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# A *P*-chirogenic β-aminophosphine synthesis by diastereoselective reaction of the α-metallated PAMP–borane complex with benzaldimine

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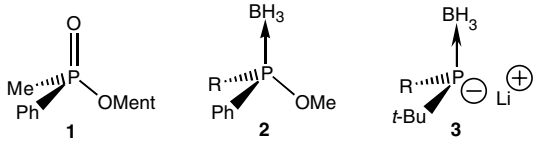
**Abstract**—The diastereoselective synthesis of a *P*-chirogenic β-aminophosphine ligand with carbon–carbon bond formation of the ethano bridge in a 3:1 ratio via reaction of an α-metallated *P*-chirogenic phosphine borane with a benzaldimine is described. The diastereoselectivity is attributed to a transition state where the lithium cation chelates the phosphine borane carbanion and the nitrogen of the imine and the attack of the C=N occurs on the face opposite to the P–B bond, due to its interaction with the antibonding P–B bond. The major diastereoisomeric β-aminophosphine borane was then separated and decomplexed into the corresponding β-aminophosphine under neutral conditions and without epimerization by heating at reflux in EtOH. This synthesis offers a short hemisynthetic route to the *P*-chirogenic β-P,N-ligands, by bridge formation starting from methylphosphine boranes.


## 1. Introduction

Chiral β-aminophosphines, which are active in numerous asymmetric reactions, such as hydrogenation, hydrosilylation, hydroformylation, allylation, Michael addition and Grignard cross-coupling,[1] are an important class of ligands for transition metal catalysis. The chelating character (hard and soft donors) of these ligands makes them particularly attractive since it allows open coordination sites during the catalytic cycle[2] or dissymmetry, causing an increase in the regioselectivity of complex–substrate reactions.[3] In addition, β-aminophosphines, especially those with a large bite angle,[4] are also used as building blocks to synthesize multidentate ligands. These β-aminophosphines have the amino group linked to the phosphorus atom by an aliphatic[5,6] or aromatic[4c,7,8b] bridge, often with the nitrogen atom arising from an imine[8] or a heterocycle.[6]

The chirogenicity of these ligands usually is borne by the backbone of the bridge or by the amino group.[5–8] In the few examples known to date of β-aminophosphines bearing the chirogenicity on the phosphorus atom, the β-aminophosphines are prepared either by resolution of a racemic mixture[9] or by stereoselective synthesis with phosphorus–carbon bond formation using a *P*-chirogenic building block, such as menthyl phosphinate **1**,[10] methyl phosphinite **2**[11] or phosphide borane complexes **3**,[12] respectively.




Having investigated the synthesis and application of *P*,*N*[13] and *P*-chirogenic[14] hybrid ligands in coordination chemistry or asymmetric catalysis in previous work, we decided to examine β-aminophosphines with a stereogenic phosphorus center.

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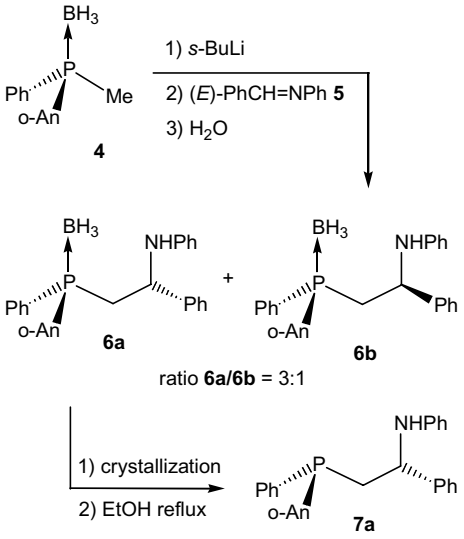
We predicted that the synthesis of these ligands would proceed via carbon–carbon bond formation of the ethano bridge, starting from a methyl phosphine borane. Even though the reaction of an α-metallated anion of a phosphine borane with a carbonyl or various electrophilic reagents has been well documented,[15] to the best of our knowledge, the reaction of this particular anion with an imine has not been studied.[16] Therefore, we herein report the first example of a diastereoselective reaction between an α-metallated *P*-chirogenic phosphine borane and an imine leading to the corresponding β-aminophosphine derivatives **6** (Scheme 1).



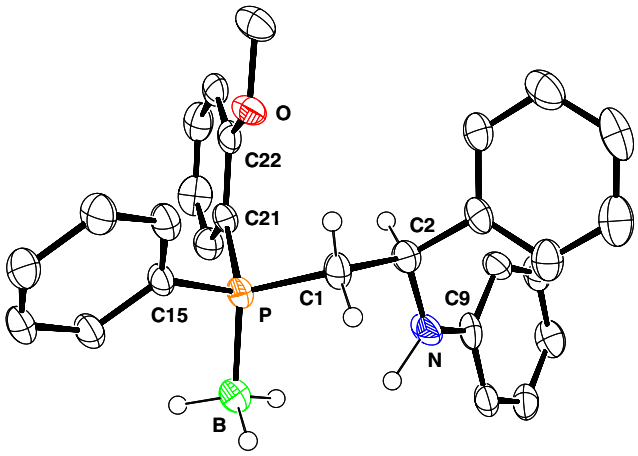

**Scheme 1.**

## 2. Results and discussion

The (*S*)-(+)-*o*-anisylmethylphenylphosphine borane **4** was prepared with 98% ee from (−)-ephedrine, according to the published procedure.[17] After deprotonation, the resulting α-metallated carbanion was reacted with benzaldimine **5** to afford the β-aminophosphine borane **6a** and **6b** as an epimeric mixture in a 3:1 ratio (Scheme 1). The major isomer **6a** was obtained with a diastereoisomeric purity of >96% by recrystallization from ethanol. Its absolute configuration was determined by X-ray analysis as *S* and *R* for the phosphorus and carbon centers, respectively (Fig. 1).

In addition, this structure showed that the molecule was in a staggered conformation with the *o*-anisyl group in the plane and in a position *anti* to the P–B bond, when the C(1)–C(2) is outside and nearly in the plane of the PC(15) bond (Fig. 1). The angle C(2)–N–C(9) is in agreement with a flattened pyramidal structure for the nitrogen atom. It is noteworthy that the minor epimer **6b** was obtained from the mother liquor in very low yield (4%) but with 96% de, with its absolute configuration was then deduced from **6a**, as *S* for both the phosphorus and carbon centers.

The stereochemistry of the α-phosphoryl carbanion reaction with an imine can be readily accounted for by




Selected bond lengths (Å), angles (°), and dihedral angles (°): P–B 1.893(5), P–C(1) 1.822(4), C(1)–C(2) 1.542(5), C(2)–N 1.432(5), C(9)–N 1.398(5), C(15)–P–C(1) 104.7(2), C(15)–P–C(21) 108.6(2), C(15)–P–B 110.3(2), B–P–C(1) 113.1(2), C(1)–C(2)–N 110.0(3), C(1)–C(2)–C(3), C(2)–N–C(9) 122.9(3); B–P–C(21)–C(22) −177.1(3); P–C(21)–C(22)–O 2.5(5), B–P–C(1)–C(2) 74.7(4), P–C(1)–C(2)–C(3) 164.1(3), P–C(1)–C(2)–N –71.5(4), C(15)–P–C(1)–C(2) 165.2(3).

**Figure 1.** Crystal structure of the β-aminophosphine borane **6a**.

the formation of a chelated cyclic transition state with electrophilic assistance of the lithium cation, bridging the oxygen and nitrogen atoms; however in the case of the phosphine borane this model failed. Since the major β-aminophosphine **6a** was formed with an (*R*)-configuration at the stereogenic carbon center, the approach of the carbanion occurs preferentially on the *si* face of the imine **5**. Therefore, we suggest that the stereochemical outcome of the reaction arises from the diastereofacial selectivity of the phosphine borane carbanion due to the lithium chelate with the imine (Fig. 2). In this case, the *si* face of the imine must approach the face opposite to the P–B bond, affording an interaction between the C=N and the antibonding P–B bond. Furthermore, the *N*-phenyl group may give π–π stacking interactions with the phenyl substituent, since both rings could be parallel, contributing also to the position of the imine with regard to the phosphorus reagent. It may be noted that this mechanism looks like a Wittig transition state,[18] where the hydrogen of the benzaldimine is on the same side as the phosphine substituents, in order to minimize steric hindrance (Fig. 2).

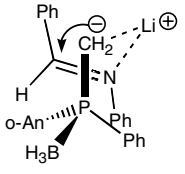



**Figure 2.**

Finally, the decomplexation of the β-aminophosphine borane **6a** was investigated in order to obtain the cor-

responding P,N-ligand **7a**. Although, the decomplexation is usually carried out by exchange with DABCO,[19] we ran the reaction under neutral conditions to avoid possible side reactions due to the presence of the amino group, as observed in the case of β-hydroxyarylphosphine.[14] Thus, we found that the free β-aminophosphine **7a** could be obtained in 78% isolated yield without epimerization by simply heating its borane complex **6a** at reflux in ethanol for 6 h (Scheme 1). Since decomplexation of borane occurs with retention of configuration,[14] the absolute configuration of **7a** was attributed as 1*S*,2*R*.

Preliminary studies of chiral ligand **7a** were performed in styrene asymmetric hydroformylation, using the precatalyst [Rh(acac)(CO)$_2$]. Under mild conditions, the catalytic system gave complete conversion after 3 h (TOF=320 h$^{-1}$), leading to high branched/linear aldehydes in a 8.1:1 ratio, as usually observed for rhodium catalyzed hydroformylation.[20] However, the (2*S*)-phenylpropanal was obtained with only 10% ee, which could be due to the hemilabile character of the P,N-ligand under CO pressure[21a] and/or the weak asymmetric induction of chiral monophosphines for the asymmetric catalysis.[21b,c] Nevertheless, the synthesis and application of new *P*-chirogenic β-P,N-ligands for further asymmetric catalyzed reactions are currently in progress in our laboratory.

## 3. Conclusion

We have herein reported the first diastereoselective synthesis of a *P*-chirogenic β-aminophosphine ligand using a borane complexation methodology. This synthesis is based on the reaction of the α-metallated *P*-chirogenic phosphine borane with a benzaldimine affording the corresponding β-*P*,*N* derivative with carbon–carbon bond formation of the ethano bridge, as an epimeric mixture in a 3:1 ratio. This diastereoselectivity is attributed to a transition state where lithium chelates the phosphine borane carbanion and the imine nitrogen while the attack on the C=N occurs on the face opposite to the P–B bond, due to its interaction with the antibonding P–B bond. It was shown that the β-aminophosphine borane was decomplexed into the free β-P,N-ligand in good yield and without epimerization by heating at reflux in EtOH. Finally, the reaction of the α-metallated phosphine borane with an imine offers a promising, new route to *P*-chirogenic β-P,N-ligands with an aliphatic bridge.

## 4. Experimental

### 4.1. General

All manipulations were carried out under argon using standard Schlenk techniques. All solvents were dried and deoxygenated prior to use by standard methods. The commercial compounds [Rh(acac)(CO)$_2$] and styrene were used as received. Aniline and benzaldehyde were distilled prior to use. The (*S*)-(+)-*o*-anisylmethylphenylphosphine borane **4**,[17] and the *N*-benzylideneaniline **5**[22] were prepared according to the literature. Thin-layer chromatography was performed on silica chromagel (60 $F_{254}$) and visualized by UV, iodine or permanganate treatment. Flash chromatography was performed on silica gel (60ACC, 6–35 microns and 35–70 microns). NMR spectra data were recorded on Bruker 300 and 500 MHz spectrometers, using TMS as the internal reference for $^1$H and $^{13}$C NMR and 85% phosphoric acid as the external reference for $^{31}$P NMR. IR spectra were recorded with golden gate equipment on a Bruker Vector 22 spectrophotometer. Melting points were measured on a Büchi 530 melting point apparatus and are uncorrected. Optical rotations values were determined at 20 °C on a 141 polarimeter. Elemental analyses were carried out by the analytical service at the Burgundy (Dijon) University with a Fisons Instruments EA1108 analyzer. The X-ray structure was determined on Enraf Nonius KappaCCD diffractometer at the Burgundy (Dijon) University.

### 4.2. Preparation of 2-*N*-phenylamino-2-phenyl-1-(*o*-anisylphenylphosphino borane)ethane 6

In a 50 mL three-necked flask equipped with a magnetic stirrer and an argon inlet, 0.47 g of (*S*)-PAMP(BH$_3$) **4** (1.9 mmol) was dissolved in 10 mL of anhydrous THF. The solution was cooled to −78 °C, and 1.7 mL of *s*-BuLi in hexane (1.3 M, 1.9 mmol) added dropwise. The mixture was stirred for another 2 h at low temperature, after which a solution of *N*-benzylideneaniline **5** (0.37 g, 2.1 mmol) in THF (3 mL) was slowly added. The temperature was raised and the solution stirred overnight at room temperature. The reaction mixture was then hydrolyzed by addition of water (15 mL). After phase separation, the aqueous phase was extracted with diethyl ether (3×15 mL). The organic phase was dried over $MgSO_4$ and the solvents evaporated under reduced pressure to give a residue, which was purified by chromatography on a silica column with a 1:10 $Et_2O$/pentane mixture. The solvents were evaporated and then pentane added to precipitate compound **6** as a white microcrystalline powder, which was filtered, washed with pentane, and dried (0.61 g, 76%). The product was recrystallized from hot ethanol and repeated crystallizations leading to epimer (1*S*,2*R*)-**6a** with 96% de (0.18 g, 30%). The mother solution was concentrated and placed at −30 °C for several days, yielding few crystals. After filtration, the mother liquor was evaporated to dryness. The residue was then washed with pentane to afford the epimer (*S*,2*S*)-**6b**, which was obtained with 96% de as a white powder (24 mg, 4%).

(1*S*,2*R*)-**6a**: White powder; $R_f = 0.1$ ($Et_2O$/pentane 1:10); mp 130 °C; IR(neat): 3404 cm$^{-1}$ (w, $\nu_{NH}$), 2400 cm$^{-1}$ (m, $\nu_{BH}$); $[\alpha]_D = -76$ (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 0.75–1.47 (br q, 3H, B$H_3$), 2.65 (ddd, 1H, $^2J_{HP} = 4.3$, $^3J_{HH} = 9.4$, $^2J_{HH} = 13.9$, PC*H*), 3.13 (dt, 1H, $^3J_{HH} = 4.5$, $^2J_{HP} = {}^2J_{HH} = 14.3$, PC*H*), 3.62 (s, 3H, C$H_3$O), 4.36 (dt, 1H, $^3J_{HH} = 4.3$, $^3J_{HP} = {}^3J_{HH} = 9.4$, NC*H*), 4.63 (br s, 1H, N*H*), 6.32 (d, 2H, $^3J_{HH} = 7.7$, *H* arom), 6.53 (t, 1H, $^3J_{HH} = 7.3$, *H* arom), 6.74 (dd, 1H, $^4J_{HH} = 3.2$, $^3J_{HH} = 8.3$, *H* arom), 6.82–6.88 (m, 3H,

*H* arom) 7.08–7.37 (m, 9H, *H* arom), 7.47 (ddd, 1H, $^4J_{HH} = 1.7$, $^3J_{HH} = 8.1$, $^2J_{HP} = 10.9$, *H* arom), 7.81 (ddd, 1H, $^4J_{HH} = 1.5$, $^3J_{HH} = 7.7$, $^3J_{HP} = 14.3$, *H* arom); $^{13}$C NMR ($CDCl_3$): $\delta$ 34.0 (d, $^2J_{CP} = 34$, P*C*H$_2$), 55.3 (N*C*H), 55.6 (*C*H$_3$O), 111.1 (d, $^3J_{CP} = 4$, *C* arom), 113.9 (*C* arom), 114.5 ($C_i$ arom), 117.8 (*C* arom), 121.9 (d, $^3J_{CP} = 13$, *C* arom), 126.4 (*C* arom), 127.7 (*C* arom), 128.8 (d, $^2J_{CP} = 10$, *C* arom), 129.1 (*C* arom), 129.2 (*C* arom), 130.9 (d, $^4J_{CP} = 2$, *C* arom), 131.4 (d, $^3J_{CP} = 9$, *C* arom), 131.6 ($C_{ipso}$ arom), 134.5 (d, $^4J_{CP} = 2$, *C* arom), 137.7 (d, $^2J_{CP} = 16$, *C* arom), 144.4 (d, $^1J_{CP} = 9$, *C* arom), 147.1 (*C* arom), 161.4 (d, $^2J_{CP} = 2$, *C* arom); $^{31}$P NMR ($CDCl_3$): $\delta$ +13.8 (m, $^1J_{PB} = 55$); Anal. Calcd for $C_{27}H_{29}NOBP$ (425.3): C, 76.24; H, 6.87; N, 3.29. Found: C, 76.06; H, 6.94; N, 3.75.

Crystal data:[23] tetragonal; *a* (Å) = *b* (Å) = 10.0832(2); *c* (Å) = 46.171(1); *V* (Å) = 4694.3(2); $Z = 8$; space group: $P4_32_12$; crystal color: colorless; $\mu$ (mm$^{-1}$): 0.136; $F(000)$ : 1808; density $\rho$ (g/cm$^3$): 1.204; $\lambda = 0.71073$ Å; $\sin\theta/\lambda_{max}$ (Å$^{-1}$): 0.65; limits *h*/*k*/*l*: $-13 < h < 13$; $-9 < k < 9$; $-59 < l < 19$; absorption correction: Scalepack; temperature of measurement: 110(2) K; Nb of reflections collected: 6989; Nb of independent reflections: 5369 [$R$(int) = 0.095]; Nb of reflections with [$I > 2\sigma(I)$]: 2987; refinement method: full-matrix L.S. on F$^2$; constraint parameters for data: 284; $R = \Sigma(||Fo| - |Fc||)/\Sigma|Fo|$: $R^1 = 0.0735$, $wR^2 = 0.1326$; $R = [\Sigma w(||Fo|^2 - |Fc||^2)^2 / \Sigma wFo^2]^{1/2}$: $R^1 = 0.1590$, $wR^2 = 0.1625$; $\Delta\rho$ min (e/Å$^{-3}$) −0.508; $\Delta\rho_{max}$ (e/Å$^{-3}$) 0.264.

(1*S*,2*S*)-**6b**: white powder; $R_f = 0.1$ ($Et_2O$/pentane 1:10); $^1$H NMR ($CDCl_3$): $\delta$ 0.75–1.47 (br q, 3H, B*H*$_3$), 2.67 (dt, 1H, $^3J_{HH} = 3.0$, $^3J_{HP} = {}^3J_{HH} = 10.2$, PC*H*), 3.12 (m, 1H, $^3J_{HH} = 3.0$, $^3J_{HP} = {}^3J_{HH} = 10.2$, PC*H*), 3.65 (s, 3H, C*H*$_3$O), 4.23 (br s, 1H, N*H*), 4.71 (dt, 1H, $^3J_{HH} = 3.0$, $^3J_{HP} = {}^3J_{HH} = 10.2$, NC*H*), 6.11 (d, 2H, $^3J_{HH} = 7.7$, *H* arom), 6.33 (d, 1H, $^3J_{HH} = 7.9$, *H* arom), 6.51 (t, 1H, $^3J_{HH} = 7.4$, *H* arom), 6.83–7.54 (m, 14H, *H* arom), 7.75 (ddd, 1H, $^4J_{HH} = 1.5$, $^3J_{HH} = 7.7$, $^3J_{HP} = 14.3$, *H* arom); $^{13}$C NMR ($CDCl_3$): $\delta$ 33.9 (d, $^2J_{CP} = 33$, P*C*H$_2$), 54.7 (N*C*H), 55.8 (*C*H$_3$O), 111.6 (d, $^3J_{CP} = 4$, *C* arom), 113.6 (*C* arom), 113.7 (*C* arom), 117.7 (*C* arom), 121.9 (d, $^3J_{CP} = 12$, *C* arom), 126.3 (*C* arom), 127.5 (*C* arom), 128.6–129.1 (*C* arom), 130.9 (d, $^4J_{CP} = 2$, *C* arom), 131.2 ($C_i$ arom), 131.9 (d, $^3J_{CP} = 9$, *C* arom), 134.2 (d, $^4J_{CP} = 2$, *C* arom), 136.6 (d, $^2J_{CP} = 14$, *C* arom), 144.4 (d, $^1J_{CP} = 11$, *C* arom), 146.8 (*C* arom), 161.1 (*C* arom); $^{31}$P NMR ($CDCl_3$): $\delta$ +13.8 (m, $^1J_{PB} = 55$).

### 4.3. Preparation of 2-*N*-phenylamino-2-phenyl-1-(*o*-anisylphenylphosphino)ethane 7

Borane complex **6a** (170 mg, 0.4 mmol) was dissolved in degassed ethanol (10 mL) and refluxed for 6 h. The solvent was then evaporated under reduced pressure and the residue purified by chromatography on silica gel under an inert atmosphere with a 1:4 $Et_2O$/pentane mixture. The solvents were evaporated until a white powdery precipitate formed. The product was washed with pentane and dried under vacuum (128 mg, 78% yield).

(1*S*,2*R*)-**7a**: white powder; $R_f = 0.6$ ($Et_2O$/pentane 1:4); mp 132 °C; IR(neat): 3390 cm$^{-1}$ (w, $\nu_{NH}$); $[\alpha] = -10$ (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 2.46 (ddd, 1H, $^2J_{HP} = 1.8$, $^3J_{HH} = 9.6$, $^2J_{HH} = 14.0$, PC*H*), 2.68 (ddd, 1H, $^2J_{HP} = 0.9$, $^3J_{HH} = 4.6$, $^2J_{HH} = 14.0$, PC*H*), 3.61 (s, 3H, C*H*$_3$O), 4.36 (br s, 1H, N*H*), 4.43 (ddd, 1H, $^3J_{HH} = 4.5$, $^3J_{HP} = 6.8$, $^3J_{HH} = 9.9$, NC*H*), 6.32 (d, 2H, $^3J_{HH} = 7.9$, *H* arom), 6.59 (t, 1H, $^3J_{HH} = 7.2$, *H* arom), 6.79 (1H, dd, $^3J_{HP} = 4.2$, $^3J_{HH} = 8.3$, *H* arom), 6.88 (t, 1H, $^3J_{HH} = 7.2$, *H* arom), 7.00 (t, 2H, $^3J_{HH} = 7.8$, *H* arom), 7.09–7.49 (m, 12H, *H* arom); $^{13}$C NMR ($CDCl_3$): $\delta$ 38.1 (d, $^2J_{CP} = 16$, P*C*H$_2$), 56.0 (*C*H$_3$O), 56.7 (d, $^3J_{CP} = 15$, N*C*H), 109.3 (*C* arom), 113.8 (*C* arom), 117.5 (*C* arom), 121.3 (*C* arom), 126.3–132.8 (m, *C* arom), 133.7 (d, $^2J_{CP} = 20$, *C* arom), 136.6 (d, $^1J_{CP} = 11$, *C* arom), 145.1 (d, $^1J_{CP} = 6$, *C* arom), 147.6 (*C* arom), 161.1 (d, $^2J_{CP} = 13$, *C* arom); $^{31}$P NMR ($CDCl_3$): $\delta$ −31.1; Anal. Calcd for $C_{27}H_{26}NOP$ (411.48): C, 78.81; H, 6.37; N, 3.01. Found: C, 79.02; H, 6.58; N, 3.48.

The minor epimer **7b** was characterized by decomplexation of the mixture **6a** and **6b**.

(1*S*,2*S*)-**7b**: $^1$H NMR ($CDCl_3$): $\delta$ 2.50 (td, 1H, $J = 6.8$, 13.0), 2.59 (ddd, 1H, $J = 4.2$, 10.0, 10.3), 3.74 (s, 3H, C*H*$_3$O), 4.28 (m, 1H, NC*H*), 4.55 (br s, 1H, N*H*), 6.37 (d, 2H, $^3J_{HH} = 7.9$, *H* arom), 6.59 (t, 1H, 7.2, *H* arom), 6.82 (1H, dd, $^3J_{HP} = 4.2$, $^3J_{HH} = 8.3$, *H* arom), 6.86 (t, 1H, $^3J_{HH} = 7.2$, *H* arom), 7.03–7.48 (m, 12H, *H* arom); $^{13}$C NMR ($CDCl_3$): $\delta$ 38.3 (d, $^2J_{CP} = 16$, P*C*H$_2$), 56.2 (*C*H$_3$O), 57.2 (d, $^3J_{CP} = 15$, N*C*H), 109.3 (*C* arom), 113.9 (*C* arom), 117.5 (*C* arom), 121.3 (*C* arom), 126.4–132.9 (*C* arom), 133.8 (d, $^2J_{CP} = 20$, *C* arom), 137.6 (d, $^1J_{CP} = 11$, *C* arom), 145.2 (d, $^1J_{CP} = 6$, *C* arom), 147.6 (*C* arom), 161.5 (d, $^2J_{CP} = 13$, *C* arom); $^{31}$P NMR ($CDCl_3$): $\delta$ −30.8.

### 4.4. Catalytic experiments

The hydroformylation reactions were carried out in a 300 mL stainless-steel Parr autoclave equipped with a magnetic drive and an immersion tube connected to a valve for solution withdrawals under pressure. The temperature was controlled by a rigid heating mantle and a single loop cooling coil. The autoclave was purged three times under vacuum/argon before introducing the catalytic solution. The 1:1 $CO/H_2$ mixture was prepared by mixing the pure gases in a 500 mL stainless steel cylinder. A solution of [Rh(acac)(CO)$_2$] (0.070 mmol), the ligand **7a** (0.070 mmol) and styrene (8 mL, 70 mmol) in 40 mL of benzene was introduced in the autoclave, followed by syngas until 600 psi, and the mixture was heated at 55 °C. After completion of the reaction, the organic solvent was removed under vacuum at room temperature, leading to a yellow-orange residue, which was analyzed by $^1$H and $^{13}$C NMR spectroscopy. The ee were determined using the NMR chiral shift reagent [Eu(hfc)$_3$], according to the literature.[24]

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