EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402203

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

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Keywords: Synthetic methods / Chiral resolution / Phosphates / Phosphoric acids

Four synthetic equivalents of $(i\mathrm{Pr_2N})_2$P-$\mathrm{OCH_2CH_2CN}$ (**1**) have been prepared from readily available enantiomerically pure β-hydroxynitriles as well as from chiral β-hydroxy esters. 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 through separation of the diastereomeric phosphates. The method should favorably compete with other resolution procedures, e.g. fractional crystallization 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 other areas, for the synthesis of biologically relevant compounds.

Introduction

Commercially available 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite (**1**) is a common reagent for the generation of cyanoethyl phosphates $(\mathrm{RO})_2$P(O)-$(\mathrm{OCH_2CH_2CN})$ from alcohols or diols, mainly used in bioorganic chemistry e.g. in carbohydrates, nucleotides and phospholipids chemistry. From these phosphates, the cyanoethyl group can be easily removed through base-induced elimination of acrylonitrile, to generate the corresponding phosphoric acids, phosphodiesters and others.[1,2] Chiral variants of phosphorodiamidite **1** might be highly useful auxiliaries for asymmetric syntheses through 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.

We report here on the synthesis of new, structurally diverse chiral *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidites 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.

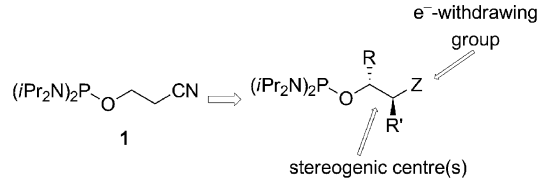

Figure 1. Targeted chiral analogues of **1**.

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 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. SPINOLs,[6] BINOLs,[7] VANOLs and VAPOLs.[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, whereas 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

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402203.

through P-OR functions, and chromatographic separation of epimeric phosphites or the corresponding phosphates (Figure 2).

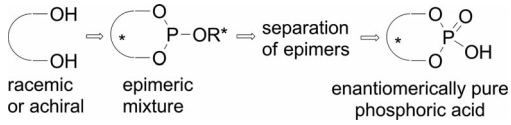
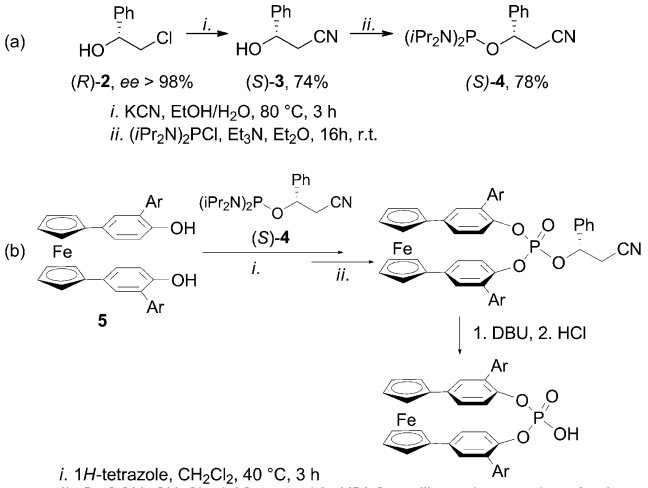


Figure 2. Proposed synthesis and resolution procedure.

For such purposes, the chiral auxiliary must be easy to remove 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 1 (b),[3] we faced a crucial issue: the diol precursors being achiral, the common strategy of resolving the diol precursors could not be applied in this series. Although chiral HPLC allowed resolution of the final chiral acids, this technique prevented 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. Thus, at the outset of this study, we considered (*S*)-3-hydroxy-3-phenylpropanenitrile-derived phosphorodiamidite [(*S*)-**4**] as a chiral synthetic equivalent of **1** [Scheme 1 (a)], i.e. as a precursor for the phosphoric acid function.



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

Nitrile (*S*)-**3** is accessed easily from commercially available, enantiomerically enriched (*R*)-1-phenyl-2-chloroethanol **2**: conversion of chloride **2** into nitrile **3** with KCN occurs in 74% yield at a 7 g 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 through a silica gel column with heptane/EtOAc (7:3)/Et_3N (1%) as the eluent. Compound (*S*)-**4** was obtained in 78% yield on a multigram scale as a stable, easy to handle crystalline solid.

This chiral auxiliary was used then in the synthesis and resolution of paracyclophane-based phosphoric acids as detailed in Scheme 1 (b).[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 best performed on corresponding phosphates **6**, which are obtained after oxidation of phosphorus with *tert*-butyl hydroperoxide. 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 were assigned afterwards, from the sign of the optical rotation of corresponding acids **7a**–**7c**.[8a,10]

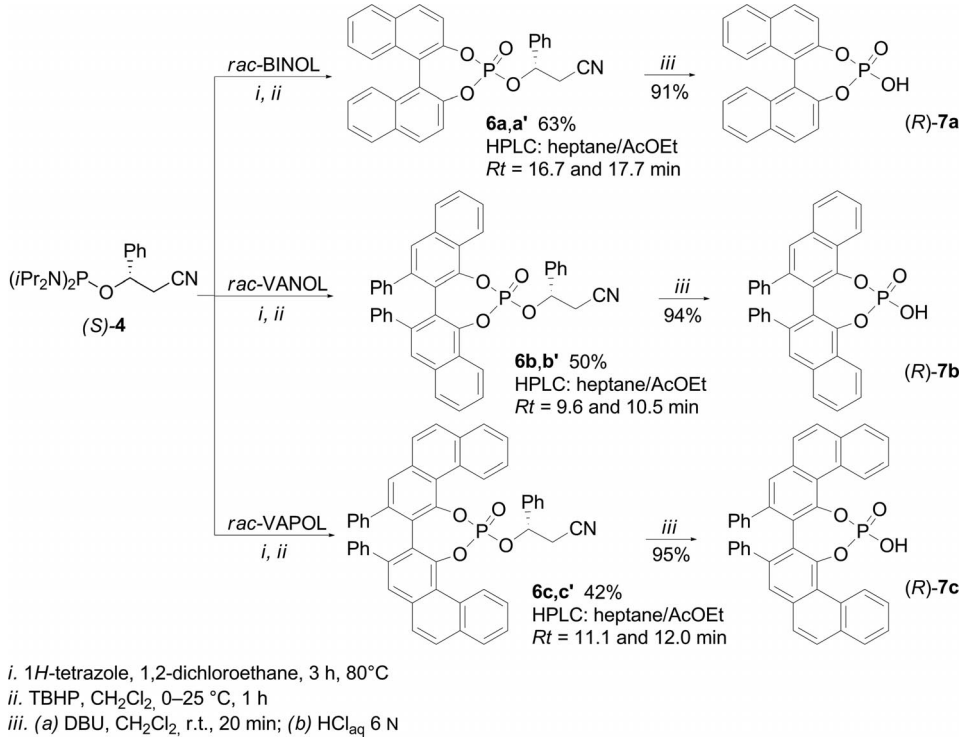
Finally, the cyanoethyl group was removed by treatment with 1,8-diazabicycloundec-7-ene (DBU), at room temperature in dichloromethane. Pure acids **7** have been isolated after filtration of the DBU salts on a short silica gel column (removal of excess DBU and cinnamonitrile) and washing of the salt with a concentrated HCl solution.

Beyond the atropisomeric biaryl derivatives in Scheme 2, the method is illustrated also by the efficient separation of spiranic phosphates **6d**,**d′**, which are precursors for 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 (*R*)-configuration.

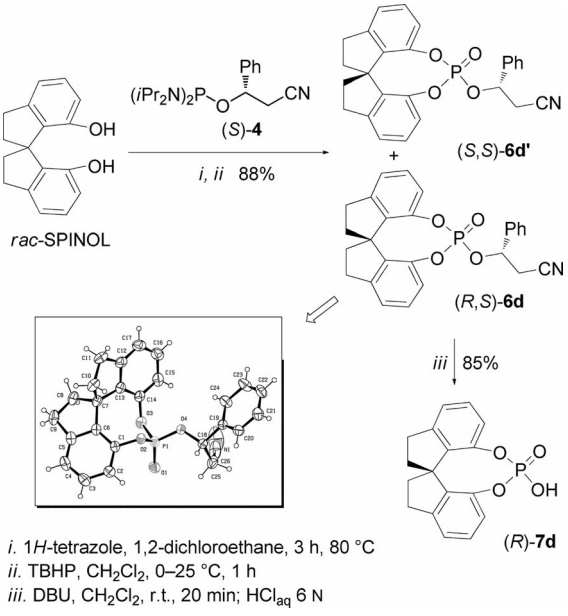
Phosphates **6d** and **6d′** have been converted into the corresponding acids by reaction with DBU, under the usual conditions.

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, in other instances, phosphates made by combining (*S*)-**4** with other chiral alcohols might be a challenge for 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 considered some new phosphorodiamidites as potential resolution agents (Scheme 4). Thus, we have prepared ethyl (*R*)-4-cyano-3-hydroxybutanoate derived phosphorodiamidite (*R*)-**8**. This compound

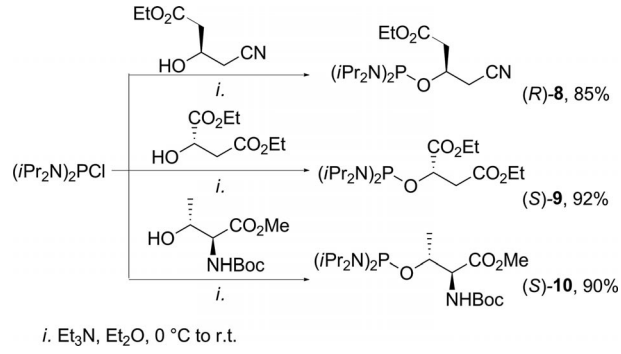


Scheme 2. Synthesis of the phosphoric acids **7a**–**7c** by means of the chiral auxiliary (*S*)-**4**.



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

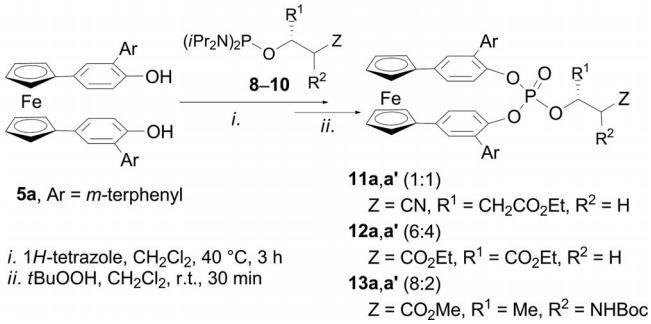
was anticipated to afford suitable phosphoric acid precursors, given its structural analogy to (*S*)-**4**, related to the presence of the β-cyano function. We have also envisioned that the range of phosphinating/resolving agents might be extended to phosphorodiamidites bearing withdrawing functions other than nitrile in their β-positions. To check this point, we prepared new phosphorodiamidites **9** and **10**, which display esters as withdrawing functions (Scheme 4). These two compounds have the main advantage of being readily prepared from commercially available, chiral pool substrates, i.e. malic acid and threonine esters, respectively.



Scheme 4. Synthesis of chiral phosphorodiamidites **8**–**10**.

Phosphorodiamidites **8**–**10** have been obtained in good yields from the corresponding chiral alcohols[11] by reaction with $(iPr_2N)_2PCl$ and have been used most often without further purification. If needed, they can be purified by filtration through a short alumina column.

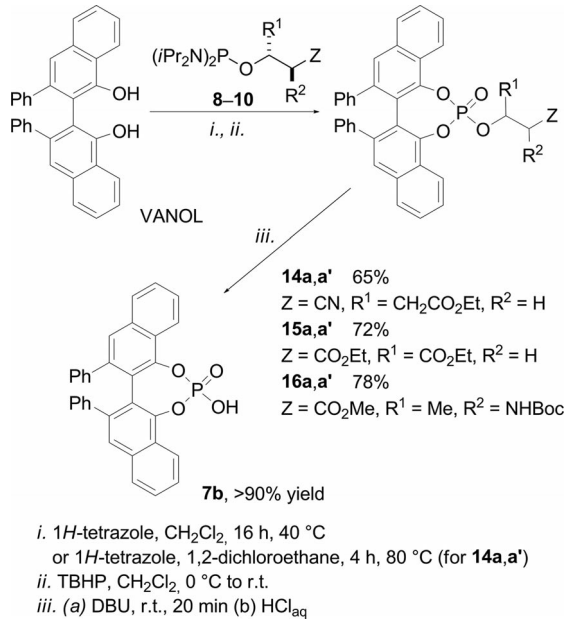
The phosphorodiamidites **8**–**10** were tested initially as chiral resolving agents in the synthesis of planar chiral phosphoric acids with paracyclophane structures (Scheme 5). During these studies, we succeeded in the synthesis of the desired phosphates **11**–**13** [**11a**,**a′**: $\delta^{31}P$ = –15.0 and –15.2 ppm (1:1 ratio); **12a**,**a′**: $\delta^{31}P$ = –14.0 and –14.5 ppm (6:4 ratio); **13a**,**a′**: $\delta^{31}P$ = –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. Synthesis of epimeric mixtures of phosphates **11**–**13**.

Nevertheless, an interesting point was noticed during these studies: the cyclization reaction between the ferrocenic diol **5a** and the threonine-derived phosphorodiamidite (*S*)-**10** generates cyclic phosphates **13a**,**a′** as a 8:2 epimeric mixture, i.e. with a significant level of chiral induction during the ring-closing step. Although the stereoselectivity level of these cyclizations can 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 have been reacted with VANOL in the presence of 1*H*-tetrazole in mild conditions to give the desired phosphites that have been converted in situ into phosphates **14**–**16** (Scheme 6).



Scheme 6. Synthesis of VANOL-derived phosphoric acid **7b** through 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 VANOL-derived phosphoric acid **7b** (Scheme 6). 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**.

Conclusions

The successful experiments in Schemes 2 and 6 expand the scope of our new strategy to use 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-hydroxy esters derivatives. It highlights phosphorodiamidites **4**, **8**, **9** and **10** as chiral auxiliaries with potentially broad scope in different fields and applications, including chemical biology in which 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*′-tetraisopropylphosphorodiamidite (*S*)-**4** was been prepared as reported previously.[3b]

Ethyl (*R*)-3-{[Bis(diisopropylamino)phosphanyl]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 warmed to room temperature and stirred overnight. The white solid was filtered off, the solution was evaporated under reduced pressure to afford desired phosphorodiamidite **(*R*)-8** (1.05 g, 85%). ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 113.0 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 4.22–4.17 (m, 1 H, OCH), 4.15–4.10 (m, 2 H, OCH_2), 3.55–3.47 (m, 4 H, NCH), 2.86 (d, J = 15.9, 4.8 Hz, 2 H), 2.77 (dd, J = 15.9, 4.5 Hz, 1 H), 2.70 (dd, J = 15.9, 8.4 Hz, 1 H), 1.25 (t, J = 7.0 Hz, 3 H, Me), 1.17–1.15 (24 H, $CHMe_2$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.1 (CO), 116.9 (CN), 65.6 (d, J = 18.9 Hz, OCH), 60.5 (CH_2), 44.8 (NCH), 44.6 (NCH), 39.5 (CH_2), 39.4 (CH_2), 24.3 (CH_3), 24.1 (CH_3), 24.0 (CH_3), 14.0 (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 2969, 2932, 2872, 1733, 1459, 1392, 1378, 1363, 1310, 1183, 1116, 1055, 1023, 954, 867, 708 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{41}N_3O_4P$ [M + H_2O + H]$^+$ 406.2835; found 406.2831. $[\alpha]_D^{20}$ = –16 (*c* = 1.5, $CHCl_3$).

(*S*)-Diethyl Malate *N*,*N*,*N*′,*N*′-Tetraisopropylphosphorodiamidite [(*S*)-9]: Phosphorodiamidite (*S*)-**9** was obtained in 92% yield (1.02 g) from bis(diisopropylamino)chlorophosphine (0.70 g, 2.6 mmol) and L-(–)-malate (500 mg, 2.6 mmol). ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 118.9 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 4.52–4.44 (m, 1 H, OCH), 4.19 (q, J = 7.2 Hz, 2 H, OCH_2),

4.12 (q, J = 7.2 Hz, 2 H, OCH_2), 3.60–3.47 (m, 4 H, NCH), 2.87 (dd, J = 15.2, 6.1 Hz, 1 H), 2.80 (dd, J = 15.2, 6.6 Hz, 1 H), 1.29–1.21 (m, 6 H, Me), 1.17 (s, 12 H, CHMe_2), 1.15 (s, 12 H, CHMe_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.1 (CO), 170.3 (CO), 69.6 (d, J = 18.2 Hz, OCH), 61.0 (CH_2), 60.7 (CH_2), 45.1 (NCH), 44.9 (NCH), 39.5 (d, J = 4.6 Hz, CH_2), 24.5 (CH_3), 24.4 (CH_3), 24.3 (CH_3), 14.3 (CH_3), 14.2 (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 2970, 2934, 2873, 1737, 1464, 1369, 1245, 1180, 1157, 1116, 1095, 1024, 1024, 953, 867 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{44}N_2O_6P$ [M + H_2O + H]$^+$ 439.2937; found 439.2939. $[\alpha]_D^{20}$ = –4.5 (c = 0.5, $CHCl_3$).

***N*-(*tert*-Butoxycarbonyl)-L-threonine Methyl Ester *N*,*N*,*N*′,*N*′-Tetraisopropylphosphorodiamidite, [(2*S*,3*R*)-10]:** Phosphorodiamidite (2*S*,3*R*)-**10** was obtained quantitative yield (3.5 g) from bis(diisopropylamino)chlorophosphine (2.0 g, 7.55 mmol) and *N*-(*tert*-butoxycarbonyl)-L-threonine methyl ester (1.76 g, 7.55 mmol). ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 111.5 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 5.22 (d, J = 9.6 Hz, 1 H), 4.37–4.32 (m, 1 H, OCH), 4.21 (d, J = 9.6 Hz, 1 H), 3.71 (s, 3 H, Me), 3.53–3.40 (m, 4 H, NCH), 1.45 (s, 9 H, CMe_3), 1.32 (d, J = 6.6 Hz, 3 H, Me), 1.18–1.15 (m, 24 H, CHMe_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.5 (CO), 156.1 (CO), 79.5 (CMe_3), 69.9 (d, J = 16.6 Hz, OCH), 59.0 (d, J = 4.1 Hz, CH), 52.0 (OCH_3), 44.9 (NCH), 44.7 (NCH), 44.5 (NCH), 28.3 (CMe_3), 24.5 (CH_3), 24.4 (CH_3), 24.2 (CH_3), 24.1 (CH_3), 19.3 (d, J = 8.1 Hz, CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 3447, 2968, 2930, 1758, 1717, 1485, 1460, 1362, 1318, 1183, 1156, 1118, 1087, 1069, 1024, 1002, 953, 902, 866 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{22}H_{49}N_3O_6P$ [M + H_2O + H]$^+$ 482.3359; found 482.3344. $[\alpha]_D^{20}$ = +7.0 (c = 1.5, $CHCl_3$).

Representative Procedure for the Synthesis of Phosphates 6: See Schemes 2 and 3. A solution of (1*S*)-2-cyanoethyl-1-phenyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite (*S*)-**4** (180 mg, 0.48 mmol) in anhydrous 1,2-dichloroethane (5 mL) was added dropwise at room temp. 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 $NaHCO_3$ (20 mL) and the mixture was extracted twice with CH_2Cl_2 (2× 20 mL). The organic phase was dried with $MgSO_4$ and the solvents were removed under reduced pressure. The crude phosphites (1:1 mixture of diastereomers, ^{31}P = 146.7 and 135.2 ppm) were engaged in the next step without further purification. Phosphites were dissolved in CH_2Cl_2 (1 mL). *Tert*-butyl hydroperoxide (TBHP; 218 μL, 5.5 M in decane, 1.20 mmol) was added to the solution at 0 °C. Then the reaction mixture was warmed to room temperature and stirred for 30 min. After addition of saturated aqueous $Na_2S_2O_3$ the layers were separated, and the organic layer was dried with $MgSO_4$ 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 × 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, $CDCl_3$): δ = 1.5 ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.9 Hz, 1 H), 7.99 (d, J = 9.1 Hz, 1 H), 7.97 (d, J = 9.1 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.62 (d, J = 8.6 Hz, 1 H), 7.49 (t, J = 6.6 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.36–7.27 (m, 9 H), 5.89 (ddd, $J_{H,P}$ = 7.6, J = 6.5, 5.3 Hz, 1 H, OCH), 3.10 (dd, J = 16.9, 5.3 Hz, 1 H, CH_2CN), 3.01 (dd, J = 16.9, 6.5 Hz, 1 H, CH_2CN) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 147.5 (d, $J_{C,P}$ = 11.8 Hz, C-O), 146.2 (d, $J_{C,P}$ = 8.2 Hz, C-O), 136.6 (d, $J_{C,P}$ = 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, $J_{C,P}$ = 4.6 Hz, CH, OCH), 27.8 (d, $J_{C,P}$ = 6.7 Hz, CH_2) ppm. IR: $\tilde{\nu}_{max}$ = 3064, 3015, 2927, 2853, 1620, 1591, 1508, 1465, 1434, 1362, 1296, 1227, 1010, 977, 951, 748, 697 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{29}H_{21}NO_4P$ [M + H]$^+$ 478.1208; found 478.1249. $[\alpha]_D^{20}$ = +296 (c = 1, $CHCl_3$).

6a′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 2.1 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.04 (d, J = 9.0 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 1 H), 7.83 (d, J = 8.8 Hz, 1 H), 7.61 (d, J = 8.9 Hz, 1 H), 7.50–7.43 (7 H), 7.35 (d, J = 8.8 Hz, 1 H), 7.31–7.25 (3 H), 6.76 (d, J = 8.8 Hz, 1 H), 5.93 (m, 1 H, OCH), 3.04 (dd, J = 17.0, 6.3 Hz, 1 H, CH_2CN), 3.00 (dd, J = 17.0, 6.3 Hz, 1 H, CH_2CN) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 147.0 (d, $J_{C,P}$ = 11.5 Hz, C-O), 146.0 (d, $J_{C,P}$ = 7.7 Hz, C-O), 136.3 (d, $J_{C,P}$ = 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, $J_{C,P}$ = 3.7 Hz, OCH), 27.1 (d, $J_{C,P}$ = 6.5 Hz, CH_2CN) ppm. IR: $\tilde{\nu}_{max}$ = 3067, 2928, 2854, 1620, 1591, 1508, 1464, 1294, 1227, 1009, 976, 951, 896, 816, 729 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{29}H_{21}NO_4P$ [M + H]$^+$ 478.1208; found 478.1203, $[\alpha]_D^{20}$ = –329 (c = 1, $CHCl_3$).

Phosphates **6b** and **6b**′ were obtained through the same procedure (50% yield). They were separated by semi-preparative HPLC on a SiO_2 column (250 × 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, $CDCl_3$): δ = 1.9 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.45 (d, J = 8.3 Hz, 1 H), 7.82 (d, J = 8.2 Hz, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 1 H), 7.68 (t, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.50–7.48 (m, 3 H), 7.43 (t, J = 7.4 Hz, 1 H), 7.37–7.34 (m, 2 H), 7.28 (d, J = 7.3 Hz, 2 H), 7.20 (t, J = 7.4 Hz, 1 H), 7.11–7.05 (m, 2 H), 6.93 (t, J = 7.5 Hz, 2 H), 6.89 (t, J = 7.5 Hz, 2 H), 6.47 (d, J = 7.5 Hz, 2 H), 6.43 (d, J = 7.5 Hz, 2 H), 6.11 (ddd, J_{H-P} = 9.0, J = 7.2, 5.5 Hz, 1 H, OCH), 3.05 (dd, J = 16.9, 7.2 Hz, 1 H, CH_2CN), 2.96 (dd, J = 16.9, 5.5 Hz, 1 H, CH_2CN) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 145.8 (d, $J_{C,P}$ = 11.8 Hz, C-O), 144.8 (d, $J_{C,P}$ = 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, $J_{C,P}$ = 4.5 Hz, OCH), 27.5 (d, $J_{C,P}$ = 4.5 Hz, CH_2CN) ppm. IR: $\tilde{\nu}_{max}$ = 3058, 3022, 2959, 2927, 1593, 1566, 1489, 1362, 1289, 1009, 1000, 946, 760 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{41}H_{29}NO_4P$ [M + H]$^+$ 630.1834; found 630.1829. $[\alpha]_D^{20}$ = –177 (c = 1, $CHCl_3$).

6b′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 1.4 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.44 (d, J = 8.2 Hz, 1 H), 7.84 (d, J = 8.2 Hz, 1 H), 7.77 (d, J = 8.2 Hz, 2 H), 7.67 (t, J = 7.9 Hz, 1 H), 7.61 (t, J = 7.9 Hz, 1 H), 7.55–7.47 (m, 4 H), 7.39–7.32 (m, 5 H), 7.10–7.06 (m, 2 H), 6.90 (t, J = 7.9 Hz, 4 H), 6.44 (d, J = 7.9 Hz, 2 H), 6.41 (d, J = 7.9 Hz, 2 H), 5.99 (ddd, J = 7.0, 6.3, $J_{H,P}$ = 6.3 Hz, 1 H), 3.04 (dd, J = 16.7, 7.0 Hz, 1 H); 2.97 (ddd, J = 16.7, 6.3, $J_{H,P}$ = 1.9 Hz, 1 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 146.0 (d, J = 11.4 Hz, C), 144.8 (d, $J_{C,P}$ = 9.0 Hz, C), 140.2 (d, $J_{C,P}$ = 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, $J_{C,P}$ = 5.5 Hz, OCH), 27.3 (d, $J_{C,P}$ = 9.7 Hz, CH_2CN) ppm. IR: $\tilde{\nu}_{max}$ = 3057, 2927, 2855, 1633, 1593, 1566, 1488, 1362, 1287, 998, 945, 906, 761 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{41}H_{29}NO_4P$ [M + H]$^+$ 630.1834; found 630.1863. $[\alpha]_D^{20}$ = +96 (*c* = 1, $CHCl_3$).

Phosphates **6c** and **6c′** were obtained through the same procedure (42% yield). They were separated by semi-preparative HPLC on a SiO_2 column (250 × 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, $CDCl_3$): δ = –3.0 ppm. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 9.42–9.38 (m, 2 H), 7.95 (d, *J* = 7.7 Hz, 1 H), 7.83 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 7.72–7.68 (m, 4 H), 7.64 (d, *J* = 8.6 Hz, 1 H), 7.59 (s, 2 H), 7.56–7.51 (m, 2 H), 7.11 (t, *J* = 7.6 Hz, 2 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.99–6.90 (m, 6 H), 6.70 (d, *J* = 7.6 Hz, 2 H), 6.51 (t, *J* = 7.0 Hz, 4 H), 5.51 (ddd, $J_{H,P}$ = 7.7 Hz, *J* = 6.7, 4.7 Hz, 1 H, OCH), 2.97 (dd, *J* = 16.8, 6.7 Hz, 1 H, CH_2CN); 2.65 (dd, *J* = 16.8, 4.7 Hz, 1 H, CH_2CN) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 147.6 (d, $J_{C,P}$ = 11.1 Hz, C), 146.6 (d, $J_{C,P}$ = 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, $J_{C,P}$ = 5.3 Hz, OCH), 27.7 (d, $J_{C,P}$ = 4.6 Hz, CH_2CN) ppm. IR: $\tilde{\nu}_{max}$ = 3056, 2926, 1598, 1487, 1456, 1425, 1388, 1300, 1232, 1124, 1016, 914, 890, 869, 751 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{49}H_{33}NO_4P$ [M + H]$^+$ 730.2147; found 730.2153. $[\alpha]_D^{20}$ = –367 (*c* = 1.5, $CHCl_3$).

6c′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = –2.2 ppm. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 9.67 (d, *J* = 8.6 Hz, 1 H), 8.89 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.89–7.84 (m, 3 H), 7.78–7.74 (m, 3 H), 7.65 (d, *J* = 8.7 Hz, 1 H), 7.61 (s, 1 H), 7.57 (s, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.47–7.39 (m, 5 H), 7.12–7.08 (m, 3 H), 6.95–6.91 (m, 4 H), 6.55 (d, *J* = 8.6 Hz, 2 H), 6.46 (d, *J* = 8.0 Hz, 2 H), 5.85 (ddd, $J_{H,P}$ = 8.0, *J* = 8.0, 3.8 Hz, 1 H, OCH), 2.14 (dd, *J* = 16.5, 8.0 Hz, 1 H, CH_2CN), 2.02 (dd, *J* = 16.5, 3.8 Hz, 1 H, CH_2CN) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 3059, 2926, 2854, 1598, 1558, 1456, 1387, 1300, 1231, 1023, 1010, 914, 751 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{49}H_{33}NO_4P$ [M + H]$^+$ 730.2147; found 730.2151. $[\alpha]_D^{20}$ = +303 (*c* = 1.5, $CHCl_3$).

Phosphates **6d** and **6d′** were obtained through 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_f = 0.2 (toluene/THF = 90:10), 48% yield; **6d′**: R_f = 0.17, 40% yield.

6d: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = –10.7 ppm. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 3 H), 7.41–7.38 (m, 2 H), 7.26 (t, *J* = 7.4 Hz, 1 H), 7.17 (d, *J* = 7.4 Hz, 1 H), 7.12 (t, *J* = 7.4 Hz, 2 H), 7.03 (t, *J* = 7.4 Hz, 1 H), 6.47 (d, *J* = 7.4 Hz, 1 H), 5.81 (dt, $J_{H,P}$ = 8.2, *J* = 5.5 Hz, 1 H, OCH), 3.14–3.06 (m, 2 H), 2.96 (d, *J* = 5.5 Hz, 2 H), 2.90–2.81 (m, 2 H), 2.31–2.24 (m, 2 H), 2.08–1.98 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 3018, 2956, 2856, 1616, 1584, 1466, 1293, 1222, 1159, 1052, 1013, 997, 931, 905 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{26}H_{23}NO_4P$ [M + H]$^+$ 444.1365; found 444.1356. $[\alpha]_D^{20}$ = –183 (*c* = 1, $CHCl_3$).

6d′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = –11.4 ppm. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 3 H), 7.26–7.10 (m, 7 H), 6.88 (d, *J* = 7.7 Hz, 1 H), 5.73 (dt, $J_{H,P}$ = 5.5, *J* = 5.5 Hz, 1 H), 3.10 (dd, *J* = 16.9, 5.5 Hz, 1 H), 3.08–3.02 (m, 2 H), 2.98 (dd, *J* = 16.9, 5.5 Hz, 1 H), 2.84–2.78 (m, 2 H), 2.25–2.20 (m, 2 H), 2.05–1.98 (m, 1 H), 1.92–1.86 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 3013, 2956, 2855, 1616, 1584, 1466, 1294, 1222, 1159, 1132, 1054, 1014, 998, 931, 906, 790, 755 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{26}H_{22}NO_4PNa$ [M + Na]$^+$ 466.1184; found 466.1176. $[\alpha]_D^{20}$ = +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 CH_2Cl_2 (7.5 mL) was added dropwise a solution of ethyl 3-{[bis(diisopropylamino)-phosphanyl]oxy}-4-cyanobutanoate [(*R*)-**7**; 70 mg, 0.18 mmol, 1.2 equiv.] in anhydrous CH_2Cl_2 (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 with $MgSO_4$ and the solvents were removed under reduced pressure [^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 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 warmed to room temperature and stirred for 30 min. The reaction was treated with saturated aqueous $Na_2S_2O_3$. The layers were separated the organic layer was dried with $MgSO_4$ 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 × 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, $CDCl_3$): δ = 1.4 ppm. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.5 Hz, 1 H), 8.30 (d, *J* = 8.5 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.66–7.60 (m, 3 H), 7.53 (s, 2 H), 7.12 (m, 2 H), 6.96–6.91 (m, 4 H), 6.49–6.46 (m, 4 H), 5.49–5.43 (m, 1 H, OCH), 4.24 (q, *J* = 7.2 Hz, 2 H, OCH_2), 3.09 (dd, *J* = 17.0, 5.0 Hz, 1 H), 2.98–2.93 (m, 2 H), 2.85 (dd, *J* = 17.0, 7.5 Hz, 1 H, CH_2), 1.31 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 3054, 3028, 2986, 1737, 1489, 1362, 1301, 1290, 1025, 762, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{39}H_{31}NO_6P$ [M + H]$^+$ 640.1889; found 640.1880. $[\alpha]_D^{20}$ = +51 (c = 1, $CHCl_3$).

14a′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 1.7 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.45 (d, J = 8.5 Hz, 1 H), 8.38 (d, J = 8.5 Hz, 1 H), 7.85 (m, 2 H), 7.85 (m, 2 H), 7.71 (t, J = 7.6 Hz, 2 H), 7.65–7.61 (m, 2 H), 7.53 (s, 1 H), 7.52 (s, 1 H), 7.13–7.09 (m, 2 H), 6.95–6.92 (m, 4 H), 6.47–6.46 (m, 4 H), 5.52–5.45 (m, 1 H, OCH), 4.12 (q, J = 7.5 Hz, 2 H, OCH_2), 3.13 (dd, J = 17.0, 5.4 Hz, 1 H), 3.02–2.97 (m, 2 H), 2.86 (dd, J = 17.0, 7.0 Hz, 1 H), 1.19 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 3055, 3026, 2985, 2929, 1735, 1489, 1363, 1301, 1290, 1024, 967, 946, 762, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{39}H_{31}NO_6P$ [M + H]$^+$ 640.1889; found 640.1882. $[\alpha]_D^{20}$ = –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 16 h heating at 40 °C [^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 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, H_2O/MeCN/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, $CDCl_3$): δ = 2.0 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.65 (d, J = 8.4 Hz, 1 H), 8.51 (d, J = 8.4 Hz, 1 H), 7.83 (d, J = 8.1 Hz, 2 H), 7.71–7.65 (m, 2 H), 7.62–7.59 (m, 2 H), 7.51 (s, 1 H), 7.50 (s, 1 H), 7.12–7.08 (m, 2 H), 6.95–6.91 (m, 4 H), 6.48–6.46 (m, 4 H), 5.71–5.67 (m, 1 H, OCH), 4.37 (q, J = 7.2 Hz, 2 H, OCH_2), 4.11 (q, J = 7.2 Hz, 2 H, OCH_2), 3.05–3.00 (m, 1 H), 2.95–2.90 (m, 1 H), 1.38 (t, J = 7.2 Hz, 3 H, Me), 1.15 (t, J = 7.2 Hz, 3 H, Me) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 3056, 2985, 2937, 1760, 1738, 1489, 1363, 1305, 1291, 1181, 1110, 1048, 1029, 761, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{40}H_{34}O_8P$ [M + H]$^+$ 673.1991; found 673.2017. $[\alpha]_D^{20}$ = –43 (c = 1, $CHCl_3$).

15a′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 2.3 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.51 (d, J = 8.2 Hz, 1 H), 8.32 (d, J = 8.2 Hz, 1 H), 7.84–7.82 (m, 2 H), 7.68 (t, J = 7.8 Hz, 1 H), 7.64–7.57 (m, 3 H), 7.52 (s, 1 H), 7.49 (s, 1 H), 7.12–7.08 (m, 2 H), 6.95–6.91 (m, 4 H), 6.49–6.46 (m, 4 H), 5.76–5.71 (m, 1 H, OCH), 4.41–4.33 (m, 2 H, OCH_2), 4.19–4.11 (m, 2 H, O CH_2), 3.05 (dd, J = 16.5, 4.8 Hz, 1 H, CH_2), 2.96 (dd, J = 16.5, 6.4 Hz, 1 H, CH_2), 1.36 (t, J = 7.1 Hz, 3 H, Me), 1.19 (t, J = 7.1 Hz, 3 H, Me) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 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) ppm. IR: $\tilde{\nu}_{max}$ = 2986, 2930, 1740, 1489, 1364, 1306, 1291, 1262, 1182, 1110, 1049, 1030, 762, 751, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{40}H_{34}O_8P$ [M + H]$^+$ 673.1991; found 673.2001. $[\alpha]_D^{20}$ = +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 [(2*S*,3*R*)-**10**], as described for **14a**,**a′**. The corresponding phosphites (^{31}P NMR: δ = 154.3 and 142.3 ppm ppm) were obtained after 16 h 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, H_2O/MeCN/formic acid (20:80:0.1). **16a**: retention time 12.0 min; **16a′**: retention time 15.0 min.

16a: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 1.6 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.44 (d, J = 8.1 Hz, 1 H), 8.32 (d, J = 7.8 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.71–7.59 (m, 4 H), 7.53 (s, 1 H), 7.51 (s, 1 H), 7.13–7.08 (m, 2 H), 6.95–6.91 (m, 4 H), 6.47 (d, J = 7.6 Hz, 4 H), 5.54–5.49 (m, 1 H, OCH), 4.93 (d, J = 9.6 Hz, 1 H), 4.44 (d, J = 9.6 Hz, 1 H), 3.56 (s, 3 H, OMe), 1.65 (d, J = 6.3 Hz, 3 H), 1.42 (s, 9 H, CMe_3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): 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 (*C*Me_3), 78.4 (d, J = 5.4 Hz, O-CH), 58.0 (d, J = 5.5 Hz, CH), 52.7 (OCH_3), 28.4 (C*Me*$_3$), 19.1 (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 3426, 3057, 3009, 2980, 1749, 1718, 1490, 1364, 1301, 1290, 1165, 1017, 968, 761, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{42}H_{39}NO_8P$ [M + H]$^+$ 716.2413; found 716.2431. $[\alpha]_D^{20}$ = –77 (c = 1, $CHCl_3$).

16a′: ^{31}P NMR (202.5 Hz, $CDCl_3$): δ = 2.1 ppm. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 8.47 (d, J = 8.4 Hz, 1 H), 8.36 (d, J = 8.4 Hz, 1 H), 7.87 (d, J = 8.0 Hz, 1 H), 7.84 (d, J = 8.5 Hz, 1 H), 7.79 (t, J = 7.5 Hz, 1 H), 7.69–7.59 (m, 3 H), 7.53 (s, 1 H), 7.52 (s, 1 H), 7.13–7.09 (m, 2 H), 6.95–6.92 (m, 4 H), 6.49–6.46 (m, 4 H), 5.60–5.54 (m, 1 H, OCH), 5.06 (d, J = 9.6 Hz, 1 H), 4.49 (d, J = 9.6 Hz, 1 H), 3.91 (s, 3 H, OMe), 1.46 (d, J = 6.6 Hz, 3 H, Me), 1.42 (s, 9 H, C*Me*$_3$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): 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 (*C*Me_3), 78.6 (d, J = 5.5 Hz, OCH), 58.1 (d, J = 5.5 Hz, CH), 53.1 (OCH_3), 28.4 (C*Me*$_3$), 18.9 (CH_3) ppm. IR: $\tilde{\nu}_{max}$ = 3430, 3056, 2979, 1752, 1721, 1490, 1363, 1302, 1291, 1165, 1017, 968, 761, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{42}H_{39}NO_8P$ [M + H]$^+$ 716.2413; found 716.2441. $[\alpha]_D^{20}$ = +118.5 (c = 1, $CHCl_3$).

Representative Procedure for the Removal of the Chiral Auxiliary: Phosphate **16a** (36 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (1 mL) and DBU (15 µL, 0.10 mmol) was added at room temperature. After 20 min, crude **7b**·DBU salt was purified by column chromatog-

raphy (eluent: CH_2Cl_2/MeOH gradient, from 100:0 to 90:10). The fractions were collected, concentrated in vacuo and diluted in CH_2Cl_2 (10 mL). This solution was treated with HCl (6 N, 3×10 mL). The layers were separated and the organic layer was 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% triethylamine, 0.5% trifluoroacetic acid, 4.7 mL/min. Retention times 5.7 min, for (*R*)-**7b** and 8.0 min, for (*S*)-**7b**.

Supporting Information (see footnote on the first page of this article): ^1H, ^{31}P and ^{13}C NMR spectra for the new compounds; X-ray data for **6d**.

Acknowledgments

This work has been carried out with the financial support of the Agence Nationale de la Recherche (ANR), within the ANR Blanc "Chiracid" project and the COST action, "ORganoCAtalysis" CM0905.

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[12] NMR spectra for epimeric mixtures of phosphates **11**–**13** are given in the Supporting Information.

Received: March 5, 2014
Published Online: May 8, 2014

