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New *P*-stereogenic triaminophosphines and their derivatives: synthesis, structure, conformational study, and application as chiral ligands

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

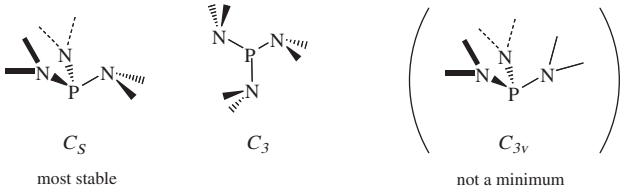
ABSTRACT

The synthesis, structural, and conformational studies of new *P*-chiral triaminophosphines, which feature an indolidine and a 1,2,3,4-tetrahydroquinolidine pattern, respectively, are reported. These compounds can feature very different 3D-structures, although they both could be seen a priori as close derivatives of the previously reported 3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane. The consequences for the use of such compounds and their derivatives in asymmetric metal-catalysis are discussed on the basis of preliminary results in asymmetric cobalt-catalyzed [6+2] cycloaddition.

1. Introduction

Within the last decade, heterosubstituted phosphines, such as phosphites or phosphoramidites, have emerged as ubiquitous classes of efficient ligands for organometallic catalysis. In particular, their easy synthesis from relatively inexpensive materials and the amazing variety of substitution patterns are key advantages for enantioselective catalysis. Indeed they facilitate the design of vast libraries of chiral ligands.[1] Among these ligands, nitrogen-trisubstituted phosphines feature special structural properties. Indeed the P–N bond cannot be classified as a regular single bond. Electrostatic effects and negative hyperconjugation involving the nitrogen lone pairs of electrons usually result in short bond lengths and sp^2-hybridized nitrogen atoms.[2] However, steric and electronic effects can easily override these geometric features. For instance, it has been known since the early 70s that the tris(dimethylamino)phosphine does not adopt a C_{3v} geometry with 3 equivalent planar amino groups (see Scheme 1). In 1996, Mitzel et al. reported the first X-ray analysis of **1**, which definitely established its C_s geometry, where only two amino groups are planar, the third one being pyramidal. According to ab initio calculations (MP2/6-311G** level of theory), the C_{3v} geometry is not even a minimum of energy on the hypersurface of potential. A second local minimum (32 kJ mol^{-1} higher in energy) was found which corresponds to a C_3 geometry where the three amino groups are pyramidal.[3–5]

Among the many described $P(NR_2)_3$ compounds, various structures have been reported, which include nitrogen environments in many variations between the extreme of planar and steeply pyramidal arrangements.[6] Such subtle geometric changes around a nitrogen atom have great implications for the electronic properties of the *P*-ligand. Indeed, a pyramidal amino substituent acts mainly as an electron-withdrawing group, whereas a sp^2-hybridized nitrogen atom acts as a π-donor because of the donation of its lone pair toward the *P* atom. As a consequence, alkyl(dipyrrolidinyl)phosphines are stronger donors than the C_s-symmetric tripyrrolidinylphosphine **2**.[6a] For similar reasons, ligand **3**, which features a C_{3v} geometry with three planar amino groups, is a strong donor,[6b] but **4a–c** are electron-withdrawing ligands because pyrrolyl, indolyl, or carbazolyl groups are weak π-donors (Scheme 2).[6c–h]



Scheme 1. Conformations of tris(dimethylamino)phosphine **1**.

Such geometric variation in nitrogen environments should also have important implications for the related *P*-chiral compounds, especially when they are used as ligands for enantioselective metal-catalysis. To our knowledge,[7,8] the only *P*-stereogenic triaminophosphines described to date is 2-dimethylamino-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **5** (Scheme 3)[9,10] and its close derivatives.[11] The X-ray structure of **5** reveals the pyramidal environment of the nitrogen of the pyrrolidine ring, whereas the two other nitrogen atoms have an almost planar configuration and are clearly sp^2-hybridized.[10] This geometric feature accounts for the highly diastereoselective formation of this compound: when reacting tris(dimethylamino)phosphine with enantiopure 2-(*S*)-anilinomethylpyrrolidine only the ($2R_P$,$5S_C$) diastereomer is obtained. Indeed the extracyclic substituent on phosphorus has to be *trans* to the 'roof' formed by the pyrrolidine ring in order to minimize steric effects. Interestingly, the same diastereoselectivity is

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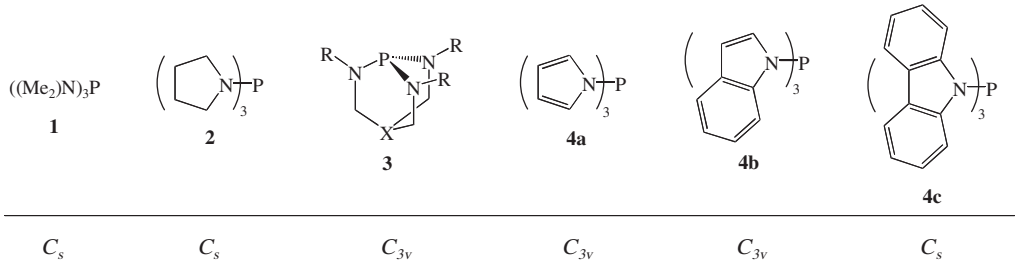
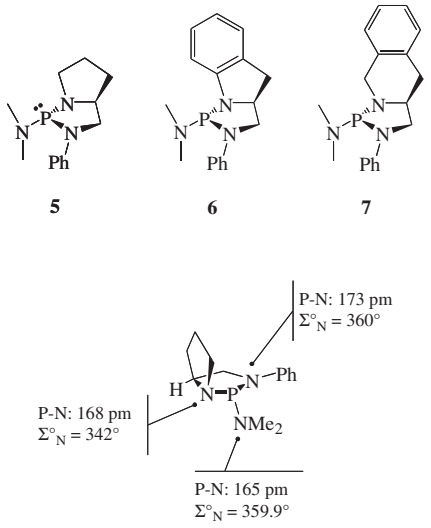


Scheme 2. Symmetry of various $P(NR_2)_3$ compounds.



Scheme 3. Compounds **5**, **6**, and **7**; geometric environment of amino groups in **5**.

observed when alkoxy, mercapto, or amino groups are introduced by exchange reactions with the remaining dimethylamino group of **5**. These *P*-stereogenic tri-, or di-, aminophosphines are efficient ligands for many enantioselective metal-catalyzed reactions.[1,12] However, despite the popularity of these ligands, and the key structural role of the pyrrolidine ring, structural modification of the latter has never been studied.

During our search for efficient chiral *P*-ligands for our recently described enantioselective cobalt-catalyzed [6+2] cycloaddition,[13] we envisioned the design of such a set of new *P*-stereogenic diazaphospholidines. Herein, we report the synthesis, and structural and conformational studies of the new chiral triaminophosphines **6** and **7**, which feature an indolidine and a 1,2,3,4-tetrahydroquinolidine pattern, respectively. These compounds can feature very different 3D-structures, although they both could be seen *a priori* as close derivatives of **5**. The consequences for the use of compounds **5–7** and their derivatives in asymmetric metal-catalysis are discussed on the basis of preliminary results in asymmetric cobalt-catalyzed [6+2] cycloaddition.

2. Results and discussion

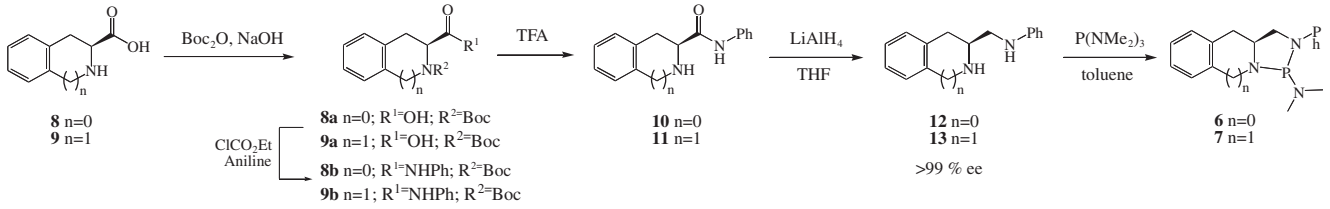
2.1. Synthesis, structural and conformational studies

The general procedure for synthesizing diazaphospholidines **6** and **7** is described in Scheme 4. The (*S*)-α-amino acids **8** and **9** are commercially available or could be synthesized in one step from (*S*)-phenylalanine.[14] After Boc-protection of the amino group, the carboxylic acid was coupled with aniline. The corresponding α-aminoamides **10** and **11** were obtained after deprotection with trifluoroacetic acid. Reduction with lithium aluminum hydride afforded β-diamines **12** and **13**.

Reaction of **12** with tris(dimethylamino)phosphine in refluxing toluene afforded **6** as a single diastereomer in 90% yield. An X-ray analysis[15] confirmed that the diastereoselective control at the *P* atom was identical to compound **5**: ($2S_P$,$5S_C$)-**6** was obtained. In marked contrast, the same reaction with **13** afforded a 1:1 mixture of the two *P*-epimers **7** and $\mathbf{7_P}$. Indeed, the $^{31}P\{^1H\}$ NMR spectrum of the crude mixture displayed two singlets at 120 and 104 ppm. Fortunately, **7** (δ = 104 ppm) could be isolated in 40% yield by crystallization from a cooled solution of toluene. An X-ray analysis[15] showed that this compound was ($6S_C$,$7R_P$)-**7**. The second singlet (δ = 120 ppm) was attributed to the *P*-epimer ($6S_C$,$7S_P$)-$\mathbf{7_P}$.

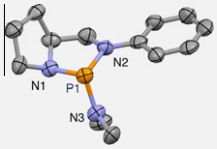
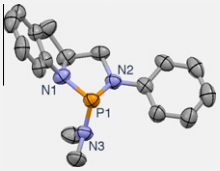
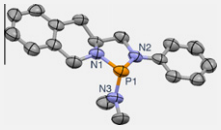
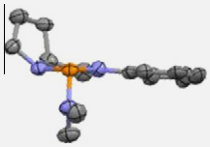
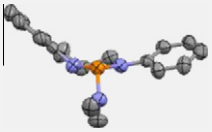
The solid-state geometry of **5**,[10b] **6,** and **7** is compared in Table 1. In the three compounds, the N2 atoms (anilino substituent) and N3 atoms (dimethylamino substituent) are clearly sp^2-hybridized. The P1N3 bonds feature short lengths (165–168 pm), which are typical of the hyperconjugation between a nitrogen lone pair and empty σ^* orbitals associated with P-substituent bonds. Conversely, the longer lengths of the P1N2 bonds can be attributed to the unfavorable overlap of the lone pairs of the two atoms, and to the concomitant conjugation of the lone pair of N2 with the π-system of the phenyl substituent. The N1 nitrogen atoms, which are involved in two fused rings, have a pyramidal environment. However, the lone pairs of N1 and P1 are *trans* in compounds **5** and **6**, but *cis* in compound **7**. As a consequence, **5** and **6** adopt sharp roof-like geometries, which control the configuration of the *P* atom. Conversely, the polycyclic backbone of **7** is roughly planar, which may explain *a posteriori* the absence of diastereoselectivity in the formation of **7** and $\mathbf{7_P}$ from tris(dimethylamino)phosphine.

In order to gain a better insight into the conformational behavior of **7**, we performed ab initio calculations at the B3LYP/



Scheme 4. General synthesis of **6** and **7**.

Table 1
Selected solid-state ORTEP representations and structural parameters of diazaphospholidines **5, 6**, and **7**

5	**6**	**7**
ORTEP representation (general view)		
		
View along the ($N_1P_1N_2$) plane		
		
Bond lengths		
P_1N_1: 168 pm	P_1N_1: 171 pm	P_1N_1: 170 pm
P_1N_2: 173 pm	P_1N_2: 173 pm	P_1N_2: 172 pm
P_1N_3: 165 pm	P_1N_3: 167 pm	P_1N_3: 168 pm
Sums of angles around phosphorus and nitrogen atoms		
$\Sigma°_P$: 300°	$\Sigma°_P$: 298°	$\Sigma°_P$: 302°
$\Sigma°_{N1}$: 342°	$\Sigma°_{N1}$: 348°	$\Sigma°_{N1}$: 347°
$\Sigma°_{N2}$: 360°	$\Sigma°_{N2}$: 356°	$\Sigma°_{N2}$: 359°
$\Sigma°_{N3}$: 360°	$\Sigma°_{N3}$: 355°	$\Sigma°_{N3}$: 360°

Hydrogen atoms are omitted for clarity. Thermal ellipsoids are set to 50% probability.

6-31+G(d,p) level of theory and evaluated the standard reaction free energies at 300 K. The solid-state geometry was well reproduced, although the PN bond was slightly longer (2–3 pm).

We found six minima on the hypersurface of energy of **7** (see Fig. 1). Inversion at the N1 atom leads to $\mathbf{7_N}$, which adopts a structure close to the roof-like geometry of **5** and **6**. The third conformer $\mathbf{7_{Nbis}}$, which results from a twist of the six-membered ring of $\mathbf{7_N}$, is 29 kJ mol^{-1} higher in energy than **7**, so that it has no significant weight in the conformational population. In marked contrast, the energetic difference between **7** and $\mathbf{7_N}$ is only 2 kJ mol^{-1}. According to our calculations, these two conformers can be assumed permanently at equilibrium at room temperature, since the standard activation free energy of the reaction leading from **7** to $\mathbf{7_N}$ is only 16 kJ mol^{-1} at 300 K, which corresponds to a half-life time

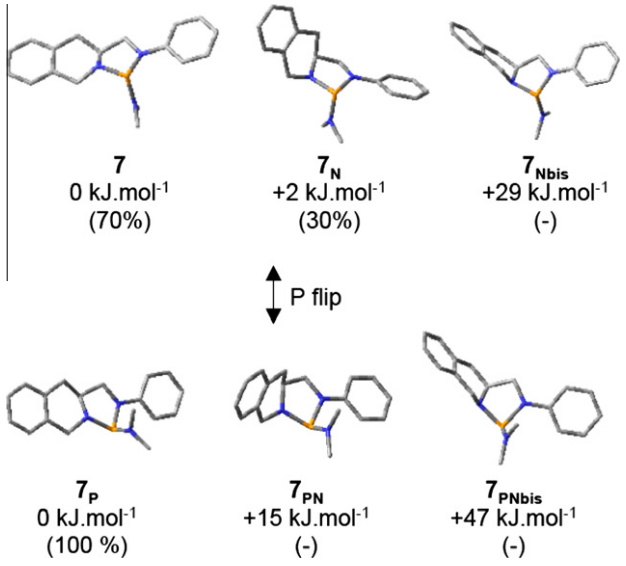


Figure 1. Calculated free energies at 300 K and the corresponding population fractions estimated within the framework of a Boltzmann distribution for the six conformers of **7** and $\mathbf{7_P}$. Hydrogen atoms are omitted for clarity.

of 68 ps. Of note, the relative disposition of the lone pairs of N1 and P1 had almost no influence on the conformational stabilities, so that lone pair repulsion could be ruled out as a major contribution to the conformational behavior of **7**, which is driven by ring strain and subtle stereoelectronic factors.

Formal inversion at the phosphorus atom of **7** led to $\mathbf{7_P}$.[16] The difference of energy between **7** and $\mathbf{7_P}$ is less than 1 kJ mol^{-1}, which is relevant to the lack of diastereoselectivity during their formation from tris(dimethylamino) phosphine. Compound $\mathbf{7_P}$ is predicted to have two conformers with a roof-like structure, $\mathbf{7_{PN}}$ and $\mathbf{7_{PNbis}}$. However, the latter are too high in energy and have no significant weight in the conformational population.

Thus, the two *P*-epimers have very different conformational behaviors: ($6S_C$,$7S_P$)-$\mathbf{7_P}$ has a rigid planar structure, whereas ($6S_C$,$7R_P$)-**7** has a flexible structure, resulting from the rapid exchange between a 'planar' conformer **7** and a 'sharp' conformer $\mathbf{7_N}$.

2.2. Derivatization of 5–7 by exchange reactions and enantioselective metal-catalysis

We then turned our attention to the derivatization of these triaminophosphines by means of exchange reactions with alcohols. Above all, compound **6** was reacted with enantiopure (−)-menthol in refluxing toluene, in order to check the enantiopurity of diamines **12** *a posteriori*.[17] As expected, ^{31}P {^{1}H} NMR indicated that a major compound was formed (δ = 114.9 ppm). The same reaction was run with a racemic mixture of menthol. As shown in Figure 2, the formation of a 1:1 mixture of diastereomers was confirmed by the presence of two singlets at 114.9 and 113.5 ppm in ^{31}P {^{1}H} NMR. This experiment allowed us to exclude the fortuitous possibility that diastereomeric adducts of ($6S_C$)-**6**/(−)-menthol and ($6R_C$)-**6**/(−)-menthol may have the same ^{31}P chemical shift. Of note is that the formation of a small amount of *P*-epimers was observed (δ = 113.2 and 111.6 ppm). The same procedure was applied to diamine **13**. As shown in Figure 2, a 1:1 mixture of two diastereomers was obtained when **7** was reacted with (−)-menthol. When *rac*-menthol was used, the formation of four diastereomers was observed. This demonstrated that

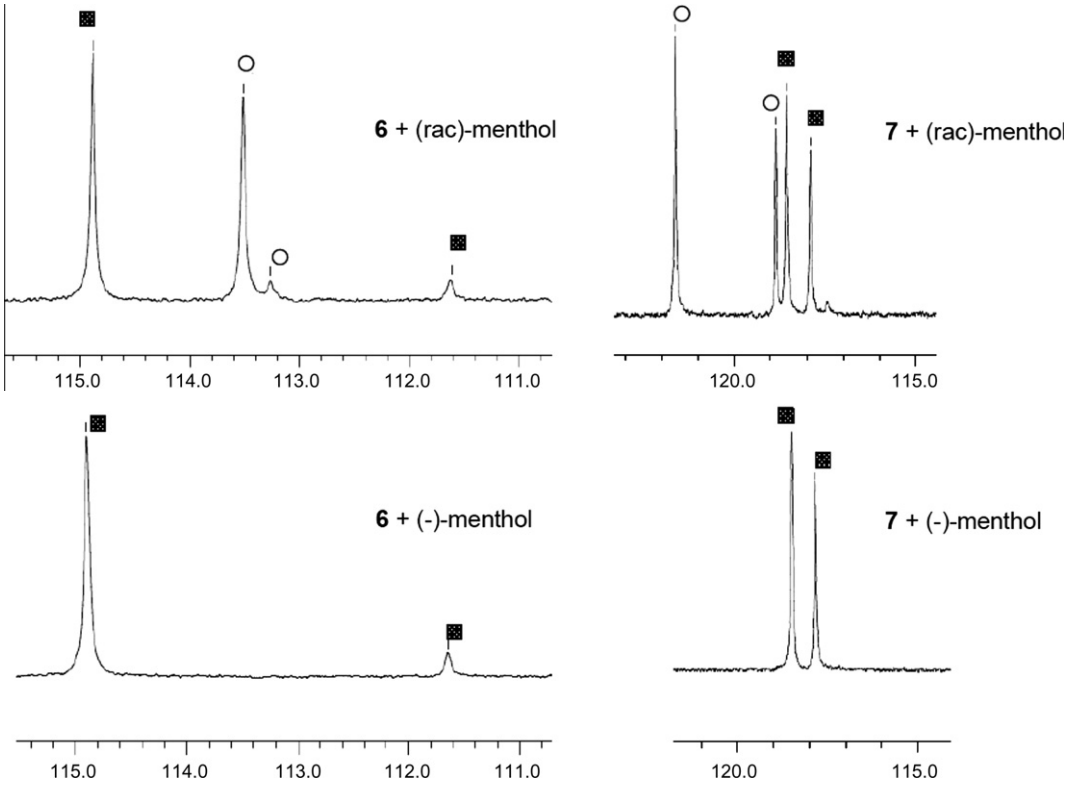


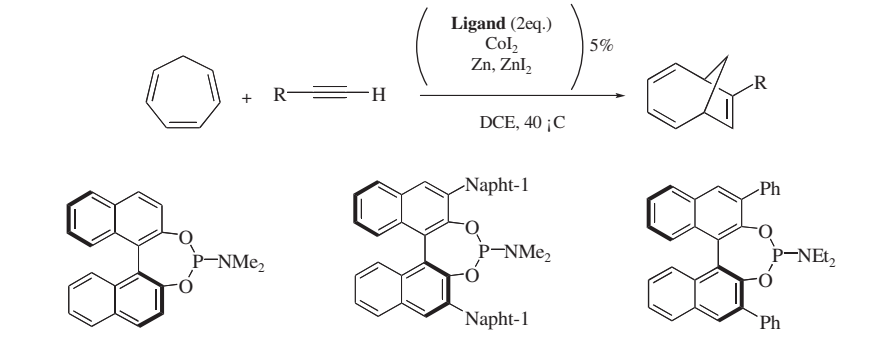
Figure 2. ^{31}P NMR of the crude reaction of **6** or **7** with menthol; ■: diastereomers with (−)-menthol moieties; ○: diastereomers with (+)-menthol moieties.

the reaction was not diastereoselective and yielded two *P*-epimers, and, thus, confirmed the excellent enantiopurity of **13**. As such exchange reactions are known to be under thermodynamic control,[18] the absence of diastereoselectivity is likely to result from the conformational behaviour of **7**, which does not adopt a rigid 'roof-like' structure.

We chose to test our chiral diazaphospholidines as ligands for the enantioselective cobalt-catalyzed cycloaddition. Indeed, we recently took advantage of a cobalt-based catalytic system (CoI_2/ligand/Zn/ZnI_2) to design the first enantioselective [6+2] cycloaddition.[13] A rough screening of ubiquitous classical chiral *P*-ligands demonstrated the difficulty in achieving the asymmetric cycloaddition of cycloheptatriene with primary alkynes. Indeed only MonoPhos afforded both a decent yield (76%) and a significant enantioselectivity (63% ee). After optimization of this promising ligand, we found that phosphoramidites based on 3,3′-substituted BINOL gave better results: the corresponding cycloadducts were obtained with 75–98% yields and up to 92% ee (Scheme 5). As we wondered whether these results could be enhanced, we started to look for alternative families of efficient chiral modular *P*-ligands.

Therefore, we synthesized a small set of ligands by reacting **5** and **6** with various phenols and alcohols, in order to evaluate the efficiency of diazaphospholidines for this reaction. The diastereoselectivities of the exchange reactions were excellent, as demonstrated by NMR data, and compounds **14a**–**e** and **15a**–**b** were obtained in good yields (>80%) (Scheme 6).

Our chiral diazaphospholidines were engaged in the enantioselective cobalt-catalyzed cycloaddition of cycloheptatriene and phenylacetylene under standard conditions. The results are reported in Table 2 (entries 1–10). We first tested triaminophosphines **5**, **6**, and **7**. Low conversions were obtained, but ligand **6** already afforded a promising 41% ee. With derivative **14**, **16a** was

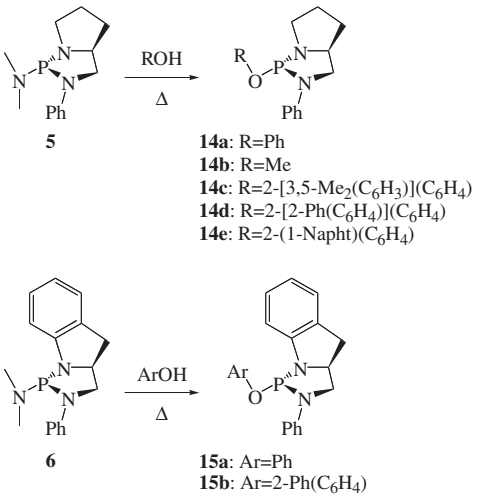


R=Ph : 76% yield, 63 % ee
R=SiMe$_3$: 33% yield, 0 % ee
R=*n*-Bu : 11% yield, 45 % ee

R=Ph : 93% yield, 90 % ee
R=SiMe$_3$: 75% yield, 85 % ee
R=*n*-Bu : 89% yield, 47 % ee

R=Ph : 99% yield, 49 % ee
R=SiMe$_3$: 86% yield, 92 % ee
R=*n*-Bu : 88% yield, 21 % ee

Scheme 5. Previously described enantioselective cobalt-catalyzed [6+2] cycloaddition.

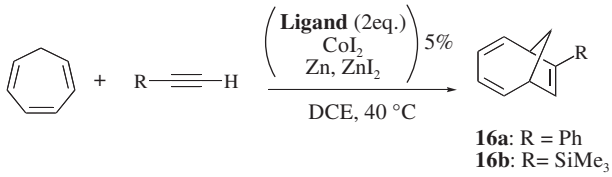


Scheme 6. Synthesis of derivatives of **5** and **6** by exchange reaction.

obtained with a better yield, but the enantioselectivities remained modest. Finally, ligands **14b**–**e** and **15a**–**b** afforded both good conversions and decent enantioselectivites. The best results were obtained with **14e**, which allowed the formation of **16a** with 92% yield and 52% ee. Interestingly with ligands **14c**–**e**, the opposite enantiomer, (+)**-16a,** was favored, whereas (−)**-16a** was favored with the other ligands. Such 'inversion of asymmetric induction' was also observed with phosphoramidite ligands in our previous study. Indeed the introduction of bulky 3,3′-substituents on the BINOL moieties favored the formation of (+)**-16a**, whereas, otherwise, (−)**-16a**–**b** were the major compounds. More generally, a dramatic variation of the enantioselectivity was observed depending upon the nature of these substituents. As a matter of fact, the same statement can be made with diazaphospholidines **5–7** and **14–15**. For instance, the introduction of an *o*-aryl substituent on the phenoxy group of **14a** appeared to be critical, whereas there is no huge difference between **15a** and **15b**.

We also considered the cycloaddition of cycloheptatriene and trimethylsilylacetylene under the same conditions (Table 2, entries 11–20). The reaction rates were significantly lower, no conversion being even observed with four ligands. Ligand **5** afforded the best ee (46%) but a poor yield. The best result was obtained with **14e**, which afforded (+)-**16b** with 41% ee and 83% isolated yield.

Table 2
Enantioselective cobalt-catalyzed [6+2] cycloaddition



Entry[a]	Chiral ligand	R	Product	Yield[b] (%)	ee[c] (%)
1	**5**	Ph	(−)-**16a**	19	5
2	**6**	Ph	(+)-**16a**	6	41
3	**7**	Ph	—	0	—
4	**14a**	Ph	(−)-**16a**	58	8
5	**14b**	Ph	(−)-**16a**	5	28
6	**14c**	Ph	(+)-**16a**	62	49
7	**14d**	Ph	(+)-**16a**	72	31
8	**14e**	Ph	(+)-**16a**	92	52
9	**15a**	Ph	(+)-**16a**	89	23
10	**15b**	Ph	(+)-**16a**	81	39
11	**5**	$SiMe_3$	(−)-**16b**	13	46
12	**6**	$SiMe_3$	(−)-**16b**	42	29
13	**7**	$SiMe_3$	—	0	—
14	**14a**	$SiMe_3$	(−)-**16b**	69	21
15	**14b**	$SiMe_3$	—	0	—
16	**14c**	$SiMe_3$	—	0	—
17	**14d**	$SiMe_3$	(+)-**16b**	38	17
18	**14e**	$SiMe_3$	(+)-**16b**	83	41
19	**15a**	$SiMe_3$	(−)-**16b**	38	27
20	**15b**	$SiMe_3$	—	0	—

[a] Triene/alkyne/CoI_2/ligand/Zn/ZnI_2 in a 1.2/1.0/0.05/0.10/0.15/0.10 molar ratio.
[b] Yields after purification.
[c] ee determined by chiral HPLC Chiralcel OD-H (R = Ph) or Chiralpak AD-RH (R = $SiMe_3$).

3. Conclusion

The new *P*-chiral triaminophosphines **6** and **7**, which feature an indolidine and a 1,2,3,4-tetrahydroquinolidine pattern, respectively, have very different 3D-structures. Compound **6** adopts a rigid 'roof-like' geometry, which is related to the structure of 3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane derivatives, such as **5**. As a consequence, exchange reactions of the dimethylamino group with alcohols can occur with high diastereoselectivity. Our preliminary study exemplified the potential of **5**, **6**, and their derivatives for the asymmetric cobalt-catalyzed [6+2] cycloaddition of cycloheptatriene with terminal alkynes.

Contrastingly, the exchange reaction of tris(dimethylamino) phosphine with 1 equivalent of (*S*)-3-(anilinomethyl)-1,2,3,4-tetrahydroisoquinoline **13** yields two *P*-epimers, **7** and $\mathbf{7_P}$, in a 1:1 ratio. Although **7** can be isolated by crystallization, it has not the modularity of ligand **5** or **6**, since its exchange reaction with alcohols is not diastereoselective at all. As a consequence, its use as a ligand for asymmetric catalysis is certainly limited. However, its flexible structure, which results from the rapid exchange between a 'planar' and a 'sharp' conformer, can also be considered as an attractive feature. Indeed compound **7** is an original member of the recently highlighted family of ligands with flexible steric bulk[19] and thus may find application as ligand for original non-asymmetric metal-catalyzed processes.

4. Experimental

4.1. General consideration

Synthesis of *P*-ligands and metal-catalyzed reactions were carried out under dry nitrogen atmosphere. Cycloheptatriene was freshly distillated before use. Zinc(II) iodide, cobalt(II) iodide, zinc powder, alkynes, 1,2-dichloroethane (DCE), were purchased, stored under nitrogen, and used as received. Compounds **5**,[10] **12**,[17] and **14a**–**e**[20] were synthesized according to previously published procedures.^{1}H NMR spectra were recorded on a Bruker Avance (200 MHz) spectrometer and reported in ppm from $CDCl_3$ as an internal standard (7.26 ppm). ^{13}C NMR spectra were recorded at 50 MHz on the same spectrometer and reported in ppm from $CDCl_3$ as an internal standard (77.0 ppm). NMR spectra were recorded on Bruker Avance (200 or 300 MHz) spectrometers. ^{31}P NMR downfield chemical shifts are expressed with a positive sign, in ppm, relative to external 85% H_3PO_4. Specific optical rotations of chiral compounds were measured on a 341 Perkin Elmer spectrometer. High resolution MS analyses were performed on a QStar Elite (Applied Biosystems SCIEX) spectrometer by 'Spectropole' at University of Aix-Marseille.

4.2. DFT calculations

Density Functional Theory (DFT) calculations were performed using the B3LYP hybrid functional and the 6-31+G(d,p) basis set.

The GAUSSIAN03[21] software suite has been used for all calculations. All structures were fully optimized using default thresholds and the nature of all minima and saddle points were confirmed using frequency calculations. Free energies were calculated using a home made Python 2.6[22] script based on the usual ideal gas—harmonic oscillator—rigid rotator approximation also used in GAUSSIAN03. Although ab initio calculations were performed in the gas phase, the solute standard was used for standard free energies (1 mol L^{-1}). The reaction rate of the reaction leading from **7** to $\mathbf{7_N}$ was calculated using the Eyring equation.[23] The corresponding transition state is characterized by a PNCC (first C: first C neighbor of N the furthest to the phenyl ring, second C: first C neighbor of N the closest to the phenyl ring) dihedral angle of 164° and a characteristic imaginary frequency of $-36\ cm^{-1}$. Population fractions were estimated using the Boltzmann distribution.

4.3. Synthesis of triaminophosphines 6 and 7

4.3.1. (2S_P,5S_C)-2-Dimethylamino-3-phenyl-1,3-diaza-2-phosphabenzo[7,8]bicyclo[3.3.0]octane 6

A solution of **12** (1.30 g; 5.80 mmol; 1 equiv) and tris(dimethylamino)phosphine (945 mg, 5.80 mmol; 1 equiv) in toluene (30 mL) was refluxed for 5 days. After removal of the solvent, **6** was crystallized in toluene to afford white crystals. 90% yield. Mp: 65 °C. $[\alpha]_D^{20} = -60$ (*c* 0.74, CH_2Cl_2). ^{31}P {^1H} NMR (50 MHz, C_6D_6) δ 102.7; ^1H NMR (200 MHz, C_6D_6) δ 2.34–2.58 (m, 2H), 2.49 (d, *J* = 9.5 Hz, 6H), 2.78–2.91 (m, 1H), 3.23 (ddd, *J* = 3.0, 6.8, 9.1 Hz, 1H), 4.13–4.29 (m, 1H), 6.76–7.06 (m, 7H), 7.19–7.27 (m, 2H); ^{13}C {^1H} NMR (50 MHz, C_6D_6) δ 34.8 (s, CH_2), 36.6 (d, *J* = 17.9 Hz, CH_3), 54.7 (d, *J* = 4.1 Hz, CH_2), 62.4 (d, *J* = 6.9 Hz, CH), 111.5 (d, *J* = 13.9 Hz, $C_{aro}H$), 115.4 (d, *J* = 11.2 Hz, $C_{aro}H$), 119.0 (s, $C_{aro}H$), 120.1 (s, $C_{aro}H$), 125.2 (s, $C_{aro}H$), 128.1 (s, $C_{aro}H$), 129.3 (d, *J* = 1.3 Hz, $C_{aro}H$), 129.9 (d, *J* = 3.6 Hz, C_{aro}), 146.9 (d, *J* = 17.6 Hz, C_{aro}), 149.7 (d, *J* = 23.8 Hz, C_{aro}). HRMS (ESI-MS) $[M+H]^+$: found 298.1467; calcd for $C_{17}H_{21}N_3P$: 298.1463.

4.3.2. (6S_C,7R_P)-9-Dimethylamino-8-phenyl-1,8-diaza-9-phosphabenzo[3,4]bicyclo[4.3.0]nonane 7

A solution of **13** (1.95 g; 8.18 mmol; 1 equiv) and tris(dimethylamino)phosphine (1.33 g mg, 8.18 mmol; 1 equiv) in toluene (40 mL) was refluxed for 5 days. The mixture was then very slowly cooled down to room temperature. White needle crystals appeared and were filtered off on Büchner and dried under vacuum. 40% yield. Mp = 130–134 °C. $[\alpha]_D^{20} = -176$ (*c* 0.80, CH_2Cl_2). ^{31}P {^1H} NMR (81 MHz, $CDCl_3$) δ 104.1 (s) (103.8 in THF); ^{13}C {^1H} NMR (50 MHz, THF) δ 36.9 (d, *J* = 17.4 Hz, CH_3), 45.0 (d, *J* = 16.8 Hz, CH_2), 48.4 (d, *J* = 42.3 Hz, CH_2), 53.4 (d, *J* = 8.3 Hz, CH_2), 54.9 (d, *J* = 10.2 Hz, CH), 113.9 (d, *J* = 13.5 Hz, $C_{aro}H$), 117.5 (s, $C_{aro}H$), 125.3 (s, $C_{aro}H$), 125.5 (d, *J* = 3.3 Hz, $C_{aro}H$), 125.8 (s, $C_{aro}H$), 128.4 (s, $C_{aro}H$), 128.7 (d, *J* = 3.1 Hz, $C_{aro}H$), 133.7 (s, C_{aro}), 134.4 (d, *J* = 7.8 Hz, C_{aro}), 146.6 (d, *J* = 16.3 Hz, C_{aro}). HRMS (ESI-MS) $[M+H]^+$: found 312.1622; calcd for $C_{18}H_{23}N_3P$: 312.1624.

4.3.3. (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid 9

A solution of (*S*)-phenylalanine (50 g; 0.3 mol; 1 equiv) in formalin (40%; 110 mL) and hydrochloric acid (35%; 380 mL) was refluxed for 30 min. Then, formalin (40%; 50 mL) and hydrochloric acid (35%; 100 mL) were added and the mixture was refluxed for three additional hours. After cooling down to room temperature, the precipitate was filtered and dissolved in water (1750 mL). The mixture was refluxed and boiling ethanol (1300 mL) was added carefully. While still hot, the solution was neutralized with a 10% solution of ammonium hydroxide and slowly cooled down to room temperature. The crude product was filtered and recrystallized in a water/ethanol mixture (75/25) to afford (*S*)-**9** as a white solid. 29% yield. Mp = 250–300 °C (decomposition). $[\alpha]_D^{20} = -168.5$ (*c* 2, 1 M $NaOH_{aq}$). ^1H NMR (200 MHz, D_2O + NaOD) δ 2.19–2.35 (m, 1H), 2.50 (dtm, *J* = 3.4, 16.6 Hz, 1H), 2.86–2.95 (m, 1H), 3.33–3.53 (m, 2H), 6.54–6.73 (m, 4H); ^{13}C {^1H} NMR (50 MHz, D_2O + NaOD) δ 31.3 (s, CH_2), 46.0 (s, CH_2), 57.2 (s, CH), 125.8 (s, $C_{aro}H$), 125.9 (s, $C_{aro}H$), 126.1 (s, $C_{aro}H$), 128.8 (s, $C_{aro}H$), 133.9 (s, C_{aro}), 134.3 (s, C_{aro}), 180.5 (s, C=O). HRMS (ESI-MS) $[M+H]^+$: found 178.0861; calcd for $C_{10}H_{12}NO_2$: 178.0863.

4.3.4. (*S*)-2-*tert*(Butyloxy)carbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid 9a

At 0 °C, a solution of Boc_2O (13.55 g; 62.1 mmol; 1.1 equiv) in dioxane (55 mL) was added dropwise to a mixture of α-amino acid (*S*)-**9** (10 g; 56.4 mmol; 1 equiv) and 1 M NaOH (110 mL) in dioxane (55 mL). After stirring for 14 h, petroleum ether (100 mL) was added and the two layers were separated. The aqueous layer was acidified with 1 M HCl (pH ≈ 5) and extracted with ethyl acetate (5 × 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Compound **9a** was obtained as a white solid and used without further purification. 94% yield. Mp: 126 °C. $[\alpha]_D^{20} = +19.0$ (*c* 1 M, methanol). R_f 0.23 (petroleum ether/ethyl acetate: 70/30). Because of the carbamate, two different conformers can be observed, in particular in ^{13}C NMR. ^1H NMR (200 MHz, DMSO) δ 1.40–1.46 (m, 9H), 3.01–3.21 (m, 2H), 4.35–4.91 (m, 3H), 7.18–7.20 (m, 4H), 12.67 (broad s, 1H); ^{13}C {^1H} NMR (75.5 MHz, DMSO) δ 27.9 (s, CH_3), 28.0 (s, CH_3), 30.6 (s, CH_2), 30.9 (s, CH_2), 43.6 (s, CH_2), 44.1 (s, CH_2), 51.9 (s, CH), 53.6 (s, CH), 79.3 (s, C), 79.5 (s, C), 126.0 (s, C_{aro} H), 126.1 (s, C_{aro} H), 126.4 (s, C_{aro} H), 126.6 (s, C_{aro} H), 127.7 (s, C_{aro} H), 128.2 (s, C_{aro} H), 131.9 (s, C_{aro}), 132.5 (s, C_{aro}), 132.8 (s, C_{aro}), 133.7 (s, C_{aro}), 154.1 (s, NC(O)O), 154.6 (s, NC(O)O), 172.5 (s, C(O)O), 172.9 (s, C(O)O). HRMS (ESI-MS) $[M+H]^+$: found 278.1388; calcd for $C_{15}H_{20}NO_4$: 278.1387.

4.3.5. (*S*)-2-*tert*(Butyloxy)carbonyl-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline 9b

At −20 °C, *N*-methylmorpholine (3.2 mL; 28.9 mmol; 1 equiv) was added to a solution **of (*S*)-9a** (8 g; 28.9 mmol; 1 equiv) in THF (180 mL). After stirring for 15 min, ethyl chloroformate (3.0 mL; 31.7 mmol; 1.1 equiv) was added dropwise and the mixture was stirred for additional 15 min. Then, aniline (2.6 mL; 28.9 mmol; 1 equiv) was added dropwise and the mixture was slowly warmed up and stirred for 20 h at room temperature. The mixture was diluted with water (100 mL) and AcOEt (100 mL) and the two layers were separated. The organic layer was successively washed with 1 M HCl (120 mL), a saturated solution of $NaHCO_3$ (120 mL) and brine (120 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate: 80/20) afforded **9b** as a white solid. 66% yield. Mp: 48 °C. $[\alpha]_D^{20} = -36$ (*c* 1 M, $CHCl_3$). R_f 0.38 (petroleum ether/ethyl acetate: 70/30). ^1H NMR (200 MHz, DMSO) δ 1.30–1.45 (m, 9H), 2.93–3.28 (m, 2H), 4.32–4.85 (m, 3H), 7.03 (tm, *J* = 7.3 Hz, 1H), 7.13–7.35 (m, 6H), 7.45–7.60 (m, 2H), 10.01 (broad s, 1H); ^{13}C {^1H} NMR (75.5 MHz, DMSO) δ 27.8 (s, CH_3), 31.8 (s, CH_2), 43.9 (s, CH_2), 56.0 (s, CH), 79.2 (s, C), 119.1 (s, C_{aro} H), 123.1 (s, C_{aro} H), 125.7 (s, C_{aro} H), 126.4 (s, C_{aro} H), 127.0 (s, C_{aro} H), 127.1 (s, C_{aro} H), 128.6 (s, C_{aro} H), 133.7 (s, C_{aro}), 135.2 (s, C_{aro}), 138.9 (s, C_{aro}), 154.0 (s, NC(O)O), 170.6 (s, NC(O)). HRMS (ESI-MS) $[M+H]^+$: found 353.1851; calcd for $C_{21}H_{25}N_2O_3$: 353.1860.

4.3.6. (*S*)-3-Anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline 11

A solution of (*S*)-**9b** (6.76 g; 19.2 mmol; 1 equiv) and trifluoroacetic acid (37 mL; 0.50 mol; 25 equiv) in dichloromethane was

stirred for 14 h at room temperature. The solvent and the excess of trifluoroacetic acid were removed and the product was dissolved in dichloromethane. The organic layer was successively washed with a saturated solution of $NaHCO_3$ (100 mL), water, (100 mL) and brine (100 mL). Then, the organic layer was dried over Na_2SO_4, filtered, and concentrated. Compound **11** was obtained as a white solid and used without further purification. 97% yield. Mp: 162 °C. $[\alpha]_D^{20} = -74$ (*c* 0.5, CH_2Cl_2). R_f 0.08 (petroleum ether/ethyl acetate: 70/30). ^1H NMR (200 MHz, $CDCl_3$) δ 1.72 (broad s, 1H), 2.91 (dd, J = 10.4, 16.4 Hz, 1H), 3.36 (dd, J = 5.3, 16.4 Hz, 1H), 3.69 (dd, J = 5.3, 10.5 Hz, 1H), 4.01 (d, J = 17.0 Hz, 1H), 4.10 (d, J = 17.0 Hz, 1H), 7.07–7.23 (m, 5H), 7.30–7.38 (m, 2H), 7.60–7.64 (m, 2H), 9.35 (broad s, 1H); ^{13}C {^1H} NMR (50 MHz, DMSO) δ 30.7 (s, CH_2), 46.7 (s, CH_2), 56.6 (s, CH), 119.2 (s, $C_{aro}H$), 123.2 (s, C_{aro} H), 125.58 (s, C_{aro} H), 125.64 (s, C_{aro} H), 125.8 (s, C_{aro} H), 128.6 (s, C_{aro} H), 128.8 (s, C_{aro} H), 134.2 (s, C_{aro}), 136.0 (s, C_{aro}), 138.7 (s, C_{aro}), 171.4 (s, NC(O)). HRMS (ESI-MS) $[M+H]^+$: found 253.1335; calcd for $C_{16}H_{17}N_2O$: 253.1335.

4.3.7. General procedure for the reduction of 10 and 11

At 0 °C, $LiAlH_4$ (2.11 g; 55.65 mmol; 3 equiv) was carefully added to a solution of amide (1 equiv) in THF (200 mL). The mixture was stirred for 14 h at room temperature and after cooling down to 0 °C, the reaction was quenched with a saturated solution of Na_2SO_4. The mixture was stirred for 2 h. Salts were filtered off on Büchner and washed with CH_2Cl_2 (3 × 100 mL). The two layers were separated and the aqueous layer was extracted with $CHCl_3$ (4 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The products were purified by column chromatography on silica gel.

4.3.7.1. (*S*)-2-(Anilinomethyl)indoline 12[17]. Brown solid. 1.41 g; 83% yield. Mp: 75 °C. $[\alpha]_D^{20} = +84$ (*c* 1.0, $CHCl_3$). R_f 0.61 (Petroleum ether/AcOEt: 70/30). ^1H NMR (200 MHz, $CDCl_3$) δ 2.89 (dd, J = 7.4, 15.6 Hz, 1H), 3.19 (dd, J = 9.0, 15.6 Hz, 1H), 3.28 (d, J = 5.7 Hz, 2H), 4.02 (br s, 2H), 4.10–4.24 (m, 1H), 6.62–6.76 (m, 5H), 7.00–7.22 (m, 4H); ^{13}C {^1H} NMR (50 MHz, $CDCl_3$) δ 33.5 (s, CH_2), 48.5 (s, CH_2), 58.4 (s, CH), 109.6 (s, $C_{aro}H$), 112.9 (s, $C_{aro}H$), 117.6 (s, $C_{aro}H$), 118.9 (s, $C_{aro}H$), 124.8 (s, $C_{aro}H$), 127.4 (s, $C_{aro}H$), 128.4 (s, C_{aro}), 129.2 (s, $C_{aro}H$), 148.1 (s, C_{aro}), 150.4 (s, C_{aro}).

4.3.7.2. (*S*)-3-(Anilinomethyl)-1,2,3,4-tetrahydroisoquinoline 13. Pale yellow solid. 4.05 g; 92% yield. Mp: 87 °C. $[\alpha]_D^{20} = -76.3$ (*c* 1.0, CH_2Cl_2). R_f 0.20 (AcOEt). ^1H NMR (200 MHz, $CDCl_3$) δ 1.60 (br s, 1H), 2.65 (dd, J = 9.9, 16.2 Hz, 1H), 2.86 (dd, J = 3.9, 16.3 Hz, 1H), 3.04–3.40 (m, 3H), 4.07 (s, 2H), 4.24 (br s, 1H), 6.67–6.76 (m, 3H), 7.02–7.24 (m, 6H); ^{13}C {^1H} NMR (50 MHz, $CDCl_3$) δ 33.0 (s, CH_2), 48.0 (s, CH_2), 49.1 (s, CH_2), 53.0 (s, CH), 112.9 (s, $C_{aro}H$), 117.4 (s, $C_{aro}H$), 125.9 (s, $C_{aro}H$), 126.0 (s, $C_{aro}H$), 126.1 (s, $C_{aro}H$), 129.2 (s, 2 $C_{aro}H$), 134.0 (s, C_{aro}), 135.6 (s, C_{aro}), 148.4 (s, C_{aro}). HRMS (ESI-MS) $[M+H]^+$: found 239.1541; calcd for $C_{16}H_{19}N_2$: 239.1543.

4.4. General procedure for the synthesis of diazaphospholidines 15a–b

A solution of diazaphospholidine **6** (1 mmol) and alcohol (1 mmol) in toluene (4 mL) was refluxed until no starting material was detected by means of ^{31}P NMR. After removal of the solvent, the ligand was obtained as a white solid after filtration on a neutral alumina column (toluene).

Following the general procedure, **15a** was obtained as a white solid. 81% yield. $[\alpha]_D^{20} = -176$ (*c* 1.0, CH_2Cl_2). ^{31}P {^1H} NMR (81 MHz, C_6D_6) δ 108.3 (s); ^1H NMR (200 MHz, C_6D_6) δ 2.17 (dd, J = 6.5, 16.0 Hz, 1H), 2.47 (td, J = 3.0, 9.0 Hz, 1H), 2.58 (dd, J = 9.6, 16.0 Hz, 1H), 2.97 (tm, J = 7.7 Hz, 1H), 3.72–3.88 (m, 1H), 6.73–7.24 (m, 14H); ^{13}C {^1H} NMR (50 MHz, $CDCl_3$) δ 35.0 (s, CH_2), 54.7 (d, J_{PC} = 7.3 Hz, CH_2), 62.8 (d, J_{PC} = 7.7 Hz, CH), 111.0 (d, J_{PC} = 11.1 Hz, $C_{aro}H$), 115.2 (d, J_{PC} = 12.9 Hz, $C_{aro}H$), 120.0 (s, $C_{aro}H$), 120.7 (s, $C_{aro}H$), 121.9 (d, J_{PC} = 4.5 Hz, $C_{aro}H$), 123.7 (s, $C_{aro}H$), 125.3 (s, $C_{aro}H$), 127.8 (s, $C_{aro}H$), 129.36 (s, $C_{aro}H$), 129.38 (d, J_{PC} = 6.8 Hz, $C_{aro}H$), 130.1 (d, J_{PC} = 3.9 Hz, C_{aro}), 144.9 (d, J_{PC} = 13.9 Hz, C_{aro}), 146.6 (d, J_{PC} = 22.9 Hz, C_{aro}), 153.0 (d, J_{PC} = 5.7 Hz, C_{aro}). HRMS (ESI-MS) $[M+Na]^+$: found 369.1123; calcd for $C_{21}H_{19}N_2NaOP$: 369.1127.

Following the general procedure, **15b** was obtained as a white solid. 80% yield. $[\alpha]_D^{20} = -187$ (*c* 0.76, CH_2Cl_2). ^{31}P {^1H} NMR (81 MHz, $CDCl_3$) δ 110.8 (s); ^1H NMR (200 MHz, C_6D_6) δ 2.18 (dd, J = 6.7, 15.8 Hz, 1H), 2.46 (td, J = 3.1, 8.9 Hz, 1H), 2.59 (dd, J = 9.5, 15.9 Hz, 1H), 3.02 (tm, J = 9.0 Hz, 1H), 3.73–3.89 (m, 1H), 6.45–7.52 (m, 18H). ^{13}C {^1H} NMR (50 MHz, $CDCl_3$) δ 35.1 (s, CH_2), 54.6 (d, J_{PC} = 7.5 Hz, CH_2), 62.8 (d, J_{PC} = 7.9 Hz, 1H), 110.8 (d, J_{PC} = 10.7 Hz, $C_{aro}H$), 115.1 (d, J_{PC} = 13.0 Hz, $C_{aro}H$), 119.8 (s, $C_{aro}H$), 120.3 (s, $C_{aro}H$), 122.6 (d, J_{PC} = 6.4 Hz, $C_{aro}H$), 124.0 (s, $C_{aro}H$), 124.8 (s, $C_{aro}H$), 126.6 (s, $C_{aro}H$), 127.5 (s, $C_{aro}H$), 127.9 (s, $C_{aro}H$), 128.3 (s, $C_{aro}H$), 129.1 (s, $C_{aro}H$), 129.4 (s, $C_{aro}H$), 129.6 (d, J_{PC} = 4.3 Hz, C_{aro}), 130.8 (s, $C_{aro}H$), 135.4 (s, C_{aro}), 138.5 (s, C_{aro}), 144.6 (d, J_{PC} = 18.8 Hz, C_{aro}), 146.1 (d, J_{PC} = 22.6 Hz, C_{aro}), 150.2 (d, J_{PC} = 4.7 Hz, C_{aro}). HRMS (ESI-MS) $[M+H]^+$: found 423.1625; calcd for $C_{27}H_{24}N_2OP$: 423.1621.

4.5. General procedure for the enantioselective Co(I)-catalyzed [6+2] cycloaddition

Under a nitrogen atmosphere, the ligand (0.10 equiv) was added to a solution of CoI_2 (13 mg; 0.042 mmol; 0.05 equiv) in 1,2-dichloroethane (1 mL). The mixture was stirred for 10 min. and powdered zinc (8.3 mg; 0.127 mmol; 0.15 equiv) was added. Then, a solution of 1,3,5-cycloheptatriene (93 mg; 1 mmol; 1.20 equiv) in 1,2-dichloroethane (1 mL) and a solution of alkyne (1 equiv) in 1,2-dichloroethane (1 mL) and zinc iodide (27 mg; 0.085 mol; 0.10 equiv) were added successively. The resulting mixture was heated at 40 °C for 20 h. After cooling to room temperature, the reaction was quenched with petroleum ether (5 mL). The reaction mixture was filtered through Celite® and removal of solvent followed by column chromatography on silica gel (petroleum ether) gave compounds **3a–c**. Analytic data, in particular the NMR spectra, are in agreement with those of known compounds. [13b]

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15. Crystallographic data for the structures of **6** and **7** were deposited in the Cambridge Crystallographic Data Centre under the number CCDC 757596 and 757597, respectively. They are available free of charge at http://www.ccdc.cam.ac.uk.
16. A detailed theoretical and experimental study of the inversion at the phosphorus center of **7**, which is configurationally stable at room temperature, will be reported in a separate article.
17. Compound **13** has never been described to the best of our knowledge. Compound **12** was reported in 2000. However, the authors assumed the synthesis was enantiospecific (in particular the last step), but they did not verify this point: Sato, S.; Watanabe, H.; Asami, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4329–4340.
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