A Modular Approach to a New Class of Monodentate Chiral Phosphorus Ligands and Their Application in Enantioselective Copper-Catalysed Conjugate Additions of Diethylzinc to Cyclohexenone

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A new family of chiral phosphorus ligands (**5**) for use in enantioselective catalysis have been synthesised. The ligands contain the electron-poor bis(sulfonyl)diazaphospholidine moiety and possess a highly modular structure which is well suited to the synthesis of a library. A small library (23 members) of ligands **5** was prepared and tested in the enantioselective copper-catalysed conjugate addition of diethylzinc to cyclohexenone. Complete conversions were obtained with enantiomeric excesses (*ee*) of up to 75%.

Introduction

Transition-metal-catalysed asymmetric transformations play an important role in the synthesis of complex organic molecules as well as in the industrial production of fine chemicals.[1] In general, a chiral ligand is used to influence both the reactivity of the metal ion (which can be enhanced or reduced by formation of the metal complex) and direct the stereochemical course of the catalysed reaction. Chiral phosphorus ligands are among the most widely used chiral ligands and have played a major role since the pioneering work of Knowles, Kagan, and Noyori.[2] In particular, both monophosphane and diphosphane ligands have been synthesised, with the latter being the most widely represented and successful of the ligands used in asymmetric catalysis [e.g. 1,4-bis(diphenylphosphanyl)-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol (DIOP), bis[2-methoxyphenyl)phenylphosphanyl]ethane (DIPAMP), and 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene (BINAP), etc.][2] In recent years, however, monophosphorus ligands have received renewed interest, particularly those structures that possess one or more P−heteroatom bonds, such as chiral phosphoramidites,[3,4] phosphonites,[5] phosphites,[6−9] and aminophosphanes.[10] Moreover, the creation of a P−X bond is easier synthetically than that of a P−C bond. Hence, several new and effective ligands that contain O and N substituents on P (e.g. phosphoramidites **1**,[3] phosphonites **2**,[5] phosphites **3**,[6] and **4**,[7] Figure 1) have been reported; these ligands have been successfully applied in a number of metal-catalysed asymmetric transformations.

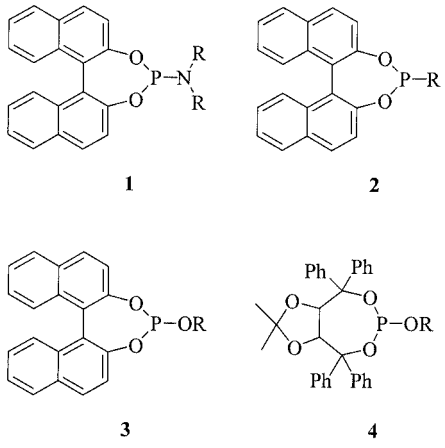

Figure 1. General structures of phosphoramidite **1**, phosphonite **2** and phosphite **3** and **4** ligands

In the search for new ligand structures that can be synthesised through a modular scheme, and that are amenable to combinatorial exploitation,[11] we became interested in bis(sulfonamido)-substituted phosphorus ligands of general structure **5** (Figure 2), where R^3 can be an alcohol, an amine or an aryl substituent. A few ligands structurally related to **5** were recently reported by Hersh,[12] Gimbert,[13] and Pfaltz[14] and their co-workers. In particular, Hilgraf and Pfaltz's chiral bis(sulfonyl)diazaphospholidine−oxazoline ligands proved effective in promoting the pal-

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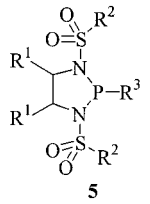
ladium-catalysed asymmetric substitution of allylic acetates with malonate anions with up to 99% enantiomeric excess (*ee*).[14]



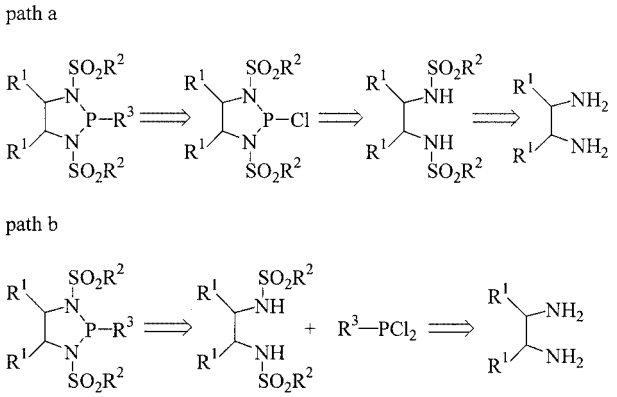
5

Figure 2. General structure of ligands **5**

Here we report the synthesis of a small library of ligands **5** (23 members) and their application in the copper-catalysed asymmetric conjugate addition of Et_2Zn to cyclohexenone.

Results and Discussion

Ligands **5** were chosen since they display several potential sites of diversity (R^1, R^2, R^3) and their synthesis can be readily accomplished through two highly modular synthetic paths (Scheme 1). The structure allows for easy adjustment of steric, electronic and conformational properties, by modification of the sulfonamide (R^2), the P (R^3) and chiral diamine (R^1) substituents. In addition, sulfonamides are strongly electron-withdrawing and should, therefore, substantially affect the π-acceptor and σ-donor ability of the P atom, thereby affecting its ability to form metal complexes, and influencing the stability and catalytic activity of the complexes. As for the stereochemical properties, in the case of a C_2-symmetric diazaphospholidine ring, the P atom is not stereogenic. The P substituents (R^3) can be achiral or chiral; in the latter case, the C_2 symmetry of the ligand is retained only with a C_2-symmetric R^3 group.

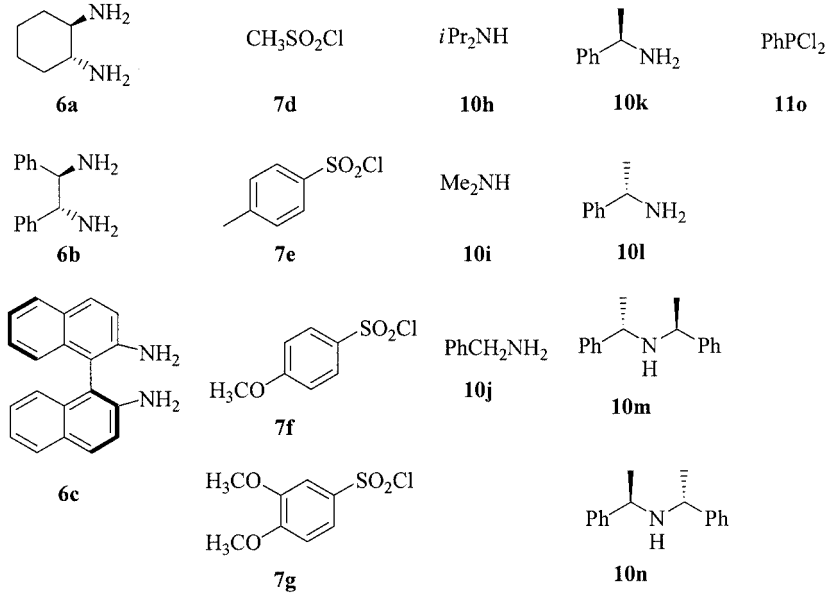


Scheme 1. Synthetic approaches to ligands **5**

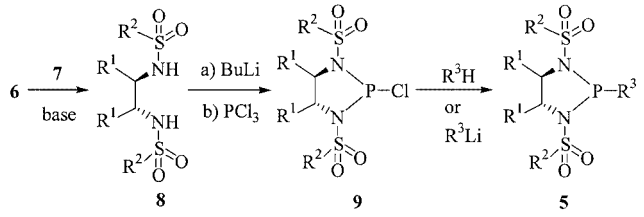
Synthesis of Ligands 5

For the synthesis of ligands **5**, three different diamine backbones were used (Scheme 2), namely (*R*,*R*)-1,2-diaminocyclohexane (**6a**), (*R*,*R*)-1,2-diphenylethylenediamine (**6b**) and (*S*)-1,1′-binaphthyl-2,2′-diamine (**6c**). The sulfonyl groups were thought to play a major role in determining the steric and electronic properties of ligands **5**; for this reason, diamines **6** were treated with a number of sulfonyl chlorides, that is, methanesulfonyl chloride (**7d**), *p*-toluenesulfonyl chloride (**7e**), *p*-methoxybenzenesulfonyl chloride (**7f**), and 3,4-dimethoxybenzenesulfonyl chloride (**7g**).[15] For the R^3 moiety, a phenyl substituent and a variety of chiral and achiral, primary and secondary amines **10h**−**10n** were used.

The synthesis of bis(sulfonamides) **8** was achieved by treating diamines **6** with sulfonyl chlorides **7** under standard conditions (Scheme 3) (see Exp. Sect.).



Scheme 2. Building blocks for the synthesis of the library of ligands **5**

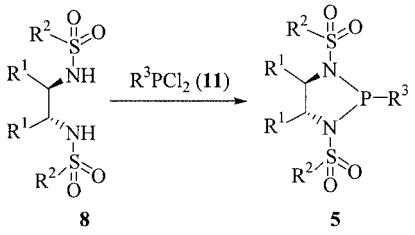


Scheme 3. Synthetic scheme for the synthesis of ligands **5**: method A (R^3 H) and method B (R^3Li)

Bis(sulfonyl)diazaphospholidines **9** were prepared by the reaction of bis(sulfonamides) **8** with PCl_3, either in the presence of a tertiary amine base (Et_3N) or after deprotonation with 2 equiv. of *n*BuLi (Scheme 3). The deprotonation method was always preferred since purer P−Cl derivatives **9** were obtained. Usually compounds **9** were not isolated but were reacted in situ with excess primary or secondary amines **10i**, **10j**, **10k**, and **10l** (method A); careful removal of LiCl and amine hydrochlorides was performed by filtration through a PTFE membrane filter. After removal of the volatiles under reduced pressure, ligands **5** were obtained that were pure enough for subsequent use in catalytic applications.

An alternative synthetic pathway was chosen for the bulky secondary amines (**10h**, **10m**, **10n**, method B); in this case, the P−Cl derivatives **9** were reacted with the preformed lithium salt of the amines. The corresponding ligands were then obtained after carrying out the work up procedure described above. Chromatographic purification could not be accomplished since ligands **5** are prone to hydrolysis and need to be stored under nitrogen.

An inverse approach (method C) was used in the case of R^3 = phenyl, or with the bulky secondary amines **10h** and **10n** (Scheme 4). In this case, R^3PCl_2 (**11**), either the commercially available $PhPCl_2$ (**11o**, Scheme 2) or the dichlorophosphinoamines **11h** and **11n** (obtained from the corresponding amines **10h**, **10n** and PCl_3), were treated with the bis(sulfonamides) **8** (R^2 = *p*Tol), derived from *p*-toluenesulfonyl chloride (**7e**). Bis(sulfonyl)diazaphospholidine formation was achieved either in the presence of a tertiary amine (R^3H = **10h**, **10n**) or after deprotonation with 2 equiv. of *n*BuLi (R^3 = Ph).



Scheme 4. Synthesis of ligands **5** (method C)

Contrary to our expectations, no reaction occurred when we tried to introduce a $P-NMe_2$ moiety by the treatment of bis(sulfonamides) **8** with hexamethylphosphorous triamide [$P(NMe_2)_3$] at room temperature or at reflux in toluene. This synthetic strategy had been applied with success to the synthesis of phosphoramidites **1** (R = Me).[3a] The desired dimethylamino derivatives (**5adi**, **5bdi**, **5cdi**, **5cfi** and **5cgi**) were obtained in good yields by treating the P−Cl derivatives **9ad**, **9bd**, **9cd**, **9cf** and **9cg** with a solution of dimethylamine (3.3 equiv.) in THF.

Table 1. Synthetic methods, yields and ^{31}P NMR chemical shifts of ligands **5**

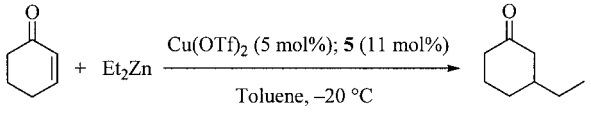
Entry	Ligand[a]	R^1	R^2	R^3	Method	Yield [%]	δ_P [ppm]
1	**5aeo**	$(CH_2)_4$	*p*Tol	Ph	C	82	95.6
2	**5aeh**	$(CH_2)_4$	*p*Tol	$N(iPr)_2$	C	96	99.3
3	**5aen**	$(CH_2)_4$	*p*Tol	$N(MeCHPh)_2$-(*R*,*R*)	C	95	100.4
4	**5ado**	$(CH_2)_4$	Me	Ph	C	84	95.8
5	**5adi**	$(CH_2)_4$	Me	NMe_2	A	75	102.7
6	**5adh**	$(CH_2)_4$	Me	$N(iPr)_2$	B	42	99.8
7	**5adj**	$(CH_2)_4$	Me	$NHCH_2Ph$	A	90	134.9
8	**5beo**	Ph	*p*Tol	Ph	C	74	107.6
9	**5beh**	Ph	*p*Tol	$N(iPr)_2$	C	80	110.1
10	**5bdo**	Ph	Me	Ph	C	89	108.2
11	**5bdi**	Ph	Me	NMe_2	A	94	112.5
12	**5bdj**	Ph	Me	$NHCH_2Ph$	A	89	101.4
13	**5ceo**	binaphth	*p*Tol	Ph	C	98	131.7
14	**5ceh**	binaphth	*p*Tol	$N(iPr)_2$	C	98	129.4
15	**5cdo**	binaphth	Me	Ph	C	99	129.8
16	**5cdi**	binaphth	Me	NMe_2	A	98	125.5
17	**5cdj**	binaphth	Me	$NHCH_2Ph$	A	85	166.6
18	**5cdl**	binaphth	Me	NHCH(Me)Ph-(*S*)	A	98	107.9
19	**5cdk**	binaphth	Me	NHCH(Me)Ph-(*R*)	A	75	113.5
20	**5cdm**	binaphth	Me	$N(MeCHPh)_2$-(*S*,*S*)	B	94	146.3
21	**5cdn**	binaphth	Me	$N(MeCHPh)_2$-(*R*,*R*)	B	98	146.4
22	**5cfi**	binaphth	4-MeO-C_6H_4	NMe_2	A	84	127.1
23	**5cgi**	binaphth	3,4-$(MeO)_2$-C_6H_3	NMe_2	A	88	127.2

Based on these synthetic methodologies a small library of 23 different ligands was prepared. Only some of all the possible combinations ($3 \times 4 \times 8 = 96$) were taken into consideration, and the choice was made following a sort of positional scanning approach[16] (vide infra the enantioselective copper-catalysed conjugate addition of diethylzinc to cyclohexenone with ligands **5**).

Ligands **5** were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy (Table 1). The ^{31}P chemical shifts of ligands **5** are typical of phosphonite and phosphoramidite ligands, and depend on the different substituents (R^1, R^2, R^3). In particular, the ^{31}P chemical shifts appear to be mostly influenced by the nature of the diamine scaffold. In fact, the ^{31}P signals are shifted downfield in the order: 1,1′-binaphthyl-2,2′-diamine > 1,2-diphenylethylenediamine > 1,2-diaminocyclohexane.

Enantioselective Copper-Catalysed Conjugate Addition of Diethylzinc to Cyclohexenone with Ligands 5

Trivalent phosphorus ligands that contain a P−heteroatom bond have frequently been used in the enantioselective copper-catalysed conjugate addition of dialkylzinc reagents to enones.[3,4,5c,7,10,17] We chose the conjugate addition of diethylzinc to cyclohexenone (Scheme 5) as a benchmark for our ligands, as this reaction is a useful reference for evaluating the activity and enantioselectivity of our catalytic system.



Scheme 5. Conjugate addition of Et_2Zn to cyclohexenone, catalysed by copper complexes of ligands **5**

All the experiments were performed under identical conditions. $Cu(OTf)_2$ (5 mol %) and the chiral ligand **5** (Cu/**5** ratio 1:2.2) were dissolved in toluene and stirred at room temperature for 1 h. The reaction mixture was then cooled to −20 °C and diethylzinc and cyclohexenone were added. The reactions were quenched with NH_4Cl after a standard reaction time of 5 h, and the crude mixtures were analysed by chiral GC (see Exp. Sect.). Complete conversions (> 98%) were obtained for all the ligands studied.

At the beginning of the screening, a small subset of ligands **5** was tested: we kept R^3 constant (R^3 = Ph) and varied the scaffolds (**6a**, **6b** and **6c**) and the sulfonyl chlorides (**7d** and **7e**). The results are summarised in Table 2. The enantioselectivities obtained were poor (max *ee* = 35%), and indicated a slight preference in favour of ligands with $R^2 = MeSO_2$ (Entries 4−6).

Table 2. Screening of ligands **5**[a]

Entry	Ligand	R^1	R^2	R^3	*ee* [%][b] (abs. conf.)[c]
1	**5ceo**	binaphth	*p*Tol	Ph	0
2	**5aeo**	$(CH_2)_4$	*p*Tol	Ph	5 (*S*)
3	**5beo**	Ph	*p*Tol	Ph	25 (*R*)
4	**5cdo**	binaphth	Me	Ph	17 (*R*)
5	**5ado**	$(CH_2)_4$	Me	Ph	0
6	**5bdo**	Ph	Me	Ph	35 (*R*)

[a] $Cu(OTf)_2$ (0.05 equiv.); ligand **5** (0.11 equiv.); Et_2Zn (2.2 equiv.); toluene; −20 °C; 5 h. [b] Determined by GC: MEGADEX DACTBSβ, 25 m, film 0.25 μm, carrier H_2 (70 kPa). [c] The absolute configuration was determined by chiral GC by comparison of the retention times with those of an unbalanced mixture of known enantiomeric composition.

Given the poor results obtained with R^3 = Ph, we decided to examine the results obtained with amine substituents. These results are summarised in Table 3.

Table 3. Screening of ligands **5**[a]

Entry	Ligand	R^1	R^2	R^3	*ee* [%][b] (abs. conf.)[c]
1	**5aeh**	$(CH_2)_4$	*p*-Tol	$N(iPr)_2$	9 (*R*)
2	**5adh**	$(CH_2)_4$	Me	$N(iPr)_2$	3 (*R*)
3	**5beh**	Ph	*p*-Tol	$N(iPr)_2$	9 (*R*)
4	**5ceh**	binaphth	*p*-Tol	$N(iPr)_2$	0
5	**5aen**	$(CH_2)_4$	*p*-Tol	$N(MeCHPh)_2$ (*S*,*S*)	0
6	**5cdm**	binaphth	Me	$N(MeCHPh)_2$ (*S*,*S*)	14 (*S*)
7	**5cdn**	binaphth	Me	$N(MeCHPh)_2$ (*R*,*R*)	19 (*R*)
8	**5adj**	$(CH_2)_4$	Me	$NHCH_2Ph$	8 (*S*)
9	**5bdj**	Ph	Me	$NHCH_2Ph$	0
10	**5cdj**	binaphth	Me	$NHCH_2Ph$	56 (*R*)
11	**5cdl**	binaphth	Me	NHCH(Me)Ph (*S*)	0
12	**5cdk**	binaphth	Me	NHCH(Me)Ph (*R*)	16 (*R*)
13	**5cdi**	binaphth	Me	NMe_2	75 (*R*)
14	**5adi**	$(CH_2)_4$	Me	NMe_2	16 (*R*)
15	**5bdi**	Ph	Me	NMe_2	23 (*R*)
16	**5cfi**	binaphth	4-MeO-C_6H_4	NMe_2	5 (*R*)
17	**5cgi**	binaphth	3,4-$(MeO)_2$-C_6H_3	NMe_2	8 (*R*)

[a] $Cu(OTf)_2$ (0.05 equiv.); ligand **5** (0.11 equiv.); Et_2Zn (2.2 equiv.); toluene; −20 °C; 5 h. [b] Determined by GC: MEGADEX DACTBSβ, 25 m, film 0.25 μm, carrier H_2 (70 kPa). [c] The absolute configuration was determined by chiral GC by comparison of the retention times with those of an unbalanced mixture of known enantiomeric composition.

It can be seen that both chiral and achiral bulky amines afford only low enantioselectivities (Entries 1−7). In addition, when chiral amines were used (Entries 6 and 7), the sense of induction was found to depend on the absolute configuration of the amine and a very minor contribution from the binaphthyl moiety was observed (the *ee*s with ligands **5cdm** and **5cdn** are very similar in magnitude). When primary amines were used, a substantial improvement in the enantioselectivity was noticed in the case of benzylamine (cf. Entry 10, *ee* = 56%, with Entries 6, 7, 11, and 12). By comparing Entries 8−10, the 1,1′-binaphthyl-2,2′-diamine was identified as the best scaffold. Dimethylamine derived ligands gave optimal results (Entries 13−17) and an enantiomeric excess as high as 75% was obtained with ligand **5cdi**.

Conclusions

In summary, we have developed a new family of chiral phosphorus ligands (**5**) for use in enantioselective catalysis. The ligands contain the electron-poor bis(sulfonyl)diazaphospholidine moiety and possess a highly modular structure which is well suited to the synthesis of a library. A small library (23 members) of ligands **5** was prepared and tested in the enantioselective copper-catalysed conjugate addition of diethylzinc to cyclohexenone. Complete conversions were obtained with enantiomeric excesses of up to 75% (with ligand **5cdi**). In particular, ligands containing the 1,1′-binaphthyl-2,2′-diamine scaffold gave superior results, followed by 1,2-diphenylethylenediamine and 1,2-diaminocyclohexane. As for the sulfonyl chlorides, it appears that methanesulfonyl chloride derivatives afford better results than arylsulfonyl chloride derivatives. It is also evident that small amine substituents at phosphorus are preferable. Work is in progress in our laboratories to apply this class of ligands to other enantioselective transformations.

Experimental Section

General Remarks: All reactions were carried out in flame-dried glassware with magnetic stirring under argon. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH_2Cl_2 (CaH_2), THF (Na), Et_2O (Na), toluene (Na), pyridine (CaH_2). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} precoated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or by staining with a ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60Å, particle size 40−64 μm. ^{1}H NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400.13 MHz, and with a Bruker AC 200 spectrometer operating at 200 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent as reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded with complete proton decoupling with a Bruker Avance 400 spectrometer operating at 100.56 MHz, and with a Bruker AC 200 spectrometer operating at 50.28 MHz. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0). ^{31}P NMR spectra were recorded with complete proton decoupling with a Bruker Avance 400 spectrometer operating at 162 MHz. Phosphorus NMR chemical shifts are reported in ppm (δ) relative to external 85% H_3PO_4 at 0 ppm (positive values downfield). Infrared spectra were recorded with a Jasco FT/IR-300E infrared spectrometer; peaks are reported in cm^{-1}. Optical rotation values were measured with a Perkin−Elmer 241 polarimeter with a 1-dm cell at the sodium D line; $[\alpha]_D$ values are given in units of $10deg \cdot cm^2 \cdot g^{-1}$. Gas chromatography was performed with a Dani GC-6500 instrument equipped with a flame ionization detector. Enantiomeric excesses were determined by chiral GC using a MEGADEX DACTBSβ, OV 1701 capillary column (25 m, film 0.25 μm) in comparison with a racemic sample. Melting point determination of ligands **5** (powders) could not be accomplished since they are unstable and tend to decompose (hydrolysis and oxidation) when exposed to air or heated. The following compounds were synthesised as originally reported: (1*R*,2*R*)-*trans*-1,2-bis(*p*-tolylsulfonylamino)cyclohexane (**8ae**),[18,19] (1*R*,2*R*)-*trans*-1,2-diphenyl-*N*,*N*′-bis(*p*-tolylsulfonyl)ethylenediamine (**8be**),[19] (*S*)-*N*,*N*′-bis(*p*-tolylsulfonyl)-1,1′-binaphthyl-2,2′-diamine (**8ce**),[20] (1*R*,2*R*)-*trans*-1,2-bis(methylsulfonylamino)cyclohexane (**8ad**),[21] (1*R*,2*R*)-*trans*-1,2-diphenyl-*N*,*N*′-bis(methylsulfonyl)ethylenediamine (**8bd**),[21,22] (*S*)-*N*,*N*′-bis(methylsulfonyl)-1,1′-binaphthyl-2,2′-diamine (**8cd**),[23] (1*R*,2*R*)-*trans*-1,2-bis(trifluoromethylsulfonylamino)cyclohexane,[21] (1*R*,2*R*)-*trans*-1,2-diphenyl-*N*,*N*′-bis(trifluoromethylsulfonyl)ethylenediamine,[21] (*S*)-*N*,*N*′-bis(trifluoromethylsulfonyl)-1,1′-binaphthyl-2,2′-diamine,[23] (*S*)-*N*,*N*′-bis(*p*-methoxyphenylsulfonyl)-1,1′-binaphthyl-2,2′-diamine (**8cf**),[20] and (*S*)-*N*,*N*′-bis(3,4-dimethoxyphenylsulfonyl)-1,1′-binaphthyl-2,2′-diamine (**8cg**).[20]

[Bis(α-methylbenzyl)amino]phosphorous Dichloride (11m, 11n): Bis(α-methylbenzyl)amine (2 mmol, 458 μL) was dissolved in dry THF (5 mL), under argon, and cooled to −78 °C. *n*BuLi (1.6 M in hexanes, 2.0 mmol, 1.25 mL) was slowly added. After 1 h, the temperature was allowed to rise to room temperature. After 2 h, the reaction mixture was cooled to −78 °C, and PCl_3 (2 mmol, 175 μL) was added dropwise. The reaction was stirred, overnight, and the temperature was allowed to rise to room temp. THF was removed, dry toluene was added and the mixture was filtered through a PTFE membrane filter to remove LiCl. The solvent was removed under reduced pressure, and the product was checked by ^{31}P NMR spectroscopy, and stored under an inert atmosphere at 0 °C.

[(*S*,*S*)-Bis(α-methylbenzyl)amino]phosphorous Dichloride (11m): Yellow viscous oil (587 mg, 90% yield). ^{1}H NMR (200 MHz, C_6D_6): δ = 7.65 (d, *J* = 6.9 Hz, 2 H, ArH), 7.14 (m, 8 H, ArH), 4.84 (m, 1 H, CH), 3.81 (m, 1 H, CH), 2.03 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.51 (d, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 138.4, 137.8, 129.3, 129.1, 127.5, 126.8, 44.5, 22.0 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 166.8 ppm.

[(*R*,*R*)-Bis(α-methylbenzyl)amino]phosphorous Dichloride (11n): Yellow viscous oil (587 mg, 90% yield). ^{1}H NMR (200 MHz, C_6D_6): δ = 7.64 (d, *J* = 7.1 Hz, 2 H, ArH), 7.14 (m, 8 H, ArH), 4.86 (m, 1 H, CH), 3.82 (m, 1 H, CH), 2.03 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.51 (d, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 138.4, 137.8, 129.3, 129.1, 127.5, 126.8, 44.5, 22.0 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 166.8 ppm.

(Diisopropylamino)phosphorous Dichloride (11h): In a dry three-necked flask, under argon, a solution of diisopropylamine (50 mmol, 7 mL) in dry diethyl ether (20 mL) was cooled to −10

°C. Phosphorus trichloride (29.4 mmol, 2.57 mL) was added dropwise over a period of 30 min. The reaction mixture warmed to room temperature and stirred overnight. The precipitate was then removed by vacuum filtration; the solution was collected, and the solvent removed under reduced pressure. The crude product was purified by vacuum distillation (72 °C at 0.5 Torr). Colourless viscous oil (2.50 g, 43% yield). ^{1}H NMR (200 MHz, C_6D_6): δ = 4.65 (m, 2 H, 2 × CH), 0.99 (d, *J* = 6.8 Hz, 12 H, 4 × CH_3) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 48.3, 48.0, 23.1, 23.0 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 170.2 ppm.

General Procedure for the Synthesis of Ligands 5, Method A: In a Schlenk tube under argon, the bis(sulfonamide) **8** (1 mmol) was dissolved in dry THF (4 mL), and cooled to −78 °C. *n*BuLi (1.6 M in hexanes, 2.1 mmol, 1.30 mL) was slowly added, and after 30 min the temperature was allowed to rise to room temperature. After 2 h, the reaction mixture was cooled to −78 °C, and PCl_3 (1.05 mmol, 92 μL) was added dropwise. The temperature was then allowed to slowly rise to room temp. After 2 h, the reaction mixture containing the bis(sulfonamide)PCl intermediate was cooled to −78 °C, and the amine [dimethylamine (2 M in THF, 3.3 mmol, 1.65 mL), benzylamine (3.3 mmol, 360 μL), α-methylbenzylamine (3.3 mmol, 421 μL)] was added dropwise under argon. After 2 h, the temperature was allowed to rise to room temperature, and the mixture was stirred overnight. The solvent and excess amine were removed under reduced pressure. Dry toluene was added, the reaction mixture was filtered through a PTFE membrane filter under argon to remove LiCl, and the solvent was removed.

Method B: In a Schlenk tube under argon, the bis(sulfonamide) **8** (0.5 mmol) was dissolved in dry THF (2 mL), and cooled to −78 °C. *n*BuLi (1.6 M solution in hexanes, 1.05 mmol, 656 μL) was slowly added, and after 30 min the temperature was allowed to rise to room temperature. After 2 h, the reaction mixture was cooled to −78 °C, and PCl_3 (0.52 mmol, 46 μL) was added dropwise. The temperature was then allowed to slowly rise to room temp. After 2 h, the reaction mixture containing the bis(sulfonamide)−PCl intermediate was cooled to −78 °C. Meanwhile the amine (0.55 mmol) was dissolved in dry THF (0.5 mL), cooled to −78 °C, treated with *n*BuLi (1.6 M solution in hexanes, 0.575 mmol, 359 μL) and stirred at room temp. for 1 h. The lithium salt of the amine was then added dropwise to the reaction mixture, under argon, at −78 °C. After 2 h, the temperature was allowed to rise to room temperature, and the reaction was stirred overnight. The solvent was removed under reduced pressure. Dry toluene was added, the reaction mixture was filtered through a PTFE membrane filter under argon to remove LiCl, and the solvent was removed.

Method C: *n*BuLi (1.6 M solution in hexanes, 1.05 mmol, 656 μL) was slowly added to a stirred solution of bis(sulfonamide) **8** (0.5 mmol) in dry THF (2.5 mL) at −78 °C under argon. Once the addition of *n*BuLi was complete, the reaction mixture was stirred at room temperature for 2 h. A Schlenk tube was charged with the appropriate phosphorous dichloride (Cl_2PR^3) **11** (0.5 mmol) and dry THF (1.5 mL), and was cooled to −78 °C. The lithium salt solution was slowly added by means of a cannula. After 1 hour, the temperature was allowed to rise to room temperature, and the mixture was stirred overnight. THF was removed, and dry toluene was added. The precipitate (LiCl) was removed by filtration through a PTFE membrane filter under argon. The solvent was then removed under reduced pressure to obtain the product as a yellow powder.

Ligand 5aeh: Method C, white powder (265 mg, 96%). ^{1}H NMR (400 MHz, C_6D_6): δ = 8.02 (d, *J* = 8.2 Hz, 2 H, ArH), 7.65 (d, *J* = 8.2 Hz, 2 H, ArH), 6.90 (d, *J* = 8.1 Hz, 2 H, ArH), 6.68 (d, *J* = 8.1 Hz, 2 H, ArH), 3.99−3.89 (m, 2 H, 2 × CHN), 4.00−3.80 (m, 1 H, CyH), 2.78−2.65 (m, 2 H, CyH), 2.34−2.27 (m, 1 H, CyH), 2.02 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 1.65 (d, *J* = 6.7 Hz, 12 H, 4 × CH_3), 1.50−0.40 (m, 6 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 143.0, 142.1, 129.4, 129.1, 128.1, 126.5, 66.1, 63.4, 48.4, 48.3, 31.4, 29.0, 24.2, 24.0, 23.6, 20.9, 20.8 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 99.3 ppm. IR (film): $\tilde{\nu}$ = 1634, 1599, 1347, 1323, 1202, 1156, 1114, 1090 cm^{-1}. $[\alpha]_D^{25}$ = −56 (*c* = 0.99, THF). MS (FAB, glycerol): *m*/*z* (%) = 552 (65), 536 (25), 451 (100), 154 (35), 139 (25). HRMS (ESI): calcd. for $C_{26}H_{39}N_3O_4PS_2$: 552.2120 $[M + H]^+$; found 552.2120.

Ligand 5aeo: Method C, white powder (217 mg, 82%). ^{1}H NMR (400 MHz, C_6D_6): δ = 8.40−8.36 (m, 2 H, PhH), 8.04 (d, *J* = 8.2 Hz, 2 H, ArH), 7.53 (d, *J* = 8.2 Hz, 2 H, ArH), 7.29−7.15 (m, 3 H, PhH), 6.88 (d, *J* = 8.1 Hz, 2 H, ArH), 6.67 (d, *J* = 8.1 Hz, 2 H, ArH), 3.33−3.27 (m, 1 H, CyH), 2.92−2.88 (m, 1 H, CyH), 2.68−2.62 (m, 1 H, CyH), 2.49−2.45 (m, 1 H, CyH), 2.05 (s, 3 H, CH_3), 1.96 (s, 3 H, CH_3), 1.40−1.30 (m, 1 H, CyH), 1.27−1.23 (m, 1 H, CyH), 1.14−1.09 (m, 1 H, CyH), 0.99−0.88 (m, 1 H, CyH), 0.66−0.55 (m, 1 H, CyH), 0.45−0.35 (m, 1 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 143.9, 143.2, 140.9, 135.7, 130.6, 130.4, 130.1, 129.8, 129.2, 127.2, 68.0, 65.3, 32.4, 28.5, 23.9, 21.5, 21.4 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 95.6 ppm. IR (film): $\tilde{\nu}$ = 1645, 1597, 1343, 1323, 1161, 1112, 1088 cm^{-1}. $[\alpha]_D^{25}$ = −35.35 (*c* = 1.01, THF). HRMS (ESI): calcd. for $C_{26}H_{29}N_2NaO_4PS_2$: 551.1204 $[M + Na]^+$; found 551.1185.

Ligand 5aen: Method C, yellow powder (321 mg, 95%). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.62−6.85 (m, 18 H, ArH), 3.79−3.77 (m, 2 H, 2 × CHN), 3.65−3.59 (m, 1 H, CyH), 2.95−2.45 (m, 2 H, CyH), 2.34−2.30 (m, 1 H, CyH), 2.09 (s, 3 H, $ArCH_3$), 2.06 (s, 3 H, $ArCH_3$), 1.95 (s, 6 H, 2 × CH_3), 1.90−0.40 (m, 6 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 143.1, 142.6, 142.1, 142.0, 129.5, 129.1, 128.8, 128.0, 126.8, 126.7, 57.3, 55.2, 31.3, 28.5, 25.5, 25.0, 23.4, 20.9, 20.8 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 100.4 ppm. IR (film): $\tilde{\nu}$ = 1653, 1598, 1159, 1118, 1076 cm^{-1}. $[\alpha]_D^{25}$ = +60.9 (*c* = 1.00, THF). HRMS (ESI): calcd. for fragment $C_{20}H_{26}N_2NaO_4S_2$: 445.1232; found 445.1247.

Ligand 5adh: Method B, white powder (84 mg, 42%). ^{1}H NMR (400 MHz, C_6D_6): δ = 3.68−3.64 (m, 2 H, CyH), 3.44−3.39 (m, 2 H, CHN), 3.24 (s, 3 H, SO_2CH_3), 3.22 (s, 3 H, SO_2CH_3), 2.61−2.48 (m, 2 H, CyH), 1.98−1.92 (m, 2 H, CyH), 1.66−1.60 (m, 2 H, CyH), 1.48 (d, *J* = 6.5 Hz, 12 H, 4 × CH_3), 1.44−1.38 (m, 2 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 57.3, 47.6, 41.6, 34.2, 24.8, 19.8, 19.3 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 99.8 ppm. IR (film): $\tilde{\nu}$ = 1653, 1261, 1091, 1021 cm^{-1}. $[\alpha]_D^{25}$ = −10.7 (*c* = 0.49, THF). HRMS (ESI): calcd. for fragment $C_8H_{18}N_2NaO_4S_2$: 293.0606; found 293.0587.

Ligand 5adi: Method A, white powder (257 mg, 75%). ^{1}H NMR (400 MHz, C_6D_6): δ = 3.40−3.35 (m, 1 H, CyH), 2.92−2.83 (m, 1 H, CyH), 2.69 (s, 3 H, SO_2CH_3), 2.67 (s, 3 H, SO_2CH_3), 2.45 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 1.52−1.40 (m, 3 H, CyH), 1.22−1.17 (m, 1 H, CyH), 1.07−0.78 (m, 4 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 65.2, 63.7, 43.8, 41.3, 37.7, 37.3, 30.3, 30.0, 24.0, 23.8 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 102.7 ppm. IR (film): $\tilde{\nu}$ = 1634, 1260, 1157, 1105, 1054 cm^{-1}. $[\alpha]_D^{25}$ = −42.2 (*c* = 1.00, THF). HRMS (ESI): calcd. for $C_{10}H_{23}N_3O_4PS_2$: 344.0868 $[M + H]^+$; found 344.0863; calcd. for $C_{10}H_{22}N_3NaO_4PS_2$: 366.0687 $[M + Na]^+$; found 366.0688.

Ligand 5ado: Method C, white powder (158 mg, 84%). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.97−7.93 (m, 1 H, ArH), 7.17−7.07 (m, 4

H, ArH), 3.13−3.00 (m, 2 H, CyH), 2.83−2.78 (m, 1 H, CyH), 2.57 (s, 3 H, SO_2CH_3), 2.37 (s, 3 H, SO_2CH_3), 2.20−2.18 (m, 1 H, CyH), 1.49−1.18 (m, 4 H, CyH), 1.00−0.80 (m, 1 H, CyH), 0.55−0.45 (m, 1 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 130.8, 130.6, 130.4, 67.9, 65.9, 43.3, 37.4, 32.7, 29.4, 24.3, 24.1 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 95.8 ppm. IR (film): $\tilde{\nu}$ = 1633, 1330, 1149, 1141, 1106, 1080, 1056 cm^{-1}. $[\alpha]_D^{25}$ = −4.1 (*c* = 1.00, THF). MS (FAB, glycerol): *m*/*z* (%) = 377 (100), 313 (45), 299 (20), 205 (30). HRMS (ESI): calcd. for $C_{14}H_{21}N_2NaO_4PS_2$: 399.0578 [M + Na]$^+$; found 399.0576.

Ligand 5adj: Method A, yellow powder (365 mg, 90%). ^1H NMR (400 MHz, C_6D_6): δ = 7.14−7.00 (m, 5 H, ArH), 3.15−3.11 (m, 2 H, CH_2), 2.36 (s, 6 H, 2 × SO_2CH_3), 2.18−2.10 (m, 2 H, CyH), 1.30−1.26 (m, 2 H, CyH), 1.05−0.60 (m, 6 H, CyH) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 129.1, 129.0, 128.6, 66.5, 43.1, 29.5, 23.6 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 134.9 ppm. IR (film): $\tilde{\nu}$ = 3392, 1653, 1159 cm^{-1}. $[\alpha]_D^{25}$ = −3.4 (*c* = 1.02, THF). HRMS (ESI): calcd. for fragment $C_8H_{18}N_2O_4S_2$: 270.0708; found 270.0710.

Ligand 5beh: Method C, brownish powder (260 mg, 80%). ^1H NMR (400 MHz, C_6D_6): δ = 7.87 (d, *J* = 8 Hz, 2 H, ArH), 7.85 (d, *J* = 8 Hz, 2 H, ArH), 7.26−7.14 (m, 6 H, ArH), 6.71−6.63 (m, 4 H, ArH), 6.46−6.39 (m, 3 H, ArH), 6.28−6.24 (m, 1 H, ArH), 5.63 (dd, *J* = 5.9 Hz, 1.18 Hz, 1 H, CHN), 4.95 (dd, *J* = 5.8 Hz, 2.4 Hz, 1 H, CHN), 3.93−3.79 (m, 2 H, 2 × CH), 1.91 (s, 3 H, $ArCH_3$), 1.87 (s, 3 H, $ArCH_3$), 1.69−1.61 (m, 12 H, 4 × CH_3) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 143.2, 141.8, 137.8, 129.7, 128.8, 128.6, 127.3, 72.5, 70.9, 63.4, 48.8, 47.5, 21.1, 19.3 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 110.1 ppm. IR (film): $\tilde{\nu}$ = 1599, 1559, 1348, 1157, 1089 cm^{-1}. $[\alpha]_D^{25}$ = +35.0 (*c* = 1.00, THF). HRMS (ESI): calcd. for $C_{34}H_{41}N_3O_4PS_2$: 650.2276 [M + H]$^+$; found 650.2250; calcd. for $C_{34}H_{40}N_3NaO_4PS_2$: 672.2096 [M + Na]$^+$; found 672.2102.

Ligand 5beo: Method C, brownish powder (232 mg, 74%). ^1H NMR (400 MHz, C_6D_6): δ = 8.46 (t, *J* = 7.3 Hz, 2 H, ArH), 8.04 (d, *J* = 8.2 Hz, 2 H, ArH), 7.71−7.67 (m, 2 H, ArH), 7.26−7.04 (m, 6 H, ArH), 6.92−6.78 (m, 5 H, ArH), 6.64−6.49 (m, 4 H, ArH), 6.24−6.22 (m, 2 H, ArH), 5.42 (d, *J* = 7.0 Hz, 1 H, CHN), 5.23 (d, *J* = 7.0 Hz, 1 H, CHN), 1.99 (s, 3 H, $ArCH_3$), 1.94 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 143.9, 142.7, 142.0, 139.7, 138.9, 137.1, 135.7, 130.7, 130.5, 130.4, 130.2, 139.4, 129.3, 129.2, 129.1, 127.0, 77.2, 74.3, 18.6, 17.2 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 107.6 ppm. IR (film): $\tilde{\nu}$ = 1348, 1156, 1088 cm^{-1}. $[\alpha]_D^{25}$ = +29.5 (*c* = 1.00, THF). HRMS (ESI): calcd. for $C_{34}H_{31}N_2NaO_4PS_2$: 649.1361 [M + Na]$^+$; found 649.1342.

Ligand 5bdi: Method A, pale yellow powder (415 mg, 94%). ^1H NMR (200 MHz, C_6D_6): δ = 7.58−7.53 (m, 2 H, ArH), 7.17−6.94 (m, 8 H, ArH), 5.48 (d, *J* = 5.8 Hz, 1 H, CHN), 5.09−5.05 (m, 1 H, CHN), 2.79 (s, 3 H, NCH_3), 2.75 (s, 3 H, NCH_3), 2.14 (s, 3 H, SO_2CH_3), 2.01 (s, 3 H, SO_2CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 138.4, 137.8, 129.5, 129.3, 129.2, 129.1, 129.0, 128.9, 70.8, 69.1, 42.6, 42.3, 37.8, 37.5 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 116.9, 112.5 ppm. IR (film): $\tilde{\nu}$ = 1602, 1146, 1079 cm^{-1}. $[\alpha]_D^{25}$ = −3.8 (*c* = 0.99, THF). MS (FAB, glycerol): *m*/*z* (%) = 441 (100). HRMS (ESI): calcd. for fragment $C_{16}H_{20}N_2NaO_4S_2$: 391.0762; found 391.0765.

Ligand 5bdo: Method C, white powder (211 mg, 89%). ^1H NMR (200 MHz, C_6D_6): δ = 8.38−8.28 (m, 1 H, ArH), 7.36−7.24 (m, 8 H, ArH), 7.22−7.15 (m, 2 H, ArH), 7.11−7.07 (m, 1 H, ArH), 7.05−6.86 (m, 3 H, ArH), 5.64 (d, *J* = 7.2 Hz, 1 H, CHN), 5.52 (d, *J* = 7.2 Hz, 1 H, CHN), 2.29 (s, 3 H, SO_2CH_3), 2.05 (s, 3 H, SO_2CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 142.2, 141.3, 138.4, 130.7, 130.6, 130.3, 129.8, 129.3, 75.8, 73.8, 43.2, 41.6 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 108.2 ppm. IR (film): $\tilde{\nu}$ = 1640, 1329, 1261, 1145, 1072 cm^{-1}. $[\alpha]_D^{25}$ = −19.6 (*c* = 1.00, THF). MS (FAB, glycerol): *m*/*z* (%) = 475 (70), 375 (20), 353 (30), 289 (20), 274 (25), 221 (35), 207 (50), 154 (90), 136 (100). HRMS (ESI): calcd. for $C_{22}H_{23}N_2NaO_4PS_2$: 497.0735 [M + Na]$^+$; found 497.0738.

Ligand 5bdj: Method A, pale yellow powder (448 mg, 89%). ^1H NMR (200 MHz, C_6D_6): δ = 7.57−6.85 (m, 15 H, ArH), 5.49−5.47 (m, 1 H, CHN), 5.13−5.09 (m, 1 H, CHN), 4.42−4.26 (m, 2 H, CH_2Ph), 3.41 (br. s, 1 H, NH), 2.09 (s, 6 H, 2 × SO_2CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 140.9, 139.7, 129.8, 129.4, 128.7, 127.9, 127.6, 70.7, 70.4, 47.9, 42.7, 42.0 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 101.4 ppm. IR (film): $\tilde{\nu}$ = 3371, 1635, 1336, 1316, 1163, 1145, 1088, 1073 cm^{-1}. $[\alpha]_D^{25}$ = −12.8 (*c* = 1.00, THF). HRMS (ESI): calcd. for $C_{23}H_{27}N_3O_4PS_2$: 504.1181 [M + H]$^+$; found 504.1197; calcd. for $C_{23}H_{26}N_3NaO_4PS_2$: 526.1000 [M + Na]$^+$; found 526.1024.

Ligand 5ceh: Method C, pale orange powder (354 mg, 98%). ^1H NMR (200 MHz, C_6D_6): δ = 7.60−5.75 (m, 20 H, ArH), 3.78−3.57 (m, 2 H, 2 × CH), 1.97 (s, 3 H, $ArCH_3$), 1.90 (s, 3 H, $ArCH_3$), 1.52−1.46 (m, 12 H, 4 × CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 141.9, 141.8, 136.9, 133.3, 132.9, 131.9, 130.9, 130.1, 129.7, 128.8, 126.8, 127.4, 51.4, 25.0, 23.4, 21.2, 20.1. ^{31}P NMR (162 MHz, C_6D_6): δ = 129.4 ppm. IR (film): $\tilde{\nu}$ = 1632, 1596, 1342, 1261, 1201, 1161, 1089, 1027 cm^{-1}. $[\alpha]_D^{25}$ = −9.0 (*c* = 1.00, THF). HRMS (ESI): calcd. for $C_{40}H_{40}N_3NaO_4PS_2$: 744.2096 [M + Na]$^+$; found 744.2112.

Ligand 5ceo: Method C, yellow powder (342 mg, 98%). ^1H NMR (200 MHz, C_6D_6): δ = 8.42−8.38 (m, 2 H, ArH), 7.79−7.48 (m, 7 H, ArH), 7.30−6.92 (m, 10 H, ArH), 6.69−6.55 (m, 4 H, ArH), 6.12 (d, *J* = 8.2 Hz, 1 H, ArH), 5.96 (d, *J* = 8.2 Hz, 1 H, ArH), 1.96 (s, 6 H, 2 × $ArCH_3$) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 144.1, 137.3, 135.1, 133.0, 131.4, 131.3, 130.2, 128.7, 127.8, 127.5, 125.7, 125.2, 120.0, 21.5 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 131.7 ppm. IR (film): $\tilde{\nu}$ = 1633, 1593, 1349, 1302, 1261, 1211, 1158, 1088 cm^{-1}. $[\alpha]_D^{25}$ = −1.48 (*c* = 1.01, THF). MS (FAB, glycerol): *m*/*z* (%) = 698 (30), 599 (90), 438 (90), 282 (95), 267 (65), 177 (100), 152 (80), 136 (45), 107 (30), 89 (60). HRMS (ESI): calcd. for $C_{40}H_{31}N_2NaO_4PS_2$: 721.1361 [M + Na]$^+$; found 721.1378.

Ligand 5cdi: Method A, yellow powder (503 mg, 98%). ^1H NMR (200 MHz, C_6D_6): δ = 8.25−6.85 (m, 12 H, ArH), 2.64 (s, 3 H, SO_2CH_3), 2.61 (s, 3 H, SO_2CH_3), 2.31 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 135.0, 131.4, 131.1, 128.7, 125.8, 125.2, 120.1, 40.3, 34.2 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 125.5 ppm. IR (film): $\tilde{\nu}$ = 1620, 1590, 1261, 1159, 1076, 1021 cm^{-1}. $[\alpha]_D^{25}$ = +24.73 (*c* = 1.01, THF). HRMS (ESI): calcd. for $C_{24}H_{24}N_3NaO_4PS_2$: 536.5607 [M + Na]$^+$; found 536.5671.

Ligand 5cdo: Method C, golden powder (270 mg, 99%). ^1H NMR (200 MHz, C_6D_6): δ = 8.28−8.01 (m, 2 H, ArH), 7.83−7.52 (m, 5 H, ArH), 7.36−6.82 (m, 10 H, ArH), 1.91 (s, 3 H, SO_2CH_3), 1.59 (s, 3 H, SO_2CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 133.8, 133.6, 133.3, 132.9, 132.1, 131.9, 131.3, 130.2, 128.9, 128.7, 128.5, 127.1, 126.9, 126.1, 125.5, 120.4, 43.1, 41.0, 40.0 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 129.8 ppm. IR (film): $\tilde{\nu}$ = 1632, 1590, 1345, 1153, 1093 cm^{-1}. $[\alpha]_D^{25}$ = +33.7 (*c* = 1.00, THF). HRMS (ESI): calcd. for $C_{28}H_{23}N_2NaO_4PS_2$: 569.0735 [M + Na]$^+$; found 569.0724.

Ligand 5cdj: Method A, yellow powder (489 mg, 85%). ^1H NMR (200 MHz, C_6D_6): δ = 8.10−6.80 (m, 17 H, ArH), 4.39 (s, 2 H, CH_2Ph), 2.15 (s, 3 H, SO_2CH_3), 2.10 (s, 3 H, SO_2CH_3) ppm. ^{13}C

NMR (50 MHz, C_6D_6): δ = 131.4, 131.1, 130.8, 129.8, 129.3, 129.0, 128.4, 128.2, 120.0, 40.9, 40.5, 25.9 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 166.6 ppm. IR (film): $\tilde{\nu}$ = 3389, 1621, 1594, 1236, 1161, 994 cm^{-1}. $[\alpha]_D^{25} = -1.8$ (c = 1.00, THF). HRMS (ESI): calcd. for $C_{29}H_{27}N_3O_4PS_2$: 576.1181 $[M + H]^+$; found 576.1195.

Ligand 5cdl: Method A, white powder (578 mg, 98%). ^1H NMR (200 MHz, C_6D_6): δ = 8.12 (d, J = 8.6 Hz, 1 H, ArH), 7.90 (d, J = 8.6 Hz, 1 H, ArH), 7.75−7.67 (m, 2 H, ArH), 7.63−7.61 (m, 3 H, ArH), 7.54 (d, J = 8.6 Hz, 1 H, ArH), 7.48 (d, J = 8.6 Hz, 1 H, ArH), 7.25−6.90 (m, 8 H, ArH), 4.89−4.87 (m, 1 H, CH), 1.76 (d, J = 6.7 Hz, 3 H, CH_3), 1.70 (s, 6 H, 2 × SO_2CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 138.9, 130.6, 129.2, 129.1, 127.6, 127.5, 126.4, 52.0, 43.9, 40.4, 20.8 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 107.9 ppm. IR (film): $\tilde{\nu}$ = 1630, 1588, 1153 cm^{-1}. $[\alpha]_D^{25} = -6.46$ (c = 0.99, THF). HRMS (ESI): calcd. for $C_{30}H_{29}N_3O_4PS_2$: 590.1337 $[M + H]^+$; found 590.1316.

Ligand 5cdk: Method A, white powder (442 mg, 75%). ^1H NMR (200 MHz, C_6D_6): δ = 8.07−6.85 (m, 17 H, ArH), 4.90−4.79 (m, 1 H, CH), 1.69 (s, 6 H, 2 × SO_2CH_3), 1.50 (d, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 138.9, 131.2, 129.2, 129.0, 128.4, 127.8, 127.0, 52.0, 44.2, 41.0, 20.8 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 113.5 ppm. IR (film): $\tilde{\nu}$ = 1632, 1597, 1154 cm^{-1}. $[\alpha]_D^{25} = -1.8$ (c = 1.00, THF). HRMS (ESI): calcd. for $C_{30}H_{29}N_3O_4PS_2$: 590.1337 $[M + H]^+$; found 590.1323.

Ligand 5cdm: Method B, pale orange powder (326 mg, 94%). ^1H NMR (200 MHz, C_6D_6): δ = 7.75−7.65 (m, 8 H, ArH), 7.30−6.95 (m, 14 H, ArH), 3.69−3.65 (m, 2 H, 2 × CH), 2.10 (s, 6 H, 2 × SO_2CH_3), 2.08 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 137.6, 129.5, 129.1, 128.9, 57.6, 41.0, 22.1 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 146.3 ppm. IR (film): $\tilde{\nu}$ = 1632, 1589, 1581, 1155, 1074 cm^{-1}. $[\alpha]_D^{25} = -2.5$ (c = 1.00, THF). HRMS (ESI): calcd. for $C_{38}H_{36}N_3NaO_4PS_2$: 716.1783 $[M + Na]^+$; found 716.1801.

Ligand 5cdn: Method B, pale orange powder (340 mg, 98%). ^1H NMR (200 MHz, C_6D_6): δ = 7.75−7.69 (m, 8 H, ArH), 7.30−7.18 (m, 10 H, ArH), 7.16−7.14 (m, 4 H, ArH), 3.70−3.68 (m, 2 H, 2 × CH), 2.11 (s, 6 H, 2 × SO_2CH_3), 2.09 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 137.5, 129.1, 129.0, 128.8, 57.6, 40.9, 22.0 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 146.4 ppm. IR (film): $\tilde{\nu}$ = 1652, 1634, 1581, 1261, 1155, 1073 cm^{-1}. $[\alpha]_D^{25} = +21.4$ (c = 1.00, THF). HRMS (ESI): calcd. for $C_{38}H_{36}N_3NaO_4PS_2$: 716.1783 $[M + Na]^+$; found 716.1775.

Ligand 5cfi: Method A, yellow powder (588 mg, 84%). ^1H NMR (200 MHz, C_6D_6): δ = 8.50−8.40 (m, 2 H, ArH), 7.80−6.81 (m, 16 H, ArH), 5.80 (d, J = 8.4 Hz, 2 H, ArH), 5.65 (d, J = 8.5 Hz, 2 H, ArH), 2.99 (s, 3 H, OCH_3), 2.95 (s, 3 H, OCH_3), 2.39 (s, 3 H, NCH_3), 2.38 (s, 3 H, NCH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 131.7, 130.3, 129.6, 128.8, 128.2, 126.2, 125.9, 125.7, 114.9, 113.3, 54.6, 54.4 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 127.1 ppm. IR (film): $\tilde{\nu}$ = 1595, 1260, 1157, 1092, 1025 cm^{-1}. $[\alpha]_D^{25} = -2.2$ (c = 0.81, THF). HRMS (ESI): calcd. for $C_{36}H_{33}N_3O_6PS_2$: 698.1548 $[M + H]^+$; found 698.1528; calcd. for $C_{36}H_{32}N_3NaO_6PS_2$: 720.1368 $[M + Na]^+$; found 720.1395.

Ligand 5cgi: Method A, brownish powder (667 mg, 88%). ^1H NMR (200 MHz, C_6D_6): δ = 8.51 (d, J = 8.7 Hz, 1 H, ArH), 8.42 (d, J = 8.7 Hz, 1 H, ArH), 7.80−6.68 (m, 14 H, ArH), 5.71 (d, J = 8.5 Hz, 1 H, ArH), 5.37 (d, J = 8.4 Hz, 1 H, ArH), 3.09 (s, 3 H, OCH_3), 3.07 (s, 3 H, OCH_3), 3.01 (s, 3 H, OCH_3), 2.78 (s, 3 H, OCH_3), 2.37 (s, 3 H, NCH_3), 2.34 (s, 3 H, NCH_3) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 131.8, 129.9, 129.7, 126.5, 126.3, 126.0, 125.7, 121.1, 120.8, 109.9, 109.8, 109.6, 55.0, 54.9, 54.8, 54.6 ppm. ^{31}P NMR (162 MHz, C_6D_6): δ = 127.2 ppm. IR (film): $\tilde{\nu}$ = 1640, 1589, 1261, 1156, 1091 cm^{-1}. $[\alpha]_D^{25} = -13.17$ (c = 1.01, THF). HRMS (ESI): calcd. for $C_{38}H_{37}N_3O_8PS_2$: 758.1760 $[M + H]^+$; found 758.1744; calcd. for $C_{38}H_{36}N_3NaO_8PS_2$: 780.1579 $[M + Na]^+$; found 780.1543.

General Procedure for the Copper-Catalysed Conjugate Addition of Et_2Zn to Cyclohexenone: In a dry Schlenk tube equipped with a stirring bar and argon inlet, copper triflate (0.005 mmol, 1.8 mg) was added to a solution of the ligand (0.11eq, 0.011 mmol) in dry toluene (500 μL), and the mixture was stirred for 30 min. The reaction mixture was cooled to −20 °C, and a solution of diethylzinc (1.1 M in toluene, 0.22 mmol, 200 μL) was added, followed by 2-cyclohexenone (0.1 mmol, 10 μL). The reaction was monitored by TLC (hex/Et_2O, 8:2). The reaction was quenched with a saturated aqueous solution of NH_4Cl after 5 h. A sample of the organic phase was injected into the chiral GC for analysis [column: MEGADEX DACTBSβ, 25 m, film 0.25 μm; carrier: H_2, 70 kPa; injector: 200 °C; detector: 200 °C; oven temperature: 50 °C, 5 °C·min^{-1} to 150 °C; t_R: 14.8 (3*R* enantiomer) and 15.1 min (3*S* enantiomer)]. The organic phase was separated, washed with brine, dried with Na_2SO_4, and the solvents evaporated under reduced pressure. Purification by flash chromatography (eluent: *n*-hexane/ethyl acetate, 95:5) gave pure 3-ethylcyclohexanone (12 mg) in 95% yield.

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