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Synthesis and resolution of diastereomers of (*R,R*)-1,2-cyclohexylenediamino-di-phenylmethylphosphonates

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ABSTRACT

Salen-like compounds, such as bis-aminophosphonic systems bearing a (*R,R*)-1,2-diamino-cyclohexyl (DACH) moiety, were synthesized by the addition of dialkyl phosphites to the azomethine bond of *N,N′*-dibenzylidene-1,2-diaminocyclohexane **2**. Five bis-aminophosphonates, dimethyl, diethyl, diisopropyl, dibenzyl, and diallyl derivatives, were obtained in high diastereoselectivity. Three of these compounds, dimethyl **3a**, diethyl **3b**, and diisopropyl **3c** derivatives, had the predominant diastereoisomers separated. A hypothetical explanation of the diastereoselectivity is also reported.

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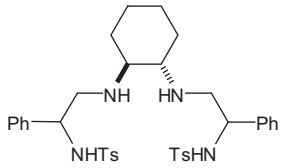
1. Introduction

Salen-ligands **1** constitute a group of compounds with a broad range of applications. They have been used as catalysts in the stereoselective Strecker synthesis of amino acids,[1] and also in the asymmetric catalysis of modifications of the Mannich reaction such as the Kabatchnik-Fields reaction.[2–6] Recently,[7] the use of saturated derivatives of *salen*-ligands, such as DACH-based, N-tosylated tetramines **1**, was reported. They were applied to the asymmetric Henry reaction as Cu(I) complexes and turned out to be very much stereoselective.



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It is well known that aminophosphonic derivatives bearing more than one amino- and more than one phosphonic moiety are as good ligands for coordinating metal ions. While the phosphonic analogue of EDTA is the most well known, there are many other aminophosphonic chelating agents.

As a result, a large number of *salen* applications involve aminophosphonic acids because optically active aminophosphonic acids and their derivatives are biologically active compounds, which are widely used in pharmaceutical applications.[8,9] Therefore, much effort has been directed toward the development of the asymmetric hydrophosphonylation of carbonyl and imine compounds.

All of these facts prompted us to perform a study on the catalytic properties of chiral *salen*-ligand derivatives bearing phosphonic moieties that had saturated, sp^3 nitrogen atoms. Our aim was to construct α-aminophosphonates, whose structure would resemble *salen*-like ligand derivatives and would combine the chelating abilities of aminophosphonic groups with the strong stereodivergence action of *salen* compounds.

Therefore, we performed the addition of phosphites to *salen*-like compounds in order to obtain aminophosphonic derivatives of *salen*-ligands, that is, bis-aminophosphonic systems bearing a (*R,R*)-1,2-diaminocyclohexyl (DACH) moiety. We expected that the presence of this optically active moiety would have a great influence on the stereoselectivity of the addition. These bis-aminophosphonic systems bearing the (*R,R*)-DACH moiety have the potential to asymmetrically catalyze the Henry reaction and possibly also the Kabachnik–Fields reaction.

2. Results and discussion

For the model compounds, we chose the benzaldehyde derivatives to prevent any of the substituents of the phenyl ring from having an additional influence on the stereochemistry. (*R,R*)-1,2-Diaminocyclohexane was isolated from a commercially available mixture of cis- and trans-isomers by crystallization of the (*R,R*)-isomer as its (+)-tartaric acid salt. Using the published procedure,[10] the condensation of (*R,R*)-cyclohexane-1,2-diammonium mono-(+)-tartrate with benzaldehyde was performed to give optically active *N,N′*-dibenzylidene-1,2-diaminocyclohexane **2**, which was easily identified by comparison with the literature data.[10,11]

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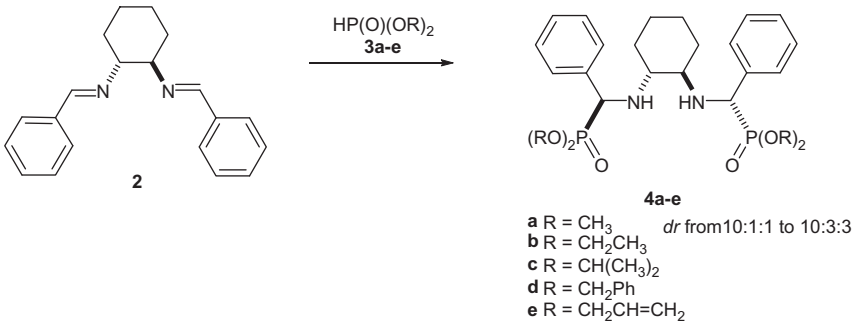

Scheme 1. Addition of phosphites **3a–e** to diimine **2**.

Table 1
Results of addition of phosphites **3a–e** to *N*,*N*′-dibenzylidene-1,2-diaminocyclohexane 2

No.	R	*Y* (%)	dr	^{31}P NMR	A single isomer[a]	
					^{31}P NMR	$[\alpha]_D^{20}$
4a	CH_3	57	10:3:3	26.20, 27.31, 27.53	26.20	−74.5 (*c* 1, CH_2Cl_2)
4b	CH_2CH_3	53[b]	10:3:3	23.90, 24.08, 24.15	23.90	−69.4 (*c* 1, CH_2Cl_2)
4c	$CH(CH_3)_2$	19[b]	10:2:2	22.27, 22.46, 22.73	22.27	−55.7 (*c* 1, CH_2Cl_2)
4d	CH_2Ph	68	10:2:2	24.77, 25.03, 25.48	—	—
4e	$CH_2CH{=}CH_2$	37	100:9:9	24.46, 24.54, 24.65	—	—

[a] Spectroscopic data of the separated diastereoisomer.
[b] Yield of a single diastereoisomer.

The Schiff base **2** was then subjected to the addition of several model phosphites **3a–e**, which lead to the formation of five bis-aminophosphonates: tetramethyl **4a**, tetraethyl **4b**, tetraisopropyl **4c**, tetrabenzyl **4d**, and tetraallyl **4e** ones (Scheme 1). Due to the influence of the optically active (*R*,*R*)-1,2-diaminocyclohexyl substituent, we expected that the additions would be diastereoselective. In all cases, analysis of the post-reaction mixture demonstrated the occurrence of one diastereoisomer in large excess with the diastereomeric ratio varying from 3:3:10 in the case of tetrabenzyl ester **4d**, up to 9:9:100 for the tetraallyl derivative **4b**. The diastereoisomeric ratios together with ^{31}P NMR data, are shown in Table 1. After preliminary purification of the product reaction mixtures, we made attempts to separate the diastereoisomers of products **4a–e** by column chromatography or fractional crystallization. However, the resolutions of the stereoisomers of tetrabenzyl **4d** and tetraallyl **4e** bis-aminophosphonates were unsuccessful, because in each fraction, the predominant diastereoisomer was accompanied by two others and we were unable to isolate any of them. However, the column chromatography of tetramethyl bis-aminophosphonate **4a** as well as the crystallization of tetraethyl **4b** and tetraisopropyl **4c** bis-aminophosphonates, allowed us to isolate the pure predominant diastereoisomers of these three compounds. While the predominant diastereoisomer of tetramethyl bis-aminophosphonate **4a** was isolated as a dense oil, the main stereoisomers of tetraethyl **4b** and tetraisopropyl **4c** bis-aminophosphonates were isolated as crystals, and so their structures were studied by X-ray single crystal diffraction.

The X-ray studies of these two predominant stereomeric forms of bis-aminophosphonates **4b**,**c** indicated clearly an (*S*,*S*)-configuration for the newly formed stereogenic centers for both bis-aminophosphonate **4b** (Fig. 1) and **4c** (Fig. 2). We suspect that tetramethyl bis-aminophosphonate **4a** as well as bis-aminophosphonates **4d-e** also occurred predominantly as the (*S*,*R*,*R*,*S*)-diastereoisomers.

The X-ray study of tetraethyl (*R*,*R*)-1,2–cyclohexylenediamino-di-(*S*,*S*)-phenylmethylphosphonate **4b** revealed two intramolecular N–H···O═P hydrogen bonds, which may stabilize the conformation adopted in the molecule (Fig. 1, Table 2). Different structural phenomena were seen for tetra-*iso*-propyl (*R*,*R*)-1,2-cyclohexylene-diamino-di-(*S*,*S*)-phenylmethylphosphonate **4c**, as it crystallized as a monohydrate with two different **4c** molecules (*A* and *B*) and two different water molecules in the asymmetric part of the unit cell. As shown in Fig. 2, each water molecule forms two O–H···O═P hydrogen bonds with two different phosphonate groups of the same molecule *A* or *B*. Therefore, water molecules, acting as linkers between the two phosphonate groups of the same molecule, influence their mutual orientation and hence play an important role in the stabilization of the molecular structures of **4c-*A*** and **4c-*B***. In addition to these intermolecular phosphonate···water···phosphonate interactions, the intramolecular N–H···O and N–H···N bonds also stabilize the molecular conformation of both **4c-*A*** and **4c-*B***.

For elemental analysis, bis-aminophosphonate **4c** was recrystallized from hexane to remove water molecules because of technical issues. The question concerning the mechanism with regards to the stereochemistry of this reaction appears logical. To answer it, we analyzed the conformation of the starting imine and considered that imine **2** adopted a *syn–syn* conformation (Fig. 3) as reported by Gawroński et al.[12] Their calculations suggested that the *syn–syn* conformer was of the lowest energy and at a global energy minimum.

The mechanism of the bis-addition of phosphite molecules to two azomethine bonds of bis-imines has been analyzed in the literature.[13,14] It was suggested that the reaction occurred in two steps; firstly attack on the first azomethine bond and then, on the second one. Taking this suggestion into account, we applied this mechanism to our case. The first step is determined by the spatial orientation of the azomethine bond in the *syn–syn* conformer. A molecule of the phosphite attacks the first azomethine bond from the less hindered *si* face. The representation using a Newman projection of the conformational state **3** shows that predominant attack comes from the site opposite to the largest, π-conjugated substituent, which is in accordance with the Felkin model. Thus,

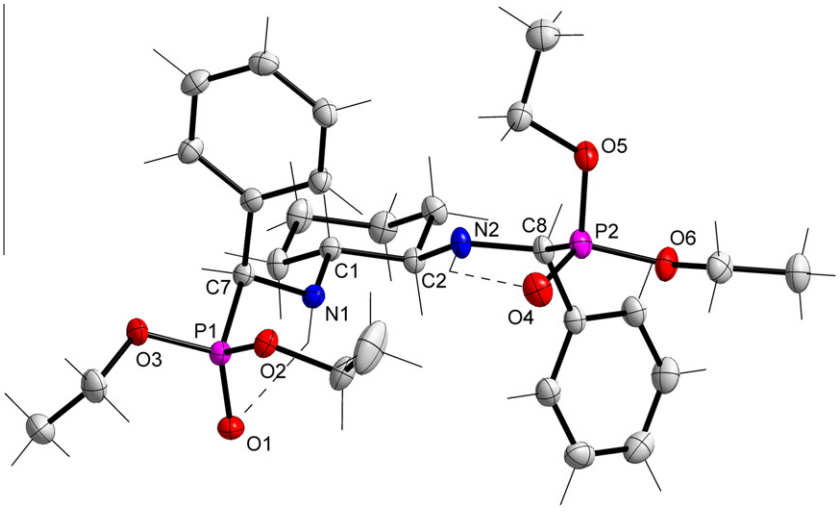

Figure 1. The X-ray structure of tetraethyl (*R,R*)-1,2–cyclohexylenediamino-di-(*S,S*)-phenylmethylphosphonate **4b** with the intramolecular N–H···O hydrogen bonds (dashed lines). Displacement ellipsoids are shown at the 50% probability level. [Selected torsion angles: O1–P1–C7–N1 −41.94(9)°; O4–P2–C8–N2 44.47(10)°.]

the predominant isomer of an imino-aminophosphonate **5** occurs in the (*S*)-configuration at the newly formed stereogenic center. The predominant attack onto the second azomethine bond of the intermediates **5b**,**c** of a phosphite molecule, which is depicted by the use of a Newman projection, comes from a *si* face too, that is, from the site opposite to the largest substituent, according to the Felkin model. Therefore, the predominant diastereoisomers, that is, (*R,R*)-1,2–cyclohexylenediamino-di-(*S,S*)-phenylmethyl-phosphonates **4b**,**c** occur with an (*S,S*)-configuration around the newly formed stereogenic centers (Fig. 3).

3. Conclusion

We have performed the bis-addition of several phosphites to azomethine bonds of a *salen*-like, imine **2** bearing (*R,R*)-1,2-diaminocyclohexane moiety, whose reactions were diastereoselective. In two cases, we managed to separate the predominant diastereoisomer, whose X-ray studies demonstrated its configuration on the newly formed stereogenic centers to be (*S,S*). In other cases, the separation of the predominant diastereoisomers was unsuccessful, but we can suppose, per analogiam, that the stereochemical behavior is, in these cases, similar and the predominant diastereoisomers also have (*S,S*)-configurations. We made some attempts, based on the literature, to give the most probable explanation for the stereochemistry of this reaction. The separated isomers of bis-aminophosphonates **4a**, **4b**, and **4c** will be further investigated as catalysts in the Tsuji-Trost reaction,[15] Henry reaction,[7] and the Kabachnik–Fields reaction.[6]

4. Experimental

4.1. General

All solvents were routinely distilled and dried prior to use. Reagents were purchased by Aldrich and used as received. NMR spectra were recorded on a Bruker Avance III 600 MHz apparatus operating at 600 MHz (^{1}H NMR) and 243 MHz (^{31}P NMR). Rotatory power was measured with a 241 MC Perkin-Elmer polarimeter. Elemental analyses were performed in the Microanalysis Laboratory of the CMMS PAS in Łódź.

4.2. *N,N′*-Dibenzylidene-(*R,R*)-1,2-diaminocyclohexane 2

The imine was synthesized following the described procedure.[10] The general method was unchanged, although it was noticed that the 2 h of heating might be shortened or even neglected without a significant decrease in the yield. The crude product was crystallized from hexane yielding 80% of pure compound. Mp: 101–104 °C, lit[11] 98–100 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.21 (s, CH=N, 2H); 7.61–7.56 (m, PhH, 4H); 7.34–7.29 (m, PhH, 6H); 3.49–3.35 (m, $NCH^{c\text{-}hex}$, 2H); 1.89–1.78 (*m*, $CH_2^{c\text{-}hex}$, 6H); 1.55–1.46 (*m*, $CH_2^{c\text{-}hex}$, 6H).

4.3. General procedure for the synthesis of phosphonates 4a–e

A 10 ml flask was charged with 2 mmol of imine and 4.4 mmol (or 6–7 mmol in a case of dimethyl phosphite due to the low solubility of the imine in it) of the appropriate phosphite. It was heated with stirring on a water bath for 2–3 min until all of the imine was dissolved in phosphite. Then the mixture was irradiated using microwaves (100 W) for 2–3 min. It should be noted that the irradiation was not needed in a case of diallyl phosphite. Purification was performed as described below.

4.3.1. Tetramethyl (*R,R*)-1,2–cyclohexylenediamino-diphenylmethylphosphonate 4a

The post-reaction mixture was dissolved in dichloromethane and washed five times with a sodium bicarbonate saturated water solution. The solvent was removed in vacuo and the residual oil was purified on a short chromatography column with Et_2O/MeOH 12:1 as an eluent. The procedure yielded 580 mg (57% based on imine) of a colorless oil. Elemental analysis: Calcd for $C_{24}H_{36}N_2O_6P_2$: C, 56.47; H, 7.11; N, 5.49. Found: C, 56.27; H, 7.14; N, 5.41. Predominant diastereoisomer: $[\alpha]_D^{20} = -74.5$ (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.48–7.32 (m, PhH, 10H); 4.22 (d, $^2J_{PH}$ = 21.2 Hz, CHP, 2H); 3.70 and 3.63 (2 d, $^3J_{PH}$ = 10.4 Hz, $P(OCH_3)_2$, 12H); 2.54–2.42 (m, $NCH^{c\text{-}hex}$, 2H); 2.06–1.96 (*m*, $CH_2^{c\text{-}hex}$, 2H; 1.61–1.52 (*m*, $CH_2^{c\text{-}hex}$, 2H; 1.09–0.86 (m, $CH_2^{c\text{-}hex}$, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.10 (C-ipso); 128.78 (d, $^3J_{PC}$ = 6.3 Hz, C_{ortho}); 128.53 (C_{arom}); 128.50 (C_{arom}); 53.86 (d, $^2J_{PC}$ = 6.8 Hz, POC); 53.57 (d, $^2J_{PC}$ = 6.6 Hz, POC); 57.45, 57.35 (C_{chex}); 57.12 (d, $^1J_{PC}$ = 153.1 Hz, PCN); 30.17, 24.42 (C_{chex}). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 26.20. IR (KBr): 3447 (NH); 2951, 2928 (C–H_{arom}); 1494, 1454 (C=C_{arom}); 1244 (P=O); 1106 (P–O); 1057, 1030. ESI-MS: *m*/*z* = 533.3 $[M+Na]^+$; 451.3 $[M\text{-}4CH_3]^+$; 423.3 $[M+Na\text{-}2P(O)(OCH_3)_2]^+$. Two minor diastereoisomers; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.43–7.30 (m, PhH, 10H); 4.28 (d, $^2J_{PH}$ = 21.4 Hz, CHP^{Id}, 2H); 4.10 (d, $^2J_{PH}$ = 21.2 Hz, CHP^{IId}, 2H); 3.83 and 3.77 (2d, $^3J_{PH}$ = 10.8 Hz, $P(OCH_3)_2^{Id}$, 12H); 3.54 and 3.52 (2d, $^3J_{PH}$ = 10.2 Hz, $P(OCH_3)2^{IId}$, 12H); 2.54–2.25 (m, $NCH^{c\text{-}hex}$, 2H);

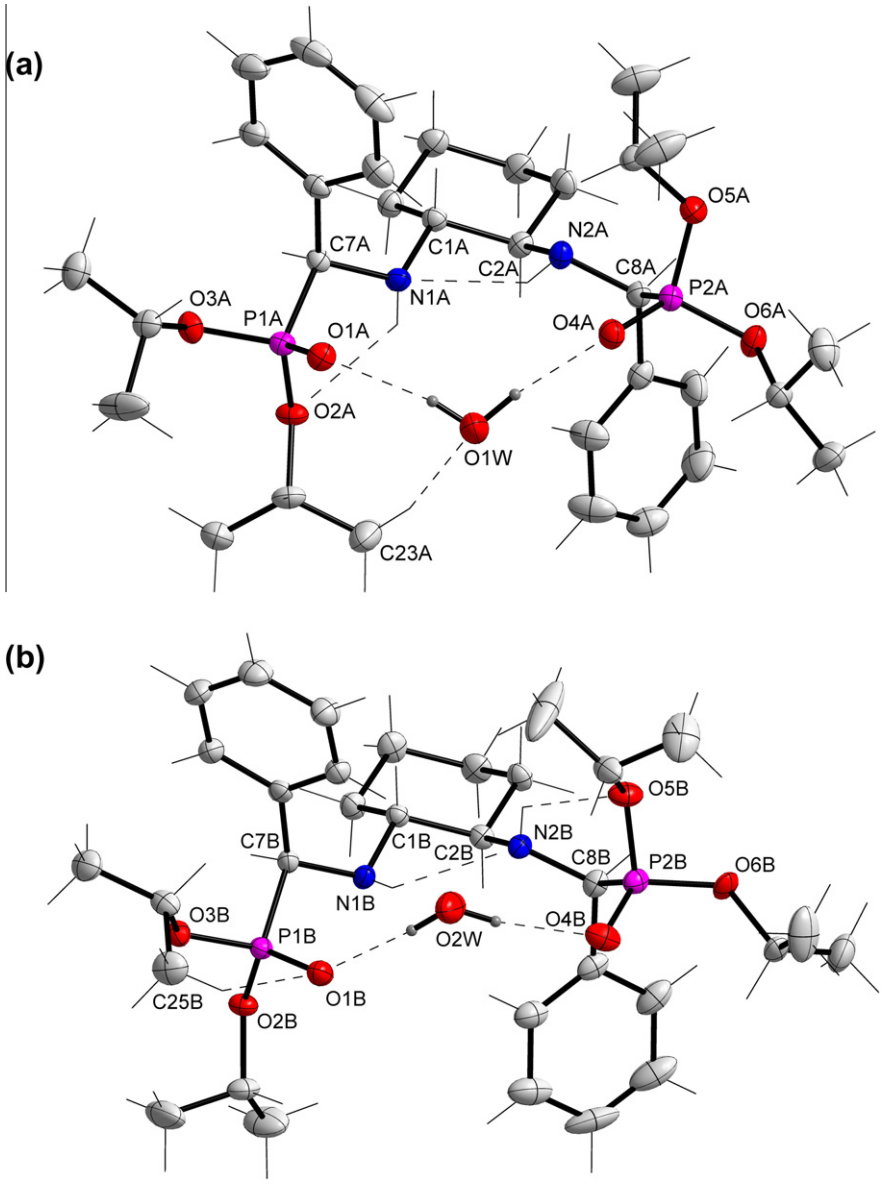

Fig. 2. The X-ray structures of two crystallographically independent molecules *A* (*a*) and *B* (*b*) of tetra-*iso*-propyl (*R,R*)-1,2–cyclohexylenediamino-di-(*S,S*)-phenylmethylphosphonate **4c** (in the crystal of **4c·H₂O**) joined with water molecules via O–H···O hydrogen bonds (dashed lines). Intermolecular hydrogen contacts – dashed lines. The disorder of two isopropoxyl groups in molecule *B* is omitted for the sake of clarity. Displacement ellipsoids are shown at the 50% probability level. [Selected torsion angles: O1*A*–P1*A*–C7*A*–N1*A* 69.81(11)°; O4*A*–P2*A*–C8*A*–N2*A* 53.57(11)°; O1*B*–P1*B*–C7*B*–N1*B* 53.16(12)°; O4*B*–P2*B*–C8*B*–N2*B* 76.19(12)°.]

2.16–1.90 (m, CH)$2^{c\text{-}hex}$, 2H); 1.65–1.39 (m, CH)$2^{c\text{-}hex}$, 2H); 1.09–0.96 (m, CH)$2^{c\text{-}hex}$, 4H). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 27.53, 27.31.

4.3.2. Tetraethyl (*R,R*)-1,2–cyclohexylenediamino-di-(S,S)-phenylmethylphosphonate 4b

A post-reaction mixture was vigorously scratched with a glass rod inside the flask followed by standing at ambient temperature for two days, after which it was found that most of the mixture had solidified. As much as possible of the residual oil was removed on a filter funnel. The residue was washed a few times with hexane and then crystallized from hexane. The procedure yielded 605 mg (53.4%) of a pure, single diastereoisomer as colorless needle crystals. Once the crystals are obtained they can be used for the direct nucleation of the crude post-reaction mixture. Mp = 109 °C. Elemental analysis: Calcd for $C_{28}H_{44}N_2O_6P_2$: C, 59.37; H, 7.87; N, 4.94. Found: C, 59.57; H, 7.57; N, 5.09. Predominant diastereoisomer: $[\alpha]_D^{20} = -69.4$ (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49–7.47 (m, PhH, 4H); 7.37–7.35 (m, PhH, 4H); 7.30–7.28 (m, PhH, 2H); 4.19 (d, $^2J_{PH}$ = 21.6 Hz, CHP, 2H); 4.07–4.01 (m, POCH_2CH$_3$, 6H); 3.97–3.90 (m, POCH_2CH$_3$, 2H); 2.45 (large s, NH, 2H); 2.05–2.00 (m, $CH_2^{c\text{-}hex}$, 4H); 1.60–1.58 (m, NCH$^{c\text{-}hex}$, 2H); 1.25 and 1.20 (2t, $^3J_{HH}$ = 7.2 Hz, P(OCH$_2$*CH*$_3$)$_2$, 2×6H); 1.03–0.99 (m, CH)$2^{c\text{-}hex}$, 2H); 0.87–0.82 (m, CH)$2^{c\text{-}hex}$, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.10 (C-ipso); 128.86 (d, $^3J_{PC}$ = 5.8 Hz, C_{ortho}); 128.34 (C_{arom}); 127.68 (C_{arom}); 63.10 (d, $^2J_{PC}$ = 6.9 Hz, POC); 62.80 (d, $^2J_{PC}$ = 6.7 Hz, POC); 57.48 (d, $^1J_{PC}$ = 152.4 Hz, PCN); 57.57, 57.46, 30.17, 24.42 (C_{chex}); 16.43 (d, $^3J_{PC}$ = 6.3 Hz, POC-C); 16.39 (d, $^3J_{PC}$ = 5.5 Hz, POC-C). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 23.88. IR (KBr): 3432 (NH); 2982, 2929 (C–H$_{arom}$); 1601, 1485, 1458 (C=C$_{arom}$); 1235 (P=O); 1102 (P–O); 1058, 1024. ESI-MS: m/z = 589.3 $[M+Na]^+$; 567.3 $[M+H]^+$. Two minor diastereoisomers; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49–7.47 (m, PhH, 4H); 7.37–7.35 (m, PhH, 4H); 7.30–7.28 (m, PhH, 2H); 4.12 (d, $^2J_{PH}$ = 21.6 Hz, CHP, 2H); 4.06 (d, $^2J_{PH}$ = 20.4 Hz, CHP, 2H); 3.99–3.95 (m,POCH$_2$ CH_3^{Id}, 6H); 3.84–3.80 (m,POCH$_2$CH$_3^{IId}$, 6H); 3.79–3.74 (*m*, POCH$_2$ CH_3^{Id}, 2H); 3.70–3.66 (*m*, POCH$_2$CH$_3^{IId}$, 6H); 2.10–2.04 (*m*, $CH_2^{c\text{-}hex}$,

Table 2
Geometry of hydrogen bonds and close contacts for **4b** and **4c** (Å, °)

Compound	*D*–H···*A*	*D*–H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*–H···*A* (°)
4b	N1–H1*N*···O1	0.87(2)	2.50(2)	2.969(2)	115(1)
	N2–H2*N*···O4	0.82(2)	2.48(2)	2.975(2)	120(2)
	C13–H13···O1^{i}	0.95	2.41	3.346(2)	169
	C27–H27*B*···O2^{ii}	0.99	2.51	3.469(2)	163
4c	N1*A*–H1N*A*···O2*A*	0.84(2)	2.46(2)	2.911(2)	114(2)
	N2*A*–H2N*A*···N1*A*	0.87(2)	2.26(2)	2.772(2)	117(2)
	N1*B*–H1N*B*···N2*B*	0.72(2)	2.34(2)	2.754(2)	118(2)
	N2*B*–H2N*B*···O5*B*	0.77(2)	2.47(2)	2.902(2)	117(2)
	O1*W*–H1*W*···O1*A*	0.85(3)	2.02(3)	2.838(2)	162(2)
	O1*W*–H2*W*···O4*A*	0.89(3)	1.92(3)	2.805(2)	172(2
	O2*W*–H3*W*···O1*B*	0.86(3)	2.01(3)	2.870(2)	174(2)
	O2*W*–H4*W*···O4*B*	0.84(3)	2.04(3)	2.867(2)	169(2)
	C19*A*–H19*A*···O3*B*	0.95	2.57	3.455(2)	156
	C23*A*–H23*A*···O1*W*	0.98	2.59	3.498(3)	154
	C25*B*–H25*D*···O1*B*	0.98	2.60	3.264(2)	125

Symmetry codes: (i) *x*−1, *y*, *z*; (ii) −*x*+1, *y*−1/2, −*z*+1/2.
/intramolecular—red, intermolecular—blue.

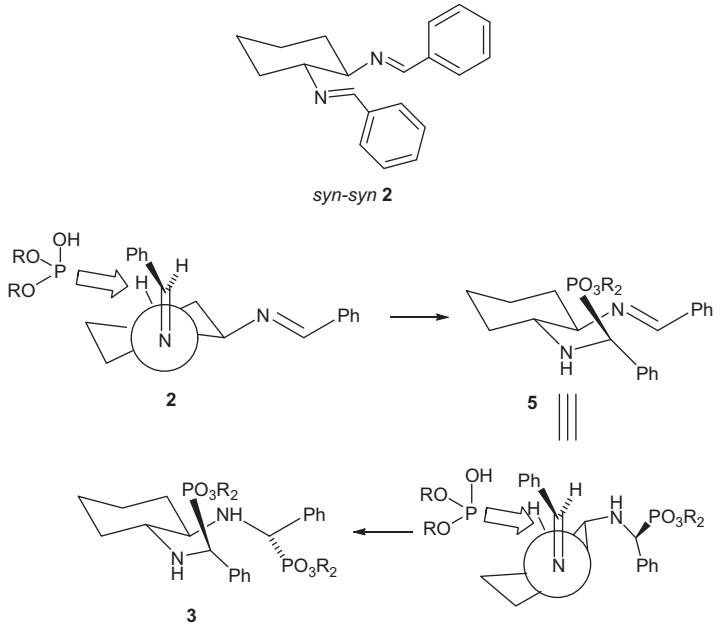

Figure 3. The probable mechanism of stereocontrol of the phosphite addition to **2**.

4H); 1.48–1.41 and 1.58–1.53 (2 m, NCH$^{c\text{-hex}}$, 2H); 1.30 and 1.13 (2t, $^{3}J_{HH}$ = 7.2 Hz, P(OCH$_2$CH$_3$)$_2^{Id}$, 12H); 1.28 and 1.12 (2t, $^{3}J_{HH}$ = 7.2 Hz, P(OCH$_2$CH$_3$)$_2^{IId}$, 12H); 1.08–1.05 (*m*, CH$_2^{c\text{-hex}}$, 2H); 0.74–0.71 (m, CH$_2^{c\text{-hex}}$, 2H). ^{31}P NMR (CDCl$_3$, 243 MHz): δ 24.15 and 24.08.

4.3.3. Tetraisopropyl (*R*,*R*)-1,2–cyclohexylenediamino-diphenylmethylphosphonate 4c

The post-reaction mixture was partially purified by using a short chromatography column using Et$_2$O/hexane 3:1 as an eluent. Fractions containing the product were merged and the solvents were removed in vacuo. The residue was kept in high vacuum for 5 h until small crystals appeared in the mixture. The flask was then left at ambient temperature and pressure for one night for further solidification. Crystals were obtained from this mixture using the method described for diethyl phosphate, yielding a pure, single diastereoisomer. Once the crystals are obtained they can be used for nucleation of the initially purified post-reaction mixture. It was found, that crystals cannot grow in a crude post-reaction mixture. Elemental analysis: Calcd for $C_{32}H_{52}N_2O_6P_2$: C, 61.72; H, 8.42; N, 4.50. Found: C, 61.47; H, 8.60; N, 4.41. Mp: 76–80 °C. Predominant diastereoisomer; $[\alpha]_D^{20} = -55.7$ (*c* 1, CH$_2$Cl$_2$); ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.50–7.49 (m, PhH, 4H); 7.35–7.33 (m, PhH, 4H); 7.28–7.26 (m, PhH, 2H); 4.67–4.62 (m, POC*H*(CH$_3$)$_2$, 2H); 4.60–4.54 (m, POC*H*(CH$_3$)$_2$, 2H); 4.11 (d, $^{2}J_{PH}$ = 22.2 Hz, CHP, 2H); 2.42 (large s, NH, 2H); 2.03–2.01 (m, CH$_2^{c\text{-hex}}$, 4H); 1.60–1.58 (m, NCH$^{c\text{-hex}}$, 2H); 1.28, 1.25, 1.22 and 1.09 (4d, $^{3}J_{HH}$ = 6.6 Hz, POCH(*CH*$_3$)$_2$, 4×6H); 1.03–0.99 (m, CH$_2^{c\text{-hex}}$, 2H); 0.81–0.80 (m, CH$_2^{c\text{-hex}}$, 2H). ^{13}C NMR (CDCl$_3$, 150 MHz): δ 136.45 (C-ipso); 129.09 (d, $^{3}J_{PC}$ = 5.9 Hz, C$_{ortho}$); 128.13 (C$_{arom}$); 127.43 (C$_{arom}$); 71.32 (POC); 71.13 (POC); 57.75 (d, $^{1}J_{PC}$ = 154.2 Hz, PCN); 57.66, 57.55, 30.12, 24.46 (C$_{chex}$); 24.22 (d, $^{3}J_{PC}$ = 3.0 Hz, POC-C); 24.15 (d, $^{3}J_{PC}$ = 4.7 Hz, POC-C); 23.85 (d, $^{3}J_{PC}$ = 5.4 Hz, POC-C); 23.63 (d, $^{3}J_{PC}$ = 5.3 Hz, POC-C). ^{31}P NMR (CDCl$_3$, 243 MHz): δ 22.31. IR (KBr): 3448 (NH); 2978, 2929 (C–H$_{arom}$); 1636, 1455 (C=C$_{arom}$); 1245 (P=O); 1106 (P–O); 994. ESI-MS: *m*/*z* = 645.5 [M+Na]$^{+}$. Two minor diastereoisomers; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 7.50–7.48

(m, PhH, 2H); 7.35–7.33 (m, PhH, 4H); 7.28–7.23 (m, PhH, 4H); 4.75–4.72 and 4.69–4.61 (2m, POC*H*(CH_3)$_2^{Id}$, 2H); 4.56–4.46 and 4.44–4.40 (2m, POC*H*(CH_3)$_2^{IId}$, 2H); 4.13 (2d, $^2J_{PH}$ = 21.0 Hz, CHP, 2H); 4.06 (2d, $^2J_{PH}$ = 20.4 Hz, CHP, 2H); 2.03–2.01 (m, $CH_2^{c\text{-}hex}$, 4H); 1.60–1.58 (m, $NCH^{c\text{-}hex}$, 2H); 1.32–1.23 (2m, POCH(*CH_3*)$_2$, 3×6H); 1.08–1.06 (2m, POCH(*CH_3*)$_2$, 1×6H); 1.02–0.98 (m, $CH_2^{c\text{-}hex}$, 2H); 0.85–0.80 (m, $CH_2^{c\text{-}hex}$, 2H). ^{31}P NMR ($CDCl_3$, 243 MHz): δ 22.73, 22.46.

4.3.4. Tetrabenzyl (*R,R*)-1,2–cyclohexylenediamino-diphenylmethylphosphonate 4d

The post-reaction mixture was dissolved in methylene chloride. Next, elemental iodide was added in small portions and if the solution was discolored within 10 min, further portions of iodine were added. If after the addition, the mixture remained brown, it was stirred for another 10 min with heating on a water bath. The mixture was then washed once with 50 ml of saturated aqueous sodium thiosulfate and 5 times with 50 ml of saturated aqueous sodium bicarbonate. The organic layer was separated and dried over sodium sulfate. The solvent was removed in vacuo. The crude product obtained was purified by chromatography on silica gel using Et$_2$O/*n*-hexane (3:1) as a mobile phase. Elemental analysis: Calcd for $C_{48}H_{52}N_2O_6P_2$: C, 70.75; H, 6.43; N, 3.44. Found: C, 70.67; H, 6.66; N, 3.56. Asterisk denotes predominant diastereoisomer; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.50–7.49 (m, PhH, 4H); 7.31–7.21 (m, PhH, 22H); 7.15–7.10 (m, PhH, 4H); 5.08–4.97 (m, $POCH_2Ph$, 4H); 4.90 and 4.71 (part of AMX system, $^2J_{HH}$ = 12.0 Hz, $^3J_{PH}$ = 8.4 and 8.2 Hz, $POCH_2Ph$); 4.95* and 4.79* (part of AMX system, $^2J_{HH}$ = 12.6 Hz, $^3J_{PH}$ = 8.4 and 7.8 Hz, $POCH_2Ph$); 4.82 and 4.63 (part of AMX system, $^2J_{HH}$ = 12.0 Hz, $^3J_{PH}$ = 8.4 and 7.2 Hz, $POCH_2Ph$); 4.28 (d, $^2J_{PH}$ = 20.4 Hz, CHP, 2H); 4.21* (d, $^2J_{PH}$ = 20.4 Hz, CHP, 2H); 4.10 (d, $^2J_{PH}$ = 19.8 Hz, CHP, 2H); 2.49–2.46 (m, $NCH^{c\text{-}hex}$, 2H); 2.42–2.39 (m, $NCH^{c\text{-}hex}$, 2H); 2.14–2.11* (m, $NCH^{c\text{-}hex}$, 2H); 2.02–2.00* (m, $CH_2^{c\text{-}hex}$, 2H); 1.92–1.90* (m, $CH_2^{c\text{-}hex}$, 2H); 1.64–1.62 (m, $CH_2^{c\text{-}hex}$, 2×2H); 1.53–1.51* (m, $CH_2^{c\text{-}hex}$, 2H); 1.47–1.43 (m, $CH_2^{c\text{-}hex}$, 2×2H); 1.09–0.97 (m, $CH_2^{c\text{-}hex}$, 2×2H); 0.95–0.91* (m, $CH_2^{c\text{-}hex}$, 2H); 0.67–0.66 (m, $CH_2^{c\text{-}hex}$, 2×2H). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 25.03, 24.97, 24.77* (2:2:10). IR (KBr): 3451 (NH); 3030, 2927 (C–H$_{arom}$); 1600, 1496, 1455 (C=C$_{arom}$); 1242 (P=O); 1105 (P–O); 1080. ESI-MS: *m*/*z* = 837.7 [M+Na]$^+$.

4.3.5. Tetraallyl (*R,R*)-1,2–cyclohexylenediamino-diphenylmethylphosphonate 4e

A post-reaction mixture was purified by chromatography, using Et$_2$O/hexane 3:1 as an eluent. Fractions containing the product were merged and solvents were removed in vacuo. Elemental analysis: Calcd for $C_{32}H_{44}N_2O_6P_2$: C, 62.53; H, 7.22; N, 4.56. Found: C, 62.38; 7.23; N, 4.32. Asterisk denotes predominant diastereoisomer; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.49–7.48 (m, PhH, 4H); 7.38–7.35 (m, PhH, 4H); 7.31–7.28 (m, PhH, 2H); 6.01–5.93 (m, $POCH_2CH$=CH_2, 2H); 5.88 (ddt, $^3J_{HH}$ = 5.4, 10.8, 17.4 Hz, $POCH_2CH$=CH_2, 2H); 5.81* (ddt, $^3J_{HH}$ = 5.4, 10.8, 17.4 Hz, $POCH_2CH$=CH_2, 2H); 5.68–5.62 (m, $POCH_2CH$=CH_2, 2H); 5.39–5.26 (m, $POCH_2CH$=CH_2, 8H); 5.26* (ddt, $^3J_{HH}$ = 1.2, 1.8, 17.4 Hz, $POCH_2CH$=CH_2, 4H); 5.22* (ddt, $^3J_{HH}$ = 1.2, 1.8, 17.4 Hz, $POCH_2CH$=CH_2, 4H); 5.17 (ddt, $^3J_{HH}$ = 1.2, 1.8, 10.8 Hz, $POCH_2CH$=CH_2, 2H); 5.14* (ddt, $^3J_{HH}$ = 1.2, 1.8, 10.8 Hz, $POCH_2CH$=CH_2, 2H); 4.62–4.60 (m, POCH_2CH=CH_2, 8H); 4.56–4.55 (m, POCH_2CH=CH_2, 8H); 4.49–4.47* (m, POCH_2CH=CH_2, 6H); 4.37–4.30* (m, POCH_2CH=CH_2, 2H); 4.26–4.22 (m, CHP, 2H); 2.45 (large s, NH, 2H); 2.06–2.00* (m,CH_2^{c-hex}, 4H); 1.73 – 1.72(m,CH_2^{c-hex}, 4H); 1.60–1.59* (m,$CH_2^{c\text{-}hex}$, 2H); 1.54–1.14 (m,$CH_2^{c\text{-}hex}$, 12H); 1.03–1.00* (m,$CH_2^{c\text{-}hex}$, 2H); 0.94–0.86 (m,$CH_2^{c\text{-}hex}$, 4H); 0.84–0.82* (m,$CH_2^{c\text{-}hex}$, 2H). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 24.65, 24.59, 24.46* (9:9:100). IR (KBr): 3466 (NH); 3026, 2928 (C–H$_{arom}$); 1648 (C=C); 1601, 1494, 1455 (C=C$_{arom}$); 1242 (P=O); 1100 (P-O); 1023. ESI-MS: *m*/*z* = 637.4 [M+Na]$^+$.

4.4. Crystal structure determination

The crystallographic measurements for **4b** and **4c** were performed on a κ-geometry *Xcalibur PX* four-circle diffractometer with graphite-monochromatized Mo Kα radiation (ω and φ scans). Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, and data reduction and analysis were carried out with the *Xcalibur PX* software, CRYSALIS CCD, and CRYSALIS RED, resp.[16] Analytical absorption corrections were applied to the data with the use of CRYSALIS RED. The structures were solved by direct methods with the SHELXS-97 program,[17] and refined using SHELXL-97[17] with anisotropic thermal parameters for non-H-atoms (except for low-occupied positions of disordered atoms in **4c**). The H atoms were found in difference Fourier maps. In the final refinement cycles, all C-bonded H atoms were treated as riding atoms in geometrically optimized positions, with C–H = 0.95–1.00 Å, and with U_{iso}(H) = 1.2U_{eq}(CH,CH$_2$) or 1.5U_{eq}(CH$_3$). N-bonded H atoms in both **4b** and **4c** were refined isotropically. H atoms from fully occupied water molecules in **4c** were refined with U_{iso}(H) = 1.5U_{eq}(O). Those from partially occupied water molecules were not found in the difference Fourier maps.

The asymmetric unit of crystal **4c·H$_2$O** contains two crystallographically independent molecules of **4c** (*A* and *B* shown in Fig. 2) and two water molecules. The highest peak in difference Fourier map was included into the final model and treated as 4% of water O atom. One of diisopropylphosphonate groups in molecule *B* is disordered and has both isopropoxyl groups at two positions (with s.o.f. = 0.77(1) and 0.23(1)). Therefore, in the final model, some geometrical restraints (SAME instructions in SHELXL-97[17]), and constraints on the fractional coordinates and anisotropic displacement parameters (EXYZ and EADP instructions) were applied to this disordered region. The figures showing the molecular and crystal structures of **4b** and **4c** were made using the Diamond program.[18]

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center [ref. CCDC 856983 and 856984]. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing deposit@ccdc.cam.ac.uk.

Crystal data for ***4b***. $C_{28}H_{44}N_2O_6P_2$, *M* = 566.59, colorless needlelike block, crystal dimensions: 0.40 × 0.20 × 0.13 mm^3; orthorhombic, space group $P2_12_12_1$; *a* = 8.679(2), *b* = 18.219(4), *c* = 19.013(4) Å; *V* = 3006.4(11) Å^3; *T* = 100(2) K; *Z* = 4; ρ_{calc} = 1.252 g cm^{-3}; μ = 0.19 mm^{-1} (for Mo Kα, λ = 0.71073 Å); *F*(000) = 1216; reflections collected = 27716; reflections independent = 12287 [R_{int} = 0.028]; reflections observed = 9405 [$I > 2\sigma(I)$]; θ range 2.48–38.57°; *h*, *k*, *l* range: $-13 \leqslant h \leqslant 12$, $-27 \leqslant k \leqslant 26$, $-32 \leqslant l \leqslant 23$; full-matrix least-squares on F^2; parameters = 351; restraints = 0; R_1 = 0.040; wR_2 = 0.084 [$F^2 > 2\sigma(F^2)$]; GooF = *S* = 1.01; largest difference in peak and hole, $\Delta\rho_{max}$ and $\Delta\rho_{min}$ = 0.53 and −0.23 e Å^{-3}; Flack parameter = −0.02(4).

Crystal data for ***4c·H$_2$O***. $C_{32}H_{52}N_2O_6P_2{\cdot}H_2O$, *M* = 641.15, colorless block, crystal dimensions: 0.48 × 0.41 × 0.27 mm^3; orthorhombic, space group $P2_12_12_1$; *a* = 14.340(4), *b* = 19.109(4), *c* = 26.148(6) Å; *V* = 7165(3) Å^3; *T* = 85(2) K; *Z* = 8; ρ_{calc} = 1.189 g cm^{-3}; μ = 0.17 mm^{-1} (for Mo Kα, λ = 0.71073 Å); *F*(000) = 2770; reflections collected = 41667; reflections independent = 20404 [R_{int} = 0.030]; reflections observed = 16815 [$I > 2\sigma(I)$]; θ range 2.56–30.06°; *h*, *k*, *l* range: $-19 \leqslant h \leqslant 17$, $-26 \leqslant k \leqslant 26$, $-27 \leqslant l \leqslant 35$; full-matrix least-squares on F^2; parameters = 837; restraints = 66; R_1 = 0.038; wR_2 = 0.083 [$F^2 > 2\sigma(F^2)$]; GooF = *S* = 1.03; largest difference in peak and hole, $\Delta\rho_{max}$ and $\Delta\rho_{min}$ = 0.34 and −0.32 e Å^{-3}; Flack parameter = 0.01(3).

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