_{CP} = 10.4 Hz), 128.77 (s), 127.10 (s), 126.50 (s), 126.43 (s), 125.12 (d, J_{CP} = 12.3 Hz), 123.41 (d, J_{CP} = 52.5 Hz), 34.20 (d, J_{CP} = 29.3 Hz).

(*S*)-2-[2-Naphthyl(phenyl)phosphino]acetic acid Borane (34) A solution of **31** (0.831 g, 3.15 mmol) in tetrahydrofuran (32 ml) was cooled to -78 °C. *sec*-Buthyllithium (2.92 ml, 4.09 mmol) was added dropwise and the solution was then stirred at -78 °C for 4 h. CO_2 gas from gas tube was bubbled through the solution while stirring at ambient temperature for 3 h. The reaction mixture was transferred to 30 ml HCl (1 M), 35 ml ethyl acetate was added and the phases separated. The aqueous phase was extracted with 3×10 ml ethyl acetate after which the combined organic layers were washed with 5×40 ml saturated Na_2CO_3. Then the pH of the basic phase was lowered to 1 by adding 70 ml concentrated HCl and this aqueous phase was extracted with 5×80 ml ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated under vacuum (0.049 g crude product). From the first organic phase crude starting material (0.742 g) was recovered.

Alternate procedure: Same proportions of reagents, 3 and 2 h reaction times. From the recovered starting material 0.055 g crude product was achieved and 0.788 g crude material was recovered from the first organic phase.

After second run the crude material of the first organic phase was purified by flash chromatography (2-30% ethyl acetate in heptane and 2-30% methanol in dichloromethane, silica gel) and it was found that it contained the desired product, though as the sodium salt of the carboxylate anion. **34** was isolated as a white solid (0.419 g, 1.27 mmol, 40% yield over both runs).

LC-MS (ES+) m/z = 235.0, 307.4, 308.6, 249.5, 277.4.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 13.3 Hz, 1H), 7.94 - 7.81 (m, 3H), 7.80 - 7.38 (m, 8H), 3.40 (d, J_{HP} = 10.9 Hz, 2H), 1.73 - 0.57 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.03 (d, J_{CP} = 3.5 Hz), 134.69 (d, J_{CP} = 11.9 Hz), 134.58 (d, J_{CP} = 2.2 Hz), 132.73 (d, J_{CP} = 12.3 Hz), 132.54 (s), 132.44 (s), 131.89 (d, J_{CP} = 2.4 Hz), 129.11 (s), 129.01 (s), 128.92 (d, J_{CP} = 1.1 Hz), 128.83 (s), 128.48 (s), 127.92 (d, J_{CP} = 0.9 Hz), 127.20 (d, J_{CP} = 0.9 Hz), 127.03 (d, J_{CP} = 8.7 Hz), 33.85 (d, J_{CP} = 28.3 Hz).

(*S*)-*N*-[2-((1-Naphthyl)phenylphosphanyl)acetoxy] succinimide Borane (35) **33** (0.111 g, 0.36 mmol) and *N*-hydroxy succinimide (0.084 g, 0.72 mmol) were dissolved in dichloromehtane (3.5 ml). DCC (0.152 g, 0.72 mmol) in dichloromethane (0.9 ml) was added dropwise. The mixture was stirred at ambient temperature for 24 h and then filtered through celite wetted with dichloromethane. The filtrate was concentrated under vacuum. Purification by flash chromatography (20-65% ethyl acetate in petroleum ether, silica gel) yielded 0.031 g white solid containing **35** and contaminants. Unpure yield: 21%.

The reaction was also run with crude starting material and the same reaction conditions. From 0.111 g crude **33** 0.025 g contaminated product was produced.

The reaction was run a third time, yielding **35** and contaminants (0.167 g) as a white solid. Unpure yield: 60%.

(*S*)-*N*-[2-((2-Naphthyl)phenylphosphanyl)acetoxy] succinimide Borane (36) **34** (0.359 g, 1.1 mmol) and *N*-hydroxy succinimide (0.28 g, 2.4 mmol) were dissolved in dichloromehtane (11 ml). DCC (0.50 g, 2.4 mmol) in dichloromethane (1 ml) was added dropwise. The mixture was stirred at ambient temperature for 24 h and then filtered through celite wetted with dichloromethane. The filtrate was concentrated under vacuum. Purification by flash chromatography (7-60% ethyl acetate in heptane, silica gel) yielded 0.291 g white solid containing **36** and contaminants. Unpure yield: 66%.

Alternative synthesis of (*S*)-*N*-[2-((1-Naphthyl)phenylphosphanyl)acetoxy] succinimide Borane (35) **30** (0.072 g, 0.27 mmol) was dissolved in 3 ml THF and cooled to -78 °C. *sec*-Buthyllithium (0.3 ml, 0.35 mmol) was added dropwise and the solution was then stirred at -78 °C for 3 h. N,N'-disuccinimidyl carbonate (0.148 g, 0.55 mmol) was added in solid form to reaction mixture an the formed suspension was stirred at ambient temperature for 1.5 h. Then 7 ml H_2O and 10 ml dichloromethane was added and the phases separated. The aqueous phase was extracted with 3×3 ml dichloromethane. The combined organic layers were washed with 2×10 ml brine and dried with Na_2SO_4 before concentrating under vacuum. Purfication by gradient flash chromatography (7-60% ethyl acetate in heptane, silica gel) only yielded starting material (0.017 g).

Alternative procedure: Same proportions of reagents and procedure, but the carbonylation was performed at 0 °C. The desired product was identified on TLC, but could not be isolated after purification.

(S_p,1*R*,2*R*)-*N*-2-Aminocyclohexyl[2-(1-naphthyl)phenylphosphanyl)]acetamide Borane (*R,R*-37) To a solution of (1*R*,2*R*)-diaminocyclohexane (0.050 g, 0.44 mmol) in dichloromethane (2.2 ml) was added **35** (0.059 g, 0.15 mmol), dissolved in dichloromethane (0.75 ml), in small portions over 1.5 h. The solution was then stirred for an additional 2.5 h at ambient temperature, until TLC (30% ethyl acetate in petroleum ether) showed reaction to be complete. Then 3 ml H_2O was added and the phases separated. The aqueous phase was extracted with 3×3 ml dichloromethane and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (2-20% methanol in dichloromethane, silica gel) yielded (*R,R*)-**37** as a white solid (0.0066 g, 0.016 mmol, 1.6% yield over two steps).

LC-MS (ES+) m/z = 393.5, 278.3, 407.7, 102.3, 149.5, 391.7.

$[\alpha]_D^{20}$ = -5.8 (c 0.005 g/ml)

IR (NaCl, thin film): 3239, 3054, 2934, 2861, 2376, 1650, 1551, 1435. 1327, 1264, 1164, 799, 775, 737, 702 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (dd, J = 15.0, 7.2 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.77 - 7.51 (m, 3H), 7.51 - 7.15 (m, 5H), 3.57 (s, 1H), 3.54 (d, J = 2.2 Hz, 2H), 2.85 - 2.54 (m, 1H), 2.00 (d, J = 13.1 Hz, 1H), 1.66 (dd, J = 40.3, 15.7 Hz, 3H), 1.48 - 0.76 (m, 7H).

^{13}C NMR (101 MHz, CD_3OD) δ 167.55 (s), 135.11 (d, J_{CP}=13.0 Hz), 134.22 (d, J_{CP}=6.9 Hz), 133.20 (d, J_{CP}=2.8 Hz), 132.81 (d, J_{CP}=20.3 Hz), 131.62 (d, J_{CP}=9.9 Hz), 130.99 (d, J_{CP}=2.6 Hz), 129.59 (s), 129.25 (s), 128.99 (s), 128.66 (d, J_{CP}=10.5 Hz), 128.39 (d, J_{CP}=7.2 Hz), 126.47 (s), 126.10 (s), 124.71 (d, J_{CP}=12.9 Hz), 67.53 (s), 54.99 (s), 52.17 (s), 30.92 (s), 30.30 (s), 25.16 (s), 23.91 (d, J_{CP}=44.4 Hz).

^{31}P NMR (162 MHz, CD_3OD) δ 17.06 (s).

(S_p,1*S*,2*S*)-*N*-2-Aminocyclohexyl[2-(1-naphthyl)phenylphosphanyl)]acetamide Borane (*S,S*-37) To a solution of (1*S*,2*S*)-diaminocyclohexane (0.141 g, 1.23 mmol) in dichloromethane (2 ml) was added **35** (0.167 g, 0.41 mmol), dissolved in dichloromethane (6 ml), dropwise over 2 h. The solution was then stirred for an additional 20 h at ambient temperature. Then 10 ml H_2O and 5 ml dichloromethane was added and the phases was separated. The aqueous phase was extracted with 4×3 ml dichloromethane and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (2-30% methanol in dichloromethane, silica gel) yielded (*S,S*)-**37** as a white solid (0.095 g, 0.23 mmol, 33% yield over two steps).

LC-MS (ES+) m/z = 391.8, 277.1, 390.8, 408.6.

$[\alpha]_D^{20}$ = -3.5 (c 0.028 g/ml)

IR (NaCl, thin film): 3259, 3054, 2934, 2859, 2385, 1642, 1546, 1435, 1327, 1266, 1168, 1142, 799, 775, 738, 701 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.51 - 8.33 (m, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.96 - 7.81 (m, 2H), 7.73 - 7.54 (m, 2H), 7.54 - 7.23 (m, 6H), 3.65 - 3.45 (m, 1H), 3.45 - 3.36 (m, 1H), 3.20 (d, J = 0.8 Hz, 1H), 2.57 - 2.36 (m, 1H), 1.98 - 1.77 (m, 1H), 1.77 - 1.48 (m, 3H), 1.47 - 0.86 (m, 7H).

^{13}C NMR (101 MHz, CD_3OD) δ 166.97 (d, J_{CP} = 1.8 Hz), 134.88 (d, J_{CP} = 11.2 Hz), 134.17

(d, J_{CP} = 7.2 Hz), 133.02 (d, J_{CP} = 2.6 Hz), 132.65 (d, J_{CP} = 20.1 Hz), 131.72 (d, J_{CP} = 9.7 Hz), 131.07 (d, J_{CP} = 2.5 Hz), 129.63 (s), 129.23 (s), 128.95 (s), 128.69 (d, J_{CP} = 10.4 Hz), 128.48 (d, J_{CP} = 6.9 Hz), 126.40 (s), 126.07 (s), 124.75 (d, J_{CP} = 12.2 Hz), 54.43 (d, J_{CP} = 6.7 Hz), 54.20 (d, J_{CP} = 6.8 Hz), 36.51 (d, J_{CP} = 17.7 Hz), 32.14 (d, J_{CP} = 7.8 Hz), 31.33 (d, J_{CP} = 11.7 Hz), 24.50 (d, J_{CP} = 2.6 Hz), 24.25 (d, J_{CP} = 4.3 Hz).

^{31}P NMR (162 MHz, CD_3OD) δ 17.47 (s).

(S_p,1*R*,2*R*)-*N*-2-Aminocyclohexyl[2-(2-naphthyl)phenylphosphanyl)]acetamide Borane (*R,R*-38) To a solution of (1*R*,2*R*)-diaminocyclohexane (0.113 g, 0.99 mmol) in dichloromethane (3 ml) was added **36** (0.132 g, 0.33 mmol), dissolved in dichloromethane (5 ml), dropwise over 3 h. The solution was then stirred for an additional 19 h at ambient temperature. Then 7 ml H_2O was added and the phases separated. The aqueous phase was extracted with 3×5 ml dichloromethane and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (2-30% methanol in dichloromethane, silica gel) yielded (*R,R*)-**38** as a white solid (0.063 g, 0.16 mmol, 39% yield over two steps).

LC-MS (ES+) m/z = 391.8, 277.4, 405.9, 407.8.

$[\alpha]_D^{20}$ = -4.4 (c 0.023 g/ml)

IR (NaCl, thin film): 3199, 3056, 2934, 2859, 2377, 1713, 1654, 1546, 1436, 1362, 1267, 1223, 1060, 739, 702 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J_{HP} = 12.8 Hz, 1H), 7.96 - 7.77 (m, 5H), 7.77 - 7.63 (m, 1H), 7.63 - 7.40 (m, 5H), 3.56 - 3.43 (m, 2H), 3.43 - 3.38 (m, 1H), 2.61 - 2.48 (m, 1H), 2.00 - 1.85 (m, 1H), 1.64 (d, J = 15.2 Hz, 3H), 1.49 - 0.71 (m, 7H).

^{13}C NMR (101 MHz, CD_3OD) δ 167.11 (d, J_{CP} = 2.3 Hz), 134.54 (d, J_{CP} = 2.1 Hz), 134.01 (d, J_{CP} = 11.0 Hz), 132.74 (d, J_{CP} = 11.9 Hz), 132.49 (s), 132.39 (s), 131.31 (d, J_{CP} = 2.5 Hz), 128.63 (s), 128.53 (s), 128.34 (s), 128.28 (d, J_{CP} = 9.7 Hz), 128.05 (s), 127.58 (d, J_{CP} = 1.0 Hz), 127.13 (d, J_{CP} = 9.0 Hz), 126.89 (d, J_{CP} = 0.6 Hz), 54.42 (s), 54.11 (s), 31.87 (s), 31.38 (s), 24.29 (d, J_{CP} = 26.9 Hz).

^{31}P NMR (162 MHz, CD_3OD) δ 16.98 (s)

(S_p,1*S*,2*S*)-*N*-2-Aminocyclohexyl[2-(2-naphthyl)phenylphosphanyl)]acetamide Borane (*S,S*-38) To a solution of (1*S*,2*S*)-diaminocyclohexane (0.116 g, 1.02 mmol) in dichloromethane (5.1 ml) was added **36** (0.136 g, 0.34 mmol), dissolved in dichloromethane (1.7 ml), in small portions over 2 h. The solution was then stirred for an additional 20 h at ambient temperature. Then 7 ml H_2O was added and the phases separated. The aqueous phase was extracted with 3×3 ml dichloromethane and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (2-30% methanol in dichloromethane, silica gel) yielded (*S,S*)-**38** as a white solid (0.051 g, 0.13 mmol, 31% yield over two steps).

LC-MS (ES+) m/z = 392.6, 393.4, 277.4, 102.1, 149.6, 407.6.

$[\alpha]_D^{20}$ = -43.5 (c 0.027 g/ml)

IR (NaCl, thin film): 3182, 3056, 2934, 2860, 2381, 1713, 1649, 1546, 1436, 1362, 1267, 1223, 1060, 739, 703 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, J_{HP} = 12.9 Hz, 1H), 7.99 - 7.83 (m, 3H), 7.83 - 7.70 (m, 3H), 7.66 - 7.41 (m, 5H), 3.55 (dd, J = 25.6, 11.9 Hz, 1H), 3.49 - 3.34 (m, 2H), 2.72 - 2.51 (m, 1H), 2.02 - 1.81 (m, 1H), 1.66 (d, J = 12.1 Hz, 3H), 1.50 - 0.70 (m, 7H).

^{13}C NMR (101 MHz, CD_3OD) δ 167.15 (d, J_{CP} = 2.1 Hz), 134.52 (d, J_{CP} = 2.1 Hz), 134.14 (d, J_{CP} = 10.9 Hz), 132.74 (d, J_{CP} = 11.9 Hz), 132.36 (s), 132.26 (s), 131.36 (d, J_{CP} = 2.6 Hz), 128.68 (s), 128.58 (s), 128.36 (s), 128.26 (d, J_{CP} = 9.8 Hz), 128.03 (s), 127.59 (d, J_{CP} = 1.0 Hz), 127.20 (d, J_{CP} = 9.2 Hz), 126.87 (d, J_{CP} = 0.8 Hz), 54.47 (s), 53.71 (s), 31.55 (s), 31.34 (s), 24.23 (d, J_{CP} = 30.9 Hz).

^{31}P NMR (162 MHz, CD_3OD) δ 16.91 (s).