Monodentate secondary phosphine oxides (SPO's), synthesis and application in asymmetric catalysis
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Chapter 3

Synthesis of racemic and enantiopure secondary phosphine oxides (SPO’s)

This chapter describes the synthesis and chiral separation by preparative HPLC of a series of secondary phosphine oxides (SPO’s, phosphinous acids).

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3.1 Synthetic routes to secondary phosphine oxides (SPO’s)

Generally, SPO’s are used as important intermediates for the preparation of phosphorus containing compounds, such as phosphines, tertiary phosphine oxides, phosphoric acids, etc. Due to their importance in synthetic phosphorus chemistry; several methods have been developed for the synthesis of this type of compounds. General methods to prepare SPO’s can be divided as follows:

3.1.1 Symmetrical SPO’s

(A) Grignard addition to phosphites

Most symmetrical SPO’s can be prepared by this route. They can be easily made via Grignard reagents adding to (EtO)2PHO in THF solution at 0 °C. Most symmetrical alkyl or aryl SPO’s, such as Me2PHO (L3.1) and Ph2PHO (L3.2), could be prepared by this method and low to medium yields (20-70%) are obtained after purification (Scheme 3.1).

(B) Hydrolysis reactions; the hydrolysis of P-Cl compounds, phosphorus esters or amides

Symmetrical SPO’s can be made by this method. A few SPO’s like (t-Bu)2PHO, Ph2PHO (L3.2) and (n-C8H17)2PHO could be obtained directly from commercially available phosphorus chlorides (Scheme 3.2). Yields are normally quite good (79-96%) and the products are easy to purify as almost no side-products are formed. Some symmetrical SPO’s such as Me2PHO (L3.1) and Ph2PHO (L3.2) can also be prepared from the hydrolysis of the corresponding phosphorus esters or amides in 70-97% yields (Scheme 3.2).

(B) Hydrolysis reactions; the hydrolysis of P-Cl compounds, phosphorus esters or amides

Several aromatic compounds or Grignard reagents can react with PCl3 followed by hydrolysis to give SPO’s in moderate yields (Scheme 3.3). Some P-X compounds, such as (n-Bu)2PX (X=Br, Cl) can be made via direct halogenation of the secondary phosphine with Br2 or COCl2 in approx. 50% yield at –30 °C. After hydrolysis of the P-halogen compounds, the SPO’s can be easily obtained in high yield (Scheme 3.3).
(C) Direct oxidation of secondary phosphines

Secondary phosphines can be directly oxidized to secondary phosphine oxides (SPO’s) with oxygen or other oxidizing reagents. However, sometimes it is quite difficult to control the oxidation to stop at this stage and the reaction will proceed to phosphoric acids (Scheme 3.4). This oxidation is normally performed in 2-propanol as solvent. $(n$-Bu)$_2$PHO and Ph$_2$PHO (L3.2) could be prepared by this method.8

![Scheme 3.4 Oxidation of secondary phosphines](image)

(D) Reduction of phosphoric acid chlorides

Via the reduction of phosphoric acid chlorides with LiAlH$_4$ at 0 °C, $(n$-C$_6$H$_{13}$)$_2$PHO, $(n$-C$_8$H$_{17}$)$_2$PHO and Ph$_2$PHO (L3.2) were obtained via this method with reasonable yields (53-54%, Scheme 3.5). At more elevated temperatures, side-products, i.e. secondary phosphines are formed. Ph$_2$POCl can also be reduced to Ph$_2$PHO (L3.2) by Mg in THF or Na in toluene in moderate yields.9

![Scheme 3.5 The synthesis of SPO’s by the reduction with LiAlH$_4$](image)

(E) Cleavage of tertiary phosphine oxides

There are a few examples in which symmetrical SPO’s have been prepared via the cleavage of a P-C bond from a tertiary phosphine oxide (Scheme 3.6). With this method, Ph$_2$PHO (L3.2) can be prepared from Ph$_3$PO or ethyl diphenyl phosphine oxide (R = Ph, R’ = Et).

![Scheme 3.6 The cleavage of tertiary phosphine oxides](image)
3.1.2 Unsymmetrical SPO’s

In this thesis, a modified literature procedure reported by Haynes and co-workers\textsuperscript{1b} is used to prepare unsymmetrical SPO’s. In our experiments, Grignard reagents are added to a R’PCI\textsubscript{2} solution at low temperature; the latter conditions are crucial to obtain the desired products. Unsymmetrical SPO’s are obtained via this procedure after hydrolysis of the formed R’R’’PCI. The synthetic route is illustrated below (Scheme 3.7).

\[ \begin{array}{c}
R'PCI_2 \\
\rightarrow \quad 1). \quad R''MgBr \\
\rightarrow \quad 2). \quad H_2O \\
\rightarrow \quad R' \neq R'' \\
\end{array} \]

Scheme 3.7 General synthetic route to unsymmetrical SPO’s

Our goal is to develop easier and more efficient methods to prepare symmetrical and unsymmetrical SPO’s and approaches to resolution to obtain the corresponding enantiopure SPO’s.

3.2 Preparation of symmetrical secondary phosphine oxides (SPO’s)

Two symmetrical SPO’s were prepared by different routes. Me\textsubscript{2}PHO (L3.1) was obtained via the method described in section 3.1.1, route A (Scheme 3.8).

\[
3 \text{MeMgBr} \quad + \quad (\text{EtO})_2\text{POH} \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{H}_2\text{O}} \quad \text{Me}_2\text{POH} \\
\text{59\%} \\
\text{L3.1}
\]

Scheme 3.8 The preparation of Me\textsubscript{2}PHO (L3.1)

The reaction seems simple, but the reaction conditions need to be controlled carefully, otherwise a low yield (<10\%) or even no desired product was obtained. The procedure is performed as follows: 3 eqs. of MeMgBr (2 M solution in Et\textsubscript{2}O) were added slowly to a (EtO\textsubscript{2})\textsubscript{2}PHO solution with ice-bath cooling to keep the temperature below 5 °C. Then the mixture was carefully hydrolyzed using an aq. K\textsubscript{2}CO\textsubscript{3} solution at 0 °C. The product L3.1 was obtained in 59\% yield.

Ph\textsubscript{2}PHO (L3.2) was prepared in high yield simply by the hydrolysis of commercially available Ph\textsubscript{2}PCI (section 3.1.1, route B) and purified by flash column chromatography (SiO\textsubscript{2} / EtOAc) (Scheme 3.9).
In view of the high efficiency of BPE and DuPhos developed by Burk and co-workers as ligands for asymmetric hydrogenation, we wanted to explore the possibility to make a \( \text{C}_2 \)-symmetric phospholane oxide and examine its behavior in asymmetric catalysis (Scheme 3.10).

**Scheme 3.10 Cyclic \( \text{C}_2 \)-symmetric SPO’s**

Toward this type of SPO, several synthetic methods were examined.

1. A method similar to that for the synthesis of DuPhos\(^\text{11}\) (Scheme 3.11)

Initially, the synthetic route for the racemic version of this type of compounds was explored. Thus a model compound \( \text{trans} \) racemic 3.1 with \( R = \text{Me} \) was selected as target. Analogues to the synthetic route of DuPhos and other analogues in the literature, racemic \( \text{trans} \) cyclic phosphine 3.3 was prepared from racemic \( \text{trans} \) cyclic sulfite 3.2, which could be made from racemic \( \text{trans} \) 2,6-hexane diol by a 2-steps procedure developed by Sharpless and co-workers. Lithium was used to reduce the P-Ph bond and the resulting P-Li was protonated to provide \( \text{trans} \) cyclic phosphine 3.4. However, the oxidation of 3.4 with \( \text{O}_2, \text{Br}_2, \text{DMSO} \) and \( \text{H}_2\text{O}_2 \)\(^8\) (30%) did not result in the desired product 3.1. The final product of these oxidations seems to be the corresponding phosphorus acid with considerable amount of unknown by-products.
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Scheme 3.11 First approach to cyclic SPO

Another route involved the addition of a MeLi solution to (TMS)$_3$P$^{12}$ followed by the reaction of the resulting lithium phosphine with racemic trans cyclic sulfate $3.2$. However, none of the desired product $3.4$ was obtained (Scheme 3.12).

Scheme 3.12 TMS phosphine route to cyclic phosphine $3.4$

Also in the reaction of the bis-Grignard reagent derived from dibromide (B3.1) with diethyl phosphite, no desired product $3.1$ was formed. Presumably the reason for the sole formation of mono-substituted product of diethyl phosphite (observed in $^{31}$P NMR) and unknown by-products lies in the difficulty of the formation of the bis-Grignard reagent (Scheme 3.13).

Scheme 3.13 Attempted Grignard addition to $3.1$

(2) Longer route

As the above attempts to synthesize trans $3.1$ failed, we investigate a somewhat longer route. Fiaud and co-workers$^{14}$ reported a synthetic route to chiral phospholane, in which C$_2$-symmetric SPO L3.3 was used as intermediate (Scheme 3.14).

\[
\begin{align*}
\text{(rac.)} \quad R = \text{Me, } 3.5, 45\%; \\
\text{(rac.)} \quad R = \text{Ph, } 3.6, 92\%; \\
\text{(rac.)} \quad R = \text{Me, } 3.7, 77\%; \\
\text{(rac.)} \quad R = \text{Ph, } 3.8, 95\%. \\
\end{align*}
\]
Scheme 3.14 The synthesis of monodentate phosphine with L3.3 as intermediate

The phosphoric amide 3.8 could be prepared in good yield and was then hydrolyzed to the corresponding trans racemic phosphoric acid followed by optical resolution with quinine to obtain enantiopure phosphoric acid L3.9. This was then converted to phosphoryl chloride followed by reduction with DIBAL-H to obtain enantiopure L3.3 (Scheme 3.14). However, we failed to reproduce this procedure to synthesize L3.3. In our hands the reduction of 3.9 with DIBAL-H failed. Using a similar procedure, its methyl analogue, trans phosphoric amide 3.7 was prepared in 55% yield (Scheme 3.14).

With trans amides 3.7 and 3.8 in hand, we tried several procedures to complete the synthesis of 3.1 and L3.3.

1. First, we attempted their reduction on phosphorus atom of trans amides 3.7 and 3.8 to the phosphorus amides (P-N compounds) that subsequently should be quite easily hydrolyzed to the desired products (see section 3.1.1, method B). Several reducing agents, such as DIBAL-H, Red-Al, LiAlH₄, and NaBH₄ were investigated. Either no reaction occurred or the formation of desired products was not observed. Raney-Ni is known to have the ability to reduce the P=S(OH) bond to give SPO’s.¹⁵ However, Raney-Ni reduction of thiophosphoric amides 3.10 (trans, racemic), which can be easily made from 3.8 (trans, racemic) with P₂S₅, only produced alkane 3.11. This might be due to the hydrogenolysis of thiophosphoric amide 3.10 with Raney-Ni (Scheme 3.15).

Scheme 3.15 Raney-Ni reduction of thiophosphoric amides 3.10

With its methyl analogue 3.7, this reaction seemed to be successful. However, after hydrolysis, only 10% of desired product 3.1 was obtained.

(2) A somewhat better alternative was the hydrolysis of 3.8 to the corresponding phosphoric acid 3.9, which was then converted into the phosphoryl chloride. Subsequent reduction with SmI₂ provided the product L3.3. However, the yield was low (approx. 10%) with SmI₂ as reducing reagent. Optimization of the reaction conditions (the use of
Synthesis of racemic and enantiomeric pure secondary phosphine oxides (SPO’s)

dry reagents, lowering of the temperature to 0°C and long reaction time) did not improve
the yield (Scheme 3.16).

![Scheme 3.16 Hydrolysis of 3.8 and reduction of its phosphoric acid chloride](image)

With trans amide 3.7 (R = Me), this procedure didn’t work at all. Other reducing reagents
such as LiAlH₄, Red-Al, Mg/I₂, DIBAL-H, Li-PBPH (lithium perhydro-9b-boraphenalyl
hydride, 0.5 M in THF) and LiB[CH₂CH(CH₃)₂]₃H were also tried, but no desired product
could be isolated. On the contrary, with model compound Ph₂POCl (from Ph₂POOH and
SO₂Cl₂) using a similar procedure, the reaction was quite successful and gave Ph₂PHO
(L3.2) in reasonable yield (45%).

(3). Direct reduction to secondary phosphines followed by oxidation to final product L3.3.
Besides general reducing reagents, silicon-containing reagents were tried. Fortunately,
PhSiH₃ or Si₂Cl₆ turned out to be quite efficient reducing agents for trans amide 3.8.
Finally the C₂-symmetrical SPO trans L3.3 was made successfully by this method in 36%
yield see experimental part for detail (Scheme 3.17).

![Scheme 3.17 The preparation of C₂-symmetrical SPO L3.3](image)

### 3.3 Preparation of unsymmetrical secondary phosphine oxides (SPO’s)

Several unsymmetrical SPO’s L3.4-L3.11, L3.14, L3.16 (Figure 3.1) have been prepared
with the method described in section 3.1.2 in reasonable yields. The addition order of the
Grignard reagents is crucial. The reactions are performed as follows: the Grignard reagent
is added to the RPCl₂ solution at –20 °C followed by hydrolysis.

![L3.4](image) ![L3.5](image) ![L3.6](image) ![L3.7](image)
The phosphorus dichloride compounds used in these experiments are PhPCl₂, t-BuPCl₂, and (mesityl)PCl₂ (3.12), respectively. The former two are commercially available, and 3.12 can be made according to reported procedure starting from mesityl bromide and n-BuLi followed by the addition to the PCl₃ solution at –78 °C (Scheme 3.18).

![Structures of unsymmetrical SPO’s](image)

**Figure 3.1** Structures of unsymmetrical SPO’s

An attempt to synthesize 2-naphthyl-PCl₂ (3.13) via a Friedel-Crafts reaction was not very successful. When naphthalene reacted with AlCl₃ and PCl₃, substitution at the α- and β-positions took place in almost equal amounts. It was not possible to separate the mixture of isomeric SPO’s L3.6 and L3.6a that were obtained after the Grignard addition and hydrolysis (Scheme 3.19). Through an alternative approach, ligand L3.6 was synthesized successfully via the addition of 2-naphthyl magnesium bromide to t-BuPCl₂, followed by hydrolysis. Details will be described in the experimental part.
Ligands L3.4, L3.5, L3.10, L3.14, L3.16 were prepared by adding t-BuMgCl, i-PrMgCl, 2-naphthyl magnesium bromide, 2-methoxyphenyl magnesium bromide and the Grignard prepared from 3.14 \([3-(diphenylphosphino)phenyl] magnesium bromide\) to a PhPCl₂ solution, respectively. The products were then hydrolyzed and purified by vacuum distillation or flash column chromatography (SiO₂, EtOAc) (Scheme 3.20, 3.21). The addition order in this procedure is crucial for getting the right products. When PhPCl₂ was added to the corresponding Grignard reagents, double addition products, namely, tertiary phosphine oxides were found as the major products. One exception to this rule is the bulky t-BuMgCl; for this reagent the addition order was unimportant. L3.4 was synthesized in high yields without any problem. The fact that only single addition occurs is most probably due to the steric hindrance of the Grignard reagent.

\[
\text{Scheme 3.20 General procedure for the synthesis of ligands L3.4, L3.5, L3.10, L3.14}
\]

L3.4, R = t-butyl, 86%; L3.5, R = i-propyl, 36%; L3.10, R = 2-naphthyl, 35%; L3.14, R = 2-methoxy-phenyl, 29%

L3.6a

L3.6

L3.6

L3.16

Scheme 3.19 Attempt to the synthesis of 3.13 (2-naphthyl-PCl₂) and L3.6

48
Ligand L3.9 was prepared using a similar procedure involving the addition of t-BuMgCl to a solution of 3.12 followed by hydrolysis. Ligands L3.6-L3.8, L3.11 were prepared using various Grignard reagents like 2-naphthyl; 2-methoxy-phenyl; 3, 5-dimethylphenyl and the Grignard prepared from 3.15 \{[2-(diphenylphosphino)phenyl] magnesium bromide\}, which were added to a t-BuPCl₂ solution at –20 °C, followed by hydrolysis and purified by flash column chromatography (SiO₂, EtOAc) (Scheme 3.22, 3.23). The addition order in this procedure is also crucial for getting the right products. If the addition order is reversed, double addition adducts, namely, tertiary phosphine oxides were found as major products.

\[
\begin{align*}
\text{Br} & \quad \text{R} & \quad \text{Mg} & \quad \text{MgBr} & \quad \text{t-BuPCl} \quad \text{L3.6, R=2-naphthyl, 14%; L3.7, R=2-methoxy-phenyl, 68%; L3.8, R=3,5-dimethyl, 65%}
\end{align*}
\]

Scheme 3.22 General procedure for the synthesis of ligands L3.6-L3.8

The successful preparation of intermediate 3.14 with n-BuLi and Ph₂PCl (see scheme 3.21) prompted us to attempt a similar procedure for the synthesis of intermediate 3.15. However, the reaction failed to give any desired product. The phosphine 3.15 was synthesized successfully by making the Grignard reagent from 1,2-dibromobenzene, followed by the addition to a PhPCl₂ solution at –20 °C (Scheme 3.23).

\[
\begin{align*}
\text{Br} & \quad \text{Br} & \quad \text{PPh}_{2} & \quad \text{P} & \quad \text{O} & \quad \text{H} & \quad \text{t-Bu}
\end{align*}
\]

Scheme 3.23 Synthetic route to ligand L3.11

For comparison purposes, some other ligands were also synthesized in order to compare with the SPO’s in various catalytic reactions (see chapter 5 and 6). Phosphite ligand L3.12 was prepared from (R,R)-Taddol and PCl₃, followed by hydrolysis according to a literature procedure. Ligand L3.13 was prepared from R-Binol and Ph₂PCl according to the literature (Figure 3.2).²¹
A sulfur analogue compound of SPO’s **L3.17** was prepared from **L3.4** with P$_2$S$_5$ in toluene in good yield according to a similar procedure reported in literature (Scheme 3.24). The disadvantage of this method is that enantiopure compounds cannot be used, as racemization occurs during the reaction and the final product is partially racemized (66% e.e. of the product was found with enantiopure starting material). Michalski and co-workers$^{23}$ reported a 3-steps procedure by which enantiopure **L3.17** could be prepared from (S)-(−)-**L3.4** with full retention of configuration (Scheme 3.24). However, attempts to repeat this procedure with racemic and enantiopure **L3.4** to prepare **L3.17** failed. The last two steps didn’t work; only the thiophosphoric acid **3.16** was left after reaction.

Compounds **L3.15**, **L3.18** were actually isolated as side-products in the attempts to synthesize pyridine-based ligands **L3.20** and **L3.21**, respectively. We have found that pyridine can be successfully used as additive in Ir-catalyzed asymmetric imine hydrogenation using enantiopure SPO’s as ligands.$^{24}$ It was found that in these reactions pyridine not only acts as a base but also as an extra ligand coordinating with the metal center (details see chapter 5). Pyridine-based SPO’s such as **L3.19**, **L3.20** and **L3.21** (Figure 3.3), which can coordinate with metals as bidentate ligands, were therefore considered to be particularly interesting ligands (Scheme 3.25). We decided to attempt
their synthesis using a similar synthetic route as shown in schemes 3.20 and 3.22.

\[ \text{Scheme 3.25 Possible coordination of Ir with “pyridine-based SPO’s”} \]

As a test reaction, we first tried to make \textbf{L3.20} using similar methods as shown in scheme 3.20 which involve the addition of 2-pyridyl magnesium bromide to a PhPCl\(_2\) solution at –20 °C. However, no desired product \textbf{L3.20} was found. Instead, the double addition products pyridine containing phosphine \textbf{L3.15} and the corresponding oxide \textbf{3.17} could be isolated as major products. A similar reaction was observed when we attempted to prepare \textbf{L3.21} (see figure 3.3) with 2- pyridyl methyllithium (prepared from α-picoline and \(n\)-BuLi). Tertiary phosphine oxide (\textbf{L3.18}) was found as the only product instead of the desired product \textbf{L3.21} (Scheme 3.26). The isolation of phosphine oxide \textbf{L3.18} instead of the phosphine under this condition taking no precaution to prevent oxidation is understandable, as it is expected that the initial formed bis-alkylphosphine will be highly sensitive towards oxidation.

\[ \text{Scheme 3.26 Synthesis of L3.15, 3.17 and L3.18 (Figure 3.2)} \]
Upon replacing the Grignard reagents with lithium reagents, similar results were obtained. It has to be mentioned that even using exactly equal amounts of Grignard reagents and PhPCl$_2$, the results are still the same. Presumably, the strong coordination of the pyridine moiety to the Grignard or lithium reagents directs the attack preferentially at the pyridine containing electrophile instead of PhPCl$_2$ (Scheme 3.27).

![Scheme 3.27 Proposed mechanism of reaction shown in scheme 3.26](image)

### 3.4 Resolution of secondary phosphine oxides (SPO’s)

After the successful synthesis of all racemic ligands, their enantiopure forms could be obtained by preparative HPLC or classic resolution. Racemic ligand **L3.4** ($t$-butyl phenyl phosphine oxide)$^{25}$ was easy to separate on an AD column ($n$-heptane/2-propanol = 90/10) due to the large difference in the retention time of the two enantiomers (up to 20 g scale with automatic injection overnight) (Figure 3.4).
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Figure 3.4 Separation of L3.4 with preparative HPLC (AD, n-heptane/2-propanol = 90/10)

Both enantiomers can be obtained with e.e. >99% in 40%-45% yields. In the literature, the classical resolution with mandelic acid has also been described.\textsuperscript{26} However, it was found later that the results of classical resolution with mandelic acid or other resolving reagents were not reproducible by the same group.\textsuperscript{26b} Haynes and coworkers reported another procedure via a 3-steps resolution on a large scale (up to 100 g), which was done by the oxidation of the racemic L3.4 with S\textsubscript{8} to thiophosphoric acid 3.16, followed by the resolution thereof with chiral amines and subsequently by de-sulfurization with Raney-Ni to provide enantiopure L3.4.\textsuperscript{1b}

Other ligands L3.3 and L3.5-L3.11 could also be separated by preparative HPLC, although the separations were not always as effective as that of ligand L3.4. All separations were performed on a preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.). Both enantiomers could be separated with e.e.>99% in most cases. After resolution, the e.e.’s of these ligands were checked by analytical HPLC.

Some ligands, like L3.14 and L3.17, could not be separated by preparative HPLC on the AD column. However, they could be separated by analytical HPLC on an OD column. As no preparative OD column was available, we were unable to obtain the enantiomers in reasonable quantities using the HPLC method.

Due to non favorable geometry (need to bend the phenyl ring in order to coordinate to metal in bidentate way) of ligand L3.16 (two phosphorus atoms in meta position) when coordinating with a metal, its separation was not performed by preparative HPLC.

3.5 Conclusions

In summary, several symmetrical (L3.1 and L3.2) and unsymmetrical SPO’s (L3.3-L3.11, L3.14 and L3.16) as well as other non-SPO type ligands (L3.12-L3.13, L3.15 and L3.17-L3.18) were prepared in reasonable yields. In the reaction, the addition order is crucial for the preparation of SPO’s. The Grignard reagents should be added to the RPCl\textsubscript{2} solution at –20 °C and not the other way around, as otherwise the double addition products tertiary phosphine oxides were observed, and in some cases even as major products. The corresponding enantiopure forms of most unsymmetrical SPO’s except L3.14 (no
separation on AD column) and \textbf{L3.16} were resolved by preparative chiral HPLC. Attempts to the synthesis of pyridine-based SPO’s \textbf{L3.19-L.21} failed and tertiary phosphine (\textbf{L3.15}) and phosphine oxide (\textbf{3.17} and \textbf{L3.18}) were isolated as major products.

### 3.6 Experiment section

**General conditions:**

Reagents were purchased from Aldrich, Acros, Fluka, Merck, Strem and used as received without any further purification unless stated otherwise. Most solvents were analytical grade and purified according to standard procedures, if necessary. $^1$H NMR (300 MHz), $^{13}$C NMR (75.4 MHz) and $^{31}$P NMR (75 MHz) spectra were recorded on a Varian VXR-300 spectrometer in CDCl$_3$. Chemical shifts were recorded in $\delta$ units (ppm) relative to the residue deuterated solvent signals of CHCl$_3$ ($^1$H: 7.25 ppm, $^{13}$C: 77.0 ppm). Coupling constants are recorded in Hertz (Hz). Melting points were measured on a Büchi B-545 melting apparatus. Optical rotations were measured on a Perkin Elmer 241 polarimeter at ambient temperature. Mass spectra were measured on an AEI-MS-902 mass spectrometer by A. Kiewiet using electron impact ionization (EI, 70 eV) or chemical ionization (CI). The enantiomeric excess (e.e.) of the ligands were measured by analytical HPLC (Daicel, chiralpak AD or OD column, $n$-heptane/2-propanol, 95/5 or 90/10).

**Dimethyl phosphine oxide (L3.1)**

In a 250 ml 3-necked flask, was placed (EtO)$_2$PHO (20 mmol, 2.6 ml) and freshly distilled dry Et$_2$O (20 ml). A solution of MeMgBr (3 M in Et$_2$O, 5 ml, 60 mmol) was added slowly at 0°C. After addition, the mixture was allowed to warm to RT and stirred overnight. A solution of aq. K$_2$CO$_3$ (60 mmol, 8.28 g) in 10 ml of ice-cold water was added to the reaction mixture, followed by filtration. After washing with 20 ml of EtOH and removing the solvent, the residue was re-dissolved in 30 ml of CHCl$_3$, 4 Å molecular sieves (10 g) were added and the mixture was stirred for 3 h then filtered and after removal of the solvent, a light yellow oil remained. The residue was further purified by vacuum distillation at 40-41 °C/1 Torr. (lit.$^{27}$ 65-67 °C/ 6 Torr.) to provide \textbf{L3.1$^{27}$} as colorless oil, which solidified at 0°C. Isolated yield 59% (0.92 g, 11.8 mmol). The spectral data were in accordance with the literature. $^1$H NMR (CDCl$_3$) $\delta$ 0.32 (dd, $J = 0.7, 3.7$ Hz, 3H, CH$_3$), 0.39 (dd, $J = 0.7, 3.7$ Hz, 3H, CH$_3$), 5.87 (dq, $J = 3.7, 7.3, 460.2$ Hz, 1H, P-H). $^{13}$C NMR (CDCl$_3$) $\delta$ 14.20, 12.85. $^{31}$P NMR (CDCl$_3$) $\delta$ 18.91 (s). In C$_6$D$_6$ $\delta$ 14.98 (s).

**Diphenyl phosphine oxide (L3.2)**

Prepared from Ph$_2$PCl (50 mmol, 9.1 ml), THF (20 ml) and H$_2$O (20 ml) at 0 °C for 1 h. After work-up and removal of the solvent, the residue was purified by flash column
chromatography (SiO$_2$, EtOAC) to give L3.2 as a colorless sticky oil, which solidified at 0°C. Isolated yield 87% (8.8 g, 43.5 mmol). The spectral data were in accordance with the literature.$^5$ $^1$H NMR (CDCl$_3$) $\delta$ 7.38-7.59 (m, 6H), 7.62-7.69 (m, 4H), 8.00 (d, $J_{P-H}$ = 481.2 Hz, 1H, P-H). $^{13}$C NMR (CDCl$_3$) $\delta$ 130.98, 130.93, 130.62, 129.07, 128.85, 128.61, 127.39, 127.13. $^{31}$P NMR (CDCl$_3$) $\delta$ 21.14 (s).

After 6 months in the air at RT, some sugar-like crystalline compound had formed in the sticky oil. Inspection of its $^1$H NMR and $^{31}$P NMR revealed that the typical P-H peak had disappeared, no P-H coupling could be observed and the $^{31}$P NMR signal had shifted to low field, which means the acid Ph$_2$POOH had formed. $^1$H NMR (CDCl$_3$) $\delta$ 7.29-7.54 (m, 6H), 7.66-7.78 (m, 4H), 10.94 (s, 1H, POOH). $^{31}$P NMR (CDCl$_3$) $\delta$ 32.46. The spectral data were in accordance with the authentic sample from Acros.

**trans-2,5-Dimethyl-1-phenylphospholane (3.3)**

This compound was prepared using a similar procedure as reported for DuPhos.

In a 100 ml double Schlenk vessel, was placed PhPH$_2$ (3 mmol, 4.8 ml, 10% wt% in n-hexane); the solution was cooled to 0°C and a solution of n-BuLi (1.6 M in n-hexane, 3.6 mmol, 2.25 ml) was added dropwise via syringe. The pale yellow solution was allowed to stir for 1 h at 0°C. To the resulting mixture was then slowly added a THF solution (10 ml) of racemic trans cyclic sulfite 3.2$^{28}$ (3 mmol, 0.54 g). After the solution was stirred for 2 h, n-BuLi (1.6 M in n-hexane, 3.6 mmol, 2.25 ml) was added again in a similar way. The mixture was allowed to stir for 1.5 h, after which 3 ml of MeOH was added to quench the remaining excess n-BuLi. The resulting colorless mixture was concentrated and extracted with 100 ml pentane under N$_2$ and filtered. The solvent was removed to yield racemic trans 3.3$^{11}$ as a colorless sticky oil. Isolated yield 71% (0.4 g, 2.1 mmol). The spectral data were in accordance with the literature. $^1$H NMR (CDCl$_3$) $\delta$ 0.73 (dd, $J = 7.0$, 11.0 Hz, 3H, CH$_3$), 0.81-0.97 (m, 2H, CH$_2$), 1.27(dd, $J = 7.0$, 18.7 Hz, 3H, CH$_3$), 1.87-1.96 (m, 1H, CH), 2.12-2.31 (m, 2H, CH$_2$), 2.62-2.70 (m, 1H, CH), 7.21-7.29 (m, 3H), 7.42-7.66 (m, 2H). $^{31}$P NMR (CDCl$_3$) $\delta$ 10.18 (s) (lit. 10.0).

The compound was then re-dissolved in 30 ml dry THF and transferred to another 100 ml double Schlenk vessel. Under argon, Li powder (0.5 g, 30% in mineral oil, 70 mmol, excess) was added and the mixture stirred at RT overnight. The mixture was then hydrolyzed carefully with Na$_2$SO$_4$.10H$_2$O, filtered and the solvent was removed to give a light yellow oil, $^{31}$P NMR (CDCl$_3$) $\delta$ -174.7 (In C$_6$D$_6$, -28.9). When the NMR tube was left open in the air for 1 d, a complicated $^{31}$P NMR spectrum was found and no major product could be identified.
1-(Dimethylamino)-2,5-diphenyl-2,5-dihydro-1H-1λ5-phosphol-1-one (3.6)

In a 100 ml Schlenk flask, was placed AlCl₃ (52 mmol, 7 g) and dry DCM (20 ml). After stirring for 30 min at RT under N₂, the solution was cooled to –30 °C. A solution of (CH₃)₂NPCl₂ (35 mmol, 4 ml) and dry DCM (5 ml) was added to this mixture. After 1 h, the solution was allowed to warm to RT, which resulted in the formation of a slightly yellow turbid solution. It was then cooled to –20 °C, and 1,4-diphenyl-1,3-butadiene (35 mmol, 7.2 g) in DCM (10 ml) was slowly added. After addition, a green solution was formed which then slowly turned into dark-red. The solution was allowed to warm to RT overnight. ³¹P NMR (CDCl₃) δ 111.62 (s, phosphorium chloride salt). It was then slowly poured into an ice-cold saturated aq. EDTA:NaHCO₃ = 30:30 ml solution. After 6 h at 0 °C, the solution was allowed to warm to RT, extracted with 3 x 50 ml DCM, washed with brine (3 x 50 ml) and dried over MgSO₄. After filtration and removing the solvent under vacuum, 3.6 was obtained as yellow oil. Isolated yield 92% over two steps (9.6 g, 32.2 mmol). The spectral data were in accordance with the literature.

trans-1-(Dimethylamino)-2,5-dimethyl-1λ5-phospholan-1-one (3.7)

Using a similar procedure, starting from 2,4-hexadiene [mixture of (2E,4E) and (2E,4Z), 1.35 g, 15 mmol] and (CH₃)₂NPCl₂ (1.7 ml, 15 mmol). 3.5 was obtained as light yellow sticky oil. Isolated yield 45% over 2 steps (1.2 g, 6.75 mmol). ¹H NMR (CDCl₃) δ 0.97 (d, J = 7.3 Hz, 3H, CH₃), 1.05 (d, J = 7.3 Hz, 3H, CH₃), 2.49 (s, 3H, CH₃), 2.53 (s, 3H, CH₃), 2.58-2.67 (m, 2H, 2CH), 5.52 (d, J = 1.5 Hz, 1H, =CH), 5.65 (d, J = 1.2 Hz, 1H, =CH). ¹³C NMR (CDCl₃) δ 142.60, 142.13, 33.12, 31.54, 28.35, 28.07, 11.71, 11.65. ³¹P NMR (CDCl₃) δ 76.92 (s). After reduction with 10% Pd/C at 50 bar H₂ in DCM followed by treatment with MeONa in MeOH, the saturated trans 3.7 was isolated as colorless oil. Isolated yield 77% over 2 steps (0.9 g, 5.2 mmol). ¹H NMR (CDCl₃) δ 1.11 (d, J = 7.0 Hz, 3H, CH₃), 1.47-1.53 (m, 2H), 1.98-2.09 (m, 4H), 2.67 (s, 3H, CH₃), 3.50 (s, 3H, CH₃). ¹³C NMR (CDCl₃) δ 35.10, 35.04, 33.12, 31.54, 28.35, 28.07, 11.71, 11.65. ³¹P NMR (CDCl₃) δ 71.74 (s).

trans-1-(Dimethylamino)-2,5-diphenyl-1λ5-phospholan-1-one (3.8)

Compound 3.6 (9.6 g, 32.2 mmol) was dissolved in DCM (30 ml) and hydrogenated using 10% Pd/C at 15 bar H₂. After 16 h, the solid was filtered off and washed with DCM (20 ml).
The solvent was removed under vacuum. The residue was purified by flash column chromatography (SiO$_2$, $n$-hexane:EtOAc, 1:1) to provide 3.8 as off-white solid. Isolated yield 95% (9.15 g, 30.6 mmol). The spectral data were in accordance with the literature. $^1$H NMR (CDCl$_3$) $\delta$ 1.79 (s, 3H, CH$_3$), 1.82 (s, 3H, CH$_3$), 2.46-2.52 (m, 4H, 2CH$_2$), 3.56-3.67 (m, 2H, 2CH), 7.19-7.31 (m, 10H). $^{13}$C NMR (CDCl$_3$) 135.12 (d, $J$ = 2.5 Hz), 126.87, 125.41, 125.33, 124.84, 124.36, 123.31, 123.71, 25.26, 25.01. $^{31}$P NMR (CDCl$_3$) $\delta$ 67.18 (s).

After treatment with MeONa in MeOH overnight, the trans compound of 3.8 was obtained as off-white powder in nearly quantitative yield. $^{31}$P NMR (CDCl$_3$) $\delta$ 61.17.

**trans-1-Hydroxy-2,5-diphenyl-1$\lambda^5$-phospholan-1-one (3.9)**

Trans 3.8 (0.59 g, 1.97 mmol) was hydrolyzed with 6 N aq. HCl (20 ml) under reflux overnight. After work-up and removing the solvents, the residue was further purified by flash column chromatography (SiO$_2$, CHCl$_3$: MeOH, 9:1) to give 3.9 as light yellow powder. Isolated yield 78% (0.42 g, 1.54 mmol). The spectral data were in accordance with the literature. m.p. 198-201 ºC (dec.). (lit. 227-228 ºC). $^1$H NMR (CD$_3$OD) $\delta$ 1.13-1.139 (m, 1H), 2.14-2.51 (m, 3H), 3.20-3.35 (m, 1H, CH), 3.43-3.67 (m, 1H, CH), 7.11 (d, $J_{P-H}$ = 471.5 Hz, 1H, P-H), 7.30-7.39 (m, 10H). $^{13}$C NMR (CD$_3$OD) $\delta$ 138.08 (d, $J$ = 4.9 Hz), 136.10, 135.49, 133.80, 127.08, 126.69, 126.41, 125.68, 125.02, 124.14, 44.12, 42.27, 32.70, 28.01. $^{31}$P NMR (CD$_3$OD) $\delta$ 59.75 (s). MS (EI$^+$) 273 (M+1), 272 (M), 271 (M-1), 206, 205, 168, 129, 117, 105, 104 (100 %), 103, 91, 78, 77, 65, 51. HRMS (EI$^+$) M$^+$ for C$_{16}$H$_{17}$O$_2$P, found 272.0957, calcd. 272.0966.

**2,5-Di-phenyl-2,5-dihydro-1H-$1\lambda^5$-phosphol-1-one (L3.3)**

Trans 3.8 (0.6 mmol, 0.18 g) was dissolved in 15 ml of dry toluene; to this solution was added Si$_2$Cl$_6$ (0.62 mmol, 0.14 ml). The solution was heated to reflux overnight under air, the solvent was removed and the residue was purified by flash column chromatography (SiO$_2$, EtOAc) to give L3.3 as white crystals. Isolated yield 36% (55.3 mg, 0.22 mmol). The spectral data were in accordance with the literature.$^{14}$ $^1$H NMR (CDCl$_3$) $\delta$ 1.87-2.20 (m, 1H), 2.22-2.67 (m, 3H), 3.20-3.35 (m, 1H, CH), 3.43-3.67 (m, 1H, CH), 7.11 (d, $J_{P,H} = 471.5$ Hz, 1H, P-H), 7.30-7.39 (m, 10H). $^{13}$C NMR (CDCl$_3$) $\delta$ 134.92 (d, $J = 3.4$ Hz), 133.76 (d, $J = 6.1$ Hz), 127.75, 127.64, 127.28, 127.13, 126.91, 126.09, 125.91(d, $J = 3.0$ Hz), 125.75 (d, $J = 2.4$ Hz), 47.20 (d, $J_{P,C} = 60.3$ Hz), 43.78 (d, $J_{P,C} = 59.9$ Hz), 31.48 (d, $J = 7.3$ Hz), 26.97 (d, $J = 11.1$ Hz). $^{31}$P NMR (CDCl$_3$) $\delta$ 54.05 (s). MS (EI$^+$) 273 (M+1), 256 (M, 100%), 255 (M-1), 207, 206, 152, 151, 139, 138, 134, 131, 129, 117, 105, 104, 91, 78, 77, 65, 51. HRMS (EI$^+$) M$^+$ for C$_{16}$H$_{17}$OP, found 256.1009, calcd. 256.1017.

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, $n$-heptane/2-propanol = 75/25, t$_1$
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= 10.5 min, \( t_2 = 13.1 \) min.

**General procedure for the synthesis of L3.4, L3.5, L3.10, L3.14, L3.16 (Scheme 3.20-3.21)**

In a 500 ml 3-necked round flask under N\(_2\) were placed Mg turnings and freshly distilled dry THF (100 ml). A solution of \( t\)-BuCl (for L3.4), 2-bromo-1-naphthalene (for L3.10), 2-methoxy-phenyl bromide (for L3.14) and 3.14 \{[3-(diphenylphosphino) phenyl] bromide\} (for L3.16) in 100 ml dry THF was added via a dropping funnel. After the reaction starts, the addition was continued slowly to maintain a gentle reflux during approx. 40 min. After addition, the solution was kept refluxing for 2 h under N\(_2\). Then the freshly prepared Grignard reagent was cooled and added slowly to a solution of PhPCl\(_2\) in 80 ml THF via a double-ended needle at -20 °C. After addition, the solution was allowed to warm to RT and heated to reflux for 3 h. The solution was cooled to 0 °C and 50 ml of H\(_2\)O was added followed by 2 M aq. HCl (20 ml). The mixture was extracted with Et\(_2\)O (3 x 100 ml). The combined organic layers were washed with saturated aq. NaHCO\(_3\) (3 x 50 ml) and brine (3 x 50 ml), dried over MgSO\(_4\) and filtered. The solvent was removed under vacuum and the residue was further purified by vacuum distillation or flash column chromatography (SiO\(_2\), EtOAc).

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.) with \( n\)-hexane/ethanol or \( n\)-heptane/2-propanol as eluents.

**tert-Butyl(oxo)phenylphosphorane (L3.4)**\(^{1b}\)

Prepared from \( t\)-BuCl (0.55 mol, 60 ml), Mg turnings (0.558 mol, 13.4 g) and PhPCl\(_2\) (0.54 mol, 73 ml). After work-up and remove all the solvent, the residue was purified by vacuum distillation 110-120 °C/0.8 Torr (lit.\(^{1b}\) bp 110 °C/0.8 Torr.) to give L3.4\(^{1b}\) as colorless oil, which solidified upon standing to a white semi-solid. Isolated yield 86% (83.7 g, 0.46 mol). The spectral data were in accordance with the literature.\(^{1b}\) \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.08 (dd, \( J_{C-H} = 1.2 \) Hz, \( J_{P-CH} = 16.6 \) Hz, 9H, CH\(_3\)), 6.98 (d, \( J_{P-H} = 454.6 \) Hz), 7.38-7.67 (m, 5H). \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 130.74, 129.16, 128.96, 126.83 (d, \( J = 90.0 \) Hz), 126.82, 126.59, 30.01 (d, \( J = 69.4 \) Hz), 21.59. \(^{31}\)P NMR (CDCl\(_3\)) \( \delta \) 47.32 (s). MS (EI \(^{+}\)) 183 (M\(^+\)), 182 (M), 181 (M-1), 149, 126, 109, 108, 91, 83, 80, 79 (100%), 77, 57, 51, 48 HRMS (EI \(^{+}\)) M\(^+\) for C\(_{10}\)H\(_{15}\)OP, found 182.0871, calcld. 182.0861.

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, \( n\)-heptane/2-propanol = 90/10, \( t_1 \) = 11.0 min, mp 73-75 °C, \([\alpha]_D = -33.5^\circ \text{ (c = 0.251, CHCl}_3\)\), \([\alpha]_D = -32.45^\circ \text{ (c = 1.20, CHCl}_3\)\), \( t_2 \) = 15.3 min, mp 75-77 °C, \([\alpha]_D = +29.5^\circ \text{ (c = 0.305, CHCl}_3\)\)

After 8-12 months at RT, most of L3.4 (up to 80%) self-disproportionated to the
phosphoric acid. In the refrigerator, this process was much slower than at RT and only 10% of phosphoric acid was found. This observation was based on $^{31}\text{P}$ and $^1\text{H}$ NMR. $^1\text{H}$ NMR (CDCl$_3$) δ 1.04 (d, $J = 15.9$ Hz, 9H, 3CH$_3$), 7.32-7.68 (m, 3H), 7.70-7.78 (m, 2H), 11.83 (s, 1H, POOH). $^{31}\text{P}$ NMR (CDCl$_3$) δ 52.77 (s). MS (EI$^+$) 199 (M+1), 198 (M, 24%), 143, 142 (100%), 78, 77, 57, 51.

Isopropyl(oxo)phenylphosphorane (L3.5)
Prepared from $i$-PrMgCl (2 M solution in THF, 20 mmol, 10 ml) and PhPCl$_2$ (32 mmol, 4.5 ml). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO$_2$, EtOAc) to give L3.5 as a colorless oil. Isolated yield 36% (1.2 g, 7.2 mmol). $^1\text{H}$ NMR (CDCl$_3$) δ 1.08-1.24 (dd, $J = 6.1$, 6.6, 6.8 Hz, 6H, 2CH$_3$), 2.03-2.22 (m, 1H), 7.22 (dd, $J = 2.2$, 458.3 Hz, 1H), 7.31-7.74 (m, 5H). $^{13}\text{C}$ NMR (CDCl$_3$) δ 129.81, 127.71, 127.56, 126.50 (d, $J = 94.0$ Hz), 126.12, 125.96, 25.70 (d, $J = 69.6$ Hz), 12.34, 11.76. $^{31}\text{P}$ NMR (CDCl$_3$) δ 39.38 (s). MS (EI$^+$) 168 (M), 167 (M-1), 126, 125, 124, 79 (100%), 77, 51, 47. HRMS (EI$^+$) M$^+$ for C$_9$H$_{13}$OP, found 168.0726, cal. 168.0704.
The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, n-hexane/ethanol = 92.5 /7.5, $t_1$ = 15.1 min, $[\alpha]_D = -14.4^\circ$ (c = 0.25, CHCl$_3$), $t_2$ = 17.3 min, $[\alpha]_D = +11.2^\circ$ (c = 0.285, CHCl$_3$). Both enantiomers are colorless sticky oils.

Diisopropyl(phenyl)phosphine oxide (3.18)
PhPCl$_2$ (65 mmol, 8.82 ml) in THF (50 ml) was added slowly to a solution of $i$-PrMgCl (2 M in THF, 60 mmol, 30 ml) at −20 °C. The solution was allowed to warm to RT and stirred overnight. After work-up and removal of the solvent, the residue was further purified by vacuum distillation (112 °C/ 0.04 Torr.) to give 3.18 as a colorless oil. Isolated yield 55% (6.9 g, 33 mmol). $^1\text{H}$ NMR (CDCl$_3$) δ 0.98 (dd, $J = 7.3$, 16.1 Hz, 6H, 2CH$_3$), 1.13 (dd, $J = 7.3$, 15.0 Hz, 6H, 2CH$_3$), 2.18-2.31 (m, 1H, CH), 7.22-7.46 (m, 3H), 7.58-7.64 (m, 2H). $^{13}\text{C}$ NMR (CDCl$_3$) δ 130.12, 129.97, 126.87, 126.66, 28.19, 24.28, 22.94, 14.47, 13.43. $^{31}\text{P}$ NMR (CDCl$_3$) δ 50.65 (s). MS (EI$^+$) 211 (M+1), 210 (M, 16%), 169, 168 (100%), 167, 140, 126, 125, 109, 105, 91, 79, 77, 44.

2-Naphthyl(oxo)phenylphosphorane (L3.10)
Prepared from 2-bromo-naphthalene (24 mmol, 5.04 g), Mg turnings (50 mmol, 1.2 g) and PhPCl$_2$ (26 mmol, 3.5 ml). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO$_2$, EtOAc) to give L3.10 as a white solid. Isolated yield 35% (2.1 g, 8.4 mmol). $^1\text{H}$ NMR (CDCl$_3$) δ 6.85-7.01 (m, 5H), 6.85, 7.01 (m, 5H), 7.22, 7.22 (dd, $J = 7.3$, 15.0 Hz, 6H, 2CH$_3$), 2.18-2.31 (m, 1H, CH), 7.22-7.46 (m, 3H), 7.58-7.64 (m, 2H). $^{13}\text{C}$ NMR (CDCl$_3$) δ 130.12, 129.97, 126.87, 126.66, 28.19, 24.28, 22.94, 14.47, 13.43. $^{31}\text{P}$ NMR (CDCl$_3$) δ 50.65 (s). MS (EI$^+$) 211 (M+1), 210 (M, 16%), 169, 168 (100%), 167, 140, 126, 125, 109, 105, 91, 79, 77, 44.
Synthesis of racemic and enantiomeric pure secondary phosphine oxides (SPO’s)

7.01-7.35 (m, 6H), 7.72 (d, J_P,H = 483.2 Hz, 1H), 7.90 (d, J = 15.6 Hz, 1H). 13C NMR (CDCl₃) δ 133.07 (d, J_P,C = 2.3 Hz), 130.92, 130.71, 130.43, 128.91, 128.68, 127.74, 127.19, 126.94, 126.88, 126.57, 126.12, 125.73, 125.33, 123.31, 123.07. 31P NMR (CDCl₃) δ 20.28 (s). MS (EI+) 253 (M+1), 252 (M), 251 (M-1, 100%), 233, 205, 202, 173, 128, 127, 77. HRMS (EI+), M⁺ for C₁₆H₁₃OP, found 252.0692, calcd. 252.0704.

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, n-hexane/2-propanol = 56/44, t₁ = 22.4 min, mp 73-75 °C, [α]D= -5.2 ° (c = 0.27, CHCl₃), t₂ = 26.9 min, mp 81-83 °C, [α]D = +6.0 ° (c = 0.25, CHCl₃) (lit. 30 mp 184-186 °C, [α]D = -0.59 °, in the literature, these data might be for the corresponding phosphoric acid).

Di(2-naphthyl)phenylphosphine oxide (3.19)

PhPCl₂ (27 mmol, 3.7 ml) in THF (20 ml) was added slowly to 2-naphthylMgBr [prepared from 2-bromo-1-naphthalene (24 mmol, 5.02 g) and Mg turnings (50 mmol, 1.2 g)] at –20 °C. The solution was allowed to warm to RT and stirred overnight. After work-up and removal of the solvent to give 3.19 as a white semi-solid. Isolated yield 30% (2.7 g, 7.2 mmol). The spectral data were in accordance with the literature. 1H NMR (CDCl₃) δ 7.42-7.94 (m, 17H), 8.29 (d, J = 0.7 Hz, 1H), 8.36 (d, J = 0.7 Hz, 1H). 31P NMR (CDCl₃) δ 29.18 (s). MS (EI+) 379 (M+1), 378 (M), 377 (M-1, 100), 376, 328, 254, 252, 251, 250, 249, 235, 233, 220, 202, 189, 188, 173, 157, 128, 127, 78, 77, 51.

Di(2-Methoxyphenyl)(oxo)phenylphosphorane (L3.14)

Prepared from 2-methoxy-1-bromo-benzene (52 mmol, 6.5 ml), Mg turnings (65 mmol, 1.56 g) and PhPCl₂ (50 mmol, 6.8 ml). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc) to give L3.14 as a white solid. Isolated yield 29% (3.4 g, 14.5 mmol). The spectral data were in accordance with the literature. mp 97-99 °C (some impurity in the sample, lit. 105-106 °C). 1H NMR (CDCl₃) δ 3.76 (s, 3H, OCH₃), 6.90 (d, J = 13.9 Hz, 1H), 7.05-7.12 (m, 1H), 7.39-7.67 (m, 4H), 7.71-7.83 (m, 3H), 8.15 (d, J_P,H = 501.0 Hz, 1H, P-H). 13C NMR (CDCl₃) δ 158.91, 158.84 (d, J = 3.4 Hz), 132.99, 131.19, 131.06, 130.49, 129.94, 128.82, 128.59, 127.01, 126.74, 119.50, 119.26, 118.03, 115.99, 109.34, 109.22, 53.86. 31P NMR (CDCl₃) δ 14.36 (s). MS (EI+) 233 (M+1), 232 (M), 231 (M-1), 214, 213, 203, 201, 199, 196, 183, 167, 141, 91, 78, 77, 47. HRMS (EI+), M⁺ for C₁₃H₁₃O₂P, found 232.0650, calcd. 232.0653.

We were unable to separate L3.14 on preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.) with different solvents combination. It could only be separated on an analytical HPLC column (Daicel, chiralpak OD column, 250 x 4.6 mm i.d.), flow rate 1 ml/min, 220 nm, gradient eluent n-heptane/2-propanol = 90/10 to 75/25, t₁ =16.5 min, t₂ =
21.0 min. However, a preparative OD column for HPLC was not available.

**tert-Butyl[3-(diphenylphosphino)phenyl]oxophosphorane (L3.16)**

In a 250 ml 3-necked round flask, was placed 1,3-dibromo-benzene (50 mmol, 6.1 ml) in dry THF (50 ml). The mixture was cooled to −78 °C and a solution of n-BuLi (1.6 M in n-hexane, 51 mmol, 32 ml) was added. This temperature was maintained for 1 h, and subsequently a solution of Ph₂PCl (50 mmol, 9.1 ml) in 50 ml of THF was added slowly. The solution was allowed to come to RT and 50 ml of water was added followed by extraction with Et₂O (3 x 100 ml). The ether layer was washed with brine (3 x 50 ml) and dried over MgSO₄. After removal of the solvent, the residue was purified by flash column chromatography [SiO₂, petroleum ether (40-60 °C):Et₂O, 1:1] to give 3.14 as a yellow sticky oil. Isolated yield 89% (15.1 g, 44.5 mmol).

The spectral data were in accordance with the literature. ¹H NMR (CDCl₃) δ 7.05-7.89 (m, 14H). ¹³C NMR (CDCl₃) δ 139.09 (d, J=15.6 Hz), 134.94, 134.73, 134.32, 132.54, 132.15, 130.85, 130.47, 130.25, 128.67, 128.53, 127.64, 127.31, 127.17, 126.41, 126.26, 121.73, 121.59. ³¹P NMR (CDCl₃) δ −5.15 (s). MS (EI⁺) 342, 341 (M+1), 340 (M, 100%), 339 (M-1), 261, 185, 184, 183, 152, 108, 107, 91, 79, 77, 65.

Prepared from 3.14 (6 mmol, 2.1 g), Mg turnings (12 mmol, 0.4 g) and PhPCl₂ (7 mmol, 1.0 ml). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc) to give L3.16 as colorless sticky oil. Isolated yield 30% (0.69 g, 1.8 mmol). ¹H NMR (CDCl₃) δ 7.20-7.78 (m, 19H), 7.94 (d, Jₚ-H= 483.4 Hz, 1H, P-H). ¹³C NMR (CDCl₃) δ 139.09 (d, J= 15.6 Hz), 134.54, 134.35, 134.32, 132.54, 132.15, 130.85, 130.47, 130.25, 128.67, 128.53, 128.27, 127.64, 127.31, 127.17, 126.41, 126.26. ³¹P NMR (CDCl₃) δ −5.78 (s), 20.92 (s). MS (EI⁺) 388, 387 (M+1), 386 (M, 100%), 385 (M-1), 259, 257, 185, 184, 183, 154, 108, 107, 77. HRMS (EI⁺) M⁺ for C₂₄H₂₀OP₂, calcd. 386.0989, found 386.0987.

**General procedure for the synthesis of L3.6-L3.9, L3.11 (Scheme 3.22-3.23)**

In a 250 ml 3-necked round bottom flask under N₂ were placed Mg turnings and freshly distilled dry THF (50 ml). A solution of 2-bromo-1-naphthalene (for L3.6), t-BuCl (for L3.9), 2-methoxy-1-bromo-benzene (for L3.7), 3, 5-dimethy-1-bromo-benzene (for L3.8), 3.15 {[2-(diphenylphosphino) phenyl] bromide} (for L3.11) in 50 ml of dry THF was added via a dropping funnel. After the reaction starts, the remaining solution was slowly added to maintain gentle reflux (40 min). After the addition was complete, heating at reflux was continued for 2 h under N₂. Then the freshly prepared Grignard reagents were cooled and added slowly to a solution of t-BuPCl₂ or 3.12 (mesityl-PCl₂) (for L3.9) in 50 ml of THF via a canula at -20 °C. After addition was complete, the solution was allowed to warm to RT and heated to reflux for 3 h to go to completion. After cooling to 0 °C, 50 ml of H₂O
followed by 2 M HCl (20 ml) were added slowly to dissolve some magnesium salts. After extraction with Et₂O (3 x 100 ml), the combined organic layers were washed with saturated NaHCO₃ (3 x 50 ml) and brine (3 x 50 ml), dried over MgSO₄ and the solvent was removed under vacuum. The residue was further purified by flash column chromatography (SiO₂, EtOAc).

The ligands were separated into their enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.) with n-hexane/ethanol or n-heptane/2-propanol as eluents.

**tert-Butyl(2-naphthyl)oxophosphorane (L3.6)**

Prepared from 2-bromo-1-naphthalene (85 mmol, 17.6 g), Mg turnings (100 mmol, 2.4 g) and t-BuPCl₂ (72 mmol, 11.5 g). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc) to give L3.6 as a white powder. Isolated yield 14% (2.34 g, 10.1 mmol).

1H NMR (CDCl₃) δ 1.18 (d, J = 16.6 Hz, 9H, 3CH₃), 7.17 (d, Jₚ-H = 453.9 Hz, 1H), 7.55-7.71 (m, 4H), 7.86-7.96 (m, 3H), 8.24 (d, J = 14.4 Hz).

13C NMR (CDCl₃) δ 133.54 (d, Jₚ-C = 12.6 Hz), 131.37, 130.65, 127.17, 126.72, 126.40, 125.54, 124.23, 124.02, 123.51, 30.72 (d, Jₚ-C = 69.1 Hz), 21.96.

31P NMR (CDCl₃) δ 47.03 (s). MS (EI+) 233 (M+1), 232 (M), 176, 130, 129, 128, 127, 77, 47. HRMS (EI+) M⁺ for C₁₄H₁₇OP, found 232.1012, calcd. 232.1017.

When t-BuPCl₂ was added to 2-naphthyl-MgBr solution at –20 °C, only about 15% based on 31P NMR of the desired product was found in the crude mixture after work-up.

**tert-Butyl(2-methoxyphenyl)oxophosphorane (L3.7)**

Prepared from 2-methoxy-1-bromo-benzene (63 mmol, 7.85 ml), Mg turnings (100 mmol, 2.4 g) and t-BuPCl₂ (62.9 mmol, 10.0 g). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc) to give L3.7 as a colorless oil. Isolated yield 68% (9.1 g, 42.8 mmol).

1H NMR (CDCl₃) δ 1.15 (d, J = 17.1 Hz, 9H, 3CH₃), 3.83 (s, 3H, OCH₃), 7.36 (d, Jₚ-H = 484.4 Hz), 7.36 (d, 1H, P-H, Jₚ-H = 484.4 Hz), 7.36-7.51 (m, 1H), 7.63-7.73 (m, 1H). 13C NMR (CDCl₃) δ 159.35 (d, J = 4.2 Hz), 132.45, 132.42, 131.90, 131.79, 119.35, 119.35, 119.14, 116.61 (d, J = 118.3 Hz), 115.31 (d, J = 90.4 Hz), 109.18, 109.05, 53.71, 32.18 (d, J = 56.5 Hz), 30.92 (d, Jₚ-C = 71.0 Hz), 22.80, 22.09, 22.06. 31P NMR (CDCl₃) δ 35.58 (s). MS (EI⁺) 233 (M+1), 212 (M), 156, 155, 149, 141, 139, 138, 137, 125, 109 (100%), 107, 94, 91, 79, 77, 65, 57, 51, 47. HRMS (EI⁺) M⁺ for C₁₄H₁₇O₂P, found 212.0979, calcd. 212.0966.
The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, n-hexane/ethanol = 67/33, $t_1 = 4.0$ min, $[\alpha]_D = -15.1^\circ$ (c = 0.35, CHCl$_3$), $t_2 = 5.9$ min, $[\alpha]_D = +11.8^\circ$ (c = 0.365, CHCl$_3$). Both enantiomers are colorless sticky oils.

**tert-Butyl(3,5-dimethylphenyl)oxophosphorane (L3.8)**

Prepared from 3, 5-dimethyl-1-bromo-benzene (63 mmol, 8.6 ml), Mg turnings (2.4 g, 100 mmol) and t-BuPCl$_2$ (62.9 mmol, 10.0 g). After work-up and removal of the solvent, the residue was purified by flash column chromatography [SiO$_2$, petroleum ether (40-60 °C):EtOAc, 1:1] to give L3.8 as a white solid. Isolated yield 65% (8.6 g, 40.9 mmol).

$^1$H NMR (CDCl$_3$) δ 1.13 (d, $J = 16.6$ Hz, 9H, 3CH$_3$), 2.35 (s, 6H, 2CH$_3$), 6.95 (d, $J_{P-H} = 452.4$ Hz, 1H, P-H), 7.17 (s, 1H, CH), 7.28 (s, 1H, CH), 7.22 (s, 1H, CH).

$^{13}$C NMR (CDCl$_3$) δ 136.65 (d, $J_{P-C} = 12.6$ Hz), 132.77, 127.30, 127.01, 126.79, 125.49, 30.24 (d, $J_{P-C} = 69.1$ Hz), 21.87, 21.84, 19.62. 

$^{31}$P NMR (CDCl$_3$) δ 47.76 (s). MS (EI$^+$) M$^+$ for C$_{12}$H$_{19}$OP, found 210.1183, calcd. 210.1174.

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, n-hexane/ethanol = 92.5/7.5, $t_1 = 7.2$ min, mp 144-147 °C, $[\alpha]_D = +9.4^\circ$ (c = 0.265, CHCl$_3$), $t_2 = 17.3$ min, mp 136-138 °C, $[\alpha]_D = -9.8^\circ$ (c = 0.275, CHCl$_3$).

**tert-Butyl(mesityl)oxophosphorane (L3.9)**

In a 250 ml 3-necked round flask, 2-bromomesitylene (50 mmol, 7.7 ml) in 20 ml of dry Et$_2$O was cooled to −20 °C and a solution of n-BuLi (1.6 M in n-hexane, 60 mmol, 37.5 ml) was added under N$_2$. After addition, the solution was allowed to warm to RT and heated to reflux for 3 h and cooled to −78 °C. A solution of PCl$_3$ (65 mmol, 5.8 ml) in 30 ml of Et$_2$O was added via a dropping funnel in 40 min. After addition, the solution was allowed to warm to RT overnight. The solvent was removed under vacuum and the desired product was purified by vacuum distillation 90-95 °C / 0.07 Torr. (lit.$^{33,34}$ 80 °C / 0.03 Torr.) to give 3.12$^{33,34}$ as a colorless sticky oil. Isolated yield 81% (40.5 mmol, 8.95 g). The spectral data were in accordance with the literature.$^{33,34}$ 

$^1$H NMR (CDCl$_3$) δ 6.92 (s, 1H, CH), 6.90 (s, 1H, CH), 2.73 (s, 3H, CH$_3$), 2.71 (s, 3H, CH$_3$), 2.37 (s, 3H, CH$_3$). $^{31}$P NMR (CDCl$_3$) δ 160.97 (s). (lit.$^{34}$ 161.0).

Compound 3.12 (40.5 mmol, 8.95 g) was immediately dissolved in 50 ml of dry THF under N$_2$ and a preformed solution of t-BuMgCl in THF [prepared from t-BuCl (60 mmol, 6.5 ml) and Mg turnings (80 mmol, 1.92 g)] was added in 30 min at −20 °C. The solution was allowed to warm to
RT overnight. After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO$_2$, n-hexane:EtOAc, 1:1) to give L3.9 as a colorless oil. Isolated yield 21% over 2 steps (2.35 g, 10.5 mmol). $^1$H NMR (CDCl$_3$) δ 1.16 (d, J$_{P-H}$ = 16.6 Hz, 9H, 3CH$_3$), 2.22 (s, 3H, CH$_3$), 2.49 (br, 6H, 2CH$_3$), 6.83 (br, 2H, 2CH), 7.55 (d, J$_{P-H}$ = 455.6 Hz, 1H). $^{13}$C NMR (CDCl$_3$) δ 139.79 (d, J$_{P-C}$ = 2.3 Hz), 128.67, 128.12, 120.23 (d, J$_{P-C}$ = 88.1 Hz), 32.70 (d, J$_{P-C}$ = 69.1 Hz), 22.78, 22.72, 20.45, 20.35, 19.12. $^{31}$P NMR (CDCl$_3$) δ 38.16 (s). MS (EI$^+$) 225 (M+1), 224 (M), 223 (M-1), 182, 168 (M-1-t-Bu), 167 (M-t-Bu), 151, 122, 121 (100%), 120, 119, 105, 91, 77, 57. HRMS (EI$^+$) M$^+$ for C$_{13}$H$_{21}$OP, found 224.1341, calcd. 224.1330.

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.), flow rate 20 ml/min, 254 nm, n-heptane/2-propanol = 95/5, $t_1$ = 9.0 min, mp 109.5-112°C, [α]$_D$ = -16.9° (c = 0.255, CHCl$_3$), $t_2$ = 13.7 min, mp 105-107°C, [α]$_D$ = +20.4° (c = 0.275, CHCl$_3$).

tert-Butyl[2-(diphenylphosphino)phenyl]oxophosphorane (L3.11)

In a 250 ml 3-necked round flask, was placed Mg turnings (70 mmol, 1.68 g) and 50 ml of freshly distilled dry THF. A solution of 1,2-dibromo-benzene (50 mmol, 6.0 ml) in dry THF (50 ml) was added via a dropping funnel. After the reaction starts, the addition was continued slowly to maintain gentle reflux (40 min). After the addition was completed, refluxing was continued for 1 h under N$_2$. After cooling to –20°C, a solution of Ph$_2$PCl (50 mmol, 9.1 ml) in 50 ml of THF was slowly added. The temperature was allowed to rise to RT, 50 ml of water was added and the mixture was extracted with Et$_2$O (3 x 100 ml), washed with brine (3 x 50 ml) and dried over MgSO$_4$. After removal of the solvent, the residue was purified by flash column chromatography [SiO$_2$, petroleum ether (40-60 °C):EtOAc, 1:1] to give 3.15$^{35}$ as a yellow sticky oil. Isolated yield 50% (8.5 g, 25 mmol). $^1$H NMR (CDCl$_3$) δ 6.88-6.94 (m, 1H), 7.23-7.51 (m, 12H), 7.71-7.76 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 137.57 (d, J = 11.8 Hz), 135.75, 134.58, 134.37, 133.13, 132.88, 132.79, 132.47, 132.06, 131.64, 128.83, 127.71, 127.43, 127.28, 127.04, 126.76, 126.09, 125.10. $^{31}$P NMR (CDCl$_3$) δ –5.31 (s). MS (EI$^+$) 342 (M+1), 341 (M, 95%), 340 (M-1), 339, 337, 277, 261, 259, 228, 184, 183 (100%), 157, 152, 130, 107, 91, 77, 51.

Prepared from 3.15 (14.7 mmol, 5.0 g), Mg turnings (30 mmol, 0.72 g) and t-BuPCl$_2$ (14 mmol, 2.27 g). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO$_2$, EtOAc) to provide L3.11 as colorless sticky oil. Isolated yield 35% (1.8 g, 4.9 mmol). $^1$H NMR (CDCl$_3$) δ 1.04 (d, J = 16.4 Hz, 9H, 3CH$_3$), 6.93-7.48 (m, 11H), 7.71-7.76 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ 138.99 (m, 1H), 2.79 (dd, J = 5.4, 471.2 Hz, 1H, P-H). $^{31}$P NMR (CDCl$_3$) δ 138.99 (dd, J$_{P-C}$ = 9.2, 29.0 Hz), 133.83 (dd, J = 28.3, 87.4 Hz), 134.22 (d, J = 9.9 Hz), 133.78 (d, J = 11.1 Hz), 133.44, 132.34, 131.96, 131.88, 131.49, 130.36, 127.48,
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127.41, 127.21, 127.07, 31.77 (d, \( J = 68.3 \) Hz), 22.78 (d, \( J = 2.3 \) Hz). \(^{31}\)P NMR (CDCl\(_3\)) \( \delta -16.03 \) (d, \( J_{P-P} = 70.1 \) Hz), 35.87 (d, \( J_{P-P} = 67.8 \) Hz). MS (CI\(^+\)) 384 (M+NH\(_4^+\)), 383 (M-1+NH\(_4^+\)), 368, 367 (M+1, 100%), 338, 325, 309, 278, 277, 248, 225, 200, 183, 147, 85, 64.

The ligand was separated into its enantiomers by preparative HPLC (Daicel, chiralpak AD column, 250 x 20 mm \( i.d. \)), flow rate 20 ml/min, 254 nm, \( n \)-hexane/2-propanol = 85/15, \( t_1 = 5.6 \) min, \( t_2 = 7.7 \) min. Both enantiomers are colorless sticky oils.

\((IR, 7R)\)-9,9-Dimethyl-4-hydrido-4-oxo-2, 6, 6-tetrapheny1-3, 5, 8, 10-tetraoxa-4-phosphabicyclo [5.3.0] decane (L3.12)\(^{36}\)

In a 100 ml Schlenk vessel, was placed \{5-\[hydroxy(diphenyl)methyl\]-2,2–dimethyl-1,3-dioxolan-4-yl(diphenyl)methanol\} (2 mmol, 0.94 g) \((R, R\)-Taddol\) and dry toluene (5 ml). The solution was cooled to \(-78^\circ C\) and PCl\(_3\) (3.0 mmol, 0.26 ml) was added in 20 min. The solution was allowed to warm to RT and stirring was continued for 3 h. The solution was cooled down to 0 \(^\circ\)C and H\(_2\)O (5 ml) was slowly added. After the addition was complete, the solution was allowed to warm to RT and stirred for 30 min. After extraction with CH\(_2\)Cl\(_2\) (3 x 20 ml), washing with brine (3 x 50 ml) and drying over MgSO\(_4\), the solvent was removed. The residue was purified by flash column chromatography (SiO\(_2\), \( n \)-hexane:EtOAc, 1:1) to give \( \text{L3.12} \) as a white powder. Isolated yield 75% (0.77 g, 1.5 mmol). The spectral data were in accordance with the literature. mp 224-226 \(^\circ\)C (dec.), \([\alpha]D = -268.4^\circ \) \( c = 0.275, \text{CHCl}_3 \), \([\alpha]D = -289.9^\circ \), \( c = 1.56, \text{CHCl}_3 \), \(^1\)H NMR (CDCl\(_3\)) \( \delta 0.56 \) (s, 3H, CH\(_3\)), 0.76 (s, 3H, CH\(_3\)), 5.21 (d, \( J = 7.8 \) Hz, 1H, CH), 5.36 (d, \( J = 8.1 \) Hz, 1H, CH), 7.08 (d, \( J_{P-H} = 726.9 \) Hz, 1H, P-H), 7.23-7.46 (m, 16H), 7.56-7.63 (m, 4H). \(^{13}\)C NMR (CDCl\(_3\)) \( \delta 142.15 \) (d), 141.65 (d), 137.66 (d), 137.45 (d), 127.27 (d), 127.00 (d), 126.77 (d), 126.45 (d), 125.95 (d), 125.34 (d), 112.90 (s), 87.31 (s), 87.14 (s), 78.57 (s), 78.30 (s), 75.28 (s), 24.79 (s). \(^{31}\)P NMR (CDCl\(_3\)) \( \delta -4.76 \) (d). MS (CI\(^+\)) 532, 531 (M+1+NH\(_4^+\)), 530 (M+NH\(_4^+\), 100%), 528, 462, 449, 448, 431, 390, 366, 340, 207, 130, 105, 88, 77, 75, 69.


Two different methods were used for the attempted synthesis of L3.19-L3.21. One is the addition of a Grignard reagent to a PhPCl\(_2\) solution at \(-20^\circ C\) (Scheme 3.20). Another one is via the use of lithium reagents, which are added to a PhPCl\(_2\) solution at \(-20^\circ C\), as illustrated below:

In a 250 ml 3-necked round flask under N\(_2\), was placed 2-methyl pyridine or 2-bromo-pyridine and dry THF (50 ml). The mixture was cooled to \(-78^\circ C\) and a solution of \( n \)-BuLi (1.6 M in \( n \)-hexane) was slowly added to form a clear red solution. After the
Synthesis of racemic and enantiomeric pure secondary phosphine oxides (SPO’s)

addition was complete, the solution was allowed to warm to RT for 2 h. It was then cooled and added to the solution of PhPCl₂ in 50 ml of THF at -20 °C. The solution was allowed to warm up to RT overnight. Water (20 ml) was added at 0 °C, the pH was adjusted to >9 with 50% aq. NaOH, followed by extraction with EtOAc (3 x 50 ml), washing with brine (3 x 50 ml) and drying over MgSO₄. After removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc:Et₃N, 90:10). L3.15, L3.18 were isolated as side-products in the attempts to synthesize L3.20-L3.21.

2-[Phenyl(2-pyridinyl)phosphino]pyridine (L3.15) and its oxide 3.17
Prepared from 2-bromo-pyridine (50 mmol, 4.8 ml), Mg turnings (90 mmol, 2.0 g) and PhPCl₂ (60 mmol, 8 ml). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc:Et₃N, 90:10) to give L3.15 as a light yellow cubic crystals. Isolated yield 33% (4.4 g, 16.5 mmol). The spectral data were in accordance with the literature. mp 95-97 °C (lit. 97-98 °C).

\[
\begin{align*}
\text{H NMR (CDCl}_3\text{)} & \delta 7.11-7.26 (m, 4H), 7.33-7.40 (m, 3H), 7.42-7.60 (m, 4H), 8.67-8.71 (m, 2H). \\
\text{C NMR (CDCl}_3\text{)} & \delta 161.47, 161.38, 148.92, 148.68, 134.42, 134.35, 134.29, 133.69, 133.44 (d, J = 98.4 Hz), 133.29, 128.10, 127.35, 127.19, 127.02, 126.67, 120.96. \\
\text{P NMR (CDCl}_3\text{)} & \delta -3.35 (s). \\
\text{MS (EI}^+\text{)} & 265 (M+1), 264 (M), 263 (M-1), 233, 187, 186, 185 (100 %), 184, 157, 109, 107, 79, 78, 77, 51.
\end{align*}
\]

In the reaction, the oxidized product 3.17 was also found and isolated as light brown-yellow solid. Isolated yield 12% (1.65 g, 6 mmol). The spectral data were in accordance with the literature. mp 95-97 °C (lit. 97-98 °C).

\[
\begin{align*}
\text{H NMR (CDCl}_3\text{)} & \delta 7.30-7.51 (m, 5H), 7.67-8.00 (m, 2H), 8.01-8.10 (m, 4H), 8.70-8.72 (m, 2H). \\
\text{C NMR (CDCl}_3\text{)} & \delta 155.57, 152.93, 148.96, 148.57, 134.60, 134.41, 130.96, 130.77, 130.62, 130.57, 128.63 (d, J = 103.4 Hz), 126.84, 126.59, 126.42, 123.93, 123.87. \\
\text{P NMR (CDCl}_3\text{)} & \delta 16.72 (s). \\
\text{MS (EI}^+\text{)} & 281 (M+1), 280 (M), 279 (M-1), 203, 202 (100%), 201, 186, 185, 184, 155, 154, 128, 107, 78, 77, 51.
\end{align*}
\]

Phenyl[bis(2-pyridinylmethyl)]phosphine oxide (L3.18)
Prepared from 2-methyl-pyridine (53.8 mmol, 5.3 ml), n-BuLi (1.6 M in n-hexane, 53.8 mmol, 33.6 ml) and PhPCl₂ (54 mmol, 7.3 ml). After work-up and removal of the solvent, the residue was purified by flash column chromatography (SiO₂, EtOAc:Et₃N, 90:10) to give L3.18 as a light yellow solid. Isolated yield 45% (75 g, 24.2 mmol). mp 102-104 °C.

\[
\begin{align*}
\text{H NMR (CDCl}_3\text{)} & \delta 3.57 (s, 2H, CH₂), 3.64 (s, 2H, CH₂), 6.95-7.20 (m, 2H), 7.22-7.56 (m, 9H), 8.34 (d, J = 4.2 Hz, 2H). \\
\text{C NMR (CDCl}_3\text{)} & \delta 151.23, 151.07, 147.84, 147.81, 134.92, 134.87, 130.23, 129.37, 129.19, 128.41, 126.78, 126.54, 123.37,
\end{align*}
\]
123.29, 120.25, 120.20, 39.52, 38.29. \( ^{31} \text{P NMR} (\text{CDCl}_3) \delta 34.81 \) (s). MS (EI) 309 (M+1), 308 (M, 12.2%), 217, 216 (M-PyCH\(_2\), 100%), 184, 169, 168, 167, 93, 92, 78, 65.

**tert-Butyl(phenyl)thioxophosphorane (L3.17)**\(^{23a}\)

A solution of racemic ligand \( \text{L3.4} (t\text{-BuPhPOH}) \) (0.11 g, 0.6 mmol) and \( \text{P}_2\text{S}_5 \) (30 mg, 0.14 mmol) in dry toluene (10 ml) were stirred at RT overnight, filtered and the solid was washed with toluene (3 x 10 ml). The solvent was removed to give a light yellow oil, which was purified by flash column chromatography [SiO\(_2\), petroleum ether (40-60 °C):Et\(_2\)O, 1:1] to provide \( \text{L3.17}^{23a} \) as a colorless oil which solidified in the refrigerator. Isolated yield 62% (73.7 mg, 0.37 mmol). The spectral data were in accordance with the literature.

\(^{1} \text{H NMR} (\text{CDCl}_3) \delta 0.93 \) (d, \( J = 18.1 \) Hz, 9H, \( 3\text{CH}_3 \)), 6.72 (d, \( J = 444.6 \) Hz, 1H, P-H), 7.11-7.39 (m, 3H), 7.42-7.62 (m, 2H).

\(^{13} \text{C NMR} (\text{CDCl}_3) \delta 130.55, 130.30, 130.09, 127.38, 127.17 \) (d, \( J = 73.6 \) Hz), 126.78, 32.05 (d, \( J = 50.4 \) Hz), 22.99 (d, \( J = 3.1 \) Hz). \(^{31} \text{P NMR} (\text{CDCl}_3) \delta 51.21 \) (s). MS (EI) 199 (M+1), 198 (M), 176, 143, 142, 141, 109, 108, 107, 91, 79 (100%), 77, 63, 57, 51. HRMS (EI) \( \text{M}^+ \) for \( \text{C}_{10}\text{H}_{15}\text{PS} \), calcd. 198.0632, found 198.0628.

Separation of \( \text{L3.17} \) on preparative chiral HPLC (Daicel, chiralpak AD column, 250 x 20 mm i.d.) with different solvents combination was not successful. It could only be separated on an analytical HPLC column (Daicel, chiralpak OD column, 250 x 4.6 mm \( i.d. \)), flow rate 1 ml/min, 220 nm, \( n\)-heptane/2-propanol = 99/1, \( t_1 = 11.5 \) min, \( t_2 = 12.8 \) min. However, no preparative OD column for HPLC is available.

Another route\(^{23} \) starts with \((S)-(-)\text{-L3.4} \) (2 mmol, 0.37 g) and \( \text{S}_8 \) (2.2 mmol, 0.56 g) in toluene (5 ml). After filtration and removal of the solvent, the residue was purified by flash column chromatography (SiO\(_2\), CHCl\(_3\):MeOH, 4:1) to give \( \text{3.16}^{23a} \) as a light yellow solid. Isolated yield 75% (0.32 g, 1.5 mmol). The spectral data were in accordance with the literature.\(^{23a} \) \(^{1} \text{H NMR} (\text{CDCl}_3) \delta 1.05 \) (d, \( J = 17.1 \) Hz, 9H, \( 3\text{CH}_3 \)), 5.11 (br, 1H, OH), 7.35-7.42 (m, 3H), 7.73-7.84 (m, 2H). \(^{31} \text{P NMR} (\text{CDCl}_3) \delta 84.80 \) (s). Subsequently, \( \text{3.16} \) was treated with \((\text{CF}_3\text{SO}_2)\text{O} \) (3.5 mmol, 0.6 ml) in dry DCM (10 ml) at \(-60^\circ\text{C}\) and the solution allowed to warm to RT overnight. CaH\(_2\) was added to destroy excess \((\text{CF}_3\text{SO}_2)\text{O} \) and formed \( \text{CF}_3\text{SO}_2\text{H} \) followed by filtration. Then the residue was dissolved in absolute EtOH (5 ml) and added to \( \text{NaBH}_4 \) (3 mmol, 0.11 g) in 10 ml of absolute EtOH at \(-40^\circ\text{C}\). The solution was allowed to warm to RT overnight. After filtration and removal of the solvent, however, no desired product \( \text{L3.17} \) was present according to \(^{31} \text{P NMR} \) and \(^{1} \text{H NMR} \). The residue was mainly \( \text{3.16} \) accompanied by a by-product with absorption at 97.01 ppm in the \(^{31} \text{P NMR} \) spectrum.

**3.7 Reference and notes**
Synthesis of racemic and enantiomeric pure secondary phosphine oxides (SPO’s)


25 (a) Hoffmann, H; Schellenbeck, P. Chem. Ber. 1966, 99, 1134. (b) See ref. 1b.