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Chiral Synthetic Equivalents of 2-Cyanoethyl Tetraisopropylphosphorodiamidite: Application to the Synthesis and Resolution of Chiral Phosphoric Acids

Kévin Isaac,^[a] Jérémie Stemper,^[a] Pascal Retailleau,^[a] Jean-François Betzer^{[a]*}
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Four synthetic equivalents of $(iPr_2N)_2P-OCH_2CH_2CN$, **1**, have been prepared from easily available enantiomerically pure β -hydroxynitriles as well as from chiral β -hydroxyesters. To demonstrate their possible use as phosphinating/resolving agents, these phosphorodiamidites have been used in the synthesis of known phosphoric acids. The method allows enantiomerically pure acids to be obtained *via* separation of the diastereomeric

phosphates. The method should favourably compete with other resolution procedures, e.g. fractional crystallisation or chiral HPLC, for the small scale synthesis of new phosphoric acids for screening purposes. As synthetic equivalents of **1**, these auxiliaries might find applications also in nucleoside chemistry for the synthesis of biologically relevant compounds.

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Introduction

The commercially available tetraisopropyl 2-cyanoethyl-phosphorodiamidite **1** is a common reagent for the generation of cyanoethyl phosphates $(RO)_2P(O)(OCH_2CH_2CN)$ from alcohols or diols, mainly used bioorganic chemistry e.g. in carbohydrates, nucleotides and phospholipids chemistry. From these phosphates, the cyanoethyl group can be easily removed *via* base-induced elimination of acrylonitrile, to generate the corresponding phosphoric acids, phosphodiester and others.^{[1][2]} Chiral variants of phosphorodiamidite **1** might be highly useful auxiliaries for asymmetric syntheses *via* either diastereoselective processes or diastereomers separation. Chiral variants of this reagent could be prepared, in principle, from a variety of chiral alcohols bearing electron-withdrawing groups in their β -positions (Figure 1), but compounds of this class have not been described in the literature.

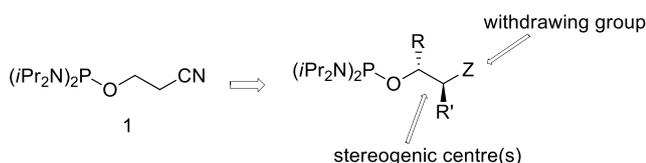


Figure 1. Targeted chiral analogues of **1**

We report here on the synthesis of new, structurally diverse chiral *N,N,N,N*-tetraisopropyl phosphorodiamidites that are easily available from chiral pool substrates. We demonstrate their use as synthetic equivalents of cyanoethyl phosphorodiamidite **1**, both as phosphorylating agents and precursors for P(O)-OH functions.

The use of these phosphorodiamidites has been typified here by a rather non-conventional application, i.e. the synthesis and resolution of chiral phosphoric acids, following to our recent work in this field.^[3] However, synthetic uses of these chiral reagents in many different applications can be easily anticipated.

Results and Discussion

Chiral phosphoric acids and the related phosphate salts have turned recently into highly useful auxiliaries and catalysts for a variety of enantioselective processes.^{[4] [5]} Chiral phosphoric acids are mainly accessed from enantiomerically pure diols, e.g. Spinol,^[6] BINOLs,^[7] VANOL and VAPOL.^[8] Alternatively, enantiomeric resolution of the phosphoric acid themselves may rely on crystallization of diastereomeric salts, e.g. brucine or cinchonidine derivatives,^[9] or preparative HPLC separation of enantiomers. Crystallization processes are perfectly suited for large scale syntheses, while chiral HPLC, although expensive, is well adapted for small scale production of chiral samples for screening purposes. We propose here an alternative approach to phosphoric acids taking advantage of chiral auxiliaries, covalently bonded to the phosphorus atom *via* P-OR functions, and chromatographic separation of epimeric phosphites, or the corresponding phosphates (Figure 2).

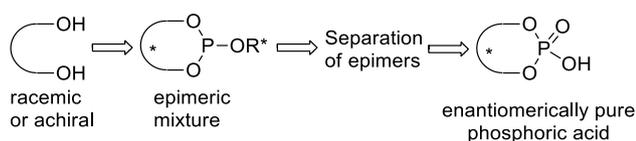


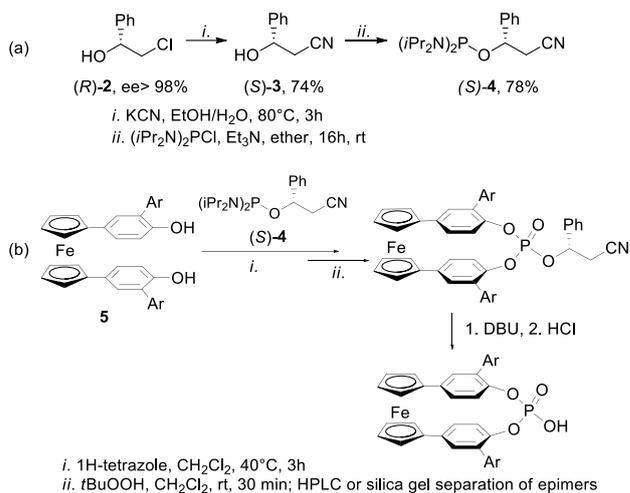
Figure 2. Proposed synthesis and resolution procedure

For such purpose, the chiral auxiliary must be easily removable so as to convert the intermediate phosphite epimers into the desired acid in a few steps. Surprisingly, this very intuitive strategy has not been applied so far to the synthesis and resolution of phosphoric acid precursors.

Recently, during our studies on the synthesis of chiral phosphoric acids based on paracyclophane scaffolds shown in Scheme 1b,^[3a] we have faced a crucial issue: the diol precursors being achiral, the common strategy of resolving the diol precursors couldn't be applied in this series. Although chiral HPLC allowed resolution of the final chiral acids, this technique prevented however an easy and economically viable scale-up. This led us to envision the design of chiral phosphinating agents as synthesis/resolution tools, according to the strategy displayed in Figure 2 above. Thus, at the outset of this study, we have considered the (*S*)-3-hydroxy-3-phenylpropanenitrile-derived phosphorodiamidite (*S*)-4 as a chiral synthetic equivalent of **1** (Scheme 1a), i.e. as a precursor for the phosphoric acid function.

Nitrile (*S*)-3 is easily available from the enantiomerically enriched (*R*)-1-phenyl-2-chloroethanol **2**: conversion of chloride **2** into nitrile **3** by means of KCN occurs in 74% yield at a 7g scale. Then, addition of bis(diisopropylamino)chlorophosphine to (*S*)-3 in the presence of triethylamine affords the desired cyanoethyl-phosphorodiamidite (*S*)-4. Purification of this compound has been performed by quick filtration on a silica gel column with heptane/EtOAc (7:3) / Et₃N (1%) as the eluent. (*S*)-4 has been obtained in 78% yield in multigram scale, as a stable, easy to handle crystalline solid.

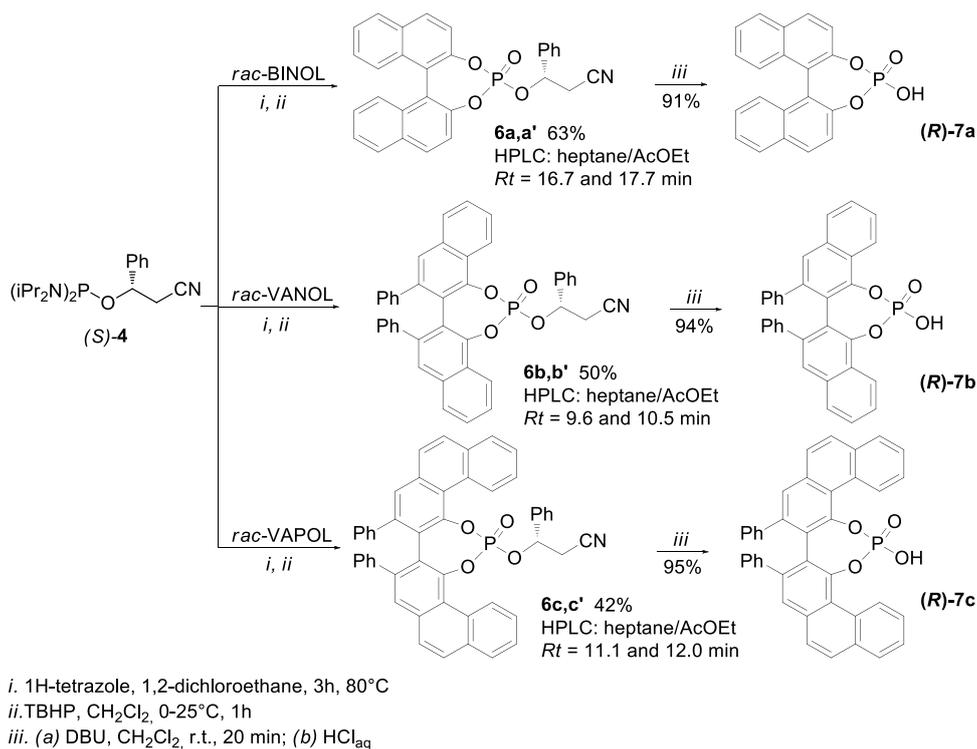
This chiral auxiliary has been used then in the synthesis and resolution of paracyclophane-based phosphoric acids as recalled in Scheme 1b.^[3b]



Scheme 1. (a) Synthesis of the chiral phosphorodiamidite (*S*)-4 and (b) use for the synthesis of paracyclophane-type phosphates.^[3b]

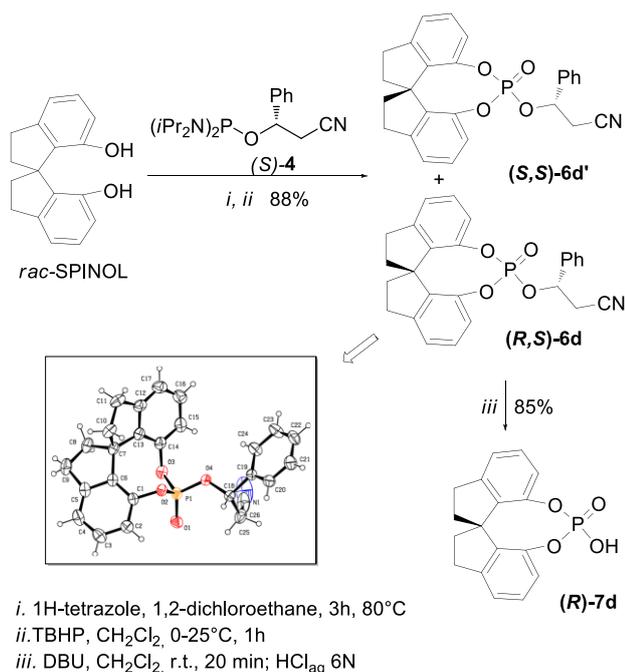
We illustrate here the potential usefulness of (*S*)-4, beyond the initially envisioned application, by typifying its use in the synthesis of some of the currently most popular chiral acids. As shown in Scheme 2, phosphorodiamidite (*S*)-4 reacts with BINOL, VANOL and VAPOL to afford mixtures of the corresponding epimeric phosphites. Phosphites being rather air-sensitive, separation of the epimers is better performed on the corresponding phosphates **6** which are obtained after oxidation of phosphorus with *t*-butylhydroperoxyde. In all cases, pairs of epimers are easily separated by preparative HPLC at a 0.1 g scale in the conditions given in Scheme 2. The single epimers of phosphates **6** have been fully characterized. The relative configurations of these phosphates have been assigned afterward, from the sign of the optical rotation of the corresponding acids **7a-c**.^[8a, 10]

Finally, the cyanoethyl group has been removed by treatment with DBU, at room temperature in dichloromethane. The pure acids **7** have been isolated after filtration of the DBU salts on a short silica gel column (removal of excess DBU and cinnamonitrile) and washing of the salt with a concentrated HCl solution.



Scheme 2. Synthesis of the phosphoric acids **7a-c** by means of the chiral auxiliary (*S*)-**4**

Beyond the atropisomeric biaryl-derivatives in Scheme 2, the method is illustrated also by the efficient separation of the spiranic phosphates **6d,d'**, which are precursors for the spinol derived acid **7d**^[6b] (Scheme 3). In this case, separation of the epimers does not require HPLC techniques, it can be carried out by column chromatography on silica gel (toluene/THF 9:1, $R_f = 0.31$ and 0.25). The (*R,S*)-phosphate **6d** has been characterized by an X-ray crystal diffraction study. An ORTEP drawing for this compound is displayed in Scheme 3, showing that the spinol scaffold of **6d** has an (*R*)-configuration.



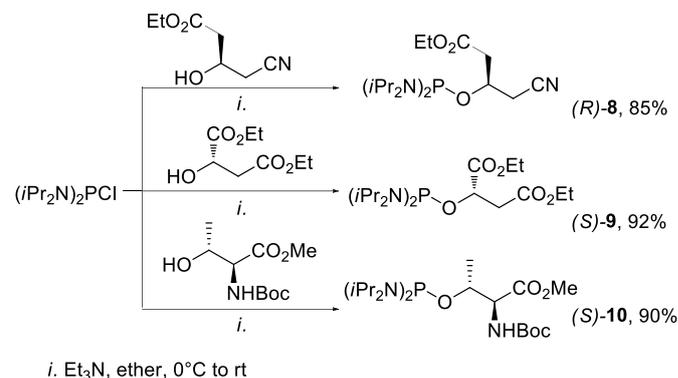
Scheme 3. Synthesis of the SPINOL-derived phosphoric acids **7d** via the chiral auxiliary (*S*)-**4**

Phosphates **6d** and **6d'** have been converted into the corresponding acids by reaction with DBU, under the above conditions.

The few experiments above validate our design of (*S*)-**4** as a chiral auxiliary in the synthesis of phosphoric acids, as far as (*S*)-**4** is readily available and allows easy separation of the diastereomeric phosphates in these four cases. Obviously, phosphates made by combining (*S*)-**4** with other chiral scaffolds might challenge however chromatographic separations. Therefore, to ensure a general applicability of the proposed method (Figure 2), it would be preferable to have at our disposal a larger set of chiral auxiliaries.

With this aim in mind, we have considered some new phosphorodiamidites as potential resolution agents (Scheme 4). Thus, we have prepared at first the (*R*)-ethyl 4-cyano-3-hydroxybutanoate derived phosphorodiamidite (*R*)-**8**. This compound was anticipated to afford suitable phosphoric acid precursors, given its structural analogy to (*S*)-**4** related to the presence of the β -cyano-function. We have also envisioned that the range of phosphinating/resolving agents might be extended to phosphorodiamidites bearing withdrawing functions other than cyanides in their β -positions. To check this point, we have prepared

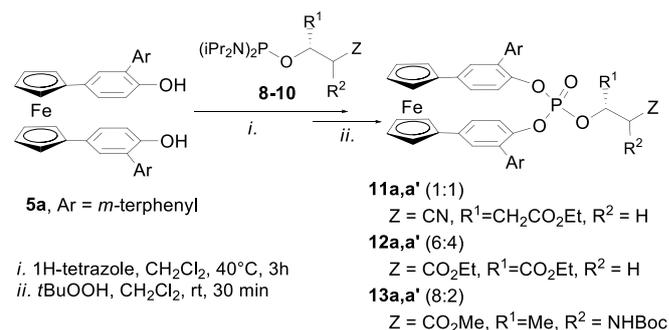
the new phosphorodiamidites **9** and **10** which display esters as the withdrawing functions (Scheme 4). These compounds have the main advantage of being easily obtained from commercially available, chiral pool substrates, i.e. malic acid and threonine esters respectively.



Scheme 4. Synthesis of the chiral phosphorodiamidites **8-10**.

Phosphorodiamidites **8-10** have been obtained in good yields from the corresponding chiral alcohols^[11] by reaction with (*i*Pr₂N)₂PCl and have been used most often without further purification. If needed, they can be purified by filtration on a short alumina column.

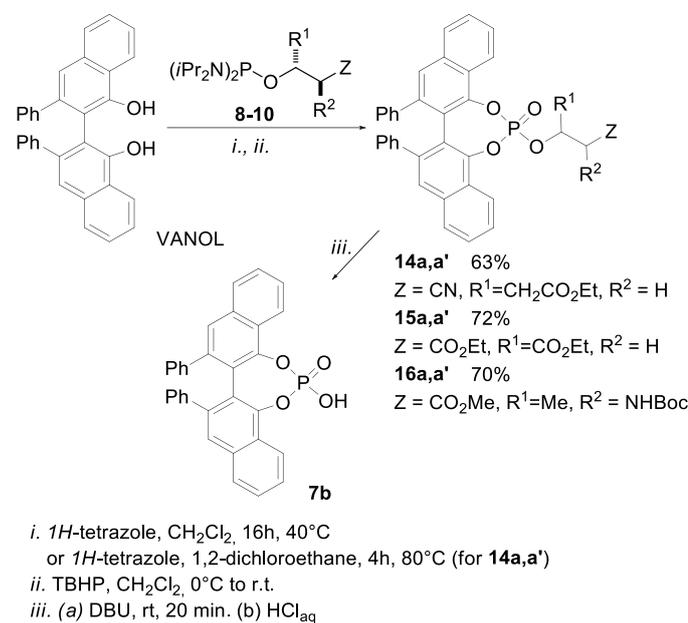
The three phosphorodiamidites **8-10** have been tested initially as chiral resolving agents in the synthesis of planar chiral phosphoric acids with paracyclophane structures (Scheme 5). During these studies, we succeeded in the synthesis of the desired phosphates **11-13** [**11a,a'**: $\delta^{31}\text{P} = -14.9$ and -15.2 ppm (1:1 ratio); **12a,a'**: $\delta^{31}\text{P} = -14.0$ and -14.5 ppm (6:4 ratio); **13a,a'**: $\delta^{31}\text{P} = -13.2$ and -14.5 ppm (2:8 ratio)] but unfortunately we couldn't find suitable conditions for the separation of these epimeric mixtures.^[12]



Scheme 5. (a) Synthesis of epimeric mixtures of phosphates **10-12**.

Nevertheless, an interesting point has been noticed during these studies: the cyclization reaction between the ferrocenic diol **5a** and the threonine-derived phosphorodiamidite (*S*)-**10** generates the cyclic phosphates **13a,a'** as a 8:2 epimeric mixture, i.e. with a significant level of chiral induction at the ring closing step. Although the stereoselectivity level of these cyclizations must still be improved, this result opens the way to asymmetric syntheses of this class of chiral paracyclophanic derivatives.

Next, to check if phosphorodiamidites **8-10** can behave as chiral equivalents of **4** in the synthesis of phosphoric acids, we have considered VANOL as the model diol. All three phosphorodiamidites react with VANOL in the presence of 1*H*-tetrazole in mild conditions to give the desired phosphites that are converted *in situ* into phosphates **14-16**.



Scheme 6. Synthesis of the VANOL-derived phosphoric acid **7b** via the chiral auxiliaries **8-10**.

The epimers of phosphates **14-16** have been separated by HPLC under the conditions specified in the experimental section. Finally, all three chiral chains, including the amino-acid derived chain of **16**, could be removed from the intermediate phosphates in the presence of DBU, leading to the VANOL derived phosphoric acid **7b**. These experiments demonstrate that the ester functions of **9** and **10** play the same role as the cyano-function in **1** by favoring deprotonation of the β-hydrogen atom and elimination of the corresponding olefins. Thus, phosphorodiamidites **8-10** can be envisioned for further uses as suitable, new chiral synthetic equivalents of the cyanoethyl phosphorodiamidite **1**.

Conclusion

The successful experiments in Scheme 4 and Scheme 6 expand the scope of our new strategy of using chiral auxiliaries for the synthesis/resolution of phosphoric acids. They demonstrate that a variety of chiral-pool derived phosphorodiamidites, easily available in enantiomerically pure form, can be used for this purpose and provide therefore a suitable toolbox. As far as it offers a suitable resolution procedure, this new synthetic method may facilitate the development of new chiral scaffolds for phosphoric acid based catalysis.

This work expands the range of chiral synthetic equivalents of cyanoethyl phosphorodiamidite **1** to β-hydroxyesters derivatives. It highlights phosphorodiamidites **4**, **8**, **9** and **10** as chiral auxiliaries with potentially broad scope in different fields and applications, including chemical biology where the achiral analogue **1** is a well-known privileged synthetic tool.

Experimental Section

Synthesis of the chiral phosphorodiamidites **4**, **8**, **9**, **10**.

(1*S*)-2-cyanoethyl-1-phenyl *N,N,N',N'*-tetra-isopropylphosphorodiamidite (*S*)-**4** has been prepared as reported previously.^[3b]

(*R*)-ethyl 3-((bis(diisopropylamino)phosphino)oxy)-4-cyanobutanoate (*R*)-**8**.

To a suspension of bis(diisopropylamino)chlorophosphine (850 mg, 3.18 mmol) in dry ether (10 mL) at 0 °C was added dropwise a solution of ethyl (*R*)-4-cyano-3-hydroxybutyrate (500 mg, 3.18 mmol) and triethylamine (488 μL, 3.50 mmol) in dry ether (5 mL). The mixture was allowed to warm to room temperature and stirred overnight. The white solid was filtered off, the solution was evaporated under reduced pressure to afford the desired phosphorodiamidite (*R*)-**8** (1.05 g, 85%). ³¹P NMR (202.5 Hz, CDCl₃): δ = 113.0 ppm; ¹H NMR (500.1 MHz, CDCl₃): δ = 4.22-4.17 (m, 1H, OCH), 4.15-4.10 (m, 2H, OCH₂), 3.55-3.47 (m, 4H, NCH), 2.86 (d, *J* = 15.9, 4.8 Hz, 2H), 2.77 (dd, *J* = 15.9, 4.5 Hz, 1H), 2.70 (dd, *J* = 15.9, 8.4 Hz, 1H), 1.25 (t, *J* = 7.0 Hz, 3H, Me), 1.17-1.15 (24H, CHMe₂); ¹³C NMR (75.5 MHz, CDCl₃): δ = 170.1 (CO), 116.9 (CN), 65.6 (d, *J* = 18.9 Hz, OCH), 60.5 (CH₂), 44.8 (NCH), 44.6 (NCH), 39.5 (CH₂), 39.4 (CH₂), 24.3 (CH₃), 24.1 (CH₃), 24.0 (CH₃), 14.0 (CH₃); IR: ν_{max}=2969, 2932, 2872, 1733, 1459, 1392, 1378, 1363, 1310, 1183, 1116, 1055, 1023, 954, 867, 708; HR-MS (ESI): *m/z* calcd. for C₁₉H₄₁N₃O₄P [M+H₂O+H]⁺, 406.2835. Found, 406.2831. [α]_D²⁰ = -16 (*c* = 1.5, CHCl₃).

(*S*)-Diethyl malate *N,N,N',N'*-tetraisopropylphosphorodiamidite, (*S*)-**9**.

Phosphorodiamidite (*S*)-**9** was obtained in 92% yield (1.02 g) from 0.70 g (2.6 mmol) of bis(diisopropylamino)chlorophosphine and 500 mg of L-(-)-malate (2.6 mmol). ³¹P NMR (202.5 Hz, CDCl₃): δ = 118.9 ppm; ¹H NMR (500.1 MHz, CDCl₃): δ 4.52-4.44 (m, 1H, OCH), 4.19 (q, *J* = 7.2 Hz, 2H, OCH₂), 4.12 (q, *J* = 7.2 Hz, 2H, OCH₂), 3.60-3.47 (m, 4H, NCH), 2.87 (dd, *J* = 15.2, 6.1 Hz, 1H), 2.80 (dd, *J* = 15.2, 6.6 Hz, 1H), 1.29-1.21 (m, 6H, Me), 1.17 (s, 12H, CHMe₂), 1.15 (s, 12H, CHMe₂); ¹³C NMR (75.5 MHz, CDCl₃): δ = 172.1 (CO), 170.3 (CO), 69.6 (d, *J* = 18.2 Hz, OCH), 61.0 (CH₂), 60.7 (CH₂), 45.1 (NCH), 44.9 (NCH), 39.5 (d, *J* = 4.6 Hz, CH₂), 24.5 (CH₃), 24.4 (CH₃), 24.3 (CH₃), 14.3 (CH₃), 14.2 (CH₃); IR: ν_{max}=2970, 2934, 2873, 1737, 1464, 1369, 1245, 1180, 1157, 1116, 1095, 1024, 1024, 953, 867; HR-MS (ESI): *m/z* calcd. for C₂₀H₄₄N₂O₆P [M+H₂O+H]⁺, 439.2937. Found, 439.2939. [α]_D²⁰ = -4.5 (*c* = 0.5, CHCl₃).

N-(*tert*-Butoxycarbonyl)-L-threonine methyl ester *N,N,N',N'*-tetraisopropylphosphorodiamidite, (*2S,3R*)-**10**.

Phosphorodiamidite (*2S,3R*)-**10** was obtained quantitative yield (3.5 g) from 2.0 g of bis(diisopropylamino)chlorophosphine (7.55 mmol) and *N*-(*tert*-butoxycarbonyl)-L-threonine methyl ester (1.76 g, 7.55 mmol). ³¹P NMR (202.5 Hz, CDCl₃): δ = 111.4 ppm; ¹H NMR (500.1 MHz, CDCl₃): δ = 5.22 (d, *J* = 9.6 Hz, 1H), 4.37-4.32 (m, 1H, OCH), 4.21 (d, *J* = 9.6 Hz, 1H), 3.71 (s, 3H, Me), 3.53-3.40 (m, 4H, NCH), 1.45 (s, 9H, CMe₃), 1.32 (d, *J* = 6.6 Hz, 3H, Me), 1.18-1.15 (m, 24H, CHMe₂); ¹³C NMR (75.5 MHz, CDCl₃): δ = 171.5 (CO), 156.1 (CO), 79.5 (CMe₃), 69.9 (d, *J* = 16.6 Hz, OCH), 59.0 (d, *J* = 4.1 Hz, CH), 52.0 (OCH₃), 44.9 (NCH), 44.7 (NCH), 44.5 (NCH), 28.3 (CMe₃), 24.5 (CH₃), 24.4 (CH₃), 24.2 (CH₃), 24.1 (CH₃), 19.3 (d, *J* = 8.1 Hz, CH₃); IR: ν_{max}=3447, 2968, 2930, 1758, 1717, 1485, 1460, 1362, 1318, 1183, 1156, 1118, 1087, 1069, 1024, 1002, 953, 902, 866; HR-MS (ESI): *m/z* calcd. for C₂₂H₄₉N₃O₆P [M+H₂O+H]⁺, 482.3359. Found, 482.3344. [α]_D²⁰ = +7.0 (*c* = 1.5, CHCl₃).

Representative procedure for the synthesis of phosphates **6** (Scheme 2 and Scheme 3).

A solution of (1*S*)-2-cyanoethyl-1-phenyl *N,N,N',N'*-tetra-isopropylphosphorodiamidite (*S*)-**4** (180 mg, 0.48 mmol) in anhydrous 1,2-dichloroethane (5 mL) was added dropwise at r.t. to a solution of *rac*-BINOL (114 mg, 0.40 mmol) and 1*H*-tetrazole (117 mg, 1.67 mmol) in 1,2-dichloroethane (20 mL). The mixture was heated at 80 °C for 3 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (20 mL) and the mixture was extracted twice with DCM (2x20 mL). The organic phase was dried over MgSO₄ and the solvents were removed under reduced

pressure. The crude phosphites (1:1 mixture of diastereomers, $\delta^{31}\text{P} = 146.7$ and 135.2 ppm) were engaged in the next step without further purification. Phosphites were dissolved in DCM (1 mL). TBHP (218 μL , 5.5M in decane, 1.20 mmol) was added to the solution at 0 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. After addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, the layers were separated, the organic layer was dried over MgSO_4 and concentrated *in vacuo*. The crude mixture was purified by chromatography on silica gel (heptane/EtOAc = 6:4 to 4:6) to afford 120 mg of **6a,a'** (63% yield). Phosphates **6a** and **6a'** were separated by semi-preparative HPLC on a SiO_2 column (250 x 10 mm, 5 mic) with a heptane/EtOAc gradient (8:2 to 4:6). **6a**: retention time 16.7 min, 40 mg, 33% yield; **6a'**: retention time 17.7 min, 48 mg, 40% yield.

6a: ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 1.5$ ppm; ^1H NMR (500 MHz, CDCl_3): $\delta = 8.04$ (d, $J = 8.9$ Hz, 1H), 7.99 (d, $J = 9.1$ Hz, 1H), 7.97 (d, $J = 9.1$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.49 (t, $J = 6.6$ Hz, 1H), 7.46 (d, $J = 8.6$ Hz, 2H), 7.36-7.27 (m, 9H), 5.89 (ddd, $J_{\text{HP}} = 7.6$ Hz, $J = 6.5$, 5.3 Hz, 1H, OCH), 3.10 (dd, $J = 16.9$, 5.3 Hz, 1H, CH_2CN), 3.01 (dd, $J = 16.9$, 6.5 Hz, 1H, CH_2CN); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 147.5$ (d, $J_{\text{C-P}} = 11.8$ Hz, C-O), 146.2 (d, $J_{\text{C-P}} = 8.2$ Hz, C-O), 136.6 (d, $J_{\text{C-P}} = 4.0$ Hz, C_{Ph}), 132.4 (C), 132.2 (C), 132.0 (C), 131.7 (CH), 131.6 (CH), 129.8 (CH), 129.2 (CH), 128.7 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 121.6 (C), 121.2 (C), 120.6 (CH), 115.8 (CN), 76.9 (d, $J_{\text{C-P}} = 4.6$ Hz, CH, OCH), 27.8 (d, $J_{\text{C-P}} = 6.7$ Hz, CH_2); IR: $\nu_{\text{max}} = 3064, 3015, 2927, 2853, 1620, 1591, 1508, 1465, 1434, 1362, 1296, 1227, 1010, 977, 951, 748, 697$. HR-MS (ESI): m/z calcd. for $\text{C}_{29}\text{H}_{21}\text{NO}_4\text{P} [\text{M}+\text{H}]^+$: 478.1208, Found: 478.1249; $[\alpha]_{\text{D}}^{20} = +296$ ($c = 1$, CHCl_3).

6a': ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 2.1$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.04$ (d, $J = 9.0$ Hz, 1H), 7.94 (d, $J = 8.3$ Hz, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.61 (d, $J = 8.9$ Hz, 1H), 7.50-7.43 (7H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.31-7.25 (3H), 6.76 (d, $J = 8.8$ Hz, 1H), 5.93 (m, 1H, OCH), 3.04 (dd, $J = 17.0$, 6.3 Hz, 1H, CH_2CN), 3.00 (dd, $J = 17.0$, 6.3 Hz, 1H, CH_2CN); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 147.0$ (d, $J_{\text{C-P}} = 11.5$ Hz, C-O), 146.0 (d, $J_{\text{C-P}} = 7.7$ Hz, C-O), 136.3 (d, $J_{\text{C-P}} = 3.1$ Hz, C_{Ph}), 132.2 (C), 132.0 (C), 131.7 (C), 131.6 (CH), 131.0 (CH), 130.1 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 126.6 (CH), 126.0 (CH), 125.9 (CH), 121.3 (C), 121.1 (C), 120.5 (CH), 120.0 (CH), 115.1 (CN), 76.1 (d, $J_{\text{C-P}} = 3.7$ Hz, OCH), 27.1 (d, $J_{\text{C-P}} = 6.5$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3067, 2928, 2854, 1620, 1591, 1508, 1464, 1294, 1227, 1009, 976, 951, 896, 816, 729$. HR-MS (ESI): m/z calcd. for $\text{C}_{29}\text{H}_{21}\text{NO}_4\text{P} [\text{M}+\text{H}]^+$, 478.1208. Found, 478.1203, $[\alpha]_{\text{D}}^{20} = -329$ ($c = 1$, CHCl_3).

Phosphates **6b** and **6b'** have been obtained *via* the same procedure (50% yield). They were separated by semi-preparative HPLC on a SiO_2 column (250 x 10 mm, 5 mic) with a heptane/EtOAc gradient (8:2 to 4:6). **6b**: retention time 9.6 min, 43% yield; **6b'**: retention time 10.5 min, 40% yield.

6b: ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 1.9$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.45$ (d, $J = 8.3$ Hz, 1H), 7.82 (d, $J = 8.2$ Hz, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.68 (t, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.50-7.48 (m, 3H), 7.43 (t, $J = 7.4$ Hz, 1H), 7.37-7.34 (m, 2H), 7.28 (d, $J = 7.3$ Hz, 2H), 7.20 (t, $J = 7.4$ Hz, 1H), 7.11-7.05 (m, 2H), 6.93 (t, $J = 7.5$ Hz, 2H), 6.89 (t, $J = 7.5$ Hz, 2H), 6.47 (d, $J = 7.5$ Hz, 2H), 6.43 (d, $J = 7.5$ Hz, 2H), 6.11 (ddd, $J_{\text{HP}} = 9.0$ Hz, $J = 7.2$, 5.5 Hz, 1H, OCH), 3.05 (dd, $J = 16.9$, 7.2 Hz, 1H, CH_2CN), 2.96 (dd, $J = 16.9$, 5.5 Hz, 1H, CH_2CN); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 145.8$ (d, $J_{\text{C-P}} = 11.8$ Hz, C-O), 144.8 (d, $J_{\text{C-P}} = 8.2$ Hz, C-O), 140.3 (C), 140.1 (C), 139.9 (d, $J = 3.4$ Hz, C), 136.4 (d, $J = 4.4$ Hz, C), 134.5 (C), 134.3 (C), 130.0 (CH), 129.2 (CH), 129.1 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 126.6 (CH), 125.9 (C), 125.7 (C), 125.1 (C), 122.7 (CH), 122.6 (C), 122.3 (C), 122.2 (CH), 115.6 (CN), 77.4 (d, $J_{\text{C-P}} = 4.5$ Hz, OCH), 27.5 (d, $J_{\text{C-P}} = 4.5$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3058, 3022, 2959, 2927, 1593, 1566, 1489, 1362, 1289, 1009, 1000, 946, 760$; HR-MS (ESI): m/z calcd. for $\text{C}_{41}\text{H}_{29}\text{NO}_4\text{P} [\text{M}+\text{H}]^+$, 630.1834. Found, 630.1829. $[\alpha]_{\text{D}}^{20} = -177$ ($c = 1$, CHCl_3).

6b': ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 1.4$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.44$ (d, $J = 8.2$ Hz, 1H), 7.84 (d, $J = 8.2$ Hz, 1H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.67 (t, $J = 7.9$ Hz, 1H), 7.61 (t, $J = 7.9$ Hz, 1H), 7.55-7.47 (m, 4H), 7.39-7.32 (m, 5H), 7.10-7.06 (m, 2H), 6.90 (t, $J = 7.9$ Hz, 4H), 6.44 (d, $J = 7.9$ Hz, 2H), 6.41 (d, $J = 7.9$ Hz, 2H), 5.99 (ddd, $J = 7.0$, 6.3 Hz, $J_{\text{HP}} = 6.3$ Hz, 1H), 3.04 (dd, $J = 16.7$, 7.0 Hz, 1H); 2.97 (ddd, $J = 16.7$, 6.3 Hz, $J_{\text{HP}} = 1.9$ Hz, 1H); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 146.0$ (d, $J = 11.4$ Hz, C), 144.8 (d, $J_{\text{C-P}} = 9.0$ Hz, C), 140.2 (d, $J_{\text{C-P}} = 5.6$ Hz, C), 140.0 (C), 139.8 (C), 136.4 (C), 134.5 (C), 134.4 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 126.7 (CH), 125.7 (C), 125.4 (C), 122.6 (CH), 122.3 (CH), 115.6 (CN), 77.9 (d, $J_{\text{C-P}} = 5.5$ Hz, OCH), 27.3 (d, $J_{\text{C-P}} = 9.7$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3057, 2927, 2855, 1633, 1593, 1566, 1488, 1362, 1287, 998, 945, 906, 761$; HR-MS (ESI): m/z calcd. for $\text{C}_{41}\text{H}_{29}\text{NO}_4\text{P} [\text{M}+\text{H}]^+$, 630.1834. Found, 630.1863, $[\alpha]_{\text{D}}^{20} = +96$ ($c = 1$, CHCl_3).

Phosphates **6c** and **6c'** have been obtained *via* the same procedure (42% yield). They were separated by semi-preparative HPLC on a SiO_2 column (250 x 10 mm, 5 mic) with a heptane/EtOAc gradient (8:2 to 5:5). **6c**: retention time 11.1 min, 50% yield; **6c'**: retention time 12.0 min, 40% yield.

6c: ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = -3.0$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 9.42$ -9.38 (m, 2H), 7.95 (d, $J = 7.7$ Hz, 1H), 7.83 (d, $J = 8.6$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.72-7.68 (m, 4H), 7.64 (d, $J = 8.6$ Hz, 1H), 7.59 (s, 2H), 7.56-7.51 (m, 2H), 7.11 (t, $J = 7.6$ Hz, 2H), 7.07 (d, $J = 7.6$ Hz, 1H), 6.99-6.90 (m, 6H), 6.70 (d, $J = 7.6$ Hz, 2H), 6.51 (t, $J = 7.0$ Hz, 4H), 5.51 (ddd, $J_{\text{HP}} = 7.7$ Hz, $J = 6.7$, 4.7 Hz, 1H, OCH), 2.97 (dd, $J = 16.8$, 6.7 Hz, 1H, CH_2CN); 2.65 (dd, $J = 16.8$, 4.7 Hz, 1H, CH_2CN); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 147.6$ (d, $J_{\text{C-P}} = 11.1$ Hz, C), 146.6 (d, $J_{\text{C-P}} = 8.1$ Hz, C), 141.6 (C), 141.3 (C), 139.4 (d, $J = 3.3$ Hz, C), 135.7 (d, $J = 6.0$ Hz, C), 135.1 (C), 134.7 (C), 133.6 (C), 133.3 (C), 129.8 (CH), 129.6 (CH), 129.5 (CH), 129.1 (CH), 129.0 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 125.7 (C), 125.5 (C), 125.2 (CH), 122.0 (C), 121.4 (C), 115.1 (CN), 76.9 (d, $J_{\text{C-P}} = 5.3$ Hz, OCH), 27.7 (d, $J_{\text{C-P}} = 4.6$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3056, 2926, 1598, 1487, 1456, 1425, 1388, 1300, 1232, 1124, 1016, 914, 890, 869, 751$; HR-MS (ESI): m/z calcd. for $\text{C}_{49}\text{H}_{33}\text{NO}_4\text{P} [\text{M}+\text{H}]^+$, 730.2147. Found, 730.2153; $[\alpha]_{\text{D}}^{20} = -367$ ($c = 1.5$, CHCl_3).

6c': ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = -2.2$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 9.67$ (d, $J = 8.6$ Hz, 1H), 8.89 (d, $J = 8.7$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.89-7.84 (m, 3H), 7.78-7.74 (m, 3H), 7.65 (d, $J = 8.7$ Hz, 1H), 7.61 (s, 1H), 7.57 (s, 1H), 7.53 (t, $J = 7.6$ Hz, 1H), 7.47-7.39 (m, 5H), 7.12-7.08 (m, 3H), 6.95-6.91 (m, 4H), 6.55 (d, $J = 8.6$ Hz, 2H), 6.46 (d, $J = 8.0$ Hz, 2H), 5.85 (ddd, $J_{\text{HP}} = 8.0$ Hz, $J = 8.0$, 3.8 Hz, 1H, OCH), 2.14 (dd, $J = 16.5$, 8.0 Hz, 1H, CH_2CN), 2.02 (dd, $J = 16.5$, 3.8 Hz, 1H, CH_2CN); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 147.6$ (d, $J = 11.1$ Hz, C), 146.8 (d, $J = 8.4$ Hz, C), 141.7 (C), 141.4 (C), 139.5 (d, $J = 3.1$ Hz, C), 137.0 (C), 135.0 (C), 134.9 (C), 133.7 (C), 133.5 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.8 (C), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.7 (CH), 126.3 (CH), 126.0 (C), 125.5 (C), 121.9 (C), 121.5 (C), 114.7 (CN), 76.9 (d, $J = 4.3$ Hz, OCH), 26.5 (d, $J = 10.9$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3059, 2926, 2854, 1598, 1558, 1456, 1387, 1300, 1231, 1023, 1010, 914, 751$; HR-MS (ESI): m/z calcd. for $\text{C}_{49}\text{H}_{33}\text{NO}_4\text{P} [\text{M}+\text{H}]^+$: 730.2147. Found, 730.2151; $[\alpha]_{\text{D}}^{20} = +303$ ($c = 1.5$, CHCl_3).

Phosphates **6d** and **6d'** have been obtained *via* the same procedure (88% total yield). They were separated on a Combiflash® system by using a silica gel column, with a toluene/THF gradient (99:1 to 94:6) as the eluent. **6d**: $R_{\text{f}} = 0.2$ (toluene/THF = 90:10), 48% yield; **6d'**: $R_{\text{f}} = 0.17$, 40% yield.

6d: ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = -10.7$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 7.46$ -7.44 (m, 3H), 7.41-7.38 (m, 2H), 7.26 (t, $J = 7.4$ Hz, 1H), 7.17 (d, $J = 7.4$ Hz, 1H), 7.12 (t, $J = 7.4$ Hz, 2H), 7.03 (t, $J = 7.4$ Hz, 1H),

6.47 (d, $J = 7.4$ Hz, 1H), 5.81 (dt, $J_{\text{HP}} = 8.2$ Hz, $J = 5.5$ Hz, 1H, OCH), 3.14-3.06 (m, 2H), 2.96 (d, $J = 5.5$ Hz, 2H), 2.90-2.81 (m, 2H), 2.31-2.24 (m, 2H), 2.08-1.98 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 146.8$ (C), 146.6 (C), 145.8 (d, $J = 10.3$ Hz, O-C), 144.3 (d, $J = 7.1$ Hz, O-C), 139.3 (d, $J = 3.6$ Hz, C), 138.8 (C), 136.3 (d, $J = 5.7$ Hz, C_{Ph}), 129.8 (CH), 129.0 (CH), 128.4 (CH), 126.4 (CH), 123.4 (CH), 123.0 (CH), 121.5 (CH), 121.0 (CH), 115.3 (CN), 76.1 (d, $J = 4.8$ Hz, OCH), 59.2 (C), 38.5 (CH_2), 38.2 (CH_2), 30.6 (CH_2), 27.3 (d, $J = 5.0$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3018, 2956, 2856, 1616, 1584, 1466, 1293, 1222, 1159, 1052, 1013, 997, 931, 905$; HR-MS (ESI): m/z calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_4\text{P}$ $[\text{M}+\text{H}]^+$, 444.1365. Found, 444.1356. $[\alpha]_{\text{D}}^{20} = -183$ ($c = 1$, CHCl_3).

6d': ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = -11.4$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 7.34$ -7.29 (m, 3H), 7.26-7.10 (m, 7H), 6.88 (d, $J = 7.7$ Hz, 1H), 5.73 (dt, $J_{\text{HP}} = 5.5$ Hz, $J = 5.5$ Hz, 1H), 3.10 (dd, $J = 16.9, 5.5$ Hz, 1H), 3.08-3.02 (m, 2H), 2.98 (dd, $J = 16.9, 5.5$ Hz, 1H), 2.84-2.78 (m, 2H), 2.25-2.20 (m, 2H), 2.05-1.98 (m, 1H), 1.92-1.86 (m, 1H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 146.8$ (C), 146.6 (C), 146.1 (d, $J = 10.4$ Hz, O-C), 144.4 (d, $J = 7.1$ Hz, O-C), 139.4 (C), 138.8 (C), 129.5 (C_{Ph}), 129.4 (CH), 128.9 (CH), 128.8 (CH), 126.0 (CH), 123.3 (CH), 123.1 (CH), 121.3 (CH), 115.6 (CN), 76.1 (d, $J = 5.1$ Hz, OCH), 59.3 (C), 38.5 (CH_2), 38.2 (CH_2), 30.6 (CH_2), 27.7 (d, $J = 7.1$ Hz, CH_2CN); IR: $\nu_{\text{max}} = 3013, 2956, 2855, 1616, 1584, 1466, 1294, 1222, 1159, 1132, 1054, 1014, 998, 931, 906, 790, 755$; HR-MS (ESI): m/z calcd. for $\text{C}_{26}\text{H}_{22}\text{NO}_4\text{PNa}$ $[\text{M}+\text{Na}]^+$, 466.1184. Found, 466.1176. $[\alpha]_{\text{D}}^{20} = +164$ ($c = 1$, CHCl_3).

Synthesis of phosphates 14a,a'. To a solution of *rac*-VANOL (66 mg, 0.15 mmol) and 1*H*-tetrazole (44 mg, 0.63 mmol) in anhydrous DCM (7.5 mL) was added dropwise a solution of ethyl 3-(bis(diisopropylamino)-phosphino)oxy)-4-cyanobutanoate (*R*)-**7** (70 mg, 0.18 mmol, 1.2 eq.) in anhydrous DCM (2 mL). The mixture was heated at 40 °C for 5 h. The reaction was then quenched by the addition of saturated aqueous NaHCO_3 (20 mL) and extracted twice with CH_2Cl_2 . The organic phase was dried over MgSO_4 and the solvents were removed under reduced pressure (^{31}P NMR (202.5 MHz, CDCl_3): $\delta = 143.6$ and 143.4 ppm). The mixture of phosphites was dissolved in CH_2Cl_2 (1 mL). TBHP (5.5*M* in decane, 82 μL , 0.45 mmol) was added to the solution at 0 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The reaction was treated with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The layers were separated, the organic layer was dried over MgSO_4 and concentrated *in vacuo*. The crude mixture was purified by chromatography on silica gel (heptane/EtOAc = 6:4 to 4:6) to afford 62 mg (65% yield) of 1:1 mixture of diastereoisomers. The phosphates **14a** and **14a'** were separated by semi-preparative HPLC on a SiO_2 column (250 x 10 mm, 5 mic), heptane/EtOAc gradient (8:2 to 4:6). **10a**: retention time 31.3 min, (22 mg, 35% yield); **14a'**: retention time 31.6 min, (20 mg, 32% yield).

14a: ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 1.4$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.44$ (d, $J = 8.5$ Hz, 1H), 8.30 (d, $J = 8.5$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.66-7.60 (m, 3H), 7.53 (s, 2H), 7.12 (m, 2H), 6.96-6.91 (m, 4H), 6.49-6.46 (m, 4H), 5.49-5.43 (m, 1H, OCH), 4.24 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.09 (dd, $J = 17.0, 5.0$ Hz, 1H), 2.98-2.93 (m, 2H), 2.85 (dd, $J = 17.0, 7.5$ Hz, 1H, CH_2), 1.31 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 168.7$ (CO), 145.8 (d, $J = 12.0$ Hz, O-C), 144.7 (d, $J = 8.3$ Hz, O-C), 140.4 (C), 140.1 (C), 139.8 (C), 134.5 (C), 134.3 (C), 129.2 (CH), 129.1 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 125.7 (C), 125.2 (d, $J = 2.8$ Hz, C), 122.6 (C), 122.5 (CH), 121.9 (CH), 115.3 (CN), 72.2 (d, $J = 4.7$ Hz, OCH), 61.7 (CH_2), 39.1 (d, $J = 6.4$ Hz, CH_2), 24.5 (CH_2), 14.3 (CH_3); IR: $\nu_{\text{max}} = 3054, 3028, 2986, 1737, 1489, 1362, 1301, 1290, 1025, 762, 700$; HR-MS (ESI): m/z calcd. for $\text{C}_{39}\text{H}_{31}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$, 640.1889. Found: 640.1880; $[\alpha]_{\text{D}}^{20} = +51$ ($c = 1$, CHCl_3).

14a': ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 1.7$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.45$ (d, $J = 8.5$ Hz, 1H), 8.38 (d, $J = 8.5$ Hz, 1H), 7.85 (m, 2H), 7.85 (m, 2H), 7.71 (t, $J = 7.6$ Hz, 2H), 7.65-7.61 (m, 2H), 7.53 (s, 1H), 7.52

(s, 1H), 7.13-7.09 (m, 2H), 6.95-6.92 (m, 4H), 6.47-6.46 (m, 4H), 5.52-5.45 (m, 1H, OCH), 4.12 (q, $J = 7.5$ Hz, 2H, OCH_2), 3.13 (dd, $J = 17.0, 5.4$ Hz, 1H), 3.02-2.97 (m, 2H), 2.86 (dd, $J = 17.0, 7.0$ Hz, 1H), 1.19 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 168.7$ (CO), 145.9 (d, $J = 12.0$ Hz, O-C), 144.7 (d, $J = 9.2$ Hz, O-C), 140.2 (C), 140.1 (C), 139.9 (C), 139.8 (C), 134.5 (C), 134.3 (C), 129.1 (CH), 129.1 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.8 (C), 126.8 (C), 125.8 (d, $J = 1.8$ Hz, C), 125.3 (d, $J = 2.8$ Hz, C), 122.7 (C), 122.5 (CH), 122.3 (C), 122.1 (CH), 115.3 (CN), 72.2 (d, $J = 4.7$ Hz, OCH), 61.5 (CH_2), 39.0 (d, $J = 4.5$ Hz, CH_2), 24.7 (d, $J = 5.5$ Hz, CH_2), 14.2 (CH_3); IR: $\nu_{\text{max}} = 3055, 3026, 2985, 2929, 1735, 1489, 1363, 1301, 1290, 1024, 967, 946, 762, 700$; HR-MS (ESI): m/z calcd. for $\text{C}_{39}\text{H}_{31}\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$, 640.1889. Found, 640.1882; $[\alpha]_{\text{D}}^{20} = -89$ ($c = 1$, CHCl_3).

Phosphates 15a,a'. Phosphates **15** have been prepared from *rac*-VANOL and diethyl (*S*)-malate *N,N,N',N'*-tetraisopropylphosphorodiamidite (**S**)-**9** as described for **14a,a'**. The corresponding phosphites were obtained after 16h heating at 40°C (^{31}P NMR (202.5 MHz, CDCl_3): $\delta = 148.4$ and 144.3 ppm). After oxidation, the crude mixture was purified by chromatography on silica gel (heptane/EtOAc = 6:4 to 4:6, 72% yield). Phosphates **15a** and **15a'** were separated by semi-preparative HPLC on a Sunfire C18 reversed phase column, $\text{H}_2\text{O}/\text{MeCN}/\text{Formic Acid}$ (23/77/0.1). **15a**: retention time 16.6 min; **15a'**: retention time 17.8 min.

15a: ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 2.0$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.65$ (d, $J = 8.4$ Hz, 1H), 8.51 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 2H), 7.71-7.65 (m, 2H), 7.62-7.59 (m, 2H), 7.51 (s, 1H), 7.50 (s, 1H), 7.12-7.08 (m, 2H), 6.93 (m, 4H), 6.48-6.46 (m, 4H), 5.71-5.67 (m, 1H, OCH), 4.37 (q, $J = 7.2$ Hz, 2H, OCH_2), 4.11 (q, $J = 7.2$ Hz, 2H, OCH_2), 3.05-3.00 (m, 1H), 2.95-2.90 (m, 1H), 1.38 (t, $J = 7.2$ Hz, 3H, Me), 1.15 (t, $J = 7.2$ Hz, 3H, Me); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 168.8$ (CO), 168.4 (d, $J = 3.6$ Hz, CO), 146.3 (d, $J = 11.8$ Hz, O-C), 144.9 (d, $J = 9.2$ Hz, O-C), 140.2 (C), 140.1 (C), 140.0 (C), 139.9 (C), 134.5 (C), 134.3 (C), 129.2 (CH), 129.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.7 (CH), 126.0 (C), 125.6 (d, $J = 2.8$ Hz, C), 123.2 (CH), 122.8 (CH), 122.3 (C), 74.3 (d, $J = 5.3$ Hz, OCH), 62.6 (OCH_2), 61.4 (OCH_2), 37.9 (d, $J = 5.4$ Hz, CH_2), 14.3 (CH_3), 14.2 (CH_3); IR: $\nu_{\text{max}} = 3056, 2985, 2937, 1760, 1738, 1489, 1363, 1305, 1291, 1181, 1110, 1048, 1029, 761, 700$; HR-MS (ESI): m/z calcd. for $\text{C}_{40}\text{H}_{34}\text{O}_8\text{P}$ $[\text{M}+\text{H}]^+$, 673.1991. Found, 673.2017; $[\alpha]_{\text{D}}^{20} = -43$ ($c = 1$, CHCl_3).

15a': ^{31}P NMR (202.5 Hz, CDCl_3): $\delta = 2.3$ ppm; ^1H NMR (500.1 MHz, CDCl_3): $\delta = 8.51$ (d, $J = 8.2$ Hz, 1H), 8.32 (d, $J = 8.2$ Hz, 1H), 7.84-7.82 (m, 2H), 7.68 (t, $J = 7.8$ Hz, 1H), 7.64-7.57 (m, 3H), 7.52 (s, 1H), 7.49 (s, 1H), 7.12-7.08 (m, 2H), 6.95-6.91 (m, 4H), 6.49-6.46 (m, 4H), 5.76-5.71 (m, 1H, OCH), 4.41-4.33 (m, 2H, OCH_2), 4.19-4.11 (m, 2H, O CH_2), 3.05 (dd, $J = 16.5, 4.8$ Hz, 1H, CH_2), 2.96 (dd, $J = 16.5, 6.4$ Hz, 1H, CH_2), 1.36 (t, $J = 7.1$ Hz, 3H, Me), 1.19 (t, $J = 7.1$ Hz, 3H, Me); ^{13}C NMR (125.8 MHz, CDCl_3): $\delta = 168.7$ (CO), 146.0 (d, $J = 11.9$ Hz, O-C), 145.0 (d, $J = 8.2$ Hz, O-C), 140.3 (C), 140.1 (C), 140.0 (C), 139.9 (C), 134.5 (C), 134.3 (C), 129.2 (CH), 129.1 (CH), 128.0 (CH), 127.9 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 126.1 (d, $J = 1.8$ Hz, C), 125.5 (d, $J = 2.6$ Hz, C), 122.8 (CH), 122.7 (C), 122.5 (C), 122.3 (CH), 74.2 (d, $J = 5.4$ Hz, OCH), 62.7 (OCH_2), 61.4 (OCH_2), 37.9 (d, $J = 7.4$ Hz, CH_2), 14.3 (CH_3), 14.2 (CH_3); IR: $\nu_{\text{max}} = 2986, 2930, 1740, 1489, 1364, 1306, 1291, 1262, 1182, 1110, 1049, 1030, 762, 751, 700$; HR-MS (ESI): m/z calcd. for $\text{C}_{40}\text{H}_{34}\text{O}_8\text{P}$ $[\text{M}+\text{H}]^+$, 673.1991. Found, 673.2001. $[\alpha]_{\text{D}}^{20} = +95$ ($c = 1$, CHCl_3).

Phosphates 16a,a'. Phosphates **16** have been prepared from *rac*-VANOL (0.2 mmol) and *N*-(*tert*-Butoxycarbonyl)-L-threonine methyl ester *N,N,N',N'*-tetraisopropylphosphorodiamidite (**2S,3R**)-**10**, as described for **14a,a'**. The corresponding phosphites (^{31}P NMR: $\delta = 154.3$ and 142.3 ppm) were obtained after 16h heating at 40°C. After oxidation, the crude mixture was purified by chromatography on silica gel (heptane/EtOAc = 6:4

to 4:6, 78% yield). Phosphates **16a** and **16a'** were separated by semi-preparative HPLC on a Sunfire C18 column, H₂O/MeCN/formic acid (20/80/0.1). **16a**: retention time 12.0 min; **16a'**: retention time 15.0 min.

16a: ³¹P NMR (202.5 Hz, CDCl₃): δ = 1.6 ppm; ¹H NMR (500.1 MHz, CDCl₃): δ 8.44 (d, *J* = 8.1 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.71-7.59 (m, 4H), 7.53 (s, 1H), 7.51 (s, 1H), 7.13-7.08 (m, 2H), 6.95-6.91 (m, 4H), 6.47 (d, *J* = 7.6 Hz, 4H), 5.54-5.49 (m, 1H, OCH), 4.93 (d, *J* = 9.6 Hz, 1H), 4.44 (d, *J* = 9.6 Hz, 1H), 3.56 (s, 3H, OMe), 1.65 (d, *J* = 6.3 Hz, 3H), 1.42 (s, 9H, CMe₃); ¹³C NMR (125.8 MHz, CDCl₃): δ = 169.9 (CO), 155.9 (CO), 146.0 (d, *J* = 11.1 Hz, O-C), 145.0 (d, *J* = 8.3 Hz, O-C), 140.3 (C), 140.1 (C), 139.9 (C), 139.8 (C), 134.5 (C), 134.4 (C), 129.1 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 125.9 (C), 125.4 (C), 122.7 (C), 122.6 (CH), 122.5 (C), 122.2 (C), 80.4 (CMe₃), 78.4 (d, *J* = 5.4 Hz, O-CH), 58.0 (d, *J* = 5.5 Hz, CH), 52.7 (OCH₃), 28.4 (CMe₃), 19.1 (CH₃); IR : ν_{max} = 3426, 3057, 3009, 2980, 1749, 1718, 1490, 1364, 1301, 1290, 1165, 1017, 968, 761, 700; HR-MS (ESI) : *m/z* calcd. for C₄₂H₃₉NO₈P [M+H]⁺, 716.2413. Found, 716.2431; [α]_D²⁰ = -77 (*c* = 1, CHCl₃).

16a': ³¹P NMR (202.5 Hz, CDCl₃): δ = 2.1 ppm; ¹H NMR (500.1 MHz, CDCl₃): δ = 8.47 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.69-7.59 (m, 3H), 7.53 (s, 1H), 7.52 (s, 1H), 7.13-7.09 (m, 2H), 6.95-6.92 (m, 4H), 6.49-6.46 (m, 4H), 5.60-5.54 (m, 1H, OCH), 5.06 (d, *J* = 9.6 Hz, 1H), 4.49 (d, *J* = 9.6 Hz, 1H), 3.91 (s, 3H, OMe), 1.46 (d, *J* = 6.6 Hz, 3H, Me), 1.42 (s, 9H, CMe₃); ¹³C NMR (125.8 MHz, CDCl₃): δ = 170.5 (CO), 156.0 (CO), 146.1 (d, *J* = 12.0 Hz, O-C), 145.2 (d, *J* = 9.2 Hz, O-C), 140.3 (C), 140.1 (C), 139.9 (C), 139.8 (C), 134.5 (C), 134.3 (C), 129.1 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.8 (CH), 126.7 (CH), 125.7 (C), 125.5 (C), 122.7 (C), 122.5 (CH), 122.4 (CH), 80.4 (CMe₃), 78.6 (d, *J* = 5.5 Hz, OCH), 58.1 (d, *J* = 5.5 Hz, CH), 53.1 (OCH₃), 28.4 (CMe₃), 18.9 (CH₃); IR : ν_{max} = 3430, 3056, 2979, 1752, 1721, 1490, 1363, 1302, 1291, 1165, 1017, 968, 761, 700; HR-MS (ESI) : *m/z* calcd. for C₄₂H₃₉NO₈P [M+H]⁺, 716.2413. Found, 716.2441; [α]_D²⁰ = +118.5 (*c* = 1, CHCl₃).

Representative procedure for the removal of the chiral auxiliary.

Phosphate **16a** (36 mg, 0.05 mmol) was dissolved in DCM (1 mL) and DBU (15 μL, 0.10 mmol) was added at room temperature. After 20 min, the crude **7b**-DBU salt was purified by column chromatography (eluent: DCM/MeOH gradient, from 100:0 to 90:10). The fractions were collected, concentrated *in vacuo* and diluted in DCM (10 mL). This solution was treated with HCl 6N (3*10 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo* to afford the chiral phosphoric acid (**R**)-**7b** (25 mg, 98% yield). Ee 98.8% by HPLC: CHIRALPAK® ID column, THF/*n*-heptane 70/30, 0.3% TEA, 0.5% TFA, 4.7 mL/min. Retention times 5.7 min, for (**R**)-**7b** and 8.0 min, for (**S**)-**7b**.

Supporting Information. ¹H, ³¹P and ¹³C NMR spectra for the new compounds; X-ray data for **6d**.

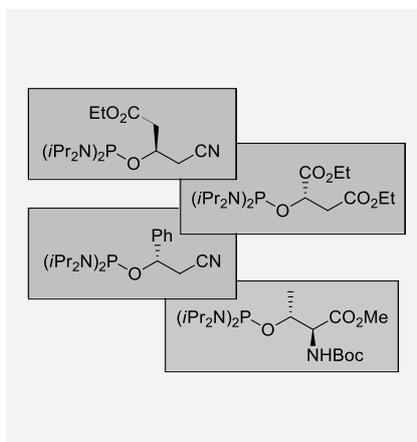
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- [12] NMR spectra for the epimeric mixtures of phosphates **11-13** are given as supporting information

Various chiral phosphorodiamidites displaying β -cyanoethyl or β -(alkoxycarbonyl)ethyl chains behave as synthetic equivalents of the well-known β -cyanoethyl tetraisopropylphosphorodiamidite. They can be used notably for the synthesis and resolution of chiral phosphoric acids *via* chromatographic separations of diastereomeric mixtures.



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Chiral Synthetic Equivalents of 2-Cyanoethyl Tetraisopropylphosphorodiamidite: Application to the Synthesis and Resolution of Chiral Phosphoric Acids

Keywords: Chiral phosphorodiamidites / resolution / phosphoric acids / phosphates