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Synthesis of some new chiral bifunctional *o*-hydroxyarylphosphonodiamides and their application as ligands in Ti(IV) complex catalyzed asymmetric silylcyanation of aromatic aldehydes

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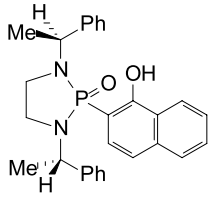
Abstract—Some new chiral bifunctional *o*-hydroxyarylphosphonodiamides were synthesized starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine and the absolute configuration of the phosphorus atom was determined by X-ray diffraction analysis. Excellent enantioselectivity (up to 98% ee) was achieved in asymmetric silylcyanation of aromatic aldehydes using a chiral titanium complex formed in situ from $Ti(O^iPr)_4$ and *o*-hydroxyarylphosphonodiamide as the catalyst.

1. Introduction

Optically active cyanohydrins are important intermediates in organic synthesis for the synthesis of a variety of valuable classes of chiral compounds, such as α-amino acids, α-hydroxy carboxylic acids, β-amino alcohols, vicinal diols, α-hydroxyketones, etc. Many efficient approaches have been reported for obtaining them by biochemical and chemical methods.[1] In the latter, the most important one is the asymmetric silylcyanation of aldehydes with trimethylsilylcyanide catalyzed by a Lewis acid, such as $Ti(O^iPr)_4$, $TiCl_4$, $AlCl_3$, $SmCl_3$ etc. in the presence of a chiral ligand. In this reaction, a wide range of chiral ligands have been elaborated, such as bis-Schiff bases (salen),[2] Schiff bases,[3] dihydroxy compounds,[4] phosphorus compounds,[5] bis-oxazolines,[6] diamides,[7] ferrocenes,[8] sulfur[9] and boron compounds,[10] etc. As shown in the literature, most of the effective chiral ligands have a free hydroxyl group or an amino group bearing at least a N–H bond which is favorable to coordinate conveniently with the metal atom in the Lewis acid. Thus the moiety of the coordinated metal atom should work as a Lewis acid center (LA) which will activate the substrate aldehyde. Moreover, if a phosphoryl group (P═O) exists at an appropriate position in the ligand molecule, the unshared electron pair on the oxygen atom should act as a Lewis base (LB) which will activate the nucleophile trimethylsilyl cyanide. If the catalyst, contains both a Lewis acid center and a Lewis base center, namely, LALB catalyst, it is a new type of chiral bifunctional catalyst.[4a,b,5e,11] Based on these findings, recently, a new chiral bifunctional cyclic *o*-hydroxynaphthylphosphonodiamide **1** was synthesized starting from (−)-α-phenylethylamine and employed in the asymmetric silylcyanation of aromatic aldehydes in the presence of $Ti(O^iPr)_4$ by our research group. The corresponding cyanohydrins were obtained in high chemical yields with good to excellent enantiomeric excesses up to 90%.[5a] In order to further improve the enantioselectivity of this type of bifunctional cyclophosphonodiamde, in this paper, we will report the synthesis of two new cyclic *o*-hydroxyarylphosphonodiamides **2** and **3** containing a phosphorus stereocenter starting from (+)-*cis*-1,2,2-trimethylcyclopentane-1,3-diamine **4** and their application in asymmetric silylcyanation of aromatic aldehydes.



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Keywords: Chiral cyclophosphonodiamide; Asymmetric silylcyanation; Catalysis; Enantioselectivity; Aromatic aldehyde.
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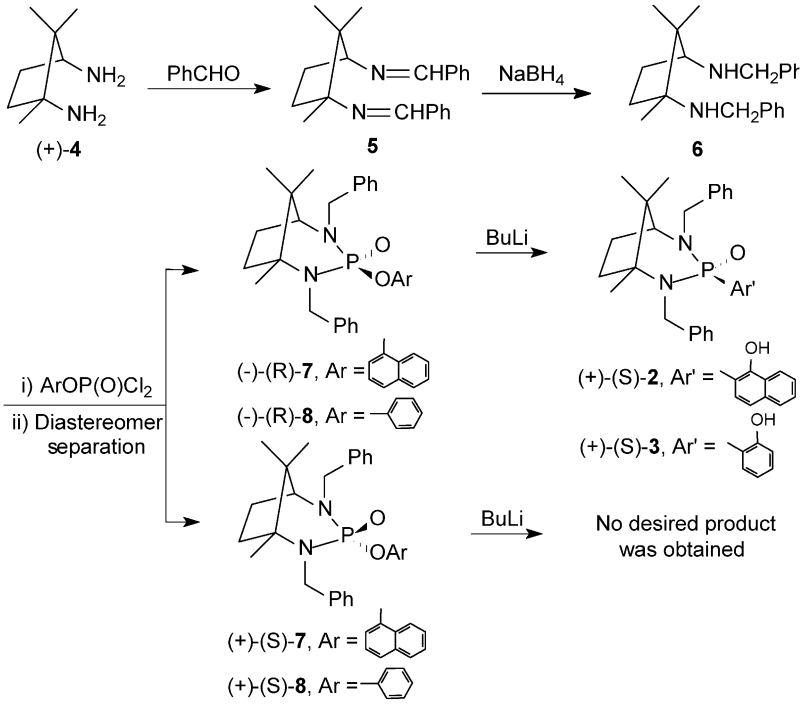


Scheme 1.

2. Results and discussion

2.1. Synthesis of ligands (+)-2, (+)-3 and determination of their stereochemistry

Condensation of 2 equiv of benzaldehyde with (+)-*cis*-trimethylcyclopentane-1,3-diamine **4**[12,13] derived from D-camphor led to *N*,*N*′-dibenzylidene-1,2,2-trimethylcyclopentane-1,3-diamine **5**. The reduction of the latter with sodium borohydride gave *N*,*N*′-dibenzyl-1,2,2-trimethylcyclopentane-1,3-diamine **6**. Then cyclization of compound **6** with *O*-aryl phosphorodichloridate afforded cyclic phosphorodiamidate **7** (Ar=1-naphthyl) or **8** (Ar=phenyl). A pair of diastereomers of **7** and **8** was obtained and separated via column chromatography. A subsequent P–O to P–C rearrangement upon treatment of (−)-**7** and (−)-**8** with *n*-BuLi resulted in the formation of (+)-cyclophosphonodiamides **2** and **3**. The rearrangement of (+)-**7** and (+)-**8** was carried out under the same condition, unfortunately, a complicated mixture rather than the desired corresponding rearrangement product was obtained (Scheme 1).

The absolute configuration of the phosphorus atom in (+)-**7** was determined as *S* via X-ray diffraction analysis (shown in Fig. 1).[14] Thus the absolute configuration of the phosphorus atom in (−)-**7** should be *R*. At the same time, a crystallographic study showed that the absolute configuration of the phosphorus atom in (+)-**2** was *S* (shown in Fig. 2).[15] Therefore, the rearrangement from (−)-(*R*)-**7** to (+)-(*S*)-**2** proceeded with retention of configuration at the phosphorus atom.

The trigonal bipyrimidal (TBP) concept and Berry's pseudorotation theory[16] could be used to explain the mechanism of this type of rearrangement. Firstly, the nucleophilic attack of carbanion formed at the α-position of the naphthalene ring in (−)-(*R*)-**7** occurs at the phosphorus opposite the N′ atom in the 1,3-diazaphosphorine, which results in the formation of the TBP-1 intermediate in which the β-carbon of naphthalene and the N′ atom are both placed at apical positions. The P–O–C in the oxaphosphetane has better apicophilicity than the N′ atom, and at the same time it is also a good leaving group. Therefore, ligand reorganization through Berry pseudorotation (BPR) of the initially formed TBP-1 to form the TBP-2 intermediate is possible.[17] Then the leaving group, naphthoxy, departs from

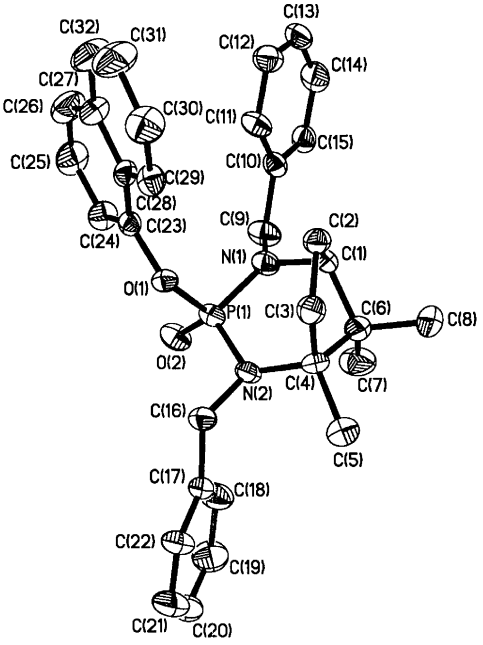


Figure 1. Molecular structure of (+)-(*S*)-**7**.

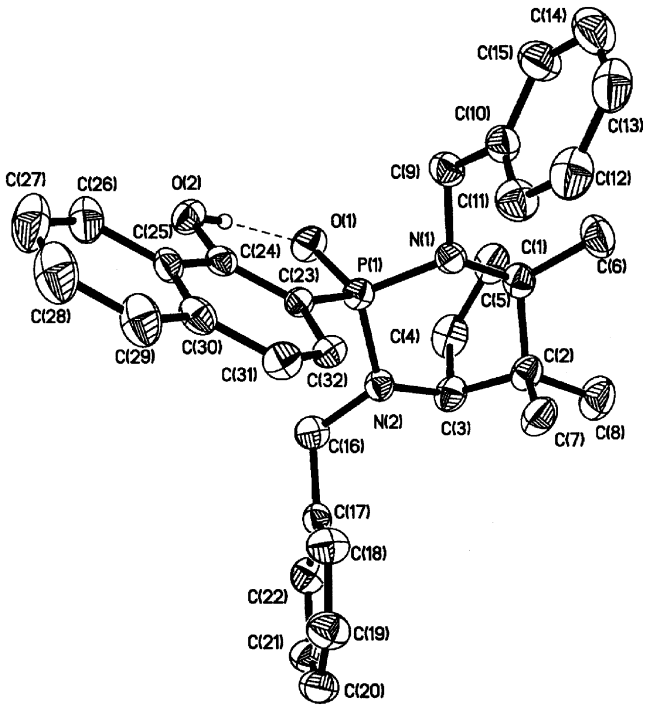


Figure 2. Molecular structure of (+)-(*S*)-**2**.

the apical position and the rearranged product with retention of configuration is obtained (Scheme 2).

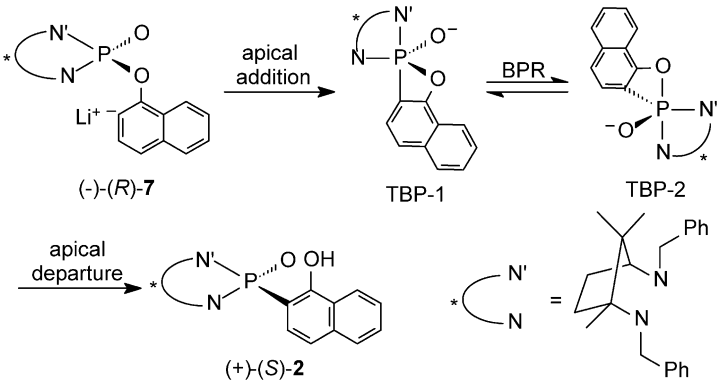
2.2. (+)-(*S*)-2/Ti(O^{i}Pr)$_4$ catalyzed asymmetric silylcyanation of aldehydes

The catalytic effect of the titanium complex formed in situ from (+)-(*S*)-**2** and Ti(O^{i}Pr)$_4$ in the asymmetric silylcyanation of aromatic aldehydes was investigated. The experimental results are listed in Table 1.

Usually, the silylcyanation reaction was best conducted in methylene chloride. We first examined the influence of the amount of ligand used on the enantioselectivity of the reaction. It was found that a decrease in yield and enantiomeric excesses value was observed, depending on the substrate employed, with a reduction of the amount of (+)-(*S*)-**2** from 40 to 20 mol%. As to the substrate, *o*-methoxybenzaldehyde the ee value for which was 98 and 97%, respectively, only a very slight change in yield and enantioselectivity was observed (entries 6 and 7). In contrast, for some other substrates, such as *p*-methoxybenzaldehyde, *m*-methoxybenzaldehyde and α-naphthyl aldehyde, this change led to an obvious decrease in enantioselectivity (entries 12 and 13, 14 and 15, 18 and 19). Further reducing the amount of (+)-(*S*)-**2** to 10 mol% resulted in a remarkable decrease both in yield and enantioselectivity (entry 8). These results showed that the change from the ligand **1** to (+)-(*S*)-**2** led to a significant improvement in the enantioselectivity. Under the same conditions, the use of 40 mol% of ligand **1** led to only 90% ee for the substrate *o*-methoxybenzaldehyde.[5a] Although a slightly high ligand loading (20–40 mol%) was required for the silylcyanation, it is gratifying that ligand (+)-(*S*)-**2** was very stable and could be readily recovered and reused without loss of its catalytic activity and asymmetric induction ability. It was found that a 4:1 molar ratio of ligand to Ti(O^{i}Pr)$_4$ resulted in better enantioselectivity, whereas the use of 1 equiv of ligand (+)-(*S*)-**2** per Ti(O^{i}Pr)$_4$ led to higher chemical yield (entries 1 and 5 and 6 and 9). Buono reported that the introduction of *i*-PrOH as an additive has a dramatic influence on the enantioselectivity in asymmetric silylcyanation.[5f] However, only a small increase in selectivity was observed in our research (entries 1 and 4 and 6 and 11). The reaction temperature was also found to be an essential factor to the reaction. The reaction at 20 °C generally led to better results than that carried out at 0 °C. An increase in reaction temperature resulted in a detrimental effect to the reaction due to the instability of the adduct silyl ether. The nature of the substrate aromatic aldehyde has a dramatic influence on the catalytic effect. Generally, the enantioselectivity of aldehydes substituted with electron donating groups (methyl and methoxy) on the benzene ring was better than that of electron withdrawing group (chloro and nitro) substituted ones. Moreover, the enantioselectivity was also affected by the position of the substituent on the benzene ring. When methoxy substituted benaldehyde was employed as the substrate, it was found that the enantioselectivity falls in the order: $o > m > p$ (entries 6, 14 and 12). This finding indicates that not only the electronic effect but also the position of the subtituent (or steric effect) had a decisive role on the enantioselectivity of the reaction.

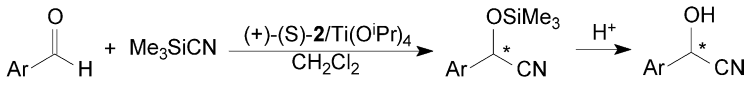
2.3. (+)-(*S*)-3/Ti(O^{i}Pr)$_4$ catalyzed asymmetric silylcyanation of aldehydes

The catalytic effect of the titanium complex formed in situ



Scheme 2.

Table 1. Asymmetric silylcyanation of aromatic aldehydes catalyzed by (+)-(*S*)-**2**/Ti(O^{i}Pr)$_4$



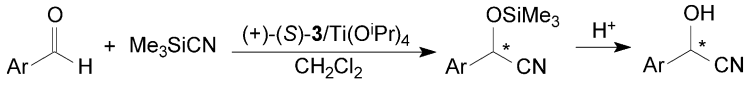
Entry	Ar	(+)-(*S*)-**2** (mol%)	Ti(O^{i}Pr)$_4$ (mol%)	*i*-PrOH (mol%)	React. temperature (°C)	Yield[a] (%)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	ee[b] (%)
1	Ph	40	10	20	20	84	+23.8	53 (54.2)[c]
2	Ph	20	5	10	20	74	+19.6	44
3	Ph	40	10	20	0	90	+15.1	34
4	Ph	40	10	/	20	90	+12.5	28
5	Ph	40	40	20	20	96	+22.2	47
6	2-MeOC$_6$H$_4$	40	10	20	20	87	+26.8	98 (98.3)[c]
7	2-MeOC$_6$H$_4$	20	5	10	20	78	+26.4	97
8	2-MeOC$_6$H$_4$	10	2.5	5	20	69	+14.4	53
9	2-MeOC$_6$H$_4$	40	40	20	20	91	+24.5	90
10	2-MeOC$_6$H$_4$	40	10	20	0	78	+25.0	92
11	2-MeOC$_6$H$_4$	40	10	/	20	86	+24.8	91
12	4-MeOC$_6$H$_4$	40	10	20	20	64	+25.5	54
13	4-MeOC$_6$H$_4$	20	5	10	20	50	+15.4	32
14	3-MeOC$_6$H$_4$	40	10	20	20	78	+34.6	84
15	3-MeOC$_6$H$_4$	20	5	10	20	73	+10.6	26
16	2-MeC$_6$H$_4$	40	10	20	20	75	+32.5	78
17	2-MeC$_6$H$_4$	20	5	10	20	74	+30.5	72 (70.0)[c]
18	α-Naphthyl	40	10	20	20	66	+55.0	84
19	α-Naphthyl	20	5	10	20	55	+37.3	57
20	4-MeC$_6$H$_4$	40	10	20	20	81	+40.0	78
21	4-ClC$_6$H$_4$	40	10	20	20	71	+22.5	55
22	4-NO$_2$C$_6$H$_4$	40	10	20	20	73	+5.5	35

[a] Isolated yield.
[b] Determined by comparison of specific rotation values: Ar=Ph, $[\alpha]_D^{20}=+45$ (*c* 1, $CHCl_3$) in Ref. 1c; Ar=2-MeOC$_6$H$_4$, $[\alpha]_D^{20}=-21.0$ (*c* 1.25, $CHCl_3$) with 77% ee in Ref. 1c; Ar=4-MeOC$_6$H$_4$, $[\alpha]_D^{20}=+45.5$ (*c* 1, $CHCl_3$) with 95% ee in Ref. 1c; Ar=3-MeOC$_6$H$_4$, $[\alpha]_D^{20}=-40.8$ (*c* 1.25, $CHCl_3$) with 99% ee in Ref. 1c; Ar=2-MeC$_6$H$_4$, $[\alpha]_D^{20}=+21.3$ (*c* 1.03, $CHCl_3$) with 99% ee in Ref. 18; Ar=α-Naphthyl, $[\alpha]_D^{20}=+48.0$ (*c* 1.325, $CHCl_3$) with 73% ee in Ref. 18; Ar=4-MeC$_6$H$_4$, $[\alpha]_D^{20}=+47.4$ (*c* 1.822, $CHCl_3$) with 92% ee in Ref. 18; Ar=4-ClC$_6$H$_4$, $[\alpha]_D^{20}=+27.2$ (*c* 1.487, $CHCl_3$) with 66% ee in Ref. 18; Ar=4-NO$_2$C$_6$H$_4$, $[\alpha]_D^{20}=+4.6$ (*c* 1.417, $CHCl_3$) with 29% ee in Ref. 18.
[c] Determined by HPLC analysis of the silyl ether on a chiralcel OD column.

from (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ in the asymmetric silylcyanation of aromatic aldehydes was also examined. The experimental results are listed in Table 2.

As shown in Table 2, the observed enantioselectivity of (+)-(*S*)-**3**/Ti(O^{i}Pr)$_4$ catalyzed asymmetric silylcyanation of aromatic aldehydes was obviously lower than that of the (+)-(*S*)-**2**/Ti(O^{i}Pr)$_4$ catalyzed process. For example, when *o*-methoxybenzaldehyde was employed as substrate, the enantioselectivity of (+)-(*S*)-**3** and (+)-(*S*)-**2** at 0 °C was 73% (Table 2, entry 8) and 92% (Table 1, entry 10), respectively. This difference was more obvious when the reaction was run at 20 °C, 57% ee (Table 2, entry 6) and 98% ee (Table 1, entry 6), respectively, was obtained. These findings show that the nature of the ligand has a dramatic influence on the enantioselectivity of the reaction. The introduction of a bulky naphthyl group into the ligand molecule has a great advantage over a phenyl group, which reveals that the steric effect of the naphthyl group plays a decisive role on the enantioselectivity of the reaction.

Table 2. Asymmetric silylcyanation of aromatic aldehydes catalyzed by (+)-(*S*)-**3**/Ti(O^{i}Pr)$_4$



Entry	Ar	(+)-(*S*)-**3** (mol%)	Ti(O^{i}Pr)$_4$ (mol%)	*i*-PrOH (mol%)	React. temperature (°C)	Yield[a] (%)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	ee[b] (%)
1	Ph	40	10	20	20	84	+19.6	44
2	Ph	40	1	/	20	90	+5.5	12
3	Ph	40	10	20	0	84	+15.1	34
4	Ph	20	10	20	20	73	+23.8	53
5	Ph	40	40	20	20	96	+21.2	47
6	2-MeOC$_6$H$_4$	40	10	20	20	64	+15.5	57
7	2-MeOC$_6$H$_4$	40	10	/	20	82	+11.2	41
8	2-MeOC$_6$H$_4$	40	10	20	0	73	+19.8	73 (70.0)[c]

[a] Isolated yield.
[b] Determined by comparison of specific rotation values: Ar=Ph, $[\alpha]_D^{20}=+45$ (*c* 1, $CHCl_3$) in Ref. 1c; Ar=2-MeOC$_6$H$_4$, $[\alpha]_D^{20}=-21.0$ (*c* 1.25, $CHCl_3$) with 77% ee in Ref. 18.
[c] Determined by HPLC analysis of the silyl ether on a chiralcel OD column.

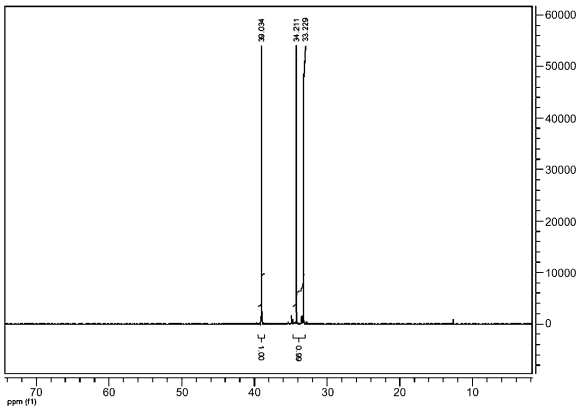


Figure 3. ^{31}P NMR spectrum of a 4:1 mixture of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$.

2.4. Mechanism of the silylcyanation

A 4:1 and 2:1 (molar ratio) mixture of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ was stirred at room temperature for 1 h and analyzed by ^{31}P nucleus magnetic resonance spectroscopy, respectively (Figs. 3 and 4). As shown in Figure 3, a new doublet peak (δ 34.21 and 33.23 ppm, respectively) corresponding to the chemical shift of the Ti(IV) complex formed in situ from (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ appeared at higher field than the single signal (δ 39.03 ppm) of (+)-(*S*)-**3**. The integral value of the signal of (+)-(*S*)-**3** and that of the Ti(IV) complex had a ratio of 1:1. Moreover, in Figure 4, the integral value of the signal of (+)-(*S*)-**3** and that of the Ti(IV) complex had a ratio of 1:10.4, which indicated that almost all of (+)-(*S*)-**3** had coordinated with the titanium atom to form the Ti(IV) complex. These results showed that it was favored to form a Ti(IV) complex with a molar ratio of 2:1 when mixing (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$ together. Based on this finding and the LALB concept a possible mechanism for this type of asymmetric silylcyanation is shown in Scheme 3.

First, intermediate complex **A** is formed from a 2:1 molar ratio of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$. With the addition of aryl aldehyde the central titanium metal acts as a Lewis acid to activate and control the orientation of the substrate aldehyde through the formation of a new complex **B** in which the oxygen of the carbonyl group is coordinated to the central titanium atom. The introduction of trimethylsilyl cyanide results in the formation of intermediate complex **C** via the interaction between the electropositive silicon and the oxygen of phosphoryl group, which leads to the activation and control of the orientation of nucleophile trimethylsilyl cyanide by the Lewis base phosphoryl group. Then the cyanide anion attacks the carbonyl of the aldehyde from its *si*-face to afford the adduct mandelonitrile silyl ether. Finally, the oxygen of the phosphoryl group is again coordinated to the central titanium atom to release the product cyanohydrin silyl ether and regenerate the intermediate complex **A**.

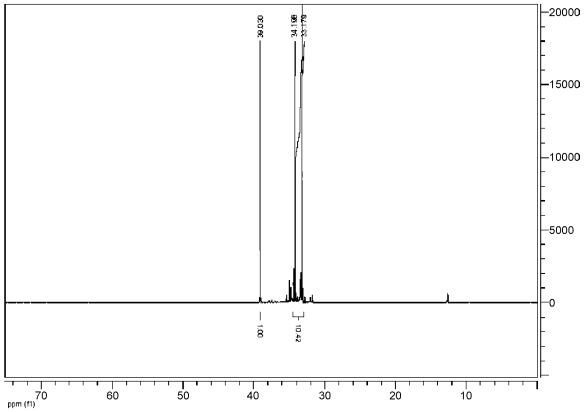


Figure 4. ^{31}P NMR spectrum of a 2:1 mixture of (+)-(*S*)-**3** and Ti(O^{i}Pr)$_4$.

3. Conclusions

In conclusion, a new type of chiral bifunctional cyclic *o*-hydroxyarylphosphonodiamide was synthesized and the absolute configuration of the phosphorus atom was determined by X-ray diffraction analysis. Excellent results (up to 98% ee) were achieved in the asymmetric silylcyanation of aromatic aldehydes using these bifunctional phosphorus reagents as the catalyst ligand in the presence of Ti(O^{i}Pr)$_4$. Investigations on further extending the range of substrates and application of this kind of bifunctional LALB catalyst for other asymmetric reaction are continuing in our laboratory.

4. Experimental

4.1. General methods

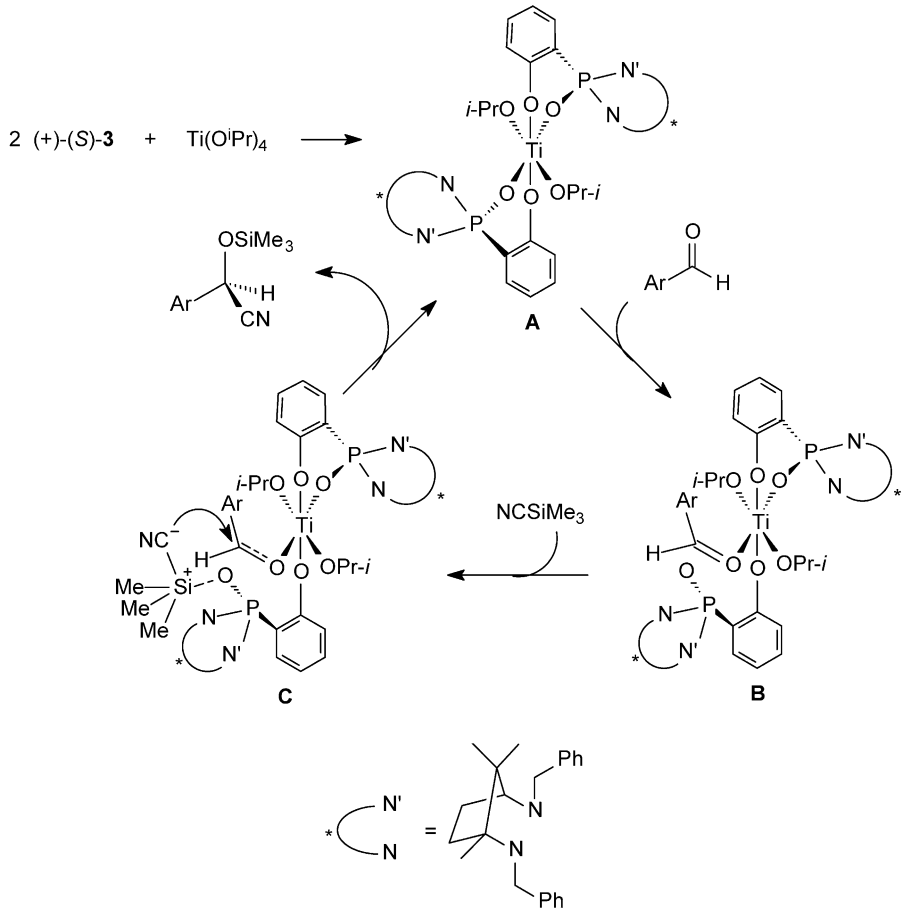
^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Bruker AC-P300 instrument using TMS as an internal standard for ^{1}H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR. Specific rotations were measured on a Perkin–Elmer 341MC polarimeter. Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined on a T-3 melting point apparatus. All temperatures and pressures were uncorrected. All solvents were dried and used after fresh distillation. Ti(O^{i}Pr)$_4$ was purchased from Fluka.

4.1.1. Trimethylsilyl cyanide.[19] Trimethylsilyl cyanide was prepared through the reaction of silver cyanide and trimethylsilyl chloride in a 68% yield, bp 116–118 °C, n_D^{20} 1.3911 (literature:[19] bp 114–117 °C).

4.1.2. *O*-Phenyl phosphorodichloridate.[20] Reaction of phenol and phosphorus trichloride in the presence of sodium chloride afforded *O*-phenyl phosphorodichloridate in 80% yield, bp 138–140 °C/2.80 kPa, n_D^{20} 1.5264 (literature:[20a] bp 106–107.5 °C/0.92 kPa).

4.1.3. *O*-Naphthyl phosphorodichloridate.[20] The reaction between 1-naphthol and phosphorus trichloride in the presence of sodium chloride resulted in the formation of *O*-1-naphthyl phosphorodichloridate in 78% yield, bp 224–226 °C/2.80 kPa, n_D^{20} 1.6012 (literature:[20b] bp 199–201 °C/2.67 kPa, n_D^{22} 1.5960).

4.1.4. (+)-*cis*-1,2,2-Trimethylcyclopentane-1,3-diamine 4. Diamine **4** was prepared from the reaction of (1*R*,3*S*)-(+)-camphoric acid with sodium azide in the presence of



Scheme 3. Proposed mechanism for silylcyanation of aromatic aldehydes.

concentrated sulfuric acid in 91% yield and used directly without further purification.

4.1.5. (+)-*cis*-*N*,*N*′-Dibenzylidene-1,2,2-trimethylcyclopentane-1,3-diamine 5. To a stirring mixture of (+)-**4** (7.11 g, 0.05 mol), *p*-toluenesulfonic acid (0.5 g) and toluene (100 mL) was added dropwise a solution of benzaldehyde (10.6 g, 0.1 mol) in toluene (40 mL) at room temperature. The resulting mixture was stirred at 80 °C for 8 h. After removal of solvent **5** (14.2 g) was obtained as a pale yellow solid. Yield: 89%; mp 77–78 °C; ^{1}H NMR (δ, $CDCl_3$): 0.91 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.66–2.40 (m, 4H, $2CH_2$), 3.57 (t, 1H, J= 8.3 Hz, CH), 7.38–7.76 (m, 10Harom), 8.26 (s, 2H, 2CH).

4.1.6. (+)-*cis*-*N*,*N*′-Dibenzyl-1,2,2-trimethylcyclopentane-1,3-diamine 6. To a solution of **5** (3.18 g, 0.01 mol) in chloroform (40 mL) was added sodium borohydride (1.14 g, 0.03 mol) at intervals at room temperature. After stirring for an additional 10 min, the reaction mixture was warmed to reflux (60–65 °C) for 10 h. The resulting mixture was cooled to room temperature and adjusted to pH 1–2 with 2 M hydrochloric acid. The organic layer was separated and washed with distilled water, the combined water phase was adjusted to pH >12 with 10% aqueous sodium hydroxide solution and extracted with chloroform. After drying over anhydrous magnesium sulfate and removal of solvent, the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford **6** (2.20 g) as a pale yellow oil. Yield: 68%; ^{1}H NMR (δ, $CDCl_3$): 1.00 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.39–2.18 (m, 6H, $2CH_2$ and 2NH), 2.88 (t, 1H, J= 7.1 Hz), 3.66–3.92 (m, 4H, $2CH_2$), 7.28–7.36 (m, 10Harom).

4.1.7. *O*-1-Naphthyl cyclophosphorodiamidate 7. To a stirring mixture of **6** (3.22 g, 0.01 mmol), triethylamine (2.40 g, 0.024 mol) and methylene chloride (40 mL) was added dropwise *O*-1-naphthyl phosphorodichloridate (3.13 g, 0.012 mol) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 24 h, then washed successively with distilled water and brine. The organic layer was separated and dried over anhydrous magnesium sulfate. After removal of solvent the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford a pair of diastereomers of **7**.

Compound (+)-(*S*)-**7**. White solid, 1.25 g. Yield: 25%; mp 140–142 °C, $[\alpha]_{578}^{20}$ = +39.9 (c=1, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$): 0.78 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.87–2.76 (m, 4H, CH_2CH_2), 2.94 (dd, 1H, $^3J_{P-H}$= 34.0 Hz, J_{H-H}=8.0 Hz, CH), 4.15–4.69 (m, 4H, $2CH_2Ph$), 7.14–8.24 (m, 17Harom); ^{31}P NMR (δ, $CDCl_3$): 12.17.

Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 75.29; H, 6.86; N, 5.49. Found: C, 75.23; H, 6.85; N, 5.59.

Compound (−)-(*R*)-**7**. Pale yellow viscous liquid, 3.14 g. Yield: 62%; $[\alpha]_{578}^{20}=-21.5$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.84 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.70–2.43 (m, 4H, CH_2CH_2), 2.98 (dd, 1H, $^3J_{P-H}=27.6$ Hz, $J_{H-H}=5.2$ Hz, CH), 3.98–4.92 (m, 4H, $2CH_2Ph$), 7.11–8.30 (m, 17Harom); ^{31}P NMR (δ, $CDCl_3$): 12.21. Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 75.29; H, 6.86; N, 5.49. Found: C, 75.26; H, 6.70; N, 5.70.

4.1.8. *O*-1-Phenyl cyclophosphorodiamidate 8. A pair of diastereomers of **8** was obtained from **6** (3.22 g, 0.01 mol), triethylamine (2.40 g, 0024 mol) and *O*-phenyl phosphorodichloridate (2.53 g, 0.012 mol) following the same procedure for the preparation of **7** (Section 4.1.7).

Compound (+)-(*S*)-**8**. White solid, 1.16 g. Yield: 25%; mp 125–126 °C, $[\alpha]_{578}^{20}=+53.3$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.74 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.76–2.75 (m, 4H, CH_2CH_2), 2.88 (dd, 1H, $^3J_{P-H}=26.0$ Hz, $J_{H-H}=6.0$ Hz, CH), 4.07–4.70 (m, 4H, $2CH_2Ph$), 7.19–7.37 (m, 15Harom); ^{31}P NMR (δ, $CDCl_3$): 12.17. Anal. Calcd for $C_{28}H_{33}N_2O_2P$: C, 73.06; H, 7.17; N, 6.08. Found: C, 72.70; H, 7.23; N, 6.24.

Compound (−)-(*R*)-**8**. Pale yellow viscous liquid, 2.53 g. Yield: 55%; $[\alpha]_{578}^{20}=-3.2$ ($c=1.5$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.78 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.70–2.45 (m, 4H, CH_2CH_2), 2.88 (dd, 1H, $^3J_{P-H}=27.2$ Hz, $J_{H-H}=5.3$ Hz, CH), 3.90–4.89 (m, 4H, $2CH_2Ph$), 7.06–7.49 (m, 15Harom); ^{31}P NMR (δ, $CDCl_3$): 14.77. Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 73.06; H, 7.17; N, 6.08. Found: C, 72.93; H, 7.25; N, 5.90.

4.1.9. (+)-(*S*)-1-Hydroxy-2-naphthyl cyclophosphonodiamidate 2. To a stirring solution of (−)-**7** (4.74 g, 8.1 mmol) in dry THF (30 mL) was added dropwise a solution of *n*-BuLi (12.7 mL, 1.8 M in *n*-hexane) at −78 °C under a nitrogen atmosphere. After 15 min the cold bath was removed and the reaction mixture was poured into saturated aqueous NH_4Cl (50 mL). The resulting mixture was extracted with ethyl acetate (3×30 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to recover (−)-**7** (3.20 g, conversion: 23%) and give compound (+)-**2** (0.51 g) as a white solid. Yield: 54%; mp 206–207 °C, $[\alpha]_{578}^{20}=+7.2$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.80 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.82–2.75 (m, 4H, CH_2CH_2), 2.99 (dd, 1H, $^3J_{P-H}=25.5$ Hz, $J_{H-H}=5.0$ Hz, CH), 3.84–4.52 (m, 4H, $2CH_2Ph$), 7.04–8.32 (m, 16Harom), 12.00 (s, 1H, OH); ^{31}P NMR (δ, $CDCl_3$): 40.59. Anal. Calcd for $C_{32}H_{35}N_2O_2P$: C, 75.29; H, 6.86; N, 5.49. Found: C, 75.29; H, 6.77; N, 5.54.

4.1.10. (+)-(*S*)-1-Hydroxyphenyl cyclophosphonodiamidate 3. In the same manner described in Section 4.1.10, (+)-**3** (0.69 g) was obtained as a white solid through the rearrangement of (−)-**8** (3.60 g, 7.8 mmol) upon treatment with *n*-BuLi. Conversion: 31% (2.50 g of (−)-**8** was recovered). Yield: 63%; mp 174–175 °C, $[\alpha]_{578}^{20}=+5.2$ ($c=1$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 0.79 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.79–2.75 (m, 4H, CH_2CH_2), 2.99 (dd, 1H, $^3J_{P-H}=25.2$ Hz, $J_{H-H}=5.4$ Hz, CH), 3.84–4.49 (m, 4H, $2CH_2Ph$), 6.80–8.00 (m, 14Harom), 11.96 (s, 1H, OH); ^{31}P NMR (δ, $CDCl_3$): 39.06. Anal. Calcd for $C_{28}H_{33}N_2O_2P$: C, 73.06; H, 7.17; N, 6.08. Found: C, 72.94; H, 7.19; N, 6.05.

4.2. (+)-2 or (+)-3/Ti(O^{i}Pr)$_4$ Catalyzed silylcyanation of aromatic aldehyde (general preceedure)

To a solution of ligand (+)-(*S*)-**2** (or (+)-(*S*)-**3**) (0.54 mmol) in methylene chloride (5 mL) was added $Ti(O^iPr)_4$ (37.2 μL, 0.13 mmol) under a nitrogen atmosphere at room temperature and the resulting mixture was stirred for 1 h. Then *iso*-propanol (15.6 μL, 0.26 mmol), methylene chloride (2 mL), aldehyde (1.34 mmol) and trimethylsilyl cyanide (200 μL, 1.6 mmol) were added and the reaction stirred for 24 h at the same temperature. Different work-up was carried out according to the methods used for determination of the enantiomeric excess.

(1) After removal of solvent, the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to afford the silyl ether of the corresponding cyanohydrin which was used for determination of the ee by chiral HPLC analysis.
(2) The reaction mixture was poured into a mixture of 1 M hydrochloric acid (30 mL) and ethyl acetate (40 mL) and stirred vigorously for 6 h at room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. After removal of solvent the residue was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to give the corresponding cyanohydrin. The ee value was determined by comparison of specific rotation values of the cyanohydrin or by chiral HPLC analysis of the corresponding acetated cyanohydrin.

Recovery of ligand (+)-**2**. (+)-**2** was recovered in 86% yield as pale yellow solid during the process of purification of the cyanohydrin by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate). Mp 205–207 °C, $[\alpha]_{578}^{20}=+7.1$ ($c=1$, $CHCl_3$).

4.2.1. (±)-*o*-Methoxymandelonitrile silyl ether.[1c] To a stirring solution of $Ti(O^iPr)_4$ (37.2 μL, 0.13 mmol) and *iso*-propanol (15.6 μL, 0.26 mmol) in methylene chloride (5 mL) was added successively *o*-methoxybenzaldehyde (0.183 g, 1.34 mmol) and trimethylsilyl cyanide (200 μL, 1.6 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 24 h. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether/ethyl acetate) to yield racemic *o*-methoxymandelonitrile silyl ether for comparison in chiral HPLC analysis.

4.2.2. *o*-Methoxymandelonitrile acetate. To a stirring mixture of *o*-methoxymandelonitrile (164 mg, 1 mmol), acetic anhydride (204 mg, 2 mmol) and methylene chloride (5 mL) was added pyridine (80 mg) at room temperature, and the reaction was stirred at the same temperature for 12 h. The mixture was washed sequentially with 5% H_2SO_4, distilled water and saturated aqueous $NaHCO_3$, and dried over anhydrous magnesium sulfate. After removal of solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, 5:1 petroleum ether/ethyl acetate as eluent) to give the acetylated cyanohydrin which was analyzed by HPLC with a chiral column to determine the ee.

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