Stereoselective Umpolung Reactions with Metalated *P*-Chiral Cyanohydrin Phosphates—Enantioselective Synthesis of Tertiary Cyanohydrins**

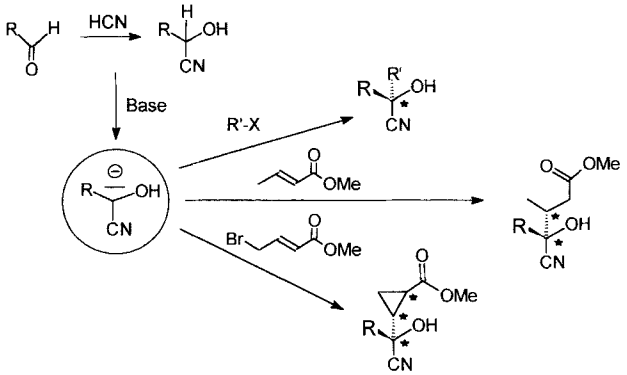
Thomas Schrader*

Abstract: We present the first cyanohydrin derivative **4** that allows diastereoselective umpolung reactions. In **4** the OH group of the cyanohydrin is linked with a chiral phosphate, which can be removed hydrolytically after asymmetric synthesis. Cyclization of pseudoephedrine **1d** with $POCl_3$ gave **2d**. This was followed by addition of racemic benzaldehyde cyanohydrin **3** to give the key intermediate **4d** with complete retention of the configuration at phosphorus. Deprotonation of **4d**, followed by addition of a wide variety of electrophiles afforded the crystalline products **5** with high diastereomeric excesses (*de* up to 94%). High asymmetric induction was also achieved for the reaction of **4**$^-$Li$^+$ with acyl halides, α-bromoacetates, 2-cycloalkenones, α,β-unsaturated esters, and γ-bromoacetates. Lewis acid assisted hydrolysis proceeded without racemization and gave high yields of ketone cyanohydrins **6**. From the ring-opened chiral auxiliary **7**, optically pure pseudoephedrine **1** was readily recovered by acid hydrolysis. Optically pure (*R*) and (*S*) ketone cyanohydrins are now accessible in a very general strategy, which circumvents the substrate limitations of enzymatic synthesis.

Keywords
asymmetric synthesis · C–C bond formation · cyanohydrins · drug research · umpolung

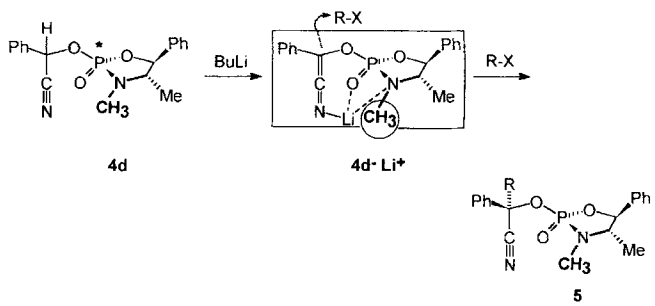
Introduction

Cyanohydrins can be regarded as umpoled carbonyl compounds, because their deprotonation results in formation of cyanohydrin carbanions and the a^1 carbonyl reactivity is thus switched to d^1.[1] When these reactive intermediates are allowed to react with electrophiles, at least one new stereogenic center is formed at the α C atom of the cyanohydrin; often several stereocenters are created, depending on the choice of electrophile (Scheme 1). Effective stereocontrol of this umpolung reaction opens the path to a wide variety of optically active compounds, which are otherwise only obtained with difficulty.[2] To the best of our knowledge, a stereoselective version of this important C–C bond forming reaction has not been reported to date. In the related field of aminonitrile chemistry, efficient asymmetric procedures are also very rare; the Michael addition developed by Enders represents a notable exception.[3] We have recently presented a solution for the above-mentioned problem involving linking the cyanohydrin oxygen atom with a chiral cyclic phosphate (Scheme 2).[4]



Scheme 1. Stereochemical potential of diastereoselective umpolung reactions with cyanohydrin carbanions.

Our *P*-chiral auxiliary has the advantage that a center of asymmetry is positioned directly next to the cyanohydrin oxygen atom; in addition, the P=O double bond provides an excellent conformational lock for the intermediate lithiated keteneimine **4d**$^-$Li$^+$ by means of a Li–O chelate.[5] One diastereotopic face is thus sterically shielded, and the attack of an electrophile should be directed towards the opposite face (Scheme 2). After alkylation, it should be possible to remove the auxiliary hydrolytically by selective P–O cleavage. The synthet-



Scheme 2. Key step of the diastereoselective alkylation of **4d** via the lithiated keteneimine **4d**$^-$Li$^+$ to give tertiary cyanohydrin phosphates **5**.

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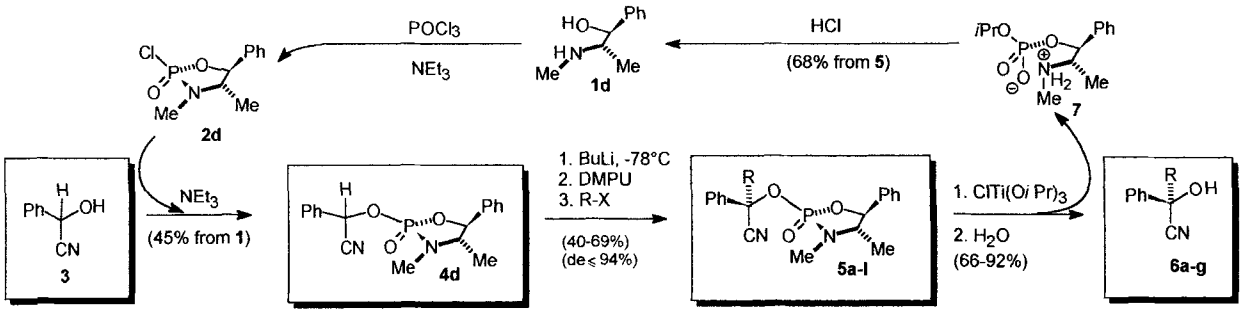
[**] Chiral Cyanohydrin Phosphates, Part 2. Part 1: see ref. [4].



Scheme 3. Transformation of racemic aldehyde cyanohydrin **3** into optically active ketone cyanohydrins **6** with recycling of the ephedrine auxiliary **1**.

ic potential of auxiliaries based on chiral phosphonates or phosphonamides would thus be substantially extended.[6] In the past, the final products of these reactions have been limited to phosphonic acid derivatives, because of the stabiliy of the P–C bond; the potential applications of these very effective auxiliaries were thus enormously restricted.[7]

From the reservoir of chiral amino alcohols we chose ephedrine derivatives **1** to construct a 1,3,2-oxazaphospholane ring system for two reasons: they are cheap, renewable resources[8a] and can be purchased in both enantiomeric forms;[8b] they are also known to form the required intermediate 2-chloro-1,3-oxazaphospholidin-2-ones **2** diastereoselectively, which can be subsequently esterified with alcohols in a highly stereospecific manner (Scheme 3).[9]

Results and Discussion

Reactions of ephedrine derivatives **1** with phosphoryl chloride led to intermediates **2**, which were esterified in the same pot with benzaldehyde cyanohydrin **3** to give cyanohydrin phosphates **4** with complete retention of configuration at the stereogenic phosphorus atom (Scheme 3).

Diastereoselective alkylations (4 → 5): The acidic α-proton of **4d** could be removed under mild conditions (at −78 °C with *n*-butyllithium) to give the light yellow lithiated keteneimine **4d**$^-$Li$^+$, which was alkylated by a range of different electrophiles in high yields. In order to optimize the optical yield, we tested different auxiliaries, solvents, temperatures, bases, and cosolvents. The best combination was found to be the following: reaction of pseudoephedrine-based cyanohydrin phosphate **4d** in THF at −78 °C with *n*-butyllithium, followed by addition of the HMPA-substitute DMPU (*N*,*N*′-dimethylpropylene urea),[10] and subsequent injection of the electrophile. In this way, tertiary cyanohydrin phosphates **5** were obtained with up to 94% *de*. After chromatographic purification the cyanohydrin phosphates were mostly obtained as crystalline material. A single recrystallization step afforded diastereomerically pure cyanohydrin phosphates **5** (*de* ≥ 98%). Surprisingly, an increase in steric bulk of the substituent at the N atom in the ephedrine auxiliary was found to have a negative influence on the asymmetric induction. In the methylation reaction, the *N*-benzyl derivative **4b** gave 20% *de* and the *N*-isopropyl derivative **4c** only 5% *de*. This may indicate that, in addition to the P=O chelate, a P–N chelate is also necessary to achieve good stereocontrol (Scheme 2). With growing steric bulk of the *N*-substituent, the latter interaction becomes more difficult; this might explain the dramatic drop in the optical yield.

Table 1 demonstrates the versatility of the alkylation reaction: a broad range of groups (e.g. long-chain alkyl, benzyl, phenylalkyl, propargyl, and allyl groups) can be attached to the cyanohydrin in good chemical and very good optical yields.

Table 1. Results of the alkylations of **4d** with electrophile RX to give cyanohydrin phosphates (*R*)-**5** and of the subsequent cleavage reactions to give tertiary cyanohydrins (*R*)-**6**.

R	X	5	Yield (%)	*de* (%)	6	Yield (%)	*ee* (%) [a]
allyl	Br	**a**	47	90	**a**	79	
methyl	I	**b**	69	83	**b**	66	>96
n-propyl	I	**c**	58	82	**c**	92	
propargyl	Br	**d**	65	82	**d**	72	
benzyl	Br	**e**	58	82	**e**	85	>96
3-phenylpropyl	I	**f**	54	80	**f**	44	
(−)-myrtenyl	Br	**g**	49	48	**g**	58	
n-octyl	I	**h**	48	81			
3,3-dimethylallyl	Br	**i**	40	94			
2-bromoallyl	Br	**k**	38	71			
cinnamyl	Br	**l**	45	90			

[a] The cleavage reaction was performed on recrystallized, diastereomerically pure **5**; in the case of **6b** and **6e** the enantiomeric purity of the product was proven by NMR shift experiments.

Normally, alkyl iodides must be used; only for activated benzyl or allyl groups is the reactivity of the bromides sufficient for complete conversion. Secondary alkyl halides such as isopropyl iodide and tertiary halides such as *tert*-butyl iodide do not react at all. The following trend can be derived from the diastereomeric excesses obtained: Alkyl halides give 80–83% *de*, and allyl halides in most cases 90–94% *de*. Among the allyl halides, a marked increase in asymmetric induction is observed according to the position of substitution in the order 2 < 3-(*E*) < 3-(*Z*) (cf. Table 1: **g**,**k** < **a**,**l** < **i**). We would like to emphasize that almost every cyanohydrin phosphate **5** can be obtained in diastereomerically pure form after a single recrystallization step.

X-ray structure of 5e:[11] The assumed conformation of the reactive intermediate (Scheme 2) predicts that an electrophile will attack the *Si* face of the metalated cyanohydrin phosphate. Thus, (1*S*,2*S*)-(+)-pseudoephedrine would be expected to induce an (*R*) configuration at the α C atom of the cyanohydrin phosphate. We were able to check this hypothesis, because the benzyl derivative **5e** gave regular single crystals suitable for X-ray structure analysis (Figure 1, Table 2).

The absolute configuration at the new cyanohydrin stereocenter can be established through its configuration relative to

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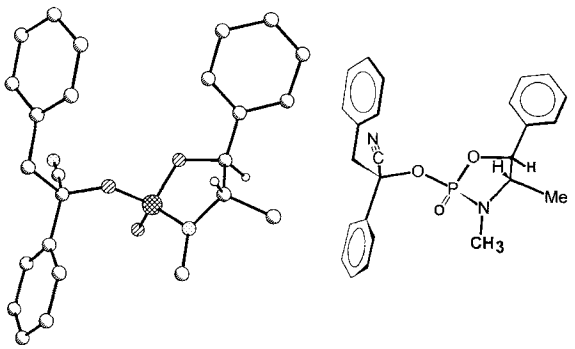


Figure 1. X-ray structure of the benzylcyanohydrin phosphate **5e** (ball-and-stick representation). The H atoms are omitted for clarity, except those at the oxazaphospholidinone ring.

Table 2. Crystal data and structural analysis results for **5e**.

formula	$C_{25}H_{25}N_2O_3P$	λ ($Mo_{K\alpha}$, Å)	0.71073
M_r	432.44	T (°C)	20
crystal system	orthorhombic	ρ_{calcd} (mg mm^{-3})	1.247
space group	$P2_12_12_1$	μ_{calcd} (mm^{-1})	0.148
a (Å)	11.472	total refl.	3769
b (Å)	11.917	obs. refl.	2517 [$I>2\sigma(I)$]
c (Å)	16.852	parameters	282
V (Å^3)	2303.9 (4)	$R1_{obs}$, $wR2_{obs}$ [a]	0.052, 0.1601
Z	4		

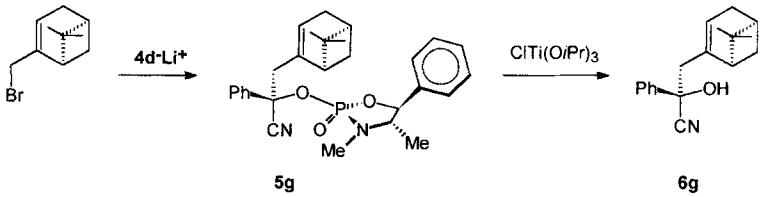
[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

the known absolute configuration of the pseudoephedrine auxiliary. The attack was thus confirmed to have taken place at the *Si* face of the lithiated keteneimine **4d**$^-$Li$^+$. Furthermore, the configuration at the phosphorus atom shows that the nucleophilic attack of the cyanohydrin OH group at oxazaphospholidinone **2d** proceeds, as expected, with retention of configuration.

Besides confirming the absolute configurations, the X-ray structure provides some interesting information about the conformation of the oxazaphospholidinone ring, which is a crucial factor for the asymmetric induction. The ring nitrogen is almost completely sp^2-hybridized and forms three bonds in one plane. This confirms earlier results on similar ring systems.[12] The favored conformation of the oxazaphospholidine in the crystal is a shallow half-chair with approximate pseudo-C_2 symmetry at the phosphorus atom. The phenyl group and the adjacent methyl group are both pseudoequatorial. Surprisingly, a completely different picture emerges in solution. From the ^{1}H NMR data, that is, from the H–H coupling constants of the secondary and tertiary cyanohydrin phosphates **4** and **5**, a twisted envelope conformation can be clearly deduced, in which the cyanohydrin substituent is located in the pseudoaxial position.[13] In addition, there is an equilibrium in solution between two conformers, namely, one with the *C*-methyl and phenyl groups pseudoaxial and one with both groups pseudoequatorial. However, the contrasting results for solution and crystal agree very well with Setzer's experiments on simple oxazaphospholidinone derivatives.[13] Because of the flexibility of the auxiliary in solution, theoretical models for the transition state to explain the high degree of asymmetric induction still appear speculative.

Cleavage of cyanohydrin phosphates (5 → 6): Cleavage of the cyanohydrin phosphates **5** to liberate the free ketone cyanohydrins **6** is not a trivial process, because the hydrolytic reaction must not only distinguish between benzyl and cyanohydrin ester, but also avoid any C–O bond cleavage, because this would lead to racemization. We used a mild Lewis acid, titanium chloride triisopropoxide, to activate the reaction (Scheme 3). Subsequent addition of water produced a two-layer system, which contained the free ketone cyanohydrin **6** in the organic phase; the ring-opened chiral auxiliary **7** was isolated from the aqueous phase. In this manner the free optically active ketone cyanohydrins **6** were obtained in high yields (Table 1). Pure (+)-pseudoephedrine **1d** could be regenerated from **7** with 5 N hydrochloric acid in 68% yield (starting from **4d**; Scheme 3).[14]

Proof of enantiomeric purity and absolute configuration of 6: NMR shift experiments were performed in order to check that the titanium-assisted cleavage was absolutely free of racemization. Since tertiary aromatic cyanohydrins are extremely sensitive to cleavage back to the respective ketones, they cannot be derivatized with Mosher's reagent and are not suitable for routine GC analysis with chiral stationary phases. However, by employing enantiomerically pure (−)-myrtenyl bromide as the electrophile, we were able to generate diastereomeric tertiary cyanohydrins **6g**; the signal ratio for the diastereomers in the ^{1}H NMR spectrum of **6g** was found to be the same as that for the corresponding cyanohydrin phosphate **5g** (Scheme 4).



Scheme 4. Proof that the cleavage of the cyanohydrin phosphates is free of racemization by comparing the ratio of diastereomers in **5g** and **6g**.

Additional proof for the optical purity of the free ketone cyanohydrins came from NMR experiments with TADDOL [(4*R*,5*R*)-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol] as shift reagent.[15] Diastereomerically pure cyanohydrin phosphates **5b** and **5e** were converted into the free tertiary cyanohydrins. The methyl and methylene signals, respectively, showed an enantiomer ratio of >98:2 after 1–2 molar equivalents of TADDOL had been added (Figure 2). From these results we conclude that all the cyanohydrin phosphates **5** which can be prepared in diastereomerically pure form are transformed into the optically pure ketone cyanohydrins **6** by the above hydrolysis procedure.

If hydrolysis of the cyanohydrin phosphates proceeds with retention of configuration at the α C atom, the absolute configuration of the tertiary cyanohydrins must be (*R*). To prove this, we hydrolyzed **5b** (recrystallized and diastereomerically pure) to the cyanohydrin **6b**. This was converted into atrolactic amide **8**, which was cyclized with sulfuric acid in acetone (Scheme 5). The purified 1,3-oxazolidin-4-one **9** showed a positive specific rotation corresponding to the the literature value for the (*R*) compound.[16]

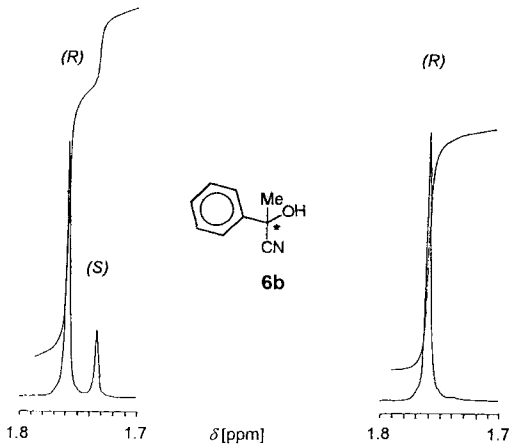
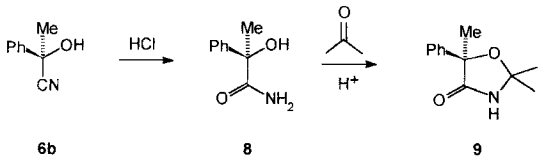


Figure 2. Determination of the enantiomeric excess by ^{1}H NMR experiments with TADDOL complexes of free ketone cyanohydrin **6b** (methyl singlet). Samples: 20 mg **6b** + 120 mg TADDOL in 0.7 mL $CDCl_3$. Left: **6b**, *ee* = 58%; right: (*R*)-**6b**, *ee* > 96%.



Scheme 5. Proof of the absolute configuration of the optically pure ketone cyanohydrin **6b** after conversion into the optically pure oxazolidinone **9**.

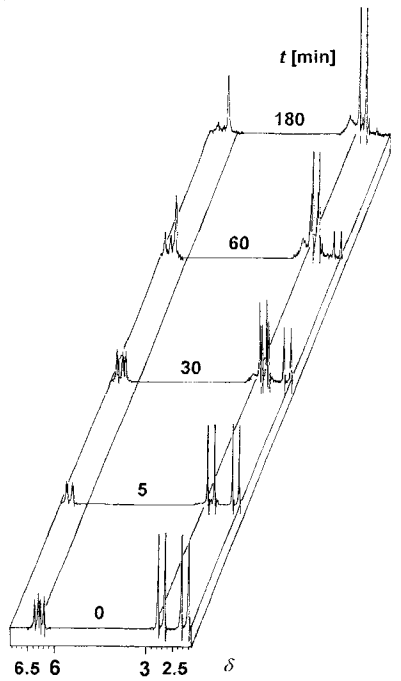
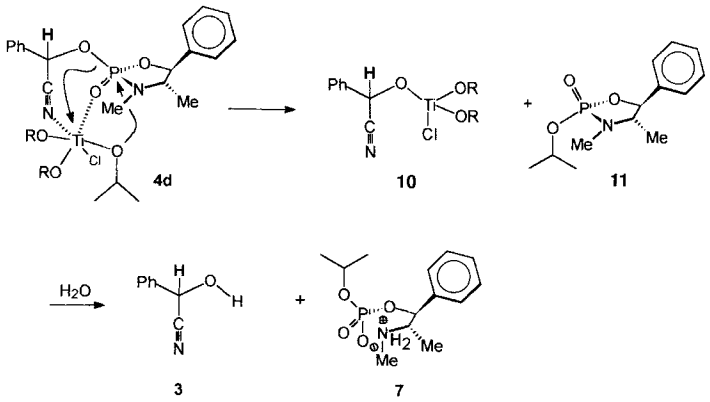


Figure 3. ^{1}H NMR experiments at different stages of the reaction shown in Scheme 6: signal changes for the cyanohydrin α-H (left) and the *N*-methyl group (right) during the development of **10** und **11**.



Scheme 6. Proposed mechanism for the $ClTi(OiPr)_3$-catalyzed cleavage of the phosphate group in **4d** to give the free cyanohydrin **3**.

Study of the cleavage mechanism (4d → 3): How does the titanium reagent manage to carry out such a highly regioselective hydrolysis of the cyanohydrin phosphates **5**? This remarkable reaction even works for **4**, the starting material for the alkylation reactions. The titanium reagent is not only able to exclusively cleave the P–O bond, but can evidently even distinguish between the secondary alcohol cyanohydrin and the secondary alcohol pseudoephedrine. To elucidate the hydrolysis mechanism, we carried out the reaction of cyanohydrin phosphate **4d** with titanium chloride triisopropoxide in an NMR tube. On addition of the Lewis acid, the signal of the cyanohydrin α-proton immediately shifted downfield (Figure 3). We assume that the titanium cation coordinatively binds not only to P=O, but also to the CN functionality (Scheme 6). During the next three hours, the signals of the starting material decreased continuously; concomitantly, a new singlet developed for the cyanohydrin α-proton, and a new doublet appeared for the *N*-methyl group, replacing the doublet of doublets. After three hours only product signals could be seen. Clearly, the cyanohydrin is cleaved from the phosphorus-containing moiety (as indicated by the missing P coupling in the magnetically equivalent enantiomers), whereas the oxazaphospholidinone ring remains intact and even epimerically pure with reference to the stereogenic phosphorus atom. At the beginning of the reaction the TLC showed a spot of the starting material on the baseline because of complex formation, but soon a new spot appeared at $R_f \approx 0.3$ (toluene/acetone 10:1). We assume that an isopropoxide anion stereospecifically attacks the phosphorus atom, facilitated by the double coordination of the titanium cation. Then the P–O bond is cleaved and the cyanohydrin titanium compound **10** and optically pure **11** are released. Subsequent hydrolysis affords the free cyanohydrin **3** and also the P–N ring-opened hydrolysis product **7**, which are present exclusively in the organic and aqueous phases, respectively, owing to their different polarities.

This mechanism shows some remarkable similarities to the action of phosphodiesterases.[17] The nuclease from staphylococci activates the P=O bond by coordinative binding to Ca^{2+}, enhanced by the electron-withdrawing effect of hydrogen-bonded arginine; then, proton transfer reactions direct a nucleophilic water molecule from the metal cation to stereospecifically cleave the P–O bond.

Extension of the concept: In view of the great importance of secondary cyanohydrins as synthetic intermediates in organic synthesis and as drugs,[18] we asked ourselves whether it would be possible to synthesize this class of compound stereoselectively by the same route. We synthesized the starting materials **12a**

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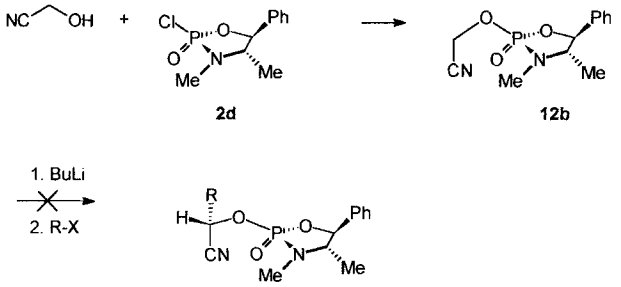
and **12b** in a *P*-epimerically pure form, starting from formaldehyde cyanohydrin and chlorooxazaphospholidinones **2a** and **2d**, respectively (Scheme 7; **2a** is the (2*R*,4*S*,5*R*) diastereomer of **2d**). All efforts to deprotonate and subsequently alkylate **12**, however, invariably led to complicated product mixtures. Here again, the prediction of Stork and others seems to apply, namely, that the carbanions of *O*-protected formaldehyde cyanohydrins will tend to self-condense and are not available as d^1 building blocks.[19]



Scheme 7. Attempted asymmetric synthesis of secondary cyanohydrin phosphates from formaldehyde cyanohydrin phosphate **12**.

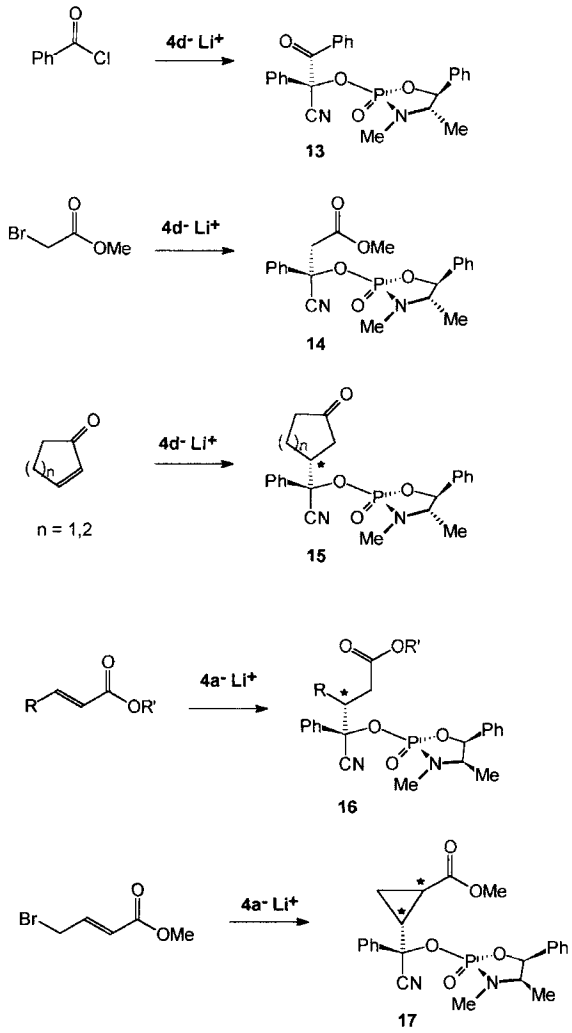
The benzaldehyde cyanohydrin carbanion **4**$^-$Li$^+$, however, allows stereoselective carbon–carbon bond formations with many more electrophiles: we first tested acyl halides and α-halocarbonyl compounds (Table 3, Scheme 8). Aromatic acyl

Table 3. Reactions of the cyanohydrin carbanion **4**$^-$Li$^+$ with electrophiles other than alkyl halides.

Electrophile	Product	Yield (%)	*dr* (%) [a]
benzoyl chloride	**13**	52	91:9
ethyl bromoacetate	**14**	53	83:17
2-cyclopentenone	**15a**	53	74:22:3:<1 [b]
2-cyclohexenone	**15b**	61	72:23:4:<1 [b]
ethyl crotonate	**16a**	55	80:13:5:<2 [b]
methyl cinnamate	**16b**	48	65:22:9:<4 [b]
methyl 4-bromocrotonate	**17**	69	55:27:12:<6 [c]

[a] *dr* = diastereomeric ratio. [b] Only three diastereomers could be detected; we assume an (*R*) configuration at C_α for both major diastereomers. [c] No other diastereomers could be detected.

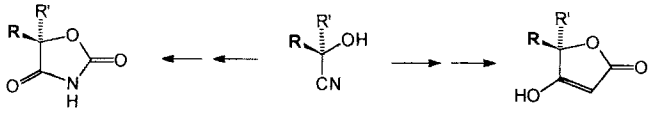
halides were found to react smoothly to give 1-acylcyanohydrin derivatives (e.g. **13**), whereas aliphatic acyl halides tended to form ketenes under the strongly basic reaction conditions. α-Haloesters formed 2-carbalkoxymethylcyanohydrins (e.g. **14**); the more reactive α-haloketones did not react cleanly (Table 3). When Michael acceptors were used as electrophiles, a new stereogenic center could be generated (Scheme 8). We found that both 2-cycloalkenones (**15**) and α,β-unsaturated esters (**16**) readily underwent Michael addition with the lithiated keteneimine **4**$^-$Li$^+$. In every case, only two major diastereomers (out of 4) were formed, in a ratio of 3–6:1 (Table 3). We assume that the strongest stereodiscrimination is operating at the cyanohydrin-α-carbon, so that we tentatively assign the (*R*) configuration at C_α to both major diastereomers. This means that a high *de* (up to 92%) is consistently produced at the cyanohydrin α-carbon, while the *de* at the β-carbon lies at around 50–70%.



Scheme 8. Electrophiles other than alkyl halides for diastereoselective umpolung reactions with cyanohydrin carbanion **4**$^-$Li$^+$: acyl halides (→**13**), α-haloacetates (→**14**), 2-cycloalkenones (→**15**), α,β-unsaturated esters (→**16**), and γ-halocrotonates (→**17**).

Cyanohydrin phosphates also provide access to cyclopropane derivatives **17**. When the carbanion **4**$^-$Li$^+$ reacted with γ-bromocrotonates, Michael addition first took place, followed by intramolecular ring closure in which the ester enolate attacked the bromide. Only three (out of 8 possible) diastereomers could be detected; the cyanohydrin stereocenter is probably again formed with high diastereoselectivity, whereas for both additional asymmetric carbons at the cyclopropane the *de* is lower (Table 3, Scheme 8). Obviously the directing influence of the small *N*-methyl group cannot sufficiently shield one of the enantiotopic faces of the Michael acceptors. For these umpolung reactions in the real sense of the word, sterically more demanding auxiliaries should be used to protect the phosphate. Model compounds are currently under investigation.[20]

From tertiary cyanohydrins α-branched α-hydroxy acids and 1,2-amino alcohols can be directly obtained; furthermore, important pharmacologically active substances are accessible in a few steps (Scheme 9): 5,5-disubstituted 2,4-oxazolidinediones **18**, which can be synthesized from ketone cyanohydrins in a one-pot procedure, play an important role as anticonvulsants and in the treatment of *Diabetes mellitus*.[21a] Cyclization of



18 6 19

Scheme 9. Chiral, pharmacologically active 2,4-oxazolidinediones **18** and tetronic acids **19** are accessible from ketone cyanohydrins **6** in one-pot reactions.

tertiary cyanohydrins with malonates and subsequent hydrolysis affords tetronic acids **19**, which are antibiotics and antitumor agents.[21b]

Conclusion

We have shown for the first time, that stereoselective umpolung reactions can be carried out with metalated *P*-chiral cyanohydrin phosphates **4**$^-$ Li$^+$, leading to tertiary cyanohydrin phosphates **5** (*de* up to 94%). After recrystallization, the latter are obtained optically pure, and titanium-assisted hydrolysis affords optically pure ketone cyanohydrins **6**. For the related aldehyde cyanohydrins a multitude of asymmetric syntheses and enzymatic procedures have been developed;[22] optically pure ketone cyanohydrins are much more difficult to obtain.[23] The presented method can be readily carried out on a multigram scale for the alkylation reaction; in addition, the starting material is synthesized in a one-pot procedure without the need for chromatographic purification. Effenberger and Kula[24] have used (*R*)-oxynitrilases as an elegant alternative to chemical synthesis, but these enzymes suffer from a limited substrate spectrum: to date, only (*R*) derivatives can be obtained enzymatically from ketones,[25] and even for these, quantitative results exist only from methyl and ethyl ketones. Our procedure offers the choice between (*R*)- and (*S*)-cyanohydrins by starting with (+)- or (−)-pseudoephedrine; furthermore, one alkyl substituent may be varied almost completely at will. The other substituent in this work is always aromatic, and our method thus complements the repertoire of the enzymes. We will show in following communications that even this substituent can be replaced by an alkenyl or alkyl group.

Experimental Section

General: ^{1}H NMR spectra were recorded at 20 °C on a Varian EM 390 (90 MHz) and a Varian VXR 300 spectrometer (300 MHz). ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts δ are given relative to an internal tetramethylsilane standard (TMS). ^{31}P NMR spectra were recorded on a Bruker AM 200 SY spectrometer with H_3PO_4 as external standard. $CDCl_3$ and [D_6]DMSO were purchased from Aldrich in 99.8% purity. TLC analyses were carried out on silica gel 60 F-254 with a layer thickness of 0.2 mm. Preparative chromatography columns were packed with silica gel 60 (70–230 mesh) from Macherey & Nagel. All solvents were dried and freshly distilled before use. THF (p.a.) was purchased from Aldrich and dried over sodium metal; for the metalation reactions and for the titanium-assisted cleavages it was always freshly distilled under nitrogen prior to use. These reactions were all carried out under rigorous exclusion of air and humidity by means of standard Schlenk techniques.

(2*R*,4*S*,5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**2a**) was synthesized according ro ref. [9].

(2*R*,4*S*,5*R*)-2-Chloro-3-benzyl-4-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**2b**) and **(2*S*,4*S*,5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one** (**2d**): These compounds were prepared in situ according to the procedure for **2c**.

(2*R*/*S*,4*S*,5*R*)-2-Chloro-4-methyl-3(1′-methylethyl)-5-phenyl-1,3,2-oxazaphospholidin-2-one (**2c**): Phosphoroxychloride (1.99 mL, 3.33 g, 21.7 mmol, 1.05 equiv) was slowly added over 30 min to a solution of (−)-*N*-isopropylnorephedrine (4.00 g, 20.7 mmol) and triethylamine (14.3 mL, 103.5 mmol, 5.0 equiv) in dichloromethane (0.25 L) at −5 °C. The reaction mixture was stirred overnight at 10 °C. After filtration of the ammonium salts and evaporation to dryness, a colorless crude product was obtained. Chromatography over silica gel (toluene/acetone 8:1) afforded 1.8 g (32%) of the minor *P*-epimer (R_f = 0.40) in addition to 3.0 g (53%) of the major *P*-epimer (R_f = 0.28) as colorless crystals.

Major *P*-epimer (2*R*): ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.93 (d, ^3J(H,H) = 6.9 Hz, 3H; C*H*$_3$-CH), 1.40 + 1.56 (2d, ^3J(H,H) = 6.9 Hz, 6H; (C*H*$_3$)$_2$CH), 3.4–4.3 (m, 2H; C*H*-N + CHMe$_2$), 5.77 (d, ^3J(H,H) = 6.9 Hz, 1H; C*H*-O), 7.3–7.5 (m, 5H$_{arom}$). ^{31}P NMR ($CDCl_3$): δ = 20.88 (s).

Minor *P*-epimer (2*S*): ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.93 (d, ^3J(H,H) = 6.9 Hz, 3H; C*H*$_3$-CH), 1.42 + 1.54 (2d, ^3J(H,H) = 6.3 Hz, 6H; (C*H*$_3$)$_2$CH), 3.2–4.1 (m, 2H; C*H*-N + CHMe$_2$), 5.60 (dd, ^3J(H,H) = 6.0 Hz, ^3J(P,H) = 1.8 Hz, 1H, C*H*-O), 7.42 (≈s, 5H$_{arom}$). ^{31}P NMR ($CDCl_3$): δ = 21.54 (s).

(1′*R*/*S*,2*R*,4*S*,5*R*)-2-[(1′-Cyano-1′-phenyl)methoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**4a**): Phosphoroxychloride (5.76 mL, 9.6 g, 0.065 mol, 1.1 equiv) was slowly added over 30 min to a solution of (−)-ephedrine (10.00 g, 0.060 mol) and triethylamine (41 mL, 0.30 mol, 5.0 equiv) in dichloromethane (0.4 L) at −5 °C. The reaction mixture was stirred overnight at 10 °C. Then benzaldehyde cyanohydrin (7.15 mL, 7.99 g, 0.060 mol, 1.0 equiv) was added, and the reaction mixture was stirred again overnight at room temperature. After filtration of the ammonium salts and evaporation to dryness a light yellow crude product was obtained. Chromatography over silica gel (toluene/acetone 5:1) gave a total yield of 11.1 g (54%) of enantiomerically and epimerically pure, colorless product **4a**. We could separate the C$_\alpha$ epimers, which were formed in equal amounts.

Epimer 1 (R_f = 0.35, 6.0 g, 29%): M.p. 88 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.76 (d, ^3J(H,H) = 6.9 Hz, 3H; C*H*$_3$-CH), 2.78 (d, ^3J(P,H) = 10.8 Hz, 3H; C*H*$_3$-N), 3.65 (ddq, ^3J(H,H) = 6.6/6.6 Hz, ^3J(P,H) = 19.2 Hz, 1H; C*H*-N), 5.58 (dd, ^3J(H,H) = 6.6 Hz, ^3J(P,H) = 1.5 Hz, 1H; C*H*-O), 6.25 (d, ^3J(P,H) = 9.6 Hz, 1H; C$_\alpha$-H), 7.0–7.7 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): δ = 19.84 (s).

Epimer 2 (R_f = 0.25, 5.1 g, 25%): ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.74 (d, ^3J(H,H) = 6.9 Hz, 3H; C*H*$_3$-CH), 2.38 (d, ^3J(P,H) = 10.5 Hz, 3H; C*H*$_3$-N), 3.64 (ddq, ^3J(H,H) = 6.6/6.6 Hz, ^3J(P,H) = 19.2 Hz, 1H; C*H*-N), 5.71 (dd, ^3J(H,H) = 6.6 Hz, ^3J(P,H) = 1.5 Hz, 1H; C*H*-O), 6.20 (d, ^3J(P,H) = 9.6 Hz, 1H; C$_\alpha$-H), 7.0–7.7 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): δ = 20.23 (s); $C_{18}H_{19}N_2O_3P$ (342.33): calcd C 63.15, H 5.59, N 8.18; found C 63.21, H 5.51, N 7.88.

(1′*R*/*S*,2*R*,4*S*,5*R*)-2-[(1′-Cyano-1′-phenyl)methoxy]-3-benzyl-4-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**4b**): Preparation analogous to **4a** from (−)-*N*-benzylnorephedrine (4.00 g, 13.6 mmol) and triethylamine (9.3 mL, 67 mmol, 5.0 equiv) in dichloromethane (0.2 L); after one day addition of phosphoroxychloride (1.88 mL, 3.03 g, 20.7 mmol, 1.5 equiv) at −5 °C and after another 24 h addition of benzaldehyde cyanohydrin (2.43 mL, 2.72 g, 20.4 mmol, 1.5 equiv). Chromatography of the crude product over silica gel (toluene/acetone 15:1) afforded 1.0 g (18%) of the minor *P*-epimer (R_f = 0.50) and 3.0 g (53%) of the major *P*-epimer (R_f = 0.40) as colorless oils **4b**. C$_\alpha$-epimeric mixture of **4b**: ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.77 (≈d, ^3J(H,H) = 6.7 Hz, 3H; C*H*$_3$-CH), 3.57 (m, 1H, C*H*-N), 4.10 + 4.47 (2 × ≈dd, 2H, C*H*$_2$-Ph, ABX system), 5.43 + 5.60 (2 × ≈d, ^3J(H,H) = 6.6 Hz, 1H, C*H*-O), 6.25 (≈d, ^3J(P,H) = 9.6 Hz, 1H; C$_\alpha$-H), 7.0–7.7 (m, 15H$_{arom}$). ^{31}P NMR ($CDCl_3$): δ = 18.03/18.69 (2s); $C_{24}H_{23}N_2O_3P$ (418.43): calcd C 68.89, H 5.54, N 6.69; found C 68.75, H 5.47, N 6.55.

(1′*R*/*S*,2*R*,4*S*,5*R*)-2-[(1′-Cyano-1′-phenyl)methoxy]-4-methyl-3(1′-methylethyl)-5-phenyl-1,3,2-oxazaphospholidin-2-one (**4c**): Preparation from **2c** (minor *P*-epimer) (1.80 g, 6.58 mmol), benzaldehyde cyanohydrin (0.83 mL, 0.92 g, 6.91 mmol, 1.05 equiv), and triethylamine (1.00 mL, 0.73 g,

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7.24 mmol, 1.1 equiv) in dichloromethane (0.15 L). Chromatography of the crude product over silica gel (toluene/acetone 15:1) gave 1.04 g (43%) of a colorless oil **4c**. C_α-epimeric mixture of **4c**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 0.85$ ($\approx$d, ^3J(H,H) = 6.4 Hz, 3H; C*H*$_3$-CH), 1.13 +1.24 +1.38 +1.53 (4d, ^3J(H,H) = 6.8 Hz, 6H, $(CH_3)_2$CH), 3.1–4.1 (m, 2H, C*H*-N +C*H*(Me)$_2$), 5.57 +5.64 (2 × $\approx$d, ^3J(H,H) = 5.7/7.5 Hz, 1H, C*H*-O), 6.26 +6.32 (2 × $\approx$d, ^3J(P,H) = 9.3/10.2 Hz, 1H; C_α-H), 7.0–7.83 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 15.93/16.56$ (2s).

(1′*R*/*S*,2*S*,4*S*,5*S*)-2-[1′-Cyano-1′-phenylmethoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (4d): Phosphoroxychloride (29 mL, 47.7 g, 0.31 mol, 1.0 equiv) was added slowly over 30 min to a solution of (+)-pseudoephedrine (51.15 g, 0.31 mol) and triethylamine (100 mL, 0.72 mol, 2.3 equiv) in dichloromethane (1 L) at 0 °C. The ice-bath was removed, and the reaction mixture was stirred at room temperature for 3 h. Triethylamine (54 mL, 39.3 g, 0.39 mol, 1.25 equiv) and benzaldehyde cyanohydrin (49 mL, 75 g, 0.56 mol, 1.82 equiv) were added, and the reaction mixture was stirred overnight at room temperature. To eliminate triethylamine hydrochloride and excess cyanohydrin, the reaction mixture was extracted with aqueous NaOH (500 mL, 1 N), and the organic phase was dried over magnesium sulfate, filtered, and evaporated to dryness. The crude product obtained (120 g) was recrystallized from hot acetone /toluene (1:6). The mother liquor was evaporated slowly and the precipitated product was filtered off giving a total yield of 60 g of light yellow crude product. This was recrystallized from ethylacetate/petroleum ether 60–80 (1:1, 700 mL) and gave 48.3 g (0.14 mol, 45.5%) of enantiomerically and analytically pure, colorless **4d**. M.p. 121 °C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.19$ +1.21 (2d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 2.30 +2.71 (2d, ^3J(P,H) = 11.1 Hz, 3H; C*H*$_3$-N), 3.31 (dq, ^3J(H,H) = 6.2/8.8 Hz, 1H; C*H*-N), 4.90 +4.92 (2dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.9 Hz, 1H; C*H*-O), 6.20 +6.32 (2d, ^3J(P,H) = 9.5 Hz, 1H; C_α-H), 7.10–7.85 (m, 10H$_{arom}$). IR (KBr): $\tilde{\nu}$ = 3045 (Ar), 2920 (CH_3), 1490 (Ar), 1450 (CH_3), 1375 +1348 (CH_3), 1260 (P=O), 1045 (P–O), 980 (P–N), 760 +730 cm^{-1} (C_6H_5); ^{31}P NMR ($CDCl_3$): $\delta = 19.04/19.49$ (2s); $C_{18}H_{19}N_2O_3P$ (342.33): calcd C 63.15, H 5.59, N 8.18; found C 62.93, H 5.64, N 8.16.

General procedure for the alkylation of 4: Compound **4** (500 mg, 1.46 mmol) was dissolved in a dry Schlenk tube under argon in abs. THF (ca. 20 mL). The solution was cooled to −78 °C, and *n*-butyllithium (1.6 N solution in hexane, 1.1 mL, 1.7 mmol, 1.2 equiv) was added dropwise during 5 min, until the color had changed from the light yellow monoanion to the orange dianion. After 20 min, DMPU (0.09 mL, 1.5 mmol, 1 equiv) was added, and the reaction mixture was stirred for another 20 min at −78 °C. Subsequently the neat electrophile (1.3 equiv; see Table 1) was injected by means of a syringe within a few seconds, and the solution was stirred for anoher 3–6 h at −78 °C. When less reactive electrophiles were used, the reaction mixture was allowed to warm to room temperature overnight. The alkylation was then quenched with saturated aqueous ammonium chloride (10 mL), and water (5 mL) was added in order to dissolve some precipitated ammonium chloride. The organic layer was separated, extracted with THF (10 mL), and the combined organic phases were dried over magnesium sulfate. After filtration and evaporation to dryness a light yellow solid was obtained. The ^{1}H NMR spectrum was used to show that complete conversion had taken place and to measure the diastereomeric excess. For further purification the crude product was either recrystallized from toluene/acetone or chromatographed over silica gel (0.04–0.063 mm) with the same solvent mixture as eluent. Analytically pure, crystalline solids **5** were obtained; oils normally crystallized during the following weeks.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-phenyl)but-3′-enoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5a): Yield 47.0%; (*R*):(*S*) = 95:5 (90% *de*); M.p. 147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (d, ^3J(H,H) = 6.0 Hz, 3H; C*H*$_3$-CH), 2.56 (d, ^3J(P,H) = 11.2 Hz, 3H; C*H*$_3$-N), 3.08 +3.33 (2dd, J = 7.0/13.9 Hz, 2H; C*H*$_2$-CH=), 3.39 (dq, ^3J(H,H) = 5.9/8.8 Hz, 1H, C*H*-N), 4.89 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.7 Hz, 1H; C*H*-O), 5.20–5.28 (m, 2H; CH_2=), 5.60–5.75 (m, 1H; -C*H*=), 7.29–7.65 (m, 10H$_{arom}$); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 15.58$ (d, ^3J(P,C) = 9.5 Hz, CH_3-C), 28.13 (d, ^2J(P,C) = 4.0 Hz, CH_3-N), 46.63 (d, ^3J(P,C) = 4.5 Hz, CH_2), 61.45 (d, ^2J(P,C) = 12.4 Hz, CH-N), 78.94 (d, ^2J(P,C) = 9.7 Hz, C_α), 85.62 (s, CH-O); 118.12 (d, ^3J(P,C) = 3.9 Hz, CN), 121.93 (s, CH_2=), 125.81, 126.85, 128.68, 128.76 (4s, 8C_{arom}, 2*o* +2*m*), 129.19, 129.37, 129.65 (3s, 3C, 2*p* +-CH=), 136.59 (d, ^3J(P,C) = 6.8 Hz, $C_{q,arom}$), 136.74 (d, ^3J(P,C) = 5.0 Hz, $C_{q,arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 15.21$ (s); HREIMS calcd for $C_{21}H_{23}N_2O_3P$ 382.1446, found 382.1454; $C_{21}H_{23}N_2O_3P$ (382.40): calcd C 65.96, H 6.06, N 7.33; found C 65.58, H 5.80, N 7.36.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-phenyl)ethoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5b): Yield 69.2%; (*R*):(*S*) = 91.5:8.5 (83% *de*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$ (d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 2.23 (s, 3H; C*H*$_3$-C-CN), 2.61 (d, ^3J(P,H) = 11.4 Hz, 3H; C*H*$_3$-N), 3.38 (dq, ^3J(H,H) = 6.2/8.8 Hz, 1H; C*H*-N), 4.93 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.9 Hz, 1H; C*H*-O), 7.32–7.67 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 15.72$ (s); HREIMS calcd for $C_{19}H_{21}N_2O_3P$ 356.1290, found 356.1298; $C_{19}H_{21}N_2O_3P$ (356.36): calcd C 64.04, H 5.94, N 7.86; found C 63.78, H 5.94, N 7.68.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-phenyl)butoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5c): Yield 58.0%; (*R*):(*S*) = 91:9 (82% *de*); M.p. 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (t, ^3J(H,H) = 7.3 Hz, 3H; CH_3-CH_2), 1.19 (d, ^3J(H,H) = 6.1 Hz, 3H; C*H*$_3$-CH), 1.2–1.6 (m, 2H; C*H*$_2$-CH_3), 2.28 +2.54 (2ddd, J = 4.7/12.8/12.8 Hz, 2H; C*H*$_2$-C_α), 2.56 (d, ^3J(P,H) = 11.1 Hz, 3H; C*H*$_3$-N), 3.41 (dq, ^3J(H,H) = 6.2/8.8 Hz, 1H, C*H*-N), 4.89 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.7 Hz, 1H; C*H*-O), 7.28–7.65 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 15.89$ (s); $C_{21}H_{25}N_2O_3P$ (384.41): calcd C 65.61, H 6.56, N 7.29; found C 65.87, H 6.72, N 7.15.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-phenyl)but-3′-inoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5d): Yield 65.0%; (*R*):(*S*) = 91:9 (82% *de*); M.p. 114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (d, ^3J(H,H) = 6.0 Hz, 3H; C*H*$_3$-CH), 2.14 (t, ^4J(H,H) = 2.6 Hz, 1H; C*H*=), 2.62 (d, ^3J(P,H) = 11.4 Hz, 3H; C*H*$_3$-N), 3.30 +3.57 (2dd, J = 2.6/16.6 Hz, 2H; C*H*$_2$-C=), 3.40 (dq, ^3J(H,H) = 6.1/8.8 Hz, 1H, C*H*-N), 4.90 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.9 Hz, 1H; C*H*-O), 7.33–7.71 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 15.52$ (s); $C_{21}H_{21}N_2O_3P$ (380.37): calcd C 66.31, H 5.56, N 7.36; found C 66.49, H 5.62, N 7.33.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′,4′-diphenyl)ethoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5e): Yield 58.0%; (*R*):(*S*) = 91:9 (82% *de*); M.p. 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (d, ^3J(H,H) = 6.1 Hz, 3H; C*H*$_3$-CH), 2.50 (d, ^3J(P,H) = 11.1 Hz, 3H; C*H*$_3$-N), 3.40 (dq, ^3J(H,H) = 6.1/8.9 Hz, 1H, C*H*-N), 3.44 (dd) +3.80 (d) (J = 1.2/13.4 +13.6 Hz, 2H; C*H*$_2$-Ph), 4.89 (dd, ^3J(H,H) = 8.9 Hz, ^3J(P,H) = 2.7 Hz, 1H; C*H*-O), 7.08–7.52 (m, 15H$_{arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 14.91$ (s); HREIMS calcd for $C_{25}H_{25}N_2O_3P$ 432.1603, found 432.1607; $C_{25}H_{25}N_2O_3P$ (432.46): calcd C 69.43, H 5.82, N 6.48; found C 69.11, H 5.92, N 6.32.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′,4′-diphenyl)butoxy)]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5f): Yield 54%; (*R*):(*S*) = 90:10 (80% *de*); M.p. 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (d, ^3J(H,H) = 6.0 Hz, 3H; C*H*$_3$-CH), 1.58–1.93 (m, 2H, C*H*$_2$-Bn), 2.36 +2.62 (2 × $\approx$ddd, 2H, C*H*$_2$-C_α), 2.54 (d, ^3J(P,H) = 11.1 Hz, 3H, C*H*$_3$-N),2.52–2.75 (m, 2H, C*H*$_2$-Ph), 3.39 (dq, ^3J(H,H) = 6.1/8.7 Hz, 1H, C*H*-N), 4.89 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.6 Hz, 1H; C*H*-O), 7.05–7.60 (m, 15H$_{arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 15.21$ (s); $C_{27}H_{29}N_2O_3P$ (460.51): calcd C 70.42, H 6.35, N 6.08; found C 70.12, H 6.27, N 5.93.

(1′*R*,2*S*,4*S*,5*S*,4″*R*,6″*S*)-2-[(1′-Cyano-(7″,7″-dimethyl-bicyclo[3.1.1]hept-1″-enyl)-1′-phenyl)ethoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5g): Yield 58%; (*R*):(*S*) = 74:26 (48% *de*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.73$ (s, 3H, CH_3), 0.96 (d, ^3J(H,H) = 8.6 Hz, 2H; CH_2-CH), 1.09 (s, 3H, CH_3), 1.17 (d, ^3J(H,H) = 6.1 Hz, 3H; C*H*$_3$-CH), 1.90–2.34 (m, 4H, 2CH, CH_2), 2.54 (d, ^3J(P,H) = 11.4 Hz, 3H; C*H*$_3$-N), 2.90 +3.42 (d, J = 13.4 Hz, 2H; C*H*$_2$-C_α), 3.37 (dq, ^3J(H,H) = 5.9/8.8 Hz, 1H, C*H*-N), 4.88 (dd, ^3J(H,H) = 8.9 Hz, ^3J(P,H) = 2.5 Hz, 1H; C*H*-O), 5.53 (s, 1H$_{olef}$), 7.30–7.67 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): $\delta = 15.84$ (s); $C_{18}H_{33}N_2O_3P$ (476.56): calcd C 70.57, H 6.98, N 5.88; found C 66.01, H 6.67, N 5.58.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-phenyl)nonoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5h): Yield 48%; (*R*):(*S*) = 90.5:9.5 (81% *de*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, ^3J(H,H) = 7.0 Hz, 3H; C*H*$_3$-CH_2), 1.18 (d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 1.18 1.58 (m, 12H, $(CH_2)_6$) 2.30 +2.54 (2 × $\approx$ddd, 2H; C*H*$_2$-C_α), 2.56 (d, ^3J(P,H) = 11.1 Hz, 3H, C*H*$_3$-N), 3.40 (dq, ^3J(H,H) = 6.2/8.8 Hz, 1H, C*H*-N), 4.90 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.6 Hz, 1H; C*H*-O), 7.26–7.65 (m, 10H$_{arom}$);

^{31}P NMR ($CDCl_3$): δ = 15.83 (s); $C_{26}H_{35}N_2O_3P$ (454.55): calcd C 68.70, H 7.76, N 6.16; found C 67.67, H 7.82, N 5.76.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-phenyl-4′-methyl)pent-3′-enoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5i): Yield 40.0%; (*R*):(*S*) = 97:3 (94% *de*); M.p. 121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, ^3J(H,H) = 6.2 Hz, 3H; CH_3-CH), 1.52 (s, 3H; CH_3-C=), 1.67 (s, 3H; CH_3-C=), 2.58 (d, ^3J(P,H) = 11.2 Hz, 3H; CH_3-N), 3.00 + 3.31 (2dd, J = 7.4/14.3 Hz, 2H; CH_2-C$_\alpha$), 3.39 (dq, ^3J(H,H) = 6.1/8.8 Hz, 1H, C*H*-N), 4.90 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.6 Hz, 1H; C*H*-O), 5.07 (thept, J = 1.4/7.4 Hz, 1H; C*H*=), 7.29–7.65 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): δ = 15.91 (s); $C_{25}H_{25}N_2O_3P$ (410.45): calcd C 67.30, H 6.63, N 6.83; found C 67.34, H 6.72, N 6.94.

(1′*R*,2*S*,4*S*,5*S*)-2-[(3′-Bromo-1′-cyano-1′-phenyl)but-3′-enoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5k): Yield 43%; (*R*):(*S*) = 85.5:14.5 (71% *de*); M.p. 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, ^3J(H,H) = 6.2 Hz, 3H; CH_3-CH), 2.61 (d, ^3J(P,H) = 11.2 Hz, 3H; CH_3-N), 3.38 + 3.74 (2d, J = 14.8 Hz, 2H; CH_2-C$_\alpha$), 3.43 (dq, ^3J(H,H) = 6.2/8.8 Hz, 1H, C*H*-N), 4.91 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.5 Hz, 1H; C*H*-O), 5.68 (d, ^1J(H,H) = 2.1 Hz, 1H, CH_{cis}), 5.84 (C*H*-O), 5.68 (d, ^1J(H,H) = 2.1 Hz, 1H, CH_{trans}), 7.32–7.70 (m, 10H$_{arom}$); ^{31}P NMR ($CDCl_3$): δ = 15.93 (s); $C_{21}H_{22}N_2O_3PBr$ (461.28): calcd C 54.68, H 4.81, N 6.07; found C 54.62, H 4.87, N 6.05.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′,4′-diphenyl)but-3′-enoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5l): Yield 44.8%; (*R*):(*S*) = 95:5 (90% *de*); M.p. 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, ^3J(H,H) = 6.0 Hz, 3H; CH_3-CH), 2.57 (d, ^3J(P,H) = 11.2 Hz, 3H; CH_3-N), 3.25 + 3.44 (2ddd, J = 7.0/13.5/14.0 Hz, 2H; CH_2-C$_\alpha$), 3.39 (dq, ^3J(H,H) = 6.0/8.8 Hz, 1H, C*H*-N), 4.90 (dd, ^3J(H,H) = 8.8 Hz, ^3J(P,H) = 2.6 Hz, 1H; C*H*-O), 6.03 (dt, J = 7.3/15.8 Hz, 1H$_{olef}$; =C*H*-CH$_2$), 6.55 (d, ^3J(H,H) = 15.8 Hz, 1H$_{olef}$; =C*H*-Ph), 7.21–7.65 (m, 15H$_{arom}$); ^{31}P NMR ($CDCl_3$): δ = 16.09 (s); $C_{27}H_{27}N_2O_3P$ (458.50): calcd C 70.73, H 5.94, N 6.11; found C 70.57, H 6.05, N 6.18.

5m und 5n: Preparation according to general procedure, but from **4b** and **4c** and without DMPU. After workup and purification the colorless oils **5m** and **5n** were obtained.

(1′*S*,2*R*,4*S*,5*R*)-2-[(1′-Cyano-1′-phenyl)ethoxy]-3-benzyl-4-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (5m): Yield 56%; (*R*):(*S*) = 60:40 (20% *de*); ^{1}H NMR (90 MHz, $CDCl_3$, epimeric mixture): δ = 0.72 (d, ^3J(H,H) = 6.3 Hz, 3H; CH_3-CH), 2.13 + 2.17 (2s, 3H, CH_3-CHPh), 3.57 (m, 1H, C*H*-N), 3.8–4.5 (2 × ≈ddd, 2H, CH_2-Ph, ABX system), 5.41–5.60 (m, 1H; C*H*O), 7.0–7.7 (m, 15H$_{arom}$). ^{31}P NMR ($CDCl_3$): δ = 14.95 (s).

(1′*R*/*S*,2*R*,4*S*,5*R*)-2-[(1′-Cyano-1′-phenyl)ethoxy]-4-methyl-3(1′-methylethyl)-5-phenyl-1,3,2-oxazaphospholidin-2-one (5n): Yield 65%; (*R*):(*S*) = 52.5:47.5 (5% *de*); ^{1}H NMR (90 MHz, $CDCl_3$, epimeric mixture): δ = 0.75 + 0.78 (2d, ^3J(H,H) = 6.3 Hz, 3H; CH_3-CH), 1.20 + 1.25 + 1.38 + 1.39 (4d, 6H, ^3J(H,H) = 6.1 Hz, $(CH_3)_2$CH), 2.13 + 2.14 (2s, 3H, CH_3), 3.13–3.96 (m, 2H, C*H*N + C*H*Me$_2$), 5.45 (≈d, 1H; ^3J(H,H) = 5.7 Hz, C*H*O), 7.0–7.7 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): δ = 14.21 + 14.45 (2s).

General procedure for the cleavage of 5 to ketone cyanohydrins 6: Under nitrogen the cyanohydrin phosphate **5** (1.0 mmol) was dissolved in abs. THF (20 mL). Titanium chloride triisopropoxide (1.0 M solution in hexane, 4.0 mL, 4 equiv) was then added at room temperature. The mixture was stirred for 3 h at room temperature, water (20 mL) was added under nitrogen, and the two-layer system was vigorously stirred for another 3 h at room temperature. After phase separation, drying over magnesium sulfate, and evaporation of the solvent, the free tertiary cyanohydrin **6** was filtered over silica gel (toluene/acetone 10:1; often a small amount of the cyanohydrin was cleaved back to the parent ketone (≈5%), but racemization never occurs). From the aqueous phase the titanium salt was precipitated as the hydroxide by addition of aqueous NaOH (ca. 5 mL, 1 N, pH = 9), and the filtrate was evaporated to dryness. The obtained material (**7**) was hydrolyzed for 2 d at 80 °C with 5 N HCl and afforded, after neutralisation with NaOH (pH ≈ 10) and extraction of the alkaline aqueous phase with dichloromethane, free (+)-pseudoephedrine, which was again extracted for 3 h with the fourfold amount of water to remove traces of (+)-ephedrine. The optical purity was determined by highfield NMR and exceeded 97% *de*.

(*R*)-2-Hydroxy-2-phenyl-4-pentenonitrile (6a): Yield 79.3%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.73 (d, ^3J(H,H) = 7.5 Hz, 2H; CH_2), 3.64 (brs, 1H; OH), 5.0–5.4 + 5.6–6.1 (m, 3H$_{allyl}$), 7.2–7.7 (m, 5H$_{arom}$); MS (70 eV): *m/z* (%): 173 (6) [M^+], 146 (24) [M^+ − HCN], 132 (100) [M^+ − C_3H_5], 105 (98) [Ph-CO$^+$], 41 (11) [$C_3H_5^+$].

(*R*)-2-Hydroxy-2-phenylpropanonitrile (6b): Yield 65.5%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.80 (s, 3H; CH_3), 4.18 (brs, 1H; OH), 7.2–7.6 (m, 5H$_{arom}$); MS (70 eV): *m/z* (%): 147 (31) [M^+], 132 (100) [M^+ − CH_3], 120 (14) [M^+ − HCN], 105 (51) [Ph-CO$^+$].

(*R*)-2-Hydroxy-2-phenylpentanonitrile (6c): Yield 91.9%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.93 (t, ^3J(H,H) = 7.5 Hz, 3H; CH_3), 1.2–2.2 (m, 4H; $(CH_2)_2$), 3.46 (brs, 1H; OH), 7.3–7.7 (m, 5H$_{arom}$); MS (70 eV): *m/z* (%): 175 (21) [M^+], 148 (4) [M^+ − HCN], 132 (100) [M^+ − C_3H_7], 105 (45) [Ph-CO$^+$], 43 (11) [$C_3H_7^+$].

(*R*)-2-Hydroxy-2-phenyl-4-pentinonitrile (6d): Yield 72%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.24 (t, ^4J(H,H) = 2 Hz, 1H; C*H*=), 2.92 (d, ^4J(H,H) = 2 Hz, 2H; CH_2-C=), 4.15 (s, 1H; OH), 7.3–7.7 (m, 5H$_{arom}$) MS (70 eV): *m/z* (%): 171 (1.9) [M^+], 144 (5) [M^+ − HCN], 132 (100) [M^+ − C_3H_3], 105 (88) [Ph-CO$^+$], 39 (10) [$C_3H_3^+$].

(*R*)-2-Hydroxy-2,3-diphenylpropanonitrile (6e): Yield 84.6%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.20 (s, 2H; CH_2), 4.25 (brs, 1H; OH), 6.9–7.6 (m, 5H$_{arom}$); MS (70 eV): *m/z* (%): 223 (3) [M^+], 196 (8) [M^+ − HCN], 132 (11) [M^+ − C_7H_7], 105 (100) [Ph-CO$^+$], 91 (63) [$C_7H_7^+$].

(*R*)-2-Hydroxy-2,5-diphenylpentanonitrile (6f): Yield 44.2%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.5–2.2 (m, 4H, $(CH_2)_2$), 2.58 (t, ^3J(H,H) = 7.5 Hz, CH_2-Ph), 3.27 (brs, 1H; OH), 7.0–7.6 (m, 10H$_{arom}$); MS (70 eV): *m/z* (%): 250 (0.8) [M^+ − H], 223 (27) [M^+ − H_2CN], 132 (5) [M^+ − C_9H_{11}], 120 (100) [$C_9H_{12}^+$], 105 (72) [Ph-CO$^+$], 91 (63) [$C_7H_7^+$].

(1*R*,4″*R*,6″*S*)-2-Hydroxy-3-(7″,7″-dimethylbicyclo[3.1.1]hept-1″-enyl)-2-phenylpropanonitrile (6g): Yield 57.5%; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH_3), 1.21 (d, ^3J(H,H) = 8.9 Hz, 2H; CH_2-CH), 1.26 (s, 3H, CH_3), 2.05–2.35 (m, 4H, 2CH, CH_2), 2.35–2.47 (m, 1H; CH_2), 2.58 + 2.68 (2d, J = 14.5 Hz, 2H; CH_2-C$_\alpha$), 3.50 (brs, 1H; OH), 5.59 (s, 1H$_{olef}$), 7.30–7.60 (m, 5H$_{arom}$); $C_{18}H_{21}NO$ (267.5) MS (70 eV): *m/z* (%): 266 (2.4) [M^+ − H], 239 (4.0) [M^+ − H_2CN], 135 (16) [M^+ − myrtenyl].

(1*S*,2*S*)-[(2-Methylammonium-1-phenyl)propyl]-(1′-methylethyl)phosphate (7): Yield 95%; ^{1}H NMR (300 MHz, D_2O): δ = 1.10 (d, ^3J(H,H) = 6.2 Hz, 3H; CH_3-CH), 1.26 + 1.37 (2d, ^3J(H,H) = 6.6 Hz, 6H; $(CH_3)_2$CH), 3.01 (s, 3H, CH_3-N), 3.86 (dq, ^3J(H,H) = 6.6/8.7 Hz, 1H, C*H*-N), 4.34 (dh, ^3J(H,H) = 6.4 Hz, ^3J(P,H) = 6.4 Hz, 1H, C*H*Me$_2$), 5.30 (dd, ^3J(H,H) = 8.7 Hz, ^3J(P,H) = 8.7 Hz, 1H, C*H*-O), 7.72 (≈s, 5H$_{arom}$). ^{31}P NMR (D_2O): δ = 0.53 (s).

Determination of the absolute cofiguration of the tertiary cyanohydrins: Cyanohydrin **6b** (200 mg, 1.36 mmol) was suspended in fuming hydrochloric acid (>37%, 1 mL). For 30 min HCl gas was bubbled through the reaction mixture, until it became a clear solution; then it was neutralized with solid sodium carbonate (0.3 g, pH ≈ 7), and the aqueous phase was extracted twice with ethyl acetate. After drying over magnesium sulfate, filtration, and evaporation of the solvent, atrolactamide **8** (120 mg) was obtained as an oil. The crude product was dissolved in dry acetone (0.4 mL), and sulfuric acid monohydrate (0.1 mL) was added slowly at 0 °C. After 24 h of stirring at room temperature, water (1 mL) was added. The reaction mixture was extracted three times with diethyl ether. After drying over magnesium sulfate, filtration, and evaporation of the solvent in vacuo, (5*R*)-5-methyl-5-phenyl-1,3-oxazolidin-4-one **9** (140 mg, 0.68 mmol, 50%) was obtained as a light yellow solid. One single recrystallization from hexane/acetone afforded colorless crystals (24 mg). $[\alpha]_{546}^{20}$ = + 38.3 (*c* = 1.2, acetone); ref. [16]: +39 (*c* = 0.64; acetone). $[\alpha]_{625}^{20}$ = + 51.8 (*c* = 1.2, acetone); ref. [16]: + 53 (*c* = 0.64; acetone).

Experiments for the determination of the enantiomeric purity of the tertiary cyanohydrins 6b und 6e: Cyanohydrin **6b** (20 mg) and (4*R*,5*R*)-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) (120 mg) were dissolved in $CDCl_3$ (0.7 mL), and the following ^{1}H NMR spectrum was recorded (300 MHz, $CDCl_3$): δ = 1.00 (s, 6H, $(CH_3)_2$C), 1.74 + 1.76 (s, 3H, CH_3-

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C-CH), 2.4–4 (brs, 1H, *HO*-C-CN), 4.43 (s, 2H, HO-C(Ph)$_2$), 4.55 (s, 2H, *H*-C), 7.20–7.54(m, 25H$_{arom}$). The shift difference between the (*R*) and (*S*) enantiomers of the cyanohydrins is 0.02 ppm. The (*R*)-cyanohydrin gives the signal at lower field (here 1.76 ppm). The same is true for the benzylic methylene singlet of cyanohydrin **6e**.

(2*R*,4*S*,5*R*)-2-Cyanomethoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (12a): Formaldehyde cyanohydrin (0.24 mL, 0.26 g, 4.68 mmol, 1.1 equiv) was slowly added at room temperature over 30 min to a solution of **2a** (1.00 g, 4.25 mmmol) and triethylamine (0.65 mL, 0.47 g, 4.68 mmol, 1.1 equiv) in dichloromethane/diethyl ether (1:1, 40 mL). The reaction mixture was stirred at room temperature overnight. After filtration of the ammonium salt and evaporation to dryness, a colorless crude product was obtained. Chromatography over silica gel (toluene/acetone 8:1) afforded 0.50 g (77%) colorless crystals. ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 0.79$ (d, ^3J(H,H) = 6.6 Hz, 3H; C*H*$_3$-CH), 2.75 (d, ^3J(P,H) = 10.2 Hz, 3H; C*H*$_3$-N), 3.72 (ddq, ^3J(H,H) = 6.5/6.5 Hz, ^3J(P,H) = 18.9 Hz, 1H; C*H*-N), 4.74 +4.88 (2× ≈dd, 2H; C*H*$_2$-O, ABX system), 5.64 (dd, ^3J(H,H) = 1.5/6.6 Hz, 1H; C*H*O), 7.0–7.6 (m, 5H$_{arom}$).

(2*S*,4*S*,5*S*)-2-Cyanomethoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (12b): Phosphoroxychloride (1.80 mL, 3.07 g, 20.0 mmol, 1 equiv) was slowly added over 30 min to a solution of (+)-pseudopehedrine (3.30 g, 20.0 mmol) and triethylamine (6.1 mL, 4.45 g, 44.0 mmol, 2.2 equiv) in dichloromethane (50 mL) at −5 °C. The reaction mixture was stirred overnight at 10 °C. Then triethylamine (3.1 mL, 2.23 g, 22.0 mmol, 1.1 equiv) was added, followed by a solution of formaldehyde cyanohydrin (1.0 mL, 1.14 g, 20.0 mmol, 1.0 equiv) in diethyl ether (20 mL). After another 24 h the ammonium salts were filtered off, and the filtrate was evaporated to dryness. The light yellow crude product was recrystallized from toluene/acetone (4:1) and afforded 2.48 g (48%) light yellow crystals. These contained a 5:1 mixture of *P*-epimers and were recrystallized once more from toluene. *P*-epimerically pure product was obtained (1.40 g, 27%). ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.21$ (d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 2.64 (d, ^3J(P,H) = 11.4 Hz, 3H; C*H*$_3$-N), 3.38 (dq, ^3J(H,H) = 6.2/9 Hz, 1H; C*H*-N), 4.74 +4.90 (2× ≈dd, 2H; C*H*$_2$O, ABX system), 4.92 (dd, ^3J(H,H) = 3/8.9 Hz, 1H; C*H*O), 7.38 (≈s, 5H$_{arom}$).

General procedure for the alkylation and acylation of the cyanohydrin phosphates 4a and 4d with new electrophiles to give products 13–17 (see Scheme 8): Compounds **4a** or **4d** (500 mg, 1.46 mmol) were dissolved in a dry Schlenk tube under argon in abs. THF (ca. 20 mL). The solution was cooled to −78 °C, and *n*-butyllithium (1.6N solution in hexane, 1.1 mL, 1.7 mmol, 1.2 equiv) was added slowly over 5 min, until the color changed from light yellow (monoanion) to orange (dianion). After stirring for 20 min, DMPU (0.09 mL, 1.5 mmol, 1 equiv) was added dropwise, and the reaction mixture was stirred for another 20 min at −78 °C. The neat electrophile (1.3 equiv) was then injected within a few seconds by means of a syringe, and the reaction mixture was stirred for another 3–6 h at −78 °C. When **14** was prepared, methylbromoacetate was added at −100 °C, followed by stirring overnight at −100 °C. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and water (5 mL) was added in order to dissolve some precipitated ammonium chloride. The organic layer was separated, the aqueous layer was extracted with THF (10 mL), and the combined organic layers were dried over magnesium sulfate. After filtration and evaporation of the solvent, a solid, light yellow crude product was obtained. The ^{1}H NMR spectrum was used show that complete conversion had taken place and to measure the diastereomeric excess. For further purification the crude product was chromatographed with toluene/acetone (2–5:1) over silica gel (0.04–0.063 mm). Oily products were initially obtained, which often crystallized during the following weeks.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′,2′-diphenyl-2′-oxo)methoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (13): Yield 52%; M.p. 35 °C; (*R*):(*S*) = 91:9 (82% *de*); ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.17$ (d, ^3J(H,H) = 6.6 Hz, 3H; C*H*$_3$-CH), 2.67 (d, ^3J(P,H) = 12 Hz, 3H; C*H*$_3$-N), 3.33 (dq, ^3J(H,H) = 6.6/9 Hz, 1H; C*H*-N), 4.83 (dd, ^3J(H,H) = 6.6 Hz, ^3J(P,H) = 4.2 Hz, 1H; C*H*-O), 7.1–8.2 (m, 15H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 16.42$ (s).

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-2′-methoxycarbonyl-1′-phenyl)ethoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (14): Yield 53%; (*R*):(*S*) = 83:17 (66% *de*); M.p. 114 °C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.16$ (d, ^3J(H,H) = 6.6 Hz, 3H; C*H*$_3$-CH), 2.57 (d, ^3J(P,H) = 11.1 Hz, 3H; C*H*$_3$-N), 3.36 (dq, ^3J(H,H) = 6.6/8.7 Hz, 1H; C*H*-N), 3.57 (s, 3H; OC*H*$_3$), 3.70 (≈dd, 2H, C*H*$_2$, ABX system), 4.83 (dd, ^3J(H,H) = 8.3 Hz, ^3J(P,H) = 3 Hz, 1H; C*H*-O), 7.1–7.8 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 15.73$ (s); $C_{21}H_{23}N_2O_5P$ (414.40): calcd C 60.87, H 5.59, N 6.76; found C 60.67, H 5.69, N 6.55.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′(3″-oxoyclopentyl)-1′-phenyl)methoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (15a): Yield 53% (*dr* = 74:22:3:<1); M.p. 130 °C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.19$ (d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 1.8–2.7 (m, 3C*H*$_2$ +C*H*$_\beta$), 2.53 (d, ^3J(P,H) = 11 Hz, 3H; C*H*$_3$-N), 3.47 (dq, ^3J(H,H) = 6.2/9 Hz, 1H; C*H*-N), 4.88 (dd, ^3J(H,H) = 9 Hz, ^3J(P,H) = 2.4 Hz, 1H; C*H*-O), 7.2–7.7 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 15.82$ (s); HREIMS calcd for $C_{23}H_{25}N_2O_4P$ 424.1552; found 424.1549.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′(3″-oxoyclohexyl)-1′-phenyl)methoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (15b): Yield 61% (*dr* = 72:23:4:<1); ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.18$ (d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 1.5–2.5 (m, 8H, 4C*H*$_2$), 2.48 (d, ^3J(P,H) = 10.8 Hz, 3H; C*H*$_3$-N), 2.67 (m 1H, C*H*$_\beta$), 3.49 (dq, ^3J(H,H) = 6.2/9 Hz, 1H; C*H*-N), 4.88 (dd, ^3J(H,H) = 9 Hz, ^3J(P,H) = 2.4 Hz, 1H; C*H*-O), 7.1–7.65 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 15.63$ (s); $C_{24}H_{27}N_2O_4P$ (438.46): calcd C 65.74, H 6.21, N 6.39; found C 65.53, H 6.32, N 6.29.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-3′-ethoxycarbonyl-2′-methyl-1′-phenyl)propoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (16a): Preparation according to the general procedure, but from **4a** and without DMPU. Yield 55% (*dr* = 80:13:5:<2); M.p. 42 °C; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 0.83$ (d, ^3J(H,H) = 6.3 Hz, 3H; C*H*$_3$-CH), 1.31 (t, ^3J(H,H) = 6.6 Hz, 3H; C*H*$_3$-CH$_2$), 1.45 (d, ^3J(H,H) = 6 Hz, 3H; C*H*$_3$-CH), 2.34 (m, 2H, C*H*$_2$-C), 2.36 (d, ^3J(P,H) = 10.8 Hz, 3H; C*H*$_3$-N), 2.98 (m, 1H, C*H*$_\beta$-CH$_2$), 3.63 (m, 1H; C*H*-N), 4.17 (q, ^3J(H,H) = 6.6 Hz, 2H, C*H*$_2$-CH$_3$), 5.63 (≈d, ^3J(H,H) = 6 Hz, 1H; C*H*O), 7.1–7.8 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 14.97$ (s); $C_{24}H_{29}N_2O_5P$ (456.48): calcd C 63.15, H 6.40, N 6.14; found C 61.32, H 6.50, N 6.05.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-3′-methoxycarbonyl-1′,2′-diphenyl)propoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (16b): Yield 48% (*dr* = 65:22:9:<4); ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 0.71$ (d, ^3J(H,H) = 6.2 Hz, 3H; C*H*$_3$-CH), 2.2–2.7 (m, 2H, C*H*$_2$-C), 2.42 (d, ^3J(P,H) = 10.2 Hz, 3H; C*H*$_3$-N), 3.40 (s, 3H, OC*H*$_3$), 3.57 (m, 1H; C*H*-N), 3.96 (m, 1H, C*H*Ph), 5.57 (≈d, ^3J(H,H) = 6.3 Hz, 1H; C*H*-O), 6.8–7.9 (m, 15H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 15.33$ (s); HREIMS calcd for $C_{28}H_{29}N_2O_5P$ 504.1814; found 504.1814.

(1′*R*,2*S*,4*S*,5*S*)-2-[(1′-Cyano-1′-(2″-methoxycarbonyl)cyclopropyl-1′-phenyl)-methoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (17): Preparation according to the general procedure, but from **4a** and without DMPU. Yield 69% (*dr* = 55:27:12:<6); ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 0.77$ (d, ^3J(H,H) = 6.6 Hz, 3H; C*H*$_3$-CH), 1.3–1.7 (m, 2H, C*H*$_\gamma$), 2.03 (m, 1H, C*H*$_\beta$), 2.3–2.5 (m, 1H, C*H*$_\gamma$), 2.62 (d, ^3J(P,H) = 9.9 Hz, 3H; C*H*$_3$-N), 3.60 (s, 3H, *OCH*$_3$), 3.61 (m, 1H; C*H*-N), 5.62 (≈d, ^3J(H,H) = 6.9 Hz, 1H; C*H*-O), 7.1–7.8 (m, 10H$_{arom}$). ^{31}P NMR ($CDCl_3$): $\delta = 15.78$ (s).

X-ray crystallography:[11] Data were collected at ambient temperature (20 °C) by means of the ω–2θ scan technique in the range of $4 < 2\theta < 60°$. Data were corrected for Lorentz and polarization effects, but no absorption correction was necessary. The structure was solved by direct methods (SHELXS-86). Refinement was carried out for all unique reflections (3769) except for 10 with very negative F^2. Calculations were performed with SHELXS-86 (Sheldrick, 1990), SHELXL-93 (Sheldrick, 1993) and SHELXTL PLUS (Siemens, 1990) on a Digital Equipment VAX station 3200 and a PC. Details of data collection and structure refinement are reported in Table 2.

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