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ARTICLE

Synthesis of P-stereogenic diarylphosphinic amides by directed lithiation. Stereospecific transformation into tertiary phosphine oxides via methanolysis, aryne chemistry and complexation behaviour toward zinc(II)

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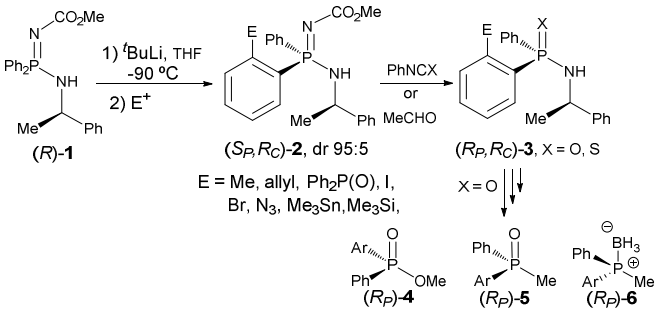
The highly diastereoselective synthesis of P-stereogenic phosphinic amides via directed ortho lithiation (DoLi) of (S_C)-*P*,*P*-diphenylphosphinic amides with *t*-BuLi followed by electrophilic quench reactions is described. Functionalised derivatives containing a wide variety of ortho substituents (Cl, Br, I, OH, N_3, $SiMe_3$, $SnMe_3$, $P(O)Ph_2$, Me, allyl, *t*-BuCO) have been prepared in high yields and a diastereomeric ratios up to 98:2. The X-ray diffraction structure of the *ortho*-stannylated and *ortho*-iodo compounds showed that the *pro-S* P-phenyl ring was stereoselectively *ortho*-deprotonated by the organolithium base. The usefulness of the method is supported by two key transformations, the synthesis of P-stereogenic methyl phosphinates through replacement of the chiral auxiliary by a methoxy group and the first example of the insertion of benzyne into the P-N bond of a P-stereogenic phosphinic amide. A DFT study of this reaction showed that the insertion proceeds through a [2 + 2] cycloaddition and a subsequent ring-opening with retention of the P-configuration. Explorative coordination chemistry of the new P-stereogenic ligands provided access to a chiral phosphinic amide-phosphine oxide Zn(II) complex, the crystal structure of which is reported.

Introduction

P-stereogenic compounds constitute a prominent family of molecules due to their applications in asymmetric synthesis as organocatalyst and ligands for transition-metal catalysed reactions.[1] Phosphorus-based chirogenicity brings asymmetry close to the catalytic center, thus promoting high chiral induction levels in these processes.[2] A number of efficient methodologies have been developed for the stereoselective synthesis of P-stereogenic compounds,[3] including substrate-controlled induction by chiral auxiliaries[4] and the desymmetrization of prochiral dimethylphosphine-boranes and sulfides via enantioselective deprotonation-trapping reactions.[5] We have used a combination of both strategies for accessing P-stereogenic *P*,*P*-diarylphosphinimidic amides **2** based on the discrimination of the diastereotopic phenyl rings of the Ph_2P group through the directed ortho lithiation (DoLi) of a C-chiral substrate **1** (Scheme 1).[6] Abstraction of the ortho proton of the *pro-S* P-phenyl ring of **1** proceeds with very high diastereoselectivity (dr 95:5).[7] The products of electrophilic trapping **2** contain additional donor sites at the ortho position, what makes these compounds interesting hybrid ligands.[8] Furthermore, phosphinimidic amides **2** are a valuable entry to a variety of enantiopure P-stereogenic compounds including phosphinic and phosphinothioic amides **3**, alkyl phosphinates **4**, phosphine oxides **5** and phosphines **6**.[9] Most of these transformations start with the stereospecific conversion of the N-P=N moiety of **2** into a phosphinic amide (N-P=O) **3** through aza-Wittig reactions (Scheme 1).



Scheme 1 Synthesis of P-stereogenic compounds via DoLi of (*R*)-**1**.

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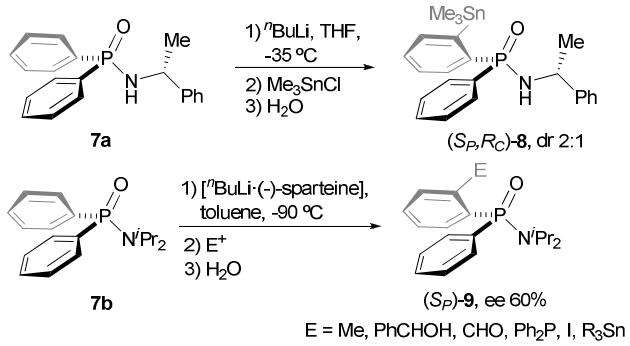
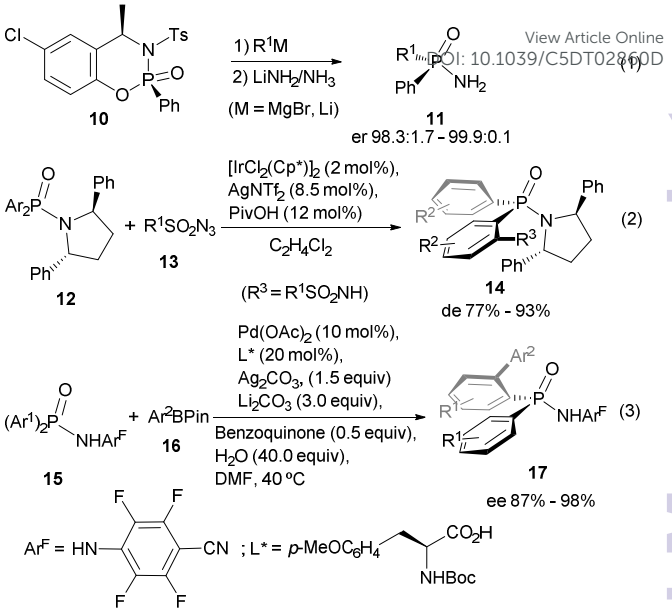
The direct synthesis of the P-stereogenic phosphinic amides **3** would be a significant methodological improvement that, in addition to simplifying the synthetic route, would avoid the use of hazardous azides. However, the analogous DoLi reaction of phosphinic amide (*R*)-**7a** afforded the *ortho*-stannylated derivative **8** with very low diastereoselectivity (dr range of 1:1 to 1:5)[10] and the enantioselective desymmetrization of the Ph_2P group of **7b** using the complex [^{n}BuLi·(-)-sparteine] as a chiral base took place with very modest stereoselectivity to give after electrophilic quench the ortho functionalized products **9** with an ee of 60% (Scheme 2).[11]



Scheme 2 Stereoselective DoLi-trapping reactions of *P*,*P*-diphenylphosphinic amides.

Very recently, the synthesis of P-stereogenic phosphinic amides has been the focus of great attention. Z. S. Han et al. used a C-chiral 1,3,2-benzoxazaphosphinine-2-oxide **10** as a phosphinyl transfer agent to prepare a variety of P-stereogenic diaryl and alkylarylphosphinic amides **11** via sequential displacement of the P-N and P-O bonds of the phosphonamidate moiety by carbon and nitrogen nucleophiles, respectively (Scheme 3, eq (1)).[12] Interestingly, Park, Chang and co-workers reported the first example of the metal assisted direct C-H stereoselective functionalization of a Ph_2P group. The reaction of C_2-symmetric chiral phosphinic amides **12** with sulfonylazides **13** catalized by $[IrCl_2(Cp^*)]_2$ in the presence of $AgNTf_2$ furnished phosphinic amides **14** in high yield (83% - 93%) and with diastereomeric excesses in the range of 77 – 93% (Scheme 3, eq (2)).[13] A breakthrough solution to the desymmetrization of diarylphosphinic amides has been reported by the group of F.-S. Han. They achieved the enantioselective direct ortho functionalization by Pd(II) catalysed C-H arylation of **15** with arylboronic acids **16**. Using *N*-Boc protected amino acids as chiral ligands, P-stereogenic derivatives **17** with enantioselectivities up to 98% were obtained (Scheme 3, eq (3)).[14] Similarly, the Pd(0)[15a] or Pd(II)[15b] catalysed intramolecular C-H arylations of *N*-(2-bromoaryl)diarylphosphinic amides using a TADDOL-phosphoramidite as chiral source were developed as valuable methods of synthesizing cyclic P-stereogenic phosphinic amides.

The elegant transformations indicated above suffer from a few weaknesses, such as the modest structural diversity introduced, which consists of variations in the substitution pattern of a given structural motif, the use of sophisticated reagents and the difficulties of accessing to both enantiomeric forms of the products.



Scheme 3 Stereoselective synthesis of P-stereogenic phosphinic amides via sequential nucleophilic substitution reactions (eq 1) and metal-assisted direct C-H functionalization (eq 2 – 3).

The DoLi pathways to P-stereogenic compounds shown in Schemes 1 and 2 remedy these limitations. However, regarding asymmetric induction with phosphinic amides there is clearly room for improvement (Scheme 2). The poor dr observed in the ortho deprotonation of phosphinic amide **7a** (Scheme 2) reflects the failure of the chiral auxiliary to control the stereoselective approach of the base to the diastereotopic P-phenyl rings.

We thought that higher chiral induction could be accomplished by increasing the difference of size of the groups attached to the stereogenic center. We describe here a very efficient procedure for the synthesis of P-stereogenic phosphinic amides based on the highly diastereoselective ortho deprotonation of a chiral 3,3-dimethylbutan-2-amino derivative and subsequent electrophilic trapping. Products bearing a wide variety of ortho substituents, such as alkyl, halides, azo, hydroxy, alkoxycarbonyl, trimethylstannyl, trimethylsilyl, and diphenylphosphinoyl were readily synthesized in high yield and with dr up to 98:2. The chiral auxiliary can be removed by acid catalysed methanolysis leading to P-stereogenic methyl phosphonates, precursors for the preparation of phosphine oxides and phosphines. Two additional applications are reported: the first example of benzyne insertion into the P-N bond of a P-stereogenic phosphinic amide and the formation of a complex of a chiral phosphinic amide-phosphine oxide with zinc chloride.

Results and discussion

Diastereoselective DoLi-stannylation of diphenylphosphinic amides

In order to increase steric encumbrance around the stereogenic center of the chiral auxiliary in phosphinic amide **7a** it was decided to replace the phenyl ring by a 1-naphthyl moiety and a *t*-Bu group.

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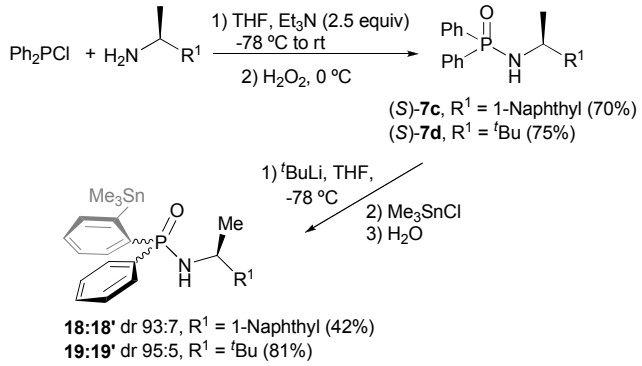
The required chiral phosphinic amides **7c** and **7d** are known in the literature. They have been prepared by enantioselective reduction of the corresponding *N*-diphenylphosphinyl ketimines.[16] The synthesis of (*R*)-**7c** by nucleophilic displacement of chloride from diphenylphosphinyl chloride with (*R*)-1-(naphthalen-1-yl)ethanamine has been also reported.[17] We used a slight modification of the latter procedure for synthesizing (*S*)-**7c** and (*S*)-**7d**, consisting of the condensation of chlorodiphenylphosphine with the corresponding amine and subsequent oxidation with H_2O_2. Column chromatography purification furnished **7c**, **7d** in high yield (Scheme 4).



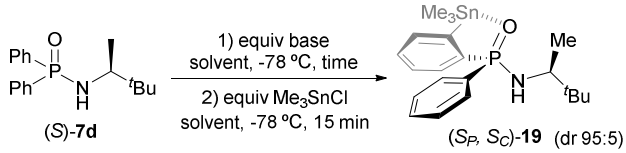
Scheme 4 Synthesis of (*S*)-**7c, 7d** and diastereoselective ortho stannylation to give **18** and **19**, respectively.

As a proof of concept, we carried out the diastereoselective ortho deprotonation-stannylation of **7c**, **7d** under reaction conditions analogue to those applied to **7a** (Scheme 2), except for the temperature and the organolithium base employed. The working temperature was lowered to -78 ºC with the aim of improving the selectivity of the proton abstraction step. This made it necessary to use a stronger base, such as ^{t}BuLi. The increased bulkiness of this base as compared with ^{n}BuLi could also benefit the chiral induction of the process.

The treatment of phosphinic amide (*S*)-**7c** bearing the (*S*)-(1-(naphthalen-1-yl)ethyl) chiral auxiliary with 3.5 equiv of ^{t}BuLi in THF (reaction concentration of 0.1 M) at -78 ºC for 16 h followed by quench with 3.5 equiv of trimethyltin chloride for 30 min afforded, after aqueous workup, a mixture of the diastereoisomers **18:18′** in a yield of 42% and a ratio of 93:7 (Scheme 4). Importantly, the analogous reaction of (*S*)-**7d** proceeded much more efficiently to give a mixture of **19:19′** in 81% yield and a ratio of 95:5 (Scheme 4). To ensure comparability of data, we achieved the same reaction using phosphinic amide **7a** as starting material. In this case, a mixture of isomers **8**:**8′** was obtained in high yield (80%), albeit with low diastereoselectivity (dr 80:20). The outcome of these reactions confirmed that steric hindrance is essential for directing the stereochemical course of the otho deprotonation of phosphinic amides **7** and revealed the superior performance of the (*S*)-3,3-dimethylbutan-2-amine as a chiral inductor with respect to that of (*S*)-1-(naphthalen-1-yl)ethanamine and (*R*)-1-phenylethanamine.

Building on these initial findings, a brief optimization of the ortho stannylation of (*S*)-**7d** was conducted (Table 1). Given that the addition of Me_3SnCl to the ortho anion produced the almost instantaneous discoloration of the solution, the time of the quenching reaction was set to 15 min for all subsequent experiments. Phosphinic amide **7d** was recovered unchanged when diethyl ether or toluene were used as solvent in the temperature range of -78 ºC to -35 ºC and the same happened in the attempted ortho deprotonation with organolithium bases such as LDA, ^{n}BuLi or the complex [^{n}BuLi·TMEDA]. Shortening the time of deprotonation with ^{t}BuLi to 1 h had an almost negligible effect on the performance of the reaction (yield to 77%, entry 2). However, the decrease of the equivalents of ^{t}BuLi and electrophile used to 2.5 was detrimental for the reaction. The yield decreased to 35% (entry 3). According to entry 2, long deprotonation times are unnecessary and may be the reason for the low yield shown in entry 3 due to partial protonation of the ortho anion. These facts suggest that abstraction of an ortho proton of **7d** could be feasible using almost stoichiometric amounts of ^{t}BuLi, which would in turn make possible to reduce the amount of electrophile added. We were pleased to see that when a 0.33 M solution of (*S*)-**7d** was deprotonated with 2.2 equiv of ^{t}BuLi for 1 h at -78 ºC in of THF and the resulting ortho anion was reacted with 1.2 equiv of Me_3SnCl allowing to reach room temperature for 15 min, compound (S_P,S_C)-**19** was obtained in 87% yield and a dr (S_P,S_C)-**19**: (R_P,S_C)-**19′** of 95:5. Column chromatography purification provided enantiomerically pure (S_P,S_C)-**19**.

Table 1 Synthesis of (S_P,S_C)-**19** via diastereoselective ortho lithiation-stannilation of **7d**.



Entry	Equiv ^{t}BuLi[a]	Equiv Me_3SnCl	Time (h)	[c] (M) THF[a]	Yield (%)
1	3.5	3.5	16	0.1	81
2	3.5	3.5	1	0.1	77
3	2.5	2.5	16	0.1	35
4	**2.2**	**1.2**	**1**	**0.33**	**87**

[a] LDA, ^{n}BuLi or [^{n}BuLi·TMEDA] failed to achieve ortho deprotonation. [b] In toluene or Et_2O as solvent **7d** was recovered quantitatively.

Recrystallization of a mixture of **19**:**19′** in ethyl acetate:hexanes afforded crystals of both compounds suitable for X-ray diffraction studies (see below). The solid-state structure revealed that the absolute configuration of the phosphorus stereocenter of the major product **19** is S_P (Fig 1a). This means that ^{t}BuLi selectively deprotonated the pro-*S P*-phenyl ring of **7d**.

Generalization of the diastereoselective DoLi-trapping of diphenylphosphinic amides

Once determined the optimized conditions for the highly diastereoselective DoLi-stannylation of (*S*)-**7d**, the scope of the methodology was investigated by treating the intermediate N,C_{ortho} dianion formed in the deprotonation step with a broad range of

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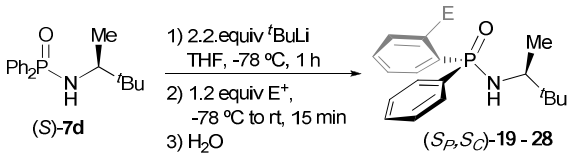
electrophiles. These were selected according to one or more of the following properties of the groups being introduced at the ortho position: (1) enable further derivatization, (2) provide a new donor site leading to a chelating hemilabile ligand and (3) increase the difference in size between the aryl groups linked to the phosphorus stereocenter. The results obtained are collected in Table 2.

Table 2 Synthesis of P-stereogenic phosphinic amides (S_P,S_C)-**19-28**.



Entry	E^+	E	Product	Yield (%)[a]	d.r.[b] (S_P:R_P)
1	Me_3SnCl	$SnMe_3$	**19**	87	95:5
2	$(ICH_2)_2$	I	**20**	80	93:7
3	$(BrCH_2)_2$	Br	**21**	72	97:3
4	C_2Cl_6	Cl	**22**	95	93:7
5	Me_3SiCl	$SiMe_3$	**23**	54	98:2
6	TsN_3	N_3	**24**	89	95:5
7	O_2	OH	**25**	66	95:5
8	Ph_2PCl	$P(O)Ph_2$	**26**	93	94:6
9	AllylBr	Allyl	**27**	74	91:9
10	AllylBr	Allyl	**27**	64	93:7[c]
11	Boc_2O	C(O)O^{t}Bu	**28**	60	96:4[d]

[a] Isolated yield. [b] Determined through integration of the ^{31}P NMR spectrum of the crude reaction mixture. [c] Reaction performed at -84 ºC. [d] Addition of electrophile at -90 ºC and hydrolysis at low temperature.

Ortho halogenation using 1,2-diiodoethane, 1,2-dibromoethane and hexachloroethane as electrophiles proceeded in high yield to give the respective iodine, bromine and chlorine derivatives **20**, **21** and **22** (entries 2-4). Compound **20** crystallised from ethyl acetate:hexanes. As expected, the solid-state structure confirmed the assignment of the *S* configuration at the phosphorus center (Fig. 1b, see below). The reaction with Me_3SiCl afforded the *ortho*-trimethylsilylaled product **23** in excellent dr (98:2), albeit in moderate yield (54%, entry 5). Phosphinic amides **19-23** provide an easy entry to more elaborated P-stereogenic products via transition-metal catalysed cross-coupling reactions. Furthermore, the *ortho*-stannylated phosphinic amide **19** is an air-stable equivalent of the *ortho*-lithiated species that can be readily regenerated through tin/lithium exchange reactions.[9]

Next, additional carbon-heteroatom bond forming reactions were assayed aimed at introducing new coordination sites that would expand the applications of P-stereogenic phosphinic amides as ligands. Tosyl azide was used as transfer reagent of the azido group to the ortho anion. The azido derivative **24** was obtained in 89% yield and a dr of 95:5 (entry 6). Organic azides are valuable ligands in coordination chemistry and can be readily converted into other important nitrogen-containing donor groups via dipolar cycloadditions, Staudinger reaction, reduction, etc. [9,18] *Ortho*-functionalization with hydroxy and diphenylphosphinoyl groups was achieved by reacting the lithiated intermediate with dioxygen and chlorodiphenylphosphine. In this way, products **25** and **26** were obtained in good to high yield, respectively (entries 7 and 8). The latter was isolated as the phosphine oxide due to quantitative oxidation of the phosphine moiety during aqueous workup.

Allyl bromide and Boc anhydride were used as representative carbon-based electrophiles for alkylation and acylation reactions. Products **27** and **28** bearing the *ortho*-allyl and the bulky *ortho*-*tert*-butylcarbonyl group, respectively were formed in good yield and high dr (entries 9 and 11).

Table 2 shows small changes of the dr depending on the electrophile used. The data are consistently reproducible through several runs, i.e., they are not a consequence of the inaccuracy of the integration of the NMR spectra. These changes may be associated to slight differences of reactivity of the electrophiles. Although the time for trapping the ortho anion is only 15 min, during that time the temperature of the reaction is allowed to increase. Less reactive electrophiles would give a chance for the appearance of competing processes such as anion traslocation[11] and thus a small degree of phosphorus epimerization would be observed. The increase of the dr in the reaction with allyl bromide as electrophile carried out at -84 ºC together with the decrease of the reaction yield (cf entries 9 and 10) support this view.

To conclude this section, one can say that we have developed a general methodology for the synthesis of enantiopure P-stereogenic phosphinic amides based on the highly diastereoselective DoLi of a C-stereogenic precursor and subsequent electrophilic quench. The method provides wide structural diversity using simple reagents and readily accessible chiral auxiliaries in both enantiomeric forms. Further derivatizations can be readily envisaged based on well-established functional group transformations.

Derivatization of P-stereogenic phosphinic amides

P-stereogenic phosphinic amides may serve as a gateway to other chiral organophosphorus compounds. Among them, without a doubt, P-stereogenic phosphines attract most attention. Access to this family of products requires the conversion of the phosphinic amide into an alkyl phosphinate. This transformation is usually achieved by acid catalysed alcoholysis of the P-N linkage.[14,19] In sterically encumbered systems harsh reaction conditions are necessary for breaking the P-N bond.[20]

The treatment of the *ortho*-iodo derivative (S_P,S_C)-**20** with a diluted methanolic solution of HCl for 48 h at ambient temperature furnished the methyl phosphinate **29** in 80% of isolated yield and with an ee of 98% (Scheme 5). In addition, the chiral auxiliary (*S*)-3,3-dimethylbutan-2-amine is recovered. As with analogue

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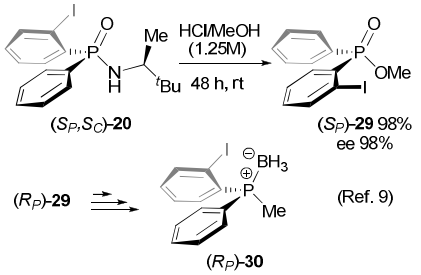
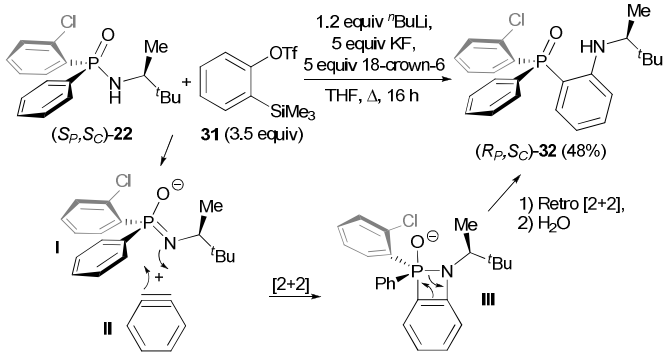
substitution reactions, inversion of the configuration at the phosphorus center is assumed.[9,19,21] Phosphinate (S_P)-**29** is the key product for the preparation of phosphines via nucleophilic displacement of the methoxy group by an organolithium or Grignard reagent and subsequent reduction of the phosphine oxide formed.[6,14] The application of this process to the synthesis of phosphine-borane complex (R_P)-**30** starting on (R_P)-**29** has been described.[9]



Scheme 5 Formal synthesis of P-stereogenic phosphines **30** via methyl phosphinate (S_P)-**29**.

Recently, it has been reported the insertion of arynes into the P-N bond of N-arylphosphinic amides as a method of synthesizing ortho aniline-substituted triarylphosphine oxides.[22] We thought that the extension of this method to P-stereogenic N-alkyl derivatives such as **19**-**28** will expand their range of applications and, at the same time, will provide insight into the stereochemical course of the reaction.

First attempt using the same reaction conditions described for *N*-arylphosphinic amides[22] was disappointing. Only a 4% conversion to unidentified products was observed. Due to this failure, we undertook a study of the parameters that may affect the reaction progress: stoichiometry of the reagents, solvent (toluene, acetonitrile, THF), base (NaH, KHMDS, Cs_2CO_3, ^{n}BuLi), temperature (range of -78 ºC to 40 ºC), time (range of 1 to 40 h) and source of benzyne (**31**, *o*-dibromobenzene). After extensive experimentation we found that the reaction of *N*-lithiated (S_P,S_C)-**22** with benzyne generated *in situ* by fluoride ion-promoted desilylation of 2-(trimethylsilyl)phenyl triflate **31** under reflux in THF in the presence of 18-crown-6 for 16 h afforded the *ortho*-aminophosphine oxide (R_P,S_C)-**32** as a single diastereoisomer in a yield of 48% (Scheme 6).



Scheme 6: Synthesis of aminophosphine oxide (R_P,S_C)-**32** by benzyne insertion into the phosphinic amide bond.

As far as we know, this is the first example of benzyne insertion into a P-stereogenic phosphinic amide bond. The use of ^{n}BuLi as a base implies that phosphinic amide **20** undergoes *N*-deprotonation to give species **I**. Charge delocalization through the P=O linkage will contribute to increase the sp^2 character of the P-N bond. In this way, benzyne insertion into the P=N bond of **I** resembles the analogous reaction of phosphazenes that provides *o*-aminophosphonium salts.[23] Assuming a stereospecific reaction pathway consisting of a [2+2] cycloaddition and subsequent [2+2] cycloreversion,[24] the benzyne insertion will take place with retention of the configuration at the phosphorus center.[25]

The aryne insertion chemistry into heteroatom-heteroatom double bonds has been very little investigated.[22,23] The mechanistic details of the process remain unknown.[26] We have carried out a DFT computational study of the formation of **32** at the M06-2X(SMD,THF)/6-311+G(d,p)//M06-2X/6-31G(d) level of theory. All energies were calculated at a temperature of 333 K. N-H deprotonation of **22** by *n*-BuLi provides species **A** in which the lithium ion is bonded to both the nitrogen and oxygen atoms of the phosphinamde moiety and completes the tetrahedral coordination by binding to two THF molecules (Figs. 1 and S18, ESI). The four-membered Li-N-P-O metallacycle of **A** is analogous to the Li-N-P-C heterocycle characteristic of C_α-lithiated phosphazenes.[27] The reaction of **A** with benzyne **II** is highly exothermic (ΔG = -35 kcal/mol), takes place through transition state **TS1** (energy barrier of $\Delta G^{\ddagger}$ = 20.0 kcal/mol) to give the [2+2] cycloadduct **E**. As in computational studies regarding Wittig olefination via 1,2-oxaphosphetane intermediates,[28] 1,2λ^5-azaphosphete **E** originates from a concerted and highly asynchronous four-center double nucleophilic addition (N to C/C to P). The structure of **TS1** reveals that the formation of the N-C1 bond is well advanced (distance of 2.463 Å) and occurs with concurrent breakdown of the N-Li bond (distance of 3.159 Å). In contrast, the interaction between C2 and the phosphorus atom is of electrostatic nature, since the P-C2 distance (4.136 Å) is larger than the sum of the respective van der Waals radii (3.5 Å). The gauche orientation of the benzyne moiety with respect to the C-N-P angle of the phosphinic amide fragment seems to be stabilized by hydrogen-bonding between the negatively charged C2 atom and the hydrogen atom linked to C3 of the nearby P-phenyl ring (distance of 2.367 Å, angle C2···H3-C3 of 162.6º).

The phosphorus atom of **E** shows a highly distorted trigonal bipyramid (TBP) geometry with the amino and *ortho*-clorophenyl ligands at the apical positions (angle N-P-C4 of 162.2º, Figs 1 and S18). The degree of distortion can be described through the topology parameter TP, having limiting values of 0 and 1 for an ideal square pyramid (SP) and TBP, respectively.[29] For **E**, the calculated TP is of 0.4. The P-N distance in **E** (2.021 Å), although longer than the sum of the van der Waals radii (1.81 Å), is almost half-way between the extreme P-N bond lengths of 1.839(6) Å[30] and 2.170(3) Å[31] found in the only two 1,2λ^5-azaphosphete characterized by X-ray crystallography. The intrinsic reaction coordinate calculation (IRC) allowed to identify three key structures, **B**, **C** and **D** in the pathway from **TS1** to **E** (Figs 1, S19). They are non stationary points lying on several plateaus along the IRC at the level of theory used. The betaine **B** arising from the formal nucleophilic addition of the nitrogen of **A** to benzyne is found at an IRC of 11.5%. Cyclization

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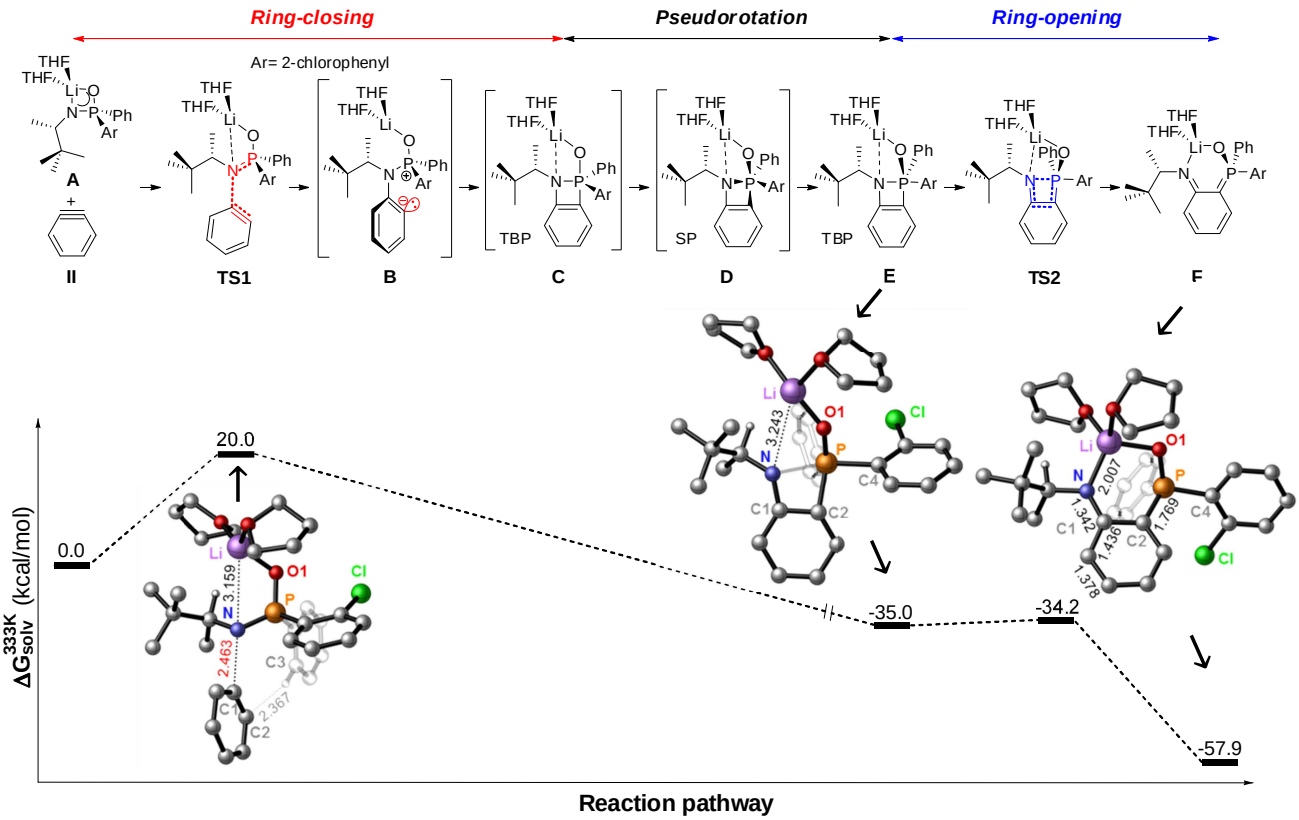

Figure 1 Computed pathway for the reaction between *N*-lithiated phosphinic amide **A** and benzyne **II**.

through nucleophilic attack of the carbanion in **B** to the positively charged phosphorus atom leads to structure **C** (IRC of 48.9%). The geometry of the phosphorus atom in **C** can be described as a distorted TBP (TP = 0.7) with the apical positions occupied by an oxygen atom and the carbon atom C2 belonging to the benzyne moiety (angle O1-P-C2 of 163.3º). P-N bond breaking in this adduct requires that the nitrogen atom departs from an apical position. The isomerization of **C** into **E** is achieved through a Berry pseudorotation using the unsubstituted P-phenyl ring as the pivot ligand.[32] The structure **D** generated halfway this process of SP geometry at the phosphorus center (TP = 0) is identified at an IRC of 72.8%. The V-shaped pattern of the topology parameter[29] connecting **C** and **E** supports the participation of a Berry pseudorotation in the **C** ⇆ **E** interconversion (Fig S19).

[2+2] Cycloreversion of **E** involves P-N/C=C bond breaking and C=N/C=P bond formation. The transformation proceeds through transition state **TS2** almost without energy barrier[32] ($\Delta G^{\ddagger}$ = 0.8 kcal/mol) to give the highly stable lithiated species of aryne insertion (R_P,S_C)-**F** (ΔG = -57.9 kcal/mol). This species is additionally stabilized by the bond formed between the nitrogen and lithium atoms (distance of 2.007 Å) that generates a six-membered metallacycle Li-N-C1-C2-P-O1. The alternating bond distances in the carbocycle bearing the nitrogen and phosphorus substituents indicate that species **F** is best described as a dearomatised phosphorus ylide stabilized by conjugation through a 1,3-cyclohexadiene system and a C=N double bond. This finding is in agreement with the structure of the intermediate identified in the insertion of benzyne into the P=N bond of phosphazenes.[23b] Importantly, the computational study predicts that the insertion reaction into (S_P,S_C)-**A** is stereospecific, which is in agreement with the experimental result, and takes place with retention of the configuration at the phosphorus atom.[33]

Finally, as an illustrative application of P-stereogenic phosphinic amides in coordination chemistry, we explored the complexation of mixed bidentate ligand **26** with zinc dichloride. Zinc complexes of phosphinic amides have received little attention. A literature search provided only one X-ray structure of this family of complexes, that of the polymeric chain generated in the reaction of *N*-(4-methyl-2-pyrimidinyl)-*P*,*P*-diphenyl-phosphinic amide with $ZnCl_2$.[34] In this

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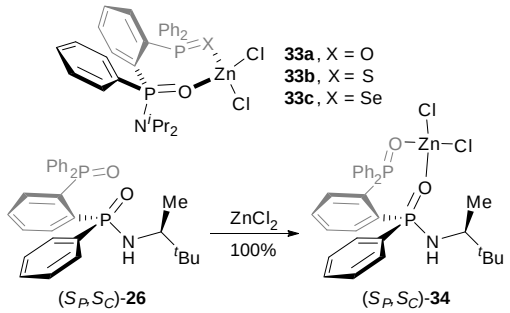
complex the ligand acts as a O,N bridging ligand through the oxygen atom of the phosphinic amide group and the less hindered nitrogen atom of the pyrimidine heterocycle. We have recently reported the synthesis and structural characterization of complexes of *o*-chalcogenophosphorylphosphinic amides (chalcogeno = oxygen, sulphur, selenium) with $ZnCl_2$, **33** (Scheme 7).[35] The reaction of ligand **26** with $ZnCl_2$ in a mixture of acetonitrile:dichloromethane (1:1) at room temperature lead to the quantitative formation of complex **34** (Scheme 7). Single crystals of **34** were obtained through slow diffusion of Et_2O into a dichloromethane:acetonitrile (1:1) solution of the compound (see next section). Molecular weight determination of the complex using soft high resolution mass spectrometry techniques failed (ESI-TOF, voltages in the range 5 V - 25 V). In all cases, only the quasimolecular ion corresponding to the free ligand was detected. This feature suggests that the ligand in complex **34** is weakly bound to the metal center.



Scheme 7 Synthesis of phosphinic amide-phosphine oxide zinc complex (S_P,S_C)-**34**.

Molecular structure of compounds 19, 19', 20 and 34

Compound **19** crystallizes in the orthorhombic space group $P2_12_12_1$ containing four discrete monomeric molecules in the unit cell. The isomer **19'** crystallizes in the tetragonal $P4_32_12$ space group with a unit cell consisting of 8 molecules. The crystal structures of **19** and **19'** are shown in Figs. 2a and 2b, and selected data are summarized in Tables S2 and S3 (see electronic supplementary information, ESI). In the following, structural data for these compounds are reported in the form **19**/**19'** due to their similarity. The P=O group is directed toward the tin atom showing an almost linear arrangement of the atoms O1, Sn1 and C19 (angle of 174.7(2)º/176.2(2)º). This linearity indicates the existence of a weak Sn-O interaction. The geometry at Sn is midway between a trigonal bipyramid and a tetrahedron as deduced from the deviation of 0.496 Å /0.474 Å of the Sn atom from the plane defined by the atoms C2, C20 and C21 (limiting value of 0.71 for an ideal tetrahedron) and the difference between the sum of the equatorial $\Sigma\theta_{eq}$ and axial $\Sigma\theta_{ax}$ angles, $\Delta\Sigma\theta = \Sigma\theta_{eq} - \Sigma\theta_{ax}$ = 35.2º/37.9º (limiting values are 0º for a tetrahedron and 90º for a trigonal bipyramid).[36] The Sn-O coordination is supported by the Sn1-O1 distance of 2.717(4) Å/2.713(4) Å, ca. 1 Å shorter than the sum of the van der Waals radii (3.69 Å), and similar to the Sn-O distance found in *ortho*-triphenylstannylphosphonates[37] (2.803(3)-2.793(2) Å). In agreement with this Sn-O contact, the Sn-Me bond distance for the pseudo-axial methyl group C20 (2.167(6) Å/ 2.196(8) Å) is slightly longer than those of the pseudo-equatorial Sn-Me bonds (limiting values of 2.118(7) and 2.149(5) Å) and the P1-O1 bond (1.492(4) Å/1.496(4) Å) is slightly elongated with respect to uncoordinated (*N*-alkyl)-*P*,*P*-diphenylphosphinic amides (average 1.485 Å).[38] However, this interaction seems to be very weak given that the P=O bond distance matches that of (*R*)-**7a**.[39,40]

Compound **20** crystallizes in the orthorhombic space group $P2_12_12_1$, having four molecules in the asymmetric unit. The molecular structure is depicted in Fig. 2c. Structural parameters for compound **20** are given in Tables S2 and S3 (ESI). Intermolecular N-H···O hydrogen bonding (H1···O1 = 2.235, <O1-H1···N1 = 162º and N1···O1^i = 2.976(5), *i*=x-1/2, -y+5/2, -z+2) generates a three-dimensional network of parallel chains running along the *a* axis Interestingly, the iodine atom and the P=O group are in the same plane (torsion angle O1-P1-C1-C2 of 176.5(3)º) with the former directed to the phosphorus atom. The I1···P1 distance of 3.607(1) Å is notably shorter than the sum of the respective van der Waals radii (3.78 Å). However, there appears to be no I···P coordination. The phosphorus atom shows the expected tetrahedral geometry with min/max bond angles of 105.0(2)º/113.2(2)º and a P1-O1 bond distance of 1.467(3) Å that is the shortest reported for *N*-alkyldiphenylphosphinic amides.[38] Only three molecular structures containing ortho P=O and iodine groups related to **20** have been reported. These are phosphine oxides in which the oxygen and iodine atoms are oriented either *syn* (torsion angle O-P-C-C of -14.40º)[41] or *gauche* (torsion angles O-P-C-C of -46.09º and 61.55º).[42] The unprecedented *anti* arrangement of the oxygen and iodine atoms of **20** may arise from the combined effect produced by the intermolecular hydrogen bonding and the intramolecular Coulombic interaction between both heteroatoms.

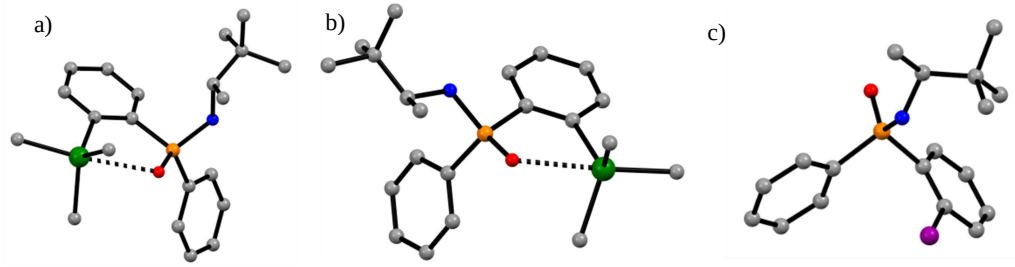


Figure 2 Crystal structures of (a) (S_P,S_C)-**19**, (b) (R_P,S_C)-**19'** and (c) (S_P,S_C)-**20**. Hydrogen atoms have been omitted for clarity. Color codes: grey:carbon; orange: phosphorus; blue: nitrogen; red: oxygen; green: tin and purple: iodine.

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Complex **34** is a monomer which crystallise in the orthorhombic space group ($P2_12_12_1$). The molecular structure is presented in Fig. 3. Selected crystal data and bond lengths and angles are given in Tables S2 and S3, respectively (ESI). The structure and bonding parameters in complex **34** are very similar to those of the analogous complex **33a**.[35] As expected, compound **26** acts as an O,O-chelate to bind to the zinc atom of $ZnCl_2$. This coordination mode gives rise to a seven-membered metallacycle that exist in a twist-boat conformation. The zinc atom is at the center of a distorted tetrahedron delimited by the two oxygen atoms and the two chlorine atoms of the molecule.

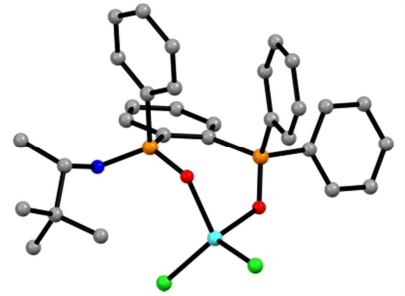

Figure 3 Crystal structure of the complex **34**. Hydrogen atoms have been omitted for clarity. Color codes: grey:carbon; orange: phosphorus; blue: nitrogen; red: oxygen; cyano: zinc and green: chlorine.

Major differences between the structures of complexes **33** and **34** proceed from the geometry of the metallacycle involving the metal center. The bond angle Cl1-Zn1-Cl2 increases from 114.89(5)º in **33** to 120.75(3)º in **34** , whereas the metallacycle of the latter complex is less twisted (cf torsion angles O1-Zn1-O2-P2 of 21.47º and 3.77º in **33** and **34**, respectively). As for the tin complexes **19**/**19'**, no hydrogen bonding is observed for the N-H bond of **34**. The geometry of the benzometallacycle fragment present in **34** can be considered as a distorted half-boat having the metal at the apex of the boat substructure connected with the plane defined by the benzo condensed ring and the two phosphorus atoms. In this arrangement, the approach to the zinc atom through the *pro-S* face would be favored. Access to the metal ion through the *pro-R* face would be hindered by the two pseudo-axial P-phenyl substituents. Compound **34** is the first example of an enantiomerically pure zinc complex of a mixed phosphinic amide-phosphine oxide ligand.

Conclusions

We have developed a new method for the efficient synthesis of enantiopure P-stereogenic diarylphosphinic amides consisting of the directed ortho lithiation of (*S*)-*N*-(3,3-dimethylbutan-2-yl)-*P*,*P*-diphenylphosphinic amide by treatment with 2.2 equiv of *t*-BuLi at -78 ºC and subsequent trapping of the ortho anion with a large variety of electrophiles. Major advantages associated with this methodology include the excellent stereocontrol of the deprotonation step affording diastereomeric ratios up to 98:2, the feasibility of introducing wide structural diversity via carbon-carbon and carbon-heteroatom bond forming reactions (C-N, C-O, C-Si, C-Sn, C-P, C-halogen with halogen = Cl, Br and I), the easy availability of both enantiomeric forms of the starting material, and the mild reaction conditions employed. The stereochemical course of the reaction has been ascertained through the X-ray structures of both *ortho*-trimethyltin diastereosiomers and the major *ortho*-iodo isomer. The chiral auxiliary can be recovered through acid catalysed methanolysis of the P-N bond. The resulting methyl phosphinate is the known entry to P-stereogenic phosphine oxides and phosphines through well established procedures. Furthermore, we have achieved for the first time the benzyne insertion into the P-N bond of a P-stereogenic phosphinic amide. The reaction provides *ortho*-aminophosphine oxides with retention of the configuration at the phosphorus center as shown by computational studies. Additional derivatisation can be envisaged through functional group transformations involving the ortho substituents. The ability of the new P-stereogenic compounds to act as ligands is supported by the synthesis and x-ray structural characterization of the complex arising from the reaction of the orto- phosphinic amide-phosphine oxide derivative with zinc dichloride.

Experimental

Materials and methods

All reactions and manipulations were carried out in a dry N_2 gas atmosphere using standard Schlenk procedures. THF was distilled from sodium/benzophenone immediately prior to use. Commercial reagents were distilled prior to their use, except alkyllithiums, quiral amines and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate. In the reaction with molecular oxygen an O_2 filled balloon was used. TLC was performed on Merck plates with aluminum backing and silica gel 60 F_{254}. Purifications were carried out by column chromatography using silica gel 60 (40-63 μm) from Scharlau and different mixtures of ethyl acetate:hexanes as eluent.

NMR spectra were measured in a Bruker Avance 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz; ^{31}P, 121.49 MHz) and a Bruker Avance 500 spectrometer equipped with a third radiofrequency channel (^{1}H, 500.13 MHz; ^{13}C, 125.76 MHz; ^{31}P, 202.45 MHz)

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using a 5 mm QNP $^{1}H/^{13}C/^{19}F/^{31}P$ probe and a direct 5 mm TBO $^{1}H/^{31}P/BB$ triple probe, respectively. The spectral references used were internal tetramethylsilane for ^{1}H and ^{13}C, external 85% H_3PO_4 for ^{31}P. Diastereoselectivities were determined by integration of ^{31}P NMR spectra of the crude reactions. Quantitative ^{31}P NMR measurements were performed by using the inverse-gated pulse sequence, an excitation pulse of 15º and a repetition delay of 2s. Standard Bruker software was used for acquisition and processing routines. Infrared spectra were recorded in a Bruker Alpha FTIR equipment. High resolution mass spectra were recorded on Agilent Technologies LC/MSD TOF and HP 1100 MSD equipment with electrospray ionization. Melting points were recorder on a Büchi B-540 capillary melting point apparatus and are uncorrected.

X-ray crystallography

Single crystal X-ray diffraction data for compounds **19** and **20** were collected on a Bruker AXS Smart Apex diffractometer using graphite monochromatic MoKα radiation (λ = 0.71069 Å) at 100(2) K and 293(2) K, respectively. Data collection and cell refinement were performed with Bruker SMART program.[43] For compound **19'** and **34**, the crystallographic data were collected on a Bruker D8 Venture diffractometer at 100 K, using CuKα radiation (λ = 1.54178 Å). Data collection and cell refinement were performed with Bruker Instrument Service v4.2.2 and APEX2,[44] respectively. Data reduction for **19**, **19'**, **20** and **34** were carried out using SAINT.[45] Empirical multiscan absorption correction using equivalent reflections was performed with the SADABS program.[46] The structure solutions and full-matrix least-squares refinements based on F^2 were performed with the SHELXS-97 and SHELXL-97 program packages.[47] All atoms except hydrogen were refined anisotropically. Hydrogen atoms were treated by a mixture of independent and constrained refinement. The structures were drawn by ORTEP-3[48] and Mercury programs.[49] The thermal ellipsoids are shown in Fig. S23-S26 (ESI).

Computational Methods

The geometries of all compounds were optimized with the meta-hybrid density functional M06-2X[50] and a 6-31G(d) basis set in gas phase. Single point energy calculations were performed with the M06-2X functional and a 6-311+G(d,p) basis. The SMD[51] solvation model was used in M06-2X single point energy calculations. THF was used as solvent. All stationary points were characterized as minimum or transition states and checked by vibrational analysis. The reported free energies and enthalpies include zero-point energies and thermal corrections calculated at 298K. All calculations were performed with Gaussian 09.[52] The 3D structures of molecules were generated using CYLView (http://www.cylview.org).

General procedure for the preparation of phosphinic amides 5 and 7. To a cooled at -78 ºC solution of 1.1 equivalents of chiral amine and 2.5 equivalents of Et_3N in THF, 1.0 equivalents of diphenylphosphine chloride was added slowly. The reaction was allowed to reach room temperature and stirred for 2 h. Then, 0.3 mL/mmol of a 33% aqueous solution of hydrogen peroxide was added at 0 ºC. After 15 min, the reaction mixture was poured into water and extracted with methylene chloride (3x5mL). The organic layers were washed with a saturated ammonium chloride solution (2x5 mL), dried over Na_2SO_4, filtered and the solvent was removed in a rotavapor. Purification was carried out by flash chromatography. See ESI for the numbering scheme used.

(*S*)-*N*-(1-(naphthalen-1-yl)ethyl)-*P,P*-diphenylphosphinic amide, 7c: Yield after chromatography (50% AcOEt:Hexanes): 70%. White solid. Mp: 165-166 ºC. $[\alpha]_D^{20}$ +60.6 (c 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.72 (d, 3H, $^{3}J_{HH}$ 6.7 Hz, H2´), 3.49 (dd, 1H, $^{3}J_{HH}$ 9.1 Hz, $^{2}J_{PH}$ 5.7 Hz, H1), 5.26 (tc, 1H, $^{3}J_{PH} = {}^{3}J_{HH}$ 9.1, $^{3}J_{HH}$ 6.7 Hz, H2), 7.26 (m, 2H, H15), 7.37 (m, 1H, H16), 7.43 (m, 1H, H6), 7.44 (m, 2H, H15´), 7.47 (m, 1H, H7), 7.49 (m, 1H, H16´), 7.50 (m, 1H, H11), 7.66 (m, 1H, H12), 7.77 (m, 1H, H10), 7.78 (m, 2H, H14), 7.84 (m, 1H, H8), 7.89 (m, 1H, H5), 7.94 (m, 2H, H14´) ppm. ^{13}C NMR ($CDCl_3$) δ 26.1 (d, $^{3}J_{PC}$ 2.5 Hz, C2´), 47.1 (d, $^{2}J_{PC}$ 0.6 Hz, C2), 122.5 (s, C12), 123.0 (s, C5), 125.4 (s, C11), 125.6 (s, C7), 126.0 (s, C6), 127.8 (s, C10), 128.3 (d, $^{3}J_{PC}$ 12.7 Hz, C15), 128.4 (d, $^{3}J_{PC}$ 12.4 Hz, C15´), 128.7 (s, C8), 130.1 (s, C4), 131.7 (d, $^{4}J_{PC}$ 2.8 Hz, C16), 131.8 (d, $^{4}J_{PC}$ 2.8 Hz, C16´), 131.9 (d, $^{2}J_{PC}$ 9.3 Hz, C14), 132.1 (d, $^{1}J_{PC}$ 130.0 Hz, C13), 132.2 (d, $^{2}J_{PC}$ 9.8 Hz, C14´), 133.3 (d, $^{1}J_{PC}$ 127.5 Hz, C13´), 133.8 (s, C9), 141.1 (s, $^{3}J_{PC}$ 7.0 Hz, C3) ppm. ^{31}P NMR ($CDCl_3$) δ 23.7 (s) ppm. IR (ATR, υ cm^{-1}): 3175 (bs, NH), 1183 (s, P=O). HRMS (ESI) calcd for $C_{24}H_{23}PNO$: 372.1517 $(MH)^+$, found: 372.1515.

(*S*)-*N*-(3,3-dimethylbutan-2-yl)-*P,P*-diphenylphosphinic amide, 7d: Yield after chromatography (50% AcOEt:Hexanes): 75%. White solid. Mp: 143-144 ºC. $[\alpha]_D^{20}$ +121.4 (c 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9H, H4), 1.21 (d, 3H, $^{3}J_{HH}$ 6.7 Hz, H2´), 2.68 (dd, 1H, $^{3}J_{HH}$ 11.1 Hz, $^{2}J_{PH}$ 5.2 Hz, H1), 2.90 (ddc, 1H, $^{3}J_{HH}$ 11.1, $^{3}J_{PH}$ = 8.7, $^{3}J_{HH}$ 6.7 Hz, H2), 7.45 (m, 6H, H7-H8), 7.92 (m, 4H, H6) ppm. ^{13}C NMR ($CDCl_3$) δ 19.2 (d, $^{3}J_{PC}$ 1.9 Hz, C2´), 26.4 (s, C4), 34.8 (d, $^{3}J_{PC}$ 7.2 Hz, C3), 56.0 (d, $^{2}J_{PC}$ 2.7 Hz, C2), 128.2 (d, $^{3}J_{PC}$ 12.6 Hz, C7), 128.4 (d, $^{3}J_{PC}$ 12.4 Hz. C7´), 131.6 (d, $^{4}J_{PC}$ 2.8 Hz, C8), 131.7 (d, $^{4}J_{PC}$ 2.7 Hz, C8´), 132.0 (d, $^{2}J_{PC}$ 9.4 Hz, C6), 132.3 (d, $^{2}J_{PC}$ 9.0 Hz, C6´), 132.6 (d, $^{1}J_{PC}$ 130.2 Hz, C5), 133.6 (d, $^{1}J_{PC}$ 127.9 Hz, C5´) ppm. ^{31}P NMR ($CDCl_3$) δ 22.5 (s) ppm. IR (ATR, υ cm^{-1}): 3298 (bs, NH), 1185 (s, P=O), 1106 (s). HRMS (ESI) calcd for $C_{18}H_{25}PNO$: 302.1674 (MH^+), found: 302.1671.

Optimized conditions for the diastereoselective synthesis of P-quiral phosphinic amides. To a solution of phosphinic amide **7** (1 g, 3.32 mmol) in 10 mL of THF, a solution of *tert*-BuLi (4.3 mL of a 1.7 M solution in pentane, 2.2 mmol) was added at -78 ºC (acetone/CO_2). After one hour of metallation, the corresponding electrophile (1.2 mmol) was added. The reaction was allowed to reach room temperature gradually stirring for 15 additional minutes. Then, the reaction was poured out into water, extracted with ethyl acetate (3x15 mL), washed with ammonium chloride (sat., 2x15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification through column chromatography (AcOEt:hexanes) afforded reaction products. Pure diastereomers were obtained by recrystallization using ethyl acetate:hexane as solvent except for **14a** where *tert*-butyl methyl ether was used. See ESI for the numbering scheme used.

(*S* *or* *R*)-*N*-((*S*)-1-(naphthalen-1-yl)ethyl)-*P*-phenyl-*P*-(2-(trimethylstannyl)phenyl)phosphinic amide, 18 or 18´: Yield after chromatography (50% AcOEt:Hexanes): 40%. White solid. Mp: 165-166 ºC. $[\alpha]_D^{20}$ +85.2 (c 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.42 (d, 9H, $^{3}J_{SnH}$ 55.6 Hz, H14´), 1.73 (d, 3H, $^{3}J_{HH}$ 6.7 Hz, H2´), 3.38 (dd, 1H, $^{3}J_{HH}$ 8.9, $^{2}J_{PH}$ 5.5 Hz, H1), 5.16 (tc, 1H, $^{3}J_{PH} = {}^{3}J_{HH}$ 8.9, $^{3}J_{HH}$ 6.7 Hz, H2), 7.13 (tdd, 1H, $^{3}J_{HH}$ 7.5, $^{4}J_{PH}$ 3.6, $^{4}J_{HH}$ 1.3 Hz, H17), 7.37 (m, 1H, H16), 7.46 (m, 2H, H21), 7.5 (m, H6+H7+H11+H22), 7.63 (m, 1H, H12), 7.65 (m, 1H, H18), 7.78 (m, 1H, H15), 7.79 (m, 1H, H10), 7.81 (m, 1H, H5), 7.86 (m, 1H, H8), 7.96 (m, 2H, H20) ppm. ^{13}C NMR ($CDCl_3$) δ -4.8 (dd, $^{4}J_{PC}$ 0.9, $^{1}J_{SnC}$ 380.1 Hz, C14´), 26.1 (d, $^{3}J_{PC}$ 2.5 Hz, C2´), 47.3 (s, C2), 122.6 (s,

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C12), 122.9 (s, C5), 125.5 (s, C11), 125.6 (s, C7), 126.1 (s, C6), 127.8 (s, C10), 127.8 (d, $^3J_{PC}$ 12.7 Hz, C17), 128.6 (d, $^3J_{PC}$ 12.3 Hz, C21), 128.9 (s, C8), 130.1 (s, C4), 130.7 (d, $^4J_{PC}$ 3.3 Hz, C16), 131.9 (d, $^4J_{PC}$ 2.9 Hz, C22), 131.9 (d, $^2J_{PC}$ 9.5 Hz, C20), 132.4 (d, $^2J_{PC}$ 13.4 Hz, C18), 133.6 (d, $^1J_{PC}$ 125.6 Hz, C19), 133.9 (s, C9), 136.4 (d, $^1J_{PC}$ 134.2 Hz, C13), 137.0 (d, $^2J_{PC}$ 17.7 Hz, C15), 141.1 (s, $^3J_{PC}$ 7.3 Hz, C3), 151.3 (d, $^2J_{PC}$ 18.7 Hz, C14) ppm. ^{31}P NMR ($CDCl_3$) δ 25.3 (d, $^3J_{SnP}$ = 19.3 Hz) ppm. IR (ATR, υ cm^{-1}): 3228 (bs, NH), 1174 (bs, P=O). HRMS (ESI) calcd for $C_{26}H_{27}NOPSn$: 520.0858 $(M\text{-}Me)^+$, found: 520.0856.

(*S*)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenyl-*P*-(2-(trimethylstannyl)phenyl)phosphinic amide, 19: Yield after chromatography (20% AcOEt:Hexanes): 80%. White solid. Mp: 123-124 ºC. $[\alpha]_D^{20}$ +234.3 (c 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.36 (d, 9H, $^2J_{SnH}$ 55.6 Hz, H6´), 0.91 (s, 9H, H4), 1.25 (d, 3H, $^3J_{HH}$ 6.5 Hz, H2´), 2.67 (dd, 1H, $^3J_{HH}$ 11.2, $^2J_{PH}$ 3.0 Hz, H1), 2.82 (ddc, 1H, $^3J_{HH}$ 11.4, $^3J_{PH}$ 8.1, $^3J_{HH}$ 6.6 Hz, H2), 7.39 (tdd, 1H, $^3J_{HH}$ 7.4, $^4J_{PH}$ 3.6, $^4J_{HH}$ 1.4 Hz, H9), 7.46 (m, 1H, H8), 7.47 (m, 3H, m, H13+H14), 7.80 (m, 1H, H7), 7.90 (m, 1H, H10), 7.95 (m, 2H, H12) ppm. ^{13}C NMR ($CDCl_3$) δ -4.7 (dd, $^4J_{PC}$ 0.9, $^1J_{SnC}$ 381.5 Hz, C6´), 19.3 (d, $^3J_{PC}$ 1.2 Hz, C2´), 26.5 (s, C4), 34.9 (d, $^3J_{PC}$ 8.4 Hz, C3), 56.0 (d, $^2J_{PC}$ 2.9 Hz, C2), 127.8 (d, $^3J_{PC}$ 12.5 Hz, C9), 128.5 (d, $^3J_{PC}$ 12.2 Hz, C13), 130.5 (d, $^4J_{PC}$ 3.4 Hz, C8), 131.7 (d, $^4J_{PC}$ 2.7 Hz, C14), 131.8 (d, $^2J_{PC}$ 9.0 Hz, C12), 132.7 (d, $^2J_{PC}$ 13.1 Hz, C10), 134.1 (d, $^1J_{PC}$ 125.8 Hz, C11), 136.5 (d, $^1J_{PC}$ 136.5 Hz, C5), 136.9 (d, $^3J_{PC}$ 17.5 Hz, C7), 151.7 (d, $^2J_{PC}$ 18.6 Hz, C6) ppm. ^{31}P NMR ($CDCl_3$) δ 24.4 (d, $^3J_{SnP}$ 17.5 Hz) ppm. IR (ATR, υ cm^{-1}): 3339 (w, NH), 1180 (s, P=O). HRMS (ESI) calcd for $C_{21}H_{32}PNOSnNa$: 488.1145 $(M+Na)^+$, found: 488.1155.

(*R*)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenyl-*P*-(2-(trimethylstannyl)phenyl)phosphinic amide, 19´: Yield after chromatography (20% AcOEt:Hexanes): 4%. White solid. Mp: 111-112 ºC. $[\alpha]_D^{20}$ -58.3 (c 0.6, CH_2Cl_2). ^{1}H NMR δ ($CDCl_3$) 0.33 (d, 9H, $^2J_{SnH}$ 55.8 Hz, H6´), 0.92 (s, 9H, H4), 1.16 (d, 3H, $^3J_{HH}$ 6.6 Hz, H2´), 2.66 (dd, 1H, $^3J_{HH}$ 11.1 Hz, $^2J_{PH}$ 6.1 Hz, H1), 2.88 (ddc, $^3J_{HH}$ 11.1, $^3J_{PH}$ 9.1, 1H, $^3J_{HH}$ 6.6 Hz, H2), 7.47 (m, 5H, H8+H9+H13+H14), 7.80 (m, 1H, H7), 7.97 (m, 3H, H10+H12) ppm. ^{13}C NMR δ ($CDCl_3$) -4.8 (dd, $^4J_{PC}$ 0.9, $^1J_{Sn,C}$ 380.5 Hz, C6´), 19.1 (d, $^3J_{PC}$ 2.5 Hz, C2´), 26.6 (s, C4), 34.8 (d, $^3J_{PC}$ 6.2 Hz, C3), 56.0 (d, $^2J_{PC}$ 2.7 Hz, C2), 127.8 (d, $^3J_{PC}$ 11.9 Hz, C9), 128.4 (d, $^3J_{PC}$ 11.9 Hz, C13), 130.6 (d, $^4J_{PC}$ 3.6 Hz, C8), 131.6 (d, $^4J_{PC}$ 2.7 Hz, C14), 132.1 (d, $^2J_{PC}$ 12.8 Hz, C10), 132.3 (d, $^2J_{PC}$ 9.6 Hz, C12), 133.2 (d, $^1J_{PC}$ 127.4 Hz, C11), 137.1 (d, $^3J_{PC}$ 17.3 Hz, C7), 138.1 (d, $^1J_{PC}$ 133.5 Hz, C5), 151.2 (d, $^2J_{PC}$ 18.4 Hz, C6) ppm. ^{31}P NMR δ ($CDCl_3$): 24.3 (d, $^3J_{SnP}$ 18.8 Hz) ppm. IR (ATR, υ cm^{-1}): 3382 (d, NH), 1193 (bs, P=O. HRMS (ESI) calcd for $C_{20}H_{29}NOPSn$: 450.1012 $(M\text{-}Me)^+$, found: 450.1012.

(*S*)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-(2-iodophenyl)-*P*-phenylphosphinic amide, 20: Yield after chromatography (50% AcOEt:Hexanes): 80%. White solid. Mp: 121-122 ºC. $[\alpha]_D^{20}$ +148.1 (c 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 9H, H4), 1.30 (d, 3H, $^3J_{HH}$ = 6.6 Hz, H2´), 3.24 (dd, 1H, $^2J_{PH}$ = 14.3 Hz, $^3J_{HH}$ 10.3 Hz, H1), 3.41 (ddc, 1H, $^3J_{PH}$ 19.7 Hz, $^3J_{HH}$ 10.1Hz, $^3J_{HH}$ 6.6 Hz, H2), 7.17 (tdd, 1H, $^3J_{HH}$ 7.8, $^4J_{PH}$ 1.2, $^4J_{HH}$ 1.7 Hz, H8), 7.42 (m, 2H, H13), 7.51 (m, 2H, H14+H9), 7.66 (m, 2H, H12), 7.91 (ddd, 1H, $^3J_{HH}$ 7.8, $^4J_{PH}$ 3.9, $^4J_{HH}$ 0.7 Hz, H7), 8.31 (ddd, 1H, $^3J_{PH}$ 12.1, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.7 Hz, H10) ppm. ^{13}C NMR ($CDCl_3$) δ 19.6 (d, $^3J_{PC}$ 3.0 Hz, C2´), 26.4 (s, C4), 34.7 (d, $^3J_{PC}$ 4.1 Hz, C3), 55.3 (d, $^2J_{PC}$ 1.8 Hz, C2), 98.8 (d, $^2J_{PC}$ 7.8 Hz, C6), 127.8 (d, $^3J_{PC}$ 10.8 Hz, C9), 128.4 (d, $^3J_{PC}$ 13.2 Hz, C13), 131.5 (d, $^2J_{PC}$ 10.8 Hz, C12), 131.8 (d, $^4J_{PC}$ 3.0 Hz, C14), 132.6 (d, $^4J_{PC}$ 2.4 Hz, C8), 133.6 (d, $^1J_{PC}$ 129.3 Hz, C11), 136.0 (d, $^2J_{PC}$ 7.8 Hz, C10), 137.2 (d, $^1J_{PC}$ 126.7 Hz, C5), 140.9 (d, $^3J_{PC}$ 9.9 Hz, C7) ppm. ^{31}P NMR ($CDCl_3$) δ 26.6 ppm. IR (ATR, υ cm^{-1}): 3402 (bs, NH), 1193 (s, P=O). HRMS (ESI) calcd for $C_{18}H_{24}PNOI$: 428.0640 $(MH)^+$, found: 428.0629.

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(*S*)-*P*-(2-bromophenyl)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenylphosphinic amide, 21: Yield after chromatography (50% AcOEt:Hexanes): 72%. White solid. Mp: 139-140 ºC. $[\alpha]_D^{20}$ +121.1 (c 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 9H, H4), 1.32 (d, 3H, $^3J_{HH}$ 6.6 Hz, H2´), 3.16 (dd, 1H, $^2J_{PH}$ 14.4, $^3J_{HH}$ 10.1 Hz, H1), 3.40 (tc, 1H, $^3J_{PH}$ = $^3J_{HH}$ 10.1, $^3J_{HH}$ 6.6 Hz, H2), 7.39 (tdd, 1H, $^3J_{HH}$ 7.9, $^4J_{HH}$ 1.9, $^4J_{PH}$ 1.4 Hz, H8), 7.43 (m, 2H, H13), 7.50 (m, 1H, H9), 7.52 (m, 1H, H14), 7.60 (ddd, 1H, $^3J_{HH}$ 7.9, $^4J_{PH}$ 4.2, $^4J_{HH}$ 1.2 Hz, H7), 7.69 (m, 2H, H12), 8.30 (ddd, 1H, $^3J_{PH}$ 12.3, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.9 Hz, H10) ppm. ^{13}C NMR ($CDCl_3$) δ 19.6 (d, $^3J_{PC}$ 2.9 Hz, C2´), 26.3 (3C, s, C4), 34.6 (d, $^3J_{PC}$ 4.1 Hz, C3), 55.1 (d, $^2J_{PC}$ 1.7 Hz, C2), 124.7 (d, $^2J_{PC}$ 5.9 Hz, C6), 127.3 (d, $^3J_{PC}$ 10.7 Hz, C9), 128.3 (d, $^3J_{PC}$ 13.3 Hz, C13), 131.1 (d, $^2J_{PC}$ 10.9 Hz, C12), 131.7 (d, $^4J_{PC}$ 2.9 Hz, C14), 132.9 (d, $^4J_{PC}$ 2.4 Hz, C8), 133.7 (1d, $^3J_{PC}$ 8.4 Hz, C7), 134.3 (1d, $^1J_{PC}$ 124.9 Hz, C11), 134.4 (d, $^1J_{PC}$ 130.7 Hz, C5), 136.0 (d, $^3J_{PC}$ 7.0 Hz, C10) ppm. ^{31}P NMR ($CDCl_3$) δ 24.9 ppm. IR (ATR, υ cm^{-1}): 3229 (bs, NH), 1184 (s, P=O). HRMS (ESI) calcd for $C_{18}H_{24}PNOBr$: 380.0779 $(MH)^+$, found: 380.0779.

(*S*)-*P*-(2-chlorophenyl)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenylphosphinic amide, 22: Yield after chromatography (50% AcOEt:Hexanes): 95%. White solid. Mp: 142-143 ºC. $[\alpha]_D^{20}$ +121.1 (c 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 9H, H4), 1.28 (d, 3H, $^3J_{HH}$ 6.6 Hz, H2´), 3.05 (dd, 1H, $^2J_{PH}$ 13.4 Hz, $^3J_{HH}$ 10.4 Hz, H1), 3.34 (ddc, 1H, $^3J_{HH}$ 10.4, $^3J_{PH}$ 9.7, $^3J_{HH}$ 6.6 Hz, H2), 7.43 (m, 6H, H8+H9+H10+H13+H14), 7.72 (m, 2H, H12), 8.23 (m, 1H, H7) ppm. ^{13}C NMR ($CDCl_3$) δ 19.4 (d, $^3J_{PC}$ 2.4 Hz, C2´), 26.3 (s, C4), 34.5 (d, $^3J_{PC}$ 4.2 Hz, C3), 55.0 (d, $^2J_{PC}$ 1.8 Hz, C2), 126.7 (d, $^2J_{PC}$ 10.8 Hz, C9), 128.2 (d, $^3J_{PC}$ 13.4 Hz, C13), 130.2 (d, $^3J_{PC}$ 7.8 Hz, C7), 131.0 (d, $^2J_{PC}$ 11.0 Hz, C12), 131.6 (d, $^4J_{PC}$ 2.9 Hz, C14), 132.3 (d, $^1J_{PC}$ 124.4 Hz, C11), 132.8 (d, $^4J_{PC}$ 2.3 Hz, C8), 134.4 (d, $^1J_{PC}$ 131.6 Hz, C5), 135.3 (d, $^2J_{PC}$ 4.7 Hz, C6), 135.4 (d, $^2J_{PC}$ 6.9 Hz, C10) ppm. ^{31}P NMR ($CDCl_3$) δ 23.5 ppm. IR (ATR, υ cm^{-1}): 3231 (bs, NH), 1186 (s, P=O). HRMS (ESI) calcd for $C_{18}H_{24}PNOCl$: 336.1284 $(MH)^+$, found: 336.1276.

(*S*)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenyl-*P*-(2-(trimethylsilyl)phenyl)phosphinic amide, 23: Yield after chromatography (20% AcOEt:Hexanes): 54%. Colorless oil. $[\alpha]_D^{20}$ +238.3 (c 0.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.45 (s, 9H, H6´), 0.90 (s, 9H, H4), 1.25 (d, 3H, $^3J_{HH}$ 6.6 Hz, H2´), 2.59 (dd, 1H, $^3J_{HH}$ 10.6 Hz, $^2J_{PH}$ 4.5 Hz, H1), 2.88 (ddc, 1H, $^3J_{HH}$ 10.6, $^3J_{PH}$ 8.3, $^3J_{HH}$ 6.6 Hz, H2), 7.41 (m, 4H, H9+H13+H14), 7.45 (m, 1H, H8), 7.78 (m, 1H, H7), 7.90 (m, 2H, H12), 7.92 (m, 1H, H10) ppm. ^{13}C NMR ($CDCl_3$) δ 2.1 (s, C6´), 19.0 (d, $^3J_{PC}$ 1.7 Hz, C2´), 26.5 (s, C4), 34.8 (d, $^3J_{PC}$ 7.2 Hz, C3), 56.2 (d, $^2J_{PC}$ 2.8 Hz, C2), 128.0 (d, $^3J_{PC}$ 12.6 Hz, C9), 128.3 (d, $^3J_{PC}$ 12.2 Hz, C13), 130.4 (d, $^4J_{PC}$ 3.1 Hz, C14), 131.3 (d, $^4J_{PC}$ 2.8 Hz, C8), 131.8 (d, $^2J_{PC}$ 9.0 Hz, C12), 133.7 (d, $^2J_{PC}$ 12.3 Hz, C10), 135.1 (d, $^1J_{PC}$ 123.4 Hz, C11), 136.1 (d, $^3J_{PC}$ 16.3 Hz, C7), 137.3 (d, $^1J_{PC}$ 133.7 Hz, C5), 147.1 (d, $^2J_{PC}$ 18.0 Hz, C6) ppm. ^{31}P NMR ($CDCl_3$) δ 25.1 ppm. IR (ATR, υ cm^{-1}): 3065 (d, NH), 1110 (s, P=O). HRMS (ESI) calcd for $C_{21}H_{33}PNOSi$: 374.2069 $(MH)^+$, found: 374.2068.

(*S*)-*P*-(2-azidophenyl)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenylphosphinic amide, 24: Yield after chromatography (50% AcOEt:Hexanes): 89%. Brown oil. $[\alpha]_D^{20}$ -45.1 (c 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9H, H4), 1.21 (m, 3H, H2´), 3.22 (m, 2H, H1+H2), 7.20 (ddd, 1H, $^3J_{HH}$ 8.1, $^4J_{PH}$ 5.1, $^4J_{HH}$ 1.0 Hz, H7), 7.27 (tdd, 1H, $^3J_{HH}$ 7.6 Hz, $^3J_{PH}$ 2.0 Hz, $^4J_{HH}$ 1.0 Hz, H9), 7.44 (m, 3H,

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H13+H14), 7.53 (tdd, 1H, $^3J_{HH}$ 7.5 Hz, $^4J_{HH}$ 1.6 Hz, $^4J_{PH}$ 1.0 Hz, H8), 7.79 (m, 2H, H12), 8.07 (ddd, 1H, $^3J_{PH}$ 13.2, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6 Hz, H10) ppm. ^{13}C NMR ($CDCl_3$) δ 19.2 (d, $^3J_{PC}$ 2.4 Hz, C2´), 26.3 (s, C4), 34.6 (d, $^3J_{PC}$ 4.8 Hz, C3), 55.1 (d, $^2J_{PC}$ 1.6 Hz, C2), 118.3 (d, $^3J_{PC}$ 7.9 Hz, C7), 124.9 (d, $^3J_{PC}$ 11.4 Hz, C9), 125.0 (d, $^1J_{PC}$ 121.5 Hz, C5), 128.2 (d, $^3J_{PC}$ 13.1 Hz, C13), 131.4 (d, $^2J_{PC}$ 10.6 Hz, C12), 131.5 (d, $^4J_{PC}$ 3.0 Hz, C14), 133.0 (d, $^4J_{PC}$ 2.4 Hz, C8), 134.8 (d, $^2J_{PC}$ 6.5 Hz, C10), 135.0 (d, $^1J_{PC}$ 130.0 Hz, C11), 140.5 (d, $^2J_{PC}$ 4.1 Hz, C6) ppm. ^{31}P NMR ($CDCl_3$) δ 23.00 ppm. IR (ATR, υ cm^{-1}): 3246 (bs, NH), 2126 (s, N=N), 2094 (s, N=N), 1189 (s, P=O). HRMS (ESI) calcd for $C_{18}H_{24}PN_4O$: 343.1688 $(MH)^+$, found: 343.1684.

(*S*)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-(2-hydroxyphenyl)-*P*-phenylphosphinic amide, 25: Yield after chromatography (50% AcOEt:Hexanes): 66%. White solid. Mp: 139-141 ºC. $[\alpha]_D^{20}$ +38.1 (c 0.5, CH_2Cl_2). ^{1}H NMR δ ($CDCl_3$) 0.92 (s, 9H, H4), 1.31 (m, 3H, H2´), 2.94 (m, 2H, H1+H2), 6.83 (dddd, 1H, $^3J_{HH}$ 7.7, $^3J_{HH}$ 7.3, $^4J_{PH}$ 2.9, $^4J_{HH}$ 1.0 Hz, H9), 6.91 (ddd, 1H, $^3J_{HH}$ 8.4, $^4J_{PH}$ 5.3, $^4J_{HH}$ 1.2 Hz, H7), 7.36 (dddd, 1H, $^3J_{HH}$ 8.5, $^3J_{HH}$ 7.3, $^4J_{HH}$ 1.8, $^4J_{PH}$ 1.3, H8), 7.41 (m, 1H, H10), 7.50 (m, 2H, H13), 7.55 (m, 1H, H14), 7.96 (m, 2H, H12) ppm. ^{13}C NMR δ ($CDCl_3$) 19.4 (d, $^3J_{PC}$ 1.4 Hz, C2´), 26.4 (s, C4), 34.8 (d, $^3J_{PC}$ 7.8 Hz, C3), 56.6 (d, $^2J_{PC}$ 2.7 Hz, C2), 110.9 (d, $^1J_{PC}$ 131.6 Hz, C5), 118.0 (d, $^3J_{PC}$ 9.5 Hz, C7), 118.8 (d, $^3J_{PC}$ 12.1 Hz, C9), 128.7 (d, $^3J_{PC}$ 12.6 Hz, C13), 131.7 (d, $^2J_{PC}$ 9.6 Hz, C12), 132.3 (d, $^4J_{PC}$ 2.9 Hz, C14), 132.4 (d, $^1J_{PC}$ 130.9 Hz, C11), 132.5 (d, $^2J_{PC}$ 7.7 Hz, C10), 134.4 (d, $^4J_{PC}$ 2.4 Hz, C8), 164.0 (d, $^2J_{PC}$ 5.4 Hz, C6) ppm. ^{31}P NMR δ ($CDCl_3$): 32.2 ppm. IR (ATR, υ cm^{-1}): 3358 (bs, NH) 1158 (bs, P=O). HRMS (ESI) calcd for $C_{18}H_{25}NO_2P$: 318.1623 $(MH)^+$, found: 318.1626.

(*S*)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-(2-(diphenylphosphoryl)-phenyl)-*P*-phenylphosphinic amide, 26: Yield after chromatography (80% AcOEt:Hexanes): 93%. White solid. Mp: 189-191 ºC. $[\alpha]_D^{20}$ -118.8 (c 0.6, CH_2Cl_2). ^{1}H NMR δ ($CDCl_3$) 0.83 (s, 9H, H4), 1.34 (d, 3H, $^3J_{HH}$ 6.7 Hz, H2´), 3.51 (tc, 1H, $^3J_{PH}$ = $^3J_{HH}$ 10.7, $^3J_{HH}$ 6.7 Hz, H2), 5.83 (dd, 1H, $^2J_{PH}$ 12.2, $^3J_{HH}$ 10.7 Hz, H1), 7.00 (m, 5HAr), 7.21 (m, 3HAr), 7.44 (m, 9HAr), 7.72 (m, 1H, H8), 8.84 (m, 1H, H7) ppm. ^{13}C NMR δ ($CDCl_3$) 19.8 (d, $^3J_{PC}$ 3.2 Hz, C2´), 26.6 (s, C4), 34.8 (d, $^3J_{PC}$ 4.0 Hz, C3), 54.2 (d, $^2J_{PC}$ 1.8 Hz, C2), 127.1 (d, $^3J_{PC}$ 13.5 Hz, CH), 128.2 (d, $^3J_{PC}$ 12.4 Hz, CH), 128.5 (d, $^3J_{PC}$ 12.3 Hz, CH), 129.6 (dd, $^3J_{PC}$ 12.7, $^4J_{PC}$ 2.6 Hz, CH), 130.4 (d, $^1J_{PC}$ 105.8 Hz, C), 130.7 (d, $^4J_{PC}$ 2.9 Hz, CH), 131.0 (d, $^2J_{PC}$ 9.6 Hz, CH), 131.0 (d, $^2J_{PC}$ 11.3 Hz, CH), 131.3 (dd, $^3J_{PC}$ 10.3, $^4J_{PC}$ 3.1 Hz, CH), 131.3 (d, $^4J_{PC}$ 3.0 Hz, CH), 131.6 (dd, $^1J_{PC}$ 100.3, $^2J_{PC}$ 10.8 Hz, C), 131.7 (d, $^2J_{PC}$ 9.9 Hz, CH), 132.0 (d, $^4J_{PC}$ 2.7 Hz, CH), 133.9 (d, $^1J_{PC}$ 106.0 Hz, C), 134.6 (dd, $^2J_{PC}$ 13.9, $^3J_{PC}$ 10.5 Hz, CH), 135.2 (dd, $^2J_{PC}$ 10.8, $^3J_{PC}$ 6.7 Hz, CH), 136.3 (d, $^1J_{PC}$ 130.0 Hz, C), 141.7 (dd, $^1J_{PC}$ 111.5 Hz, $^2J_{PC}$ 9.5 Hz, C) ppm. ^{31}P NMR δ ($CDCl_3$): 26.5 (d, $^3J_{PP}$ 11.2 Hz, PON), 33.2 (d, $^3J_{PP}$ 11.2 Hz, P=O) ppm. IR (ATR, υ cm^{-1}): 3283 (bs, NH), 1185 (bs, NP=O), 1118 (w, P=O). HRMS (ESI) calcd for $C_{30}H_{34}NO_2P_2$: 502.2065 $(MH)^+$, found: 502.2068.

(*S*)-*P*-(2-allylphenyl)-*N*-((*S*)-3,3-dimethylbutan-2-yl)-*P*-phenyl-phosphinic amide, 27: Yield after chromatography (50% AcOEt:Hexanes): 70%. White solid. Mp: 128-129 ºC. $[\alpha]_D^{20}$ +108.9 (c 1.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 9H, H4), 1.12 (d, 3H, J_{HH} 6.6 Hz, H2´), 2.66 (dd, 1H, J_{HH} 10.2 Hz, J_{PH} 9.4 Hz, H1), 3.03 (ddc, 1H, $^3J_{PH}$ 9.2, $^3J_{HH}$ 10.2, $^3J_{HH}$ 6.5 Hz, H2), 3.84 (m, 2H, H15), 4.91 (dc, 1H, $^3J_{HH}$ 17.0, $^2J_{HH}$ = $^4J_{HH}$ 1.6 Hz, $H17_{trans}$), 4.99 (dc, 1H, $^3J_{HH}$ 10.3, $^2J_{HH}$ = $^4J_{HH}$ 1.7 Hz, $H17_{cis}$), 5.88 (ddt, 1H, $^3J_{HH}$ 17.0, $^3J_{HH}$ 10.3, $^3J_{HH}$ 6.4 Hz, H16), 7.23 (tdd, 1H, $^3J_{HH}$ 7.6 Hz, $^4J_{PH}$ 2.6 Hz, $^4J_{HH}$ 1.4 Hz, H9), 7.28 (m, 1H, H7), 7.44 (tt, $^3J_{HH}$ 7.6 Hz, $^5J_{PH}$ =, $^4J_{HH}$ 1.4 Hz, H8), 7.46 (m, 2H, H13), 7.52 (m, 1H, H14), 7.73 (ddd, 1H, $^4J_{PH}$ 13.5 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.4 Hz, H10), 7.83 (m, 2H, H12) ppm. ^{13}C NMR ($CDCl_3$) δ 18.8 (d, $^3J_{PC}$ 2.8 Hz, C2´), 26.5 (s, C4), 34.8 (d, $^3J_{PC}$ 5.5 Hz, C3), 38.2 (d, $^3J_{PC}$ 3.8 Hz, C15), 56.0 (d, $^2J_{PC}$ 2.4 Hz, C2), 116.0 (s, C17), 125.6 (d, $^3J_{PC}$ 12.5 Hz, C9), 128.3 (d, $^3J_{PC}$ 12.5 Hz, C13), 131.1 (d, $^3J_{PC}$ 11.6 Hz, C7), 131.2 (d, $^3J_{PC}$ 125.8 Hz, C5), 131.5 (d, $^4J_{PC}$ 2.8 Hz, C14), 131.6 (d, $^4J_{PC}$ 2.7 Hz, C8), 132.2 (d, $^2J_{PC}$ 9.7 Hz, C12), 133.0 (d, $^2J_{PC}$ 10.6 Hz, C10), 134.2 (d, $^1J_{PC}$ 126.1 Hz, C11), 137.6 (d, $^4J_{PC}$ 0.7 Hz, C16), 144.1 (d, $^2J_{PC}$ 9.8 Hz, C6) ppm. ^{31}P NMR ($CDCl_3$) δ 25.6 ppm. IR (ATR, υ cm^{-1}): 3261 (bs, NH),, 1182 (s, P=O). HRMS (ESI) calcd for $C_{21}H_{29}PNO$: 342.1987 $(MH)^+$, found: 342.1986.

***tert*-butyl 2-((*S*)-(((*S*)-3,3-dimethylbutan-2-yl)amino)(phenyl)-phosphoryl)benzoate, 28:** Yield after chromatography (20% AcOEt:Hexanes): 60%. White solid. Mp: 126-127 ºC. $[\alpha]_D^{20}$ -37.5 (c 0.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.77 (s, 9H, H17), 1.24 (s, 9H, H4), 1.34 (d, 3H, $^3J_{HH}$ 6.7 Hz, H2´), 3.53 (tc, 1H, $^3J_{PH}$ = $^3J_{HH}$ 10.7, $^3J_{HH}$ 6.8 Hz, H2), 4.11 (dd, 1H, $^2J_{PH}$ 12.1, $^3J_{HH}$ 10.7 Hz, H1), 7.33 (m, 2H, H13), 7.39 (m, 1H, H14), 7.56 (m, 1H, H8), 7.59 (m, 2H, H12), 7.69 (ddt, 1H, $^3J_{HH}$ 7.7 Hz, $^4J_{PH}$ 1.6 Hz, $^4J_{HH}$ 1.6 Hz, H9), 7.83 (ddd, 1H, $^3J_{HH}$ 7.9 Hz, $^4J_{PH}$ 4.6 Hz, $^4J_{HH}$ 1.2 Hz, H7), 8.55 (ddd, 1H, $^3J_{PH}$ 12.6 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz, H10) ppm. ^{13}C NMR ($CDCl_3$) δ 19.9 (d, $^3J_{PC}$ 3.3 Hz, C2´), 26.4 (s, C17), 27.6 (s, C4), 34.6 (d, $^3J_{PC}$ 3.6 Hz, C3), 54.0 (d, $^2J_{PC}$ 1.6 Hz, C2), 82.0 (s, C16), 127.8 (d, $^3J_{PC}$ 13.6 Hz, C13), 130.1 (d, $^3J_{PC}$ 9.1 Hz, C7), 130.3 (d, $^2J_{PC}$ 11.3 Hz, C12), 130.6 (d, $^4J_{PC}$ 2.0 Hz, C8/C14), 130.7 (d, $^4J_{PC}$ 2.5 Hz, C14/C8), 131.4 (d, $^3J_{PC}$ 10.9 Hz, C9), 134.0 (d, $^2J_{PC}$ 7.2 Hz, C6), 134.3 (d, $^2J_{PC}$ 6.2 Hz, C10), 136.1 (d, $^1J_{PC}$ 113.6 Hz, C5), 136.9 (d, $^1J_{PC}$ 132.8 Hz, C11), 166.6 (d, $^3J_{PC}$ 3.0 Hz, C15) ppm. ^{31}P NMR ($CDCl_3$) δ 27.6 ppm. IR (ATR, υ cm^{-1}): 3403 (bs, NH), 1703 (s, C=O), 1169 (s, P=O). HRMS (ESI) calcd for $C_{23}H_{33}PNO_3$: 402.2198 $(MH)^+$, found: 402.2195.

(*S*)-Methyl (2-iodophenyl)(phenyl)phosphinate, 29: Phosphinic amide **20** (70 mg; 0.16 mmol) was dissolved into a solution of HCl in methanol (0.64 mL; 1.25 M, 0.8 mmol). The reaction was stirred for 48 h at room temperature. Then, methylene chloride (5 mL) was added and the reaction mixture was washed with 1 M NaOH (3x5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. See ESI for the numbering scheme used. Yield after chromatography (50% AcOEt:Hexanes): 75%. Colorless oil. $[\alpha]_D^{20}$ +3.8 (c 0.4, CH_2Cl_2). ^{1}H NMR δ ($CDCl_3$) 3.81 (d, 3H, $^3J_{PH}$ 11.3 Hz, H1), 7.22 (tdd, 1H, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.8, $^5J_{PH}$ 1.2 Hz, H8), 7.47 (m, 2H, H13), 7.51 (tdd, 1H, $^3J_{HH}$ 7.6, $^4J_{PH}$ 2.5, $^4J_{HH}$ 1.2 Hz, H9), 7.57 (m, 1H, H14), 7.82 (m, 2H, H12), 7.99 (ddd, 1H, $^3J_{HH}$ 7.6, $^4J_{PH}$ 4.1, $^4J_{HH}$ 1.2 Hz, H7), 8.10 (ddd, 1H, $^3J_{PH}$ 12.1 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz, H10) ppm. ^{13}C NMR δ ($CDCl_3$) 51.6 (d, $^2J_{PC}$ 6.0 Hz, C1), 98.0 (d, $^2J_{PC}$ 8.3 Hz, C6), 127.7 (d, $^3J_{PC}$ 11.3 Hz, C9), 128.4 (d, $^3J_{PC}$ 13.7 Hz, C13), 129.9 (d, $^1J_{PC}$ 141.9 Hz, C11), 132.3 (d, $^4J_{PC}$ 4.2 Hz, C14), 132.4 (d, $^2J_{PC}$ 10.7 Hz, C12), 133.5 (d, $^4J_{PC}$ 3.0 Hz, C8), 134.5 (d, $^1J_{PC}$ 138.3 Hz, C5), 135.9 (d, $^2J_{PC}$ 8.3 Hz, C10), 141.8 (d, $^3J_{PC}$ 11.3 Hz, C7) ppm. ^{31}P NMR δ ($CDCl_3$): 33.2 ppm. IR (ATR, υ cm^{-1}): 1225 (bs, P=O), 1033 (bs, C-O). HRMS (ESI) calcd for $C_{13}H_{13}IO_2P$: 358.9698 $(MH)^+$, found: 358.9699.

(*R*)-(2-chlorophenyl)(2-(((*S*)-3,3-dimethylbutan-2-yl)amino)-phenyl)(phenyl)phosphine oxide, 32: To a cooled mixture at -78 ºC of potassium floride (30 mg, 0.6 mmol), 18-crown-6 (133 mg, 0.6 mmol) and **22** (40 mg, 0.12 mmol) in THF, a solution of ^{n}BuLi (1.6 M in hexanes, 0.11 mL, 0.144 mmol) was added and the reaction was allowed to reach room temperature. Then, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.09 mL, 0.42 mmol) was added and the solution was heated to reflux and stirred for 16 h. After this time, the reaction was cooled to room temperature, poured into water, extracted with methylene dichloride

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(3x5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. See ESI for the numbering scheme used. Yield after chromatography (50% AcOEt:Hexanes): 48%. Colorless oil. $[\alpha]_D^{20}$ +22.89 (c 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 9H, H4), 1.05 (d, 3H, $^3J_{HH}$ 6.6 Hz, H2´), 3.24 (dc, 1H, $^3J_{HH}$ 8.8, $^3J_{HH}$ 6.6 Hz, H2), 6.49 (dddd, 1H, $^3J_{HH}$ 7.8, $^3J_{HH}$ 7.3, $^4J_{PH}$ 2.8, $^4J_{HH}$ 1.0 Hz, H8), 6.72 (dd, 1H, $^3J_{HH}$ 8.4, $^4J_{PH}$ 5.4 Hz, H10), 6.85 (m, 1H, H7), 6.87 (d, 1H, $^4J_{PH}$ 8.7 Hz, H1), 7.27 (m, 1H, H15), 7.33 (m, 1H, H9), 7.40 (m, 1H, H16), 7.49 (m, 4H, H13+H14+H19), 7.56 (m, 1H, H20), 7.71 (m, 2H, H18) ppm. ^{13}C NMR ($CDCl_3$) δ 15.2 (d, C2´), 26.3 (s, C4), 34.7 (d, C3), 56.5 (d, C2), 110.0 (d, $^1J_{PC}$ 110.3 Hz, C6), 111.0 (d, $^3J_{PC}$ 8.3 Hz, C10), 114.0 (d, $^3J_{PC}$ 13.7 Hz, C8), 126.4 (d, $^3J_{PC}$ 10.7 Hz, C15), 128.4 (d, $^3J_{PC}$ 12.5 Hz, C19), 131.2 (d, $^1J_{PC}$ 103.1 Hz, C11/C17), 131.3 (d, $^3J_{PC}$ 6.6 Hz, C13), 131.9 (d, $^4J_{PC}$ 3.0 Hz, C20), 132.0 (d, $^1J_{PC}$ 107.3 Hz, C17/C11), 132.2 (d, $^2J_{PC}$ 9.5 Hz, C18), 133.2 (d, $^4J_{PC}$ 2.4 Hz, C14), 133.5 (d, $^2J_{PC}$ 11.9 Hz, C7), 133.7 (d, $^4J_{PC}$ 1.8 Hz, C9), 135.2 (d, $^2J_{PC}$ 10.1 Hz, C16), 138.4 (d, $^2J_{PC}$ 3.6 Hz, C12), 153.2 (d, $^2J_{PC}$ 4.8 Hz, C5) ppm. ^{31}P NMR ($CDCl_3$) δ 36.1 ppm. IR (ATR, υ cm^{-1}): 3314 (bs, NH), 1175 (m, P=O), HRMS (ESI) calcd for $C_{24}H_{28}ClNOP$: 412.1597 $(MH)^+$, found: 412.1599.

Procedure for the synthesis of complex 34. To a solution of **26** (0.10 mmol, 50 mg) in 5 mL of a mixture methylenedichloride:acetonitrile (1:1), 0.10 mmol of $ZnCl_2$ (0.1 mL of a 1.0 M solution in diethyl ether) were added and the reaction was stirred at room temperature overnight. Then, methylenedichloride was added to dissolve the precipitate formed completely and the solution was filtered. Crystals suitable for X-ray analysis were obtained through slow vapour diffusion of diethyl ether into a solution containing the complex in methylenedichloride:acetonitrile. See ESI for the numbering scheme used.

Yield after recrystallization: 85%. White solid. Mp: 278-280 ºC (dec.). $[\alpha]_D^{20}$ -2.32 (c 0.6, CH_2Cl_2). ^{1}H NMR δ ($CDCl_3$) 0.91 (s, 9H, H4), 1.08 (dd, 3H, $^3J_{HH}$ 6.7, $^4J_{HH}$ 0.8 Hz, H2´), 2.46 (tc, 1H, $^3J_{PH}$ = $^3J_{HH}$ 11.0, $^3J_{HH}$ 6.7 Hz, H2), 3.76 (d, 1H, $^3J_{HH}$ 11.0 Hz, H1), 7.07 (m, 2HAr), 7.15 (m, 2HAr), 7.22 (m, 2HAr), 7.30 (m, 1H, H7), 7.33 (m, 3HAr), 7.45 (m, 1HAr), 7.50 (m, 2HAr), 7.61 (m, 2H, H8), 7.67 (m, 2HAr), 7.88 (tc, 1H, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.8 Hz, H9), 8.46 (m, 1H, H10) ppm. ^{13}C NMR δ ($CDCl_3$) 18.9 (d, $^3J_{PC}$ 7.5 Hz, C2´), 26.5 (s, C4), 34.7 (d, $^3J_{PC}$ 1.8 Hz, C3), 59.0 (d, $^2J_{PC}$ 2.7 Hz, C2), 126.6 (d, $^1J_{PC}$ 139.0 Hz, C), 128.3 (d, $^3J_{PC}$ 13.4 Hz, C^m), 128.6 (d, $^3J_{PC}$ 13.4 Hz, C^m), 128.7 (d, $^1J_{PC}$ 117.0 Hz, C), 128.9 (d, $^3J_{PC}$ 12.3 Hz, C^m), 129.0 (d, $^1J_{PC}$ 107.2 Hz, C), 131.0 (d, $^2J_{PC}$ 10.9 Hz, C^o), 131.6 (d, $^2J_{PC}$ 9.8 Hz, C^o), 132.1 (d, $^4J_{PC}$ 3.1 Hz, C^p), 132.2 (m, C9/C8) 132.3 (d, $^4J_{PC}$ 3.0 Hz, C^p), 132.8 (m, C8/C9), 132.9 (d, $^2J_{PC}$ 9.8 Hz, C^o), 132.9 (d, $^4J_{PC}$ 2.8 Hz, C^p), 134.4 (dd, $^1J_{PC}$ 98.6, $^2J_{PC}$ 12.4 Hz, C), 136.4 (dd, $^1J_{PC}$ 132.8, $^2J_{PC}$ 8.6 Hz, C), 137.0 (m, C10/C7), 137.1 (m, C7/C10) ppm. ^{31}P NMR δ ($CDCl_3$): 32.6 (d, $^3J_{PP}$ 7.5 Hz, PON), 42.5 (d, $^3J_{PP}$ 7.5 Hz, P=O) ppm. IR (KBr, υ cm^{-1}): 3558 (bs, NH), 1166 (bs, P=O). HRMS (ESI) calcd for $C_{30}H_{34}NO_2P_2ZnCl_2$: 636,0733 $(MH)^+$, found: 502.2059, corresponds to $[MH]^+$ of the ligand **26**.

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Notes and references

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† Electronic Supplementary Information (ESI) available: NMR spectra of the reported compounds, computed pathway for the reaction between benzyne and *N*-lithiated **22**, IRC analysis of the conversion of TS1 into intermediate **E**, Cartesian coordinates of all computed structures and ORTEP diagrams of **19**, **19'**, **20** and **34** are available in the ESI. CCDCs 1406955-1406957 and 1409186. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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Synthesis of P-stereogenic diarylphosphinic amides by directed lithiation. Stereospecific transformation into tertiary phosphine oxides via methanolysis, aryne chemistry and complexation behaviour toward zinc(II)

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Graphical Content Entry

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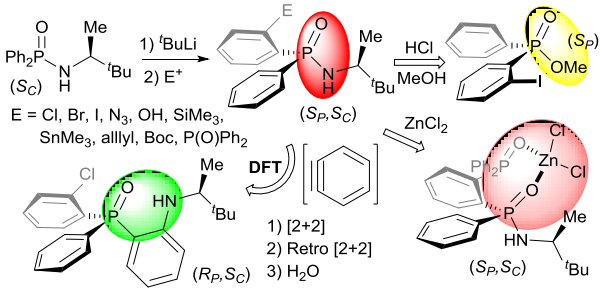

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