Binolam–AlCl: A Two-Centre Catalyst for the Synthesis of Enantioenriched Cyanohydrin *O*-Phosphates

Alejandro Baeza,[a] Carmen Nájera,*[a] José M. Sansano,[a] and José M. Saá*[b]

Abstract: The enantioselective synthesis of cyanohydrin *O*-phosphates by using in situ generated bifunctional catalysts (*R*)- or (*S*)-3,3′-bis(diethylaminomethyl)-1,1′-binaphthol–aluminium chloride (binolam–AlCl) is reported. The reaction, which can be described as an overall cyano-*O*-phosphorylation of aldehydes, has a wide scope and applicability. Evidence is also provided, including ab initio and DFT calculations, in support of supported by the Lewis acid/Brønsted base (LABB) dual role of the catalyst in inducing first the key enantioselective hydrocyanation, which is then followed by *O*-phosphorylation. A brief screening of the synthetic usefulness of the resulting cyanohydrin *O*-phosphates unveiles some interesting applications. Among them, chemoselective hydrolysis, reduction and palladium-catalysed nucleophilic allyl substitution, thereby leading to enantiomerically enriched α-*O*-phosphorylated α-hydroxy esters, β-amino alcohols and γ-cyanoallyl alcohols, respectively. Naturally occurring (−)-tembamide and (−)-aegeline are synthesised accordingly.

Keywords: aluminum · asymmetric catalysis · binaphthols · cyanohydrins · cyanophosphates

Introduction

Non-racemic cyanohydrins and their derivatives[1] are valuable chiral building blocks for the synthesis of enantiomerically pure compounds such as β-amino alcohols, α-hydroxy carboxylic acids and their derivatives.[1a,2] Both metal catalysts, organocatalysts, and enzymes as well, have been successfully employed for their enantioselective synthesis. Because of their efficiency, the metal complexes of magnesium, aluminium, titanium, yttrium, zirconium and gadolinium deserve special mention, as illustrated in recent reviews.[1a–c] Critical points of these methodologies are: a) the highly toxic nature of trimethylsilyl cyanide and hydrogen cyanide, frequently employed as the cyanide sources, b) the lability of the resulting *O*-TMS cyanohydrins (from the former procedure) which typically undergo partial desilylation under the reaction media and make compulsory a final acidic treatment with the aim of obtaining pure cyanohydrins, and c) the instability of unprotected cyanohydrins, usually requiring immediate *O*-protection in order to ensure their configurational stability. In accordance with this analysis, the direct enantioselective access to *O*-protected cyanohydrins from aldehydes and ketones is an important objective of current research. Deng, for instance, recently described the enantioselective synthesis of *O*-alkoxycarbonyl cyanohydrins by using *Cinchona* alkaloid-derived tertiary amines[3] as catalysts, whereas chiral complexes of yttrium, aluminium or titanium have been employed by Shibasaki,[4] by Nájera and Saá,[5] and by Belokon.[6] The synthesis of enantiomerically enriched *O*-acetyl cyanohydrins has also been investigated for which polymeric,[7a] as well as soluble,[7b–d] titanium-salen/potassium cyanide/acetic anhydride systems have been employed.[7] However, to the best of our knowledge, only two enantioselective synthesis of cyanohydrin *O*-phosphates, have been reported to date starting from aldehydes.[8,9] Noteworthy Schrader employed the cyanohydrin of benzaldehyde linked to a chiral phosphate as a chiral acyl anion equivalent in the enantioselective synthesis of tertiary cyanohydrins.[10] Still more surprising is the fact that, in spite of the apparent importance of *O*-phosphorylated cyanohydrins in nature, very few attempts at their racemic synthesis have

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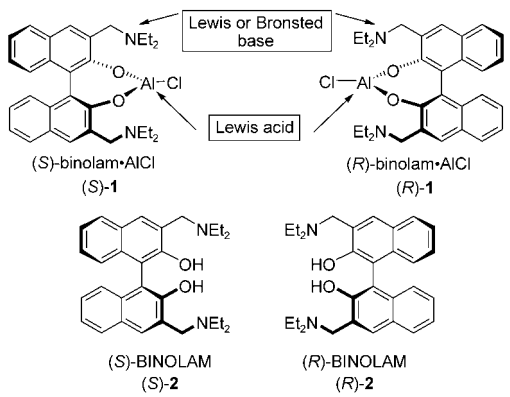
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

 DOI: 10.1002/chem.200401290

been reported. To the best of our knowledge, only the direct synthesis of racemic diethylphosphate esters of cyanohydrins by treatment of aldehydes with a mixture of lithium cyanide and diethyl chlorophosphate or by using excess diethyl cyanophosphonate in the presence of an excess of lithium cyanide, or substoichiometric amounts of lithium diisopropylamine, are known.[11] The applicability of the resulting racemic cyanohydrin *O*-phosphates in synthetic organic chemistry is also scarce, as only elimination reactions have been apparently designed for the preparation of saturated and unsaturated nitriles, indole derivatives and aromatic compounds.[11] Clearly, both the synthesis and applications of enantiomerically enriched cyanohydrin *O*-phosphates was an underdeveloped issue at the outset of our work.

We had recently found that the two-centre catalyst **1** generated from chiral ligand (*S*)-3,3′-bis(diethylaminomethyl)-1,1′-binaphthol [(*S*)-BINOLAM] **2**,[12] which bears two non-annihilating centres acting either as an LALB (Lewis acid/Lewis base) or LABB (Lewis acid/Brønsted base) system capable of activating electrophilic and nucleophilic reagents,[13] is an excellent catalyst for carrying out the enantioselective cyanosilylation[14] and cyanoformylation of aldehydes.[5] Even though both reactions appeared to be quite similar, some subtle differences impeded to clarify their precise LALB or LABB mechanism properly. In particular, the cyanosilylation reaction, which employs TMSCN as cyanation reagent, has been shown to require a low temperature (−30 to −40 °C), and the presence of 4 Å MS and triphenylphosphane oxide as additives, to yield cyanohydrins (after hydrolysis) in good chemical yields and excellent *ee* (up to 99 %).[5,12,14] In contrast, the cyanoformylation reaction, which takes place at room temperature with $NCCO_2Me$ as cyanation reagent, needs the presence of 4 Å MS as the only additive, and yields cyanoformates in lower *ee* (up to 80 %).[5] In the present work,[8] we describe in detail our studies on the enantioselective cyanophosphorylation of aldehydes catalysed by the above mentioned monometallic, two-centre aluminium complexes binolam–AlCl **1**, for which purpose diethyl cyanophosphonate was used as the cyanide source. We also report a number of evidences, together with extensive ab initio and DFT calculations (see below), which suggest that the aluminium complexes binolam–AlCl **1** work as bifunctional LABB catalysts in promoting the enantioselective hydrocyanation, that is, the addition of HCN[15] (not HNC),[16] of the aldehyde, followed by *O*-phosphorylation. In addition, we describe the configurational stability and some synthetic applications of the resulting enantiomerically enriched cyanohydrin *O*-phosphates.



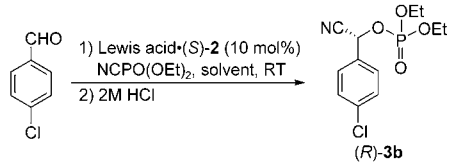
Results and Discussion

Initial studies on the enantioselective cyanophosphorylation of aldehydes were performed by treating *p*-chlorobenzaldehyde with commercial diethyl cyanophosphonate in the presence of the selected catalyst (10 mol %), under different reaction conditions (Table 1). Catalysts were freshly prepared by mixing the ligand (*S*)-BINOLAM **2** and the corresponding Lewis acid at room temperature for one hour in the appropriate solvent. Then, *p*-chlorobenzaldehyde and diethyl cyanophosphonate (3 equiv relative to the aldehyde) were added in one portion at room temperature. The reaction was monitored by GC or ^{1}H NMR spectroscopy and the enantiomeric excess (*ee*) of the product (*R*)-**3b** was determined by chiral HPLC analysis (Chiralpak AD). Its absolute configuration was assigned by comparison (HPLC) with enantiomerically enriched samples prepared by direct *O*-phosphorylation of enantiopure cyanohydrin (*R*) and (*S*)-**4b** (see below).

As depicted in Table 1, best results were achieved when operating with three equivalents of diethyl cyanophosphate and complex (*S*)-binolam–AlCl **1** as catalyst (10 mol %), generated in situ by mixing (*S*)-**2** with commercial dimethylaluminium chloride in anhydrous toluene or THF (Table 1, entries 2–3), at room temperature. Even though both THF and toluene led to excellent results (Table 1, entries 2 and 3), toluene was selected as the ideal solvent because of some marginal advantage during work-up and purification. The reaction did not work properly at lower temperatures as it turn out to be extremely slow. It is worth commenting that, in contrast with that observed for the cyanosilylation of aldehydes catalysed by **1**,[14] which required 4 Å molecular sieves and triphenylphosphane oxide as additives, both additives were found to be deleterious for the cyanophosphorylation reaction (Table 1, entries 4 and 5). We also found that the reaction was somewhat accelerated by employing diethylaluminium cyanide or aluminium methoxide, although at the expense of eroding the enantiomeric excess down to the unacceptable (Table 1, entries 6 and 7). The titanium complex derived from titanium tetraisopropoxide also gave poor *ee* values (Table 1, entry 8) therefore being abandoned too.

Using the optimised reaction conditions mentioned above, we explored the scope of the cyano-*O*-phosphorylation reaction upon a series of aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes. Except for some particular cases (see below), satisfactory enantioselective cyanophosphorylations were obtained as illustrated in Table 2. The enantiomerically enriched cyanohydrin *O*-phosphates **3**

Table 1. Enantioselective cyanophosphorylation of *p*-chlorobenzaldehyde catalysed by performed Lewis acid-(*S*)-BINOLAM **2** complexes.



(*R*)-**3b**

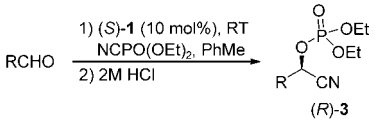
Entry	Lewis acid	Solvent	*t* [h]	Conversion [%][a]	*ee*[b]
1	Me_2AlCl	CH_2Cl_2	19	>98	70
2	Me_2AlCl	THF	24	96	98
3	Me_2AlCl	PhMe	20	>98	96
4	Me_2AlCl[c]	PhMe	48	<15	–
5	Me_2AlCl[d]	PhMe	48	–	–
6	Et_2AlCN	PhMe	7	>98	56
7	Me_2AlOMe	PhMe	0.6	>98	62
8	[Ti(*i*OPr)$_4$]	PhMe	1	>98	24

[a] Determined by ^{1}H NMR spectroscopic analyses after acidic work-up. [b] Determined by HPLC analyses on a chiral phase (Daicel Chiralpak AD). [c] 4 Å Molecular sieves added (7.5% water, 50 mg/0.25 mmol of aldehyde). [d] Triphenylphosphane oxide (20 mol%) added.

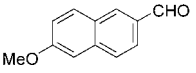
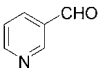
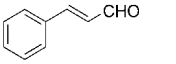
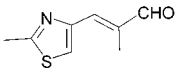
thereby obtained are stable species except for the case of **3c**, that is, that derived from 4-methoxybenzaldehyde, which partially decomposed after purification by flash chromatography. Accordingly, crude **3c** has been used for the synthesis of the naturally occurring (−)-tembamide and (−)-aegeline[1c,17] (see below). In general, aromatic aldehydes with electron-withdrawing substituents reacted at a slower rate than benzaldehyde itself (Table 2, entries 4–10), in agreement with the expected effect of substituents for an acid-catalysed addition to aryl aldehydes. The case of 4-nitrobenzaldehyde is especially notorious because we found also a significant fall of enantioselectivity (Table 2, entry 7), consistent with the importance of the competing racemic process for this case. Also mechanistically relevant is the case of basic heteroaromatic aldehydes (Table 2, entries 11 and 15). Thus, for instance, 3-pyridinecarbaldehyde afforded almost racemic **3h** (Table 2, entry 11), presumably because its basic nitrogen (pK_a 5.2) can capture HCN and therefore interfere the catalytic, enantioselective cycle. Consistent with this view, less basic (pK_a 2.4) thiazole aldehyde[18] (Table 2, entry 15) yielded cyanophosphate **3l** in good yield and *ee*. Cyanophosphate **3l** can be a key building-block in the synthesis of epothilone A.[18,19] Aliphatic as well as α,β-unsaturated aldehydes were found to be suitable starting materials for this reaction giving rise to adducts **3** in very good yields and *ee* (Table 2, entries 12–18), the only exception being that of phenylacetaldehyde, which did not give the expected result, possibly because of its easy enolisation (Table 2, entry 17). Unfortunately, ketones did not react when submitted to the above reaction conditions. As expected for a kinetically-controlled reaction, the use of the (*R*)-**1** aluminium complex (Table 2, entries 2 and 5), instead of (*S*)-**1** (Table 2, entries 1 and 4), led to the opposite enantiomers, namely (*S*)-**3a** and (*S*)-**3b** in identical chemical yield and enantiomeric excess. An additional important feature of the cyanophosphorylation reaction is that the chiral ligand **2** can be easily recovered (93% yield) from the reaction media after extractive acidic work-up, and reused again without loss of stereochemical yield: compound **3a** was actually obtained in 98% *ee* (Table 2, entry 3).[5,8,14] No further recycling has been examined.

In order to determine the absolute configuration of the new chiral cyanohydrin derivatives **3**, we attempted their preparation in enantiomerically pure form by two different methods starting from the corresponding enantiomerically enriched cyanohydrins **4a** and **4o**. The first one called for a direct, and the second for an indirect phosphorylation of these cyanohydrins. Thus, in the former

Table 2. Enantioselective synthesis of enantioenriched cyanohydrin *O*-phosphates **3**.



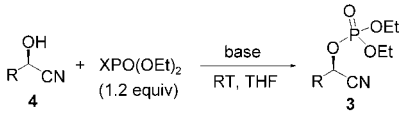
(*R*)-**3**

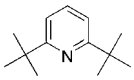
Entry	Aldehyde	*t* [h]	**3**	Yield [%][a]	*ee*[b]
1	PhCHO	4	(*R*)-**3a**	89	98
2	PhCHO	4	(*S*)-**3a**	89[c]	98
3	PhCHO	4	(*R*)-**3a**	89[d]	98
4	4-ClC_6H_4CHO	20	(*R*)-**3b**	88	96
5	4-ClC_6H_4CHO	20	(*S*)-**3b**	88[c]	96
6	4-(MeO)C_6H_4CHO	10	(*R*)-**3c**	87[e]	98
7	4-$(NO_2)C_6H_4CHO$	50	(*R*)-**3d**	87	26
8	3-(PhO)C_6H_4CHO	2	(*R*)-**3e**	90	97[f]
9	2-ClC_6H_4CHO	4	(*R*)-**3f**	89	97
10		1.5	(*R*)-**3g**	91	94
11		24	(*R*)-**3h**	90	4
12	(*E*)-$CH_3CH{=}CHCHO$	2	(*R*)-**3i**	89	88
13	(*E*)-$C_5H_{11}CH{=}CHCHO$	6	(*R*)-**3j**	90	94
14		7	(*R*)-**3k**	82	95[f]
15		4	(*R*)-**3l**	89[g]	90
16	$C_6H_{13}CHO$	3	(*R*)-**3m**	90	98[h]
17	$PhCH_2CHO$	2	(*R*)-**3n**	90	36[i]
18	$PhCH_2CH_2CHO$	2	(*R*)-**3o**	90	92[f]

[a] Isolated yields after acidic hydrolysis and column chromatography (flash silica gel). [b] The *ee* was determined by chiral HPLC analysis (Daicel Chiralpak AD). [c] The reaction was done by using chiral complex (*R*)-**1**. [d] Reaction performed with recovered ligand (*S*)-**1**. [e] Crude pure yield, partial decomposition after flash chromatography occurred. [f] The *ee* was determined by chiral HPLC analysis (Daicel Chiralpak AS). [g] After column chromatography (neutral Al_2O_3). [h] The *ee* was determined by chiral CG analysis (γ-cyclodextrin). [i] The *ee* was determined by chiral HPLC analysis (Daicel Chiralcel OD-H).

method, enantiomerically pure cyanohydrins, derived from benzaldehyde and 3-phenylpropanal, were synthesised by cyanosilylation of the corresponding aldehyde catalysed by (*S*)-binolam–AlCl, followed by acidic hydrolysis,[14] and then allowed to react in THF at room temperature with diethyl chlorophosphate or diethyl cyanophosphonate in the presence of an equivalent of the base (Table 3). It should be mentioned that, in spite of the number and type of bases (e.g., Et_3N, *N*-methylimidazole, pyridine, lutidine) and phosphorylating agents employed (Table 3), partial racemisation was found to be inevitable (Table 3, entries 1–14), thereby lending further credit to our direct, enantioselective cyano-*O*-phosphorylation as a unique method of accessing these kind of compounds. The *N*-methylimidazole (NMI)-promoted *O*-phosphorylation of benzaldehyde with diethyl chlorophosphate caused a low racemisation in the product **3a** (Table 3, entry 3). A similar result was achieved with diethyl cyanophosphonate and pyridine as base (Table 3, entry 7). However, independently of the base used, neither diethyl chlorophosphate nor diethyl cyanophosphonate were suitable reagents to give optically enriched cyanohydrin derivatives **3o** (Table 3, entries 4, 5 and 12–14).

Table 3. *O*-Phosphorylation of chiral cyanohydrins **4** under basic conditions.

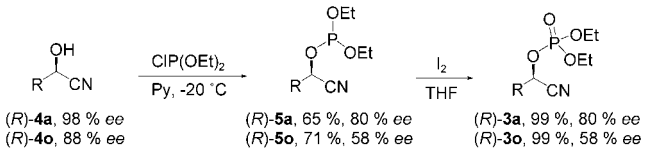


Entry	R	X	**4** (*ee*)	Base	*t* [h]	Yield [%][a]	**3** (*ee*)[b]
1	Ph	Cl	(*R*)-**4a** (98)	Et_3N	24	44	(*R*)-**3a** (48)
2	Ph	Cl	(*R*)-**4a** (98)	Py	24	–	–
3	Ph	Cl	(*R*)-**4a** (98)	NMI	3	>89	(*R*)-**3a** (82)
4	$Ph(CH_2)_2$	Cl	(*R*)-**4o** (88)	Py	22	–	–
5	$Ph(CH_2)_2$	Cl	(*R*)-**4o** (88)	NMI	1.3	83	(*R*)-**3o** (24)[c]
6	Ph	CN	(*R*)-**4a** (98)	Et_3N	1.3	87	(*R*)-**3a** (60)
7	Ph	CN	(*R*)-**4a** (98)	Py	5	88	(*R*)-**3a** (82)
8	Ph	CN	(*R*)-**4a** (98)	NMI	1.3	40	(*R*)-**3a** (80)
9	Ph	CN	(*R*)-**4a** (98)	2,6-lutidine	20	68	(*R*)-**3a** (82)
10	Ph	CN	(*R*)-**4a** (98)	DCMA[d]	2	80	(*R*)-**3a** (76)
11	Ph	CN	(*R*)-**4a** (98)		30	<10	–
12	$Ph(CH_2)_2$	CN	(*R*)-**4o** (88)	Et_3N	1.3	92	(*R*)-**3o** (64)[c]
13	$Ph(CH_2)_2$	CN[e]	(*R*)-**4o** (88)	Py	22	–	–
14	$Ph(CH_2)_2$	CN	(*R*)-**4o** (88)	NMI	24	71	(*R*)-**3o** (62)[c]

[a] Pure cyanohydrin *O*-phosphates isolated after acid hydrolysis and column chromatography. [b] Enantiomeric excess determined by chiral HPLC analysis (Daicel Chiralpak AD). [c] Enantiomeric excess determined by chiral HPLC analysis (Daicel Chiralpak AS). [d] DCMA: dicyclohexylmethylamine. [e] Two equivalents of diethyl cyanophosphonate were used.

We also checked the alternative, indirect route for preparing cyanohydrin *O*-phosphates **3** which calls for forming first the cyanohydrin *O*-phosphites followed by their oxidation with iodine[20] (Scheme 1). We examined this route for cyanohydrins **4a** and **4o**. Again, we found that phosphinoylation with diethyl chlorophosphite, in the presence of a base (triethylamine), led to partially racemised products **5**, which were immediately oxidised cleanly (in good yield and without racemisation), furnishing the desired cyanohydrin *O*-phosphates **3a** or **3o**, respectively (Scheme 1). The *ee* of the intermediate phosphites **5** was also determined by chiral HPLC analysis of a crude product sample (Chiralpak AS).

The absolute configurations given in Table 2 for cyanohydrin *O*-phosphates **3** were assigned by comparison with those prepared by the methods mentioned above. Analysis of the observed absolute configurations served also to write the following *SSR*/*RRS* mnemonic rule for the stereochemical outcome of cyanophosphorylations catalysed by binolam–AlCl: the use of the (*S*)-catalyst promotes the attack of the *Si* face thereby leading to the (*R*)-cyanohydrin derivative, and the opposite: using the (*R*)-catalyst induces the attack of the *Re* face thereby leading to the (*S*)-cyanohydrin derivative.



Scheme 1.

Mechanistic studies: What is the nature of the species formed by mixing equimolar amounts of Me_2AlCl and BINOLAM **2**? ^1H NMR analysis of a recently prepared solution (CD_2Cl_2) showed a single set of sharp signals [two doublets at δ 4.01 and 4.71 ppm, $J = 13.5$ Hz, versus two doublets at 3.82 and 4.10 ppm, $J = 15.0$ Hz observed for the pure (*S*)-BINOLAM] assignable to a symmetric species of the type $(binolam–AlCl)_n$. The ^{27}Al NMR spectrum showed an extremely wide signal centred at 47.0 ppm consistent with a pentacoordinated or rapidly exchanging tetracoordinated aluminium species. During the course of the numerous experiments performed it was observed that the catalytic asymmetric reactions carried out with catalyst prepared with enantiopure (*S*)-BINOLAM **2** took place at a faster pace than those for which we used less pure, or even racemic, **2**. Actually, kinetic measurements showed a catalytic activity of the homochiral (*S*)-**1** complex about eight times greater than that of the racemic complex (Figure 1), a priori consistent with the "reservoir effect" expected for an inactive dimeric (or higher oligomer) species being in equilibrium with the actual

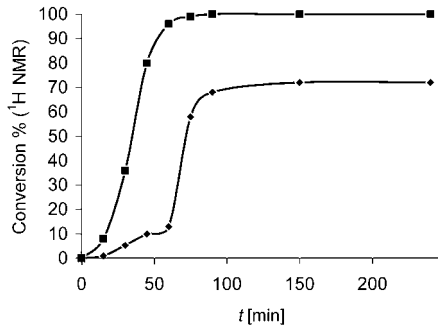


Figure 1. Catalytic activity of the homochiral complex (*S*)-**1** (■) versus the racemic complex (◆) in the cyanophosphorylation of benzaldehyde.

monomeric catalyst, as described by Kagan.[21] In fact, a strong nonlinear effect (NLE)[22] was discovered for the enantioselective cyanosilylation of aldehydes (Figure 2),[23] to the best of our knowledge the first example for an aluminium-based catalytic complex. Hartree–Fock ab initio calcu-

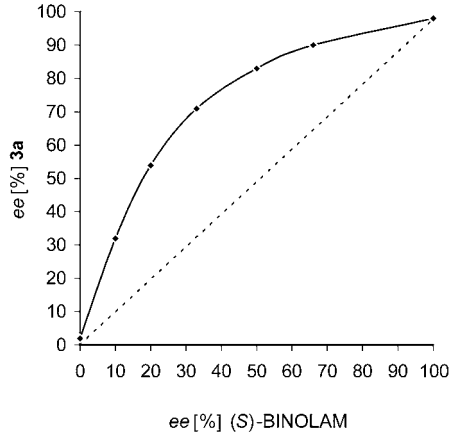
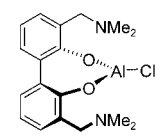
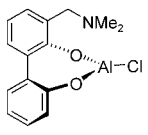


Figure 2. NLE observed in the enantioselective cyanophosphorylation of benzaldehyde.

lations at the HF/6-31G* level carried out for the dimerisation equilibrium of our model catalyst biphelam–AlCl **C** revealed that, in fact, either the homochiral (*aR*,*aR*)$\mathbf{C}_2$, or (*aS*,*aS*)$\mathbf{C}_2$, or the heterochiral (*aR*,*aS*)$\mathbf{C}_2$ dimers are more stable than the corresponding monomers. Unfortunately, at this level of calculation, the homochiral dimers were found to be slightly more stable than the heterochiral dimers, in disagreement with expectations. As expected for the above-mentioned reservoir effect, STO-3G calculations on a further simplified model phelam–AlCl **D** led us to recognise



(*S*)-biphelam•AlCl
C



(*S*)-phelam•AlCl
D

that its homochiral tetramers (*aR*,*aR*,*aR*,*aR*)$\mathbf{D}_4$ are, in fact, less stable than the corresponding heterochiral (*aR*,*aS*,*aR*,*aS*)$\mathbf{D}_4$ tetramers, as shown in Table 4. The enormous size of these species impeded further calculations on them at a higher level.

The bifunctional (either LABB or LALB) character of the presumed monomeric catalyst (binolam–AlCl) **1**, is supported by two facts. First, the presence of a competing external base such as triethylamine (20 mol%), in the cyanophosphorylation of *p*-chlorobenzaldehyde, to the otherwise standard conditions, induced a dramatic drop of enantiomeric excess down to 38% *ee* in **3b** while, at the same time, accelerates the reaction. Second, the absence of the amino function impedes the reaction: the aluminium species derived from commercial (*S*)-BINOL, generated as for the case of (*S*)-BINOLAM, led, for the case of *p*-chlorobenzaldehyde, to the racemic cyanohydrin *O*-phosphate **3b** in very low conversion (10%), after 48 h. This behaviour taken together with the above-mentioned sensitivity of the cyanophosphorylation reaction to the pK_a of basic, heterocyclic aldehydes would tend to suggest that our bifunctional catalyst is likely working as an LABB-type catalyst capable of capturing the carbonyl of an aldehyde (likely acting as a two point linker) by the Lewis acid (LA) moiety,[24] but at the same time also able to pick up HCN[15] (or HNC)[16] trough the Brønsted base unit present at the nearby arm.

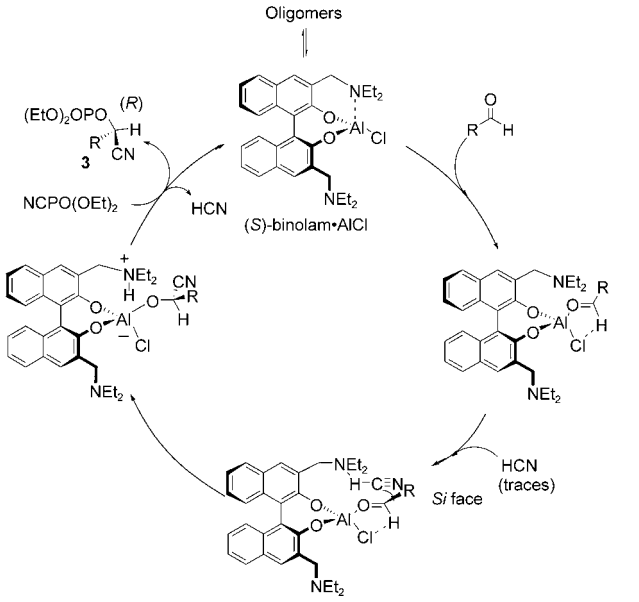
The observed enantioselective cyano-*O*-phosphorylation could either be the result of a direct process (DP), or an indirect one (IP) involving two fundamental steps: hydrocyanation and *O*-phosphorylation. Moreover, we envisioned two alternative mechanisms for the indirect route, namely racemic hydrocyanation followed by dynamic kinetic resolution upon the *O*-phosphorylation step (IP1) or,[25] instead, enantioselective hydrocyanation followed then by *O*-phosphorylation (IP2). So the question arose: where does the initial HCN (or HNC) come from? Examination by ^{13}C NMR spectroscopy of a commercial sample of diethyl cyanophosphonate (85% pure according to the supplier) showed that it does indeed contain trace amounts of HCN (δ 112.3 ppm, $CDCl_3$). Needless to say adding a hydrolytic agent to this sample led to the corresponding increase of the HCN signal, thus lending credit to the hydrocyanation–*O*-phosphorylation combined routes IP1 or IP2. The IP1 route was immediately discarded after learning that treatment of a racemic mixture of cyanohydrin **4a** with diethyl cyanophosphonate in the presence of (*S*)-binolam–AlCl **1** as catalyst (10 mol%), under otherwise identical conditions, led to a 50:50 mixture of cyanophosphates **3a** as revealed by chiral HPLC (Daicel Chiralpak AD).

At this point the indirect evidences presented so far strongly suggested a two-operation catalytic cycle, namely an enantioselective hydrocyanation followed by *O*-phosphorylation (IP2), as illustrated in Scheme 2. Nevertheless we did not fully rejected the more interesting, direct cyanophosphorylation (DP) as a plausible mechanistic scheme, specially in light of the proposed direct mechanism by Deng for the formally analogous enantioselective cyanoformyla-

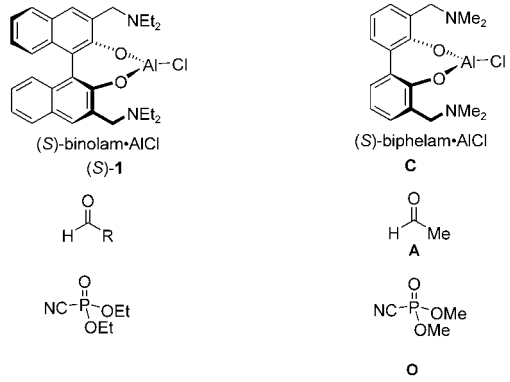
Table 4. Computed absolute and relative energies for the oligomerisation of models biphelam–AlCl **C** and phelam–AlCl **D**.

HF/6-31G* calculations[a]	$2\times\mathbf{C}_1$	$(aS,aS)\mathbf{C}_2$	$(aR,aS)\mathbf{C}_2$
absolute energy [Hartrees]	−3309, 2739632	−3309, 2860243	−3309, 2739632
relative energy[b] [kcal mol^{-1}]	+7.57	0	+1.38
HF/STO-3G calculations[a]	$4\times\mathbf{D}_1$	$(aR,aR,aR,aR)\mathbf{D}_4$	$(aR,aS,aR,aS)\mathbf{D}_4$
absolute energy[b] [Hartrees]	−5860.4099092	−5860.4258618	-5860.439724
relative energy [kcal mol^{-1}]	+18.70	+8.70	0

[a] Calculations carried out with Gaussian 98 A11 (see computational details). [b] Energies of stationary points found (all frequencies real). See Computational Details.



Scheme 2.



tion catalysed by *Cinchona* alkaloids.[3] Accordingly, we examined both routes by means of an extensive computational analysis for which purpose we selected biphelam–AlCl **C** (see below) as the ideal model catalyst for study.[26] Initial Hartree–Fock computations at the HF/6-31G* level (single-point B3LYP/6-31G*//HF/6-31G* energies were also determined) served to delimit the competitiveness of the direct cyanophosphorylation route versus the indirect route involving hydrocyanation followed by *O*-phosphorylation (Figure 3). These were eventually completed with DFT calculations at the B3LYP/6-31G* level for a more detailed assessment of the selected route.

An overall illustration of the results of our computational studies for the **C**-catalysed addition of dimethyl cyanophosphonate **O** to acetaldehyde **A** (direct cyanophosphorylation) versus the **C**-catalysed addition of hydrogen cyanide **HCN** to acetaldehyde **A** (the hydrocyanation step of the indirect cyanophosphorylation) is given in Figure 3 in terms of B3LYP/6-31G*//HF/6-31G* relative energies (absolute energies of all stationary points are provided as Supporting Information).

As illustrated in Figure 3, our (*S*)-configured model catalyst **C** is capable of forming binary complexes with HCN (**C·HCN**), or the aldehyde **A** (**C·A**), for which purpose **C** uses either the Brønsted base (BB) or Lewis acid (LA) moiety, respectively. As expected, **C** is also capable of forming a ternary complex presumably relevant for the direct cyanophosphorylation with both the aldehyde **A** and cyano-

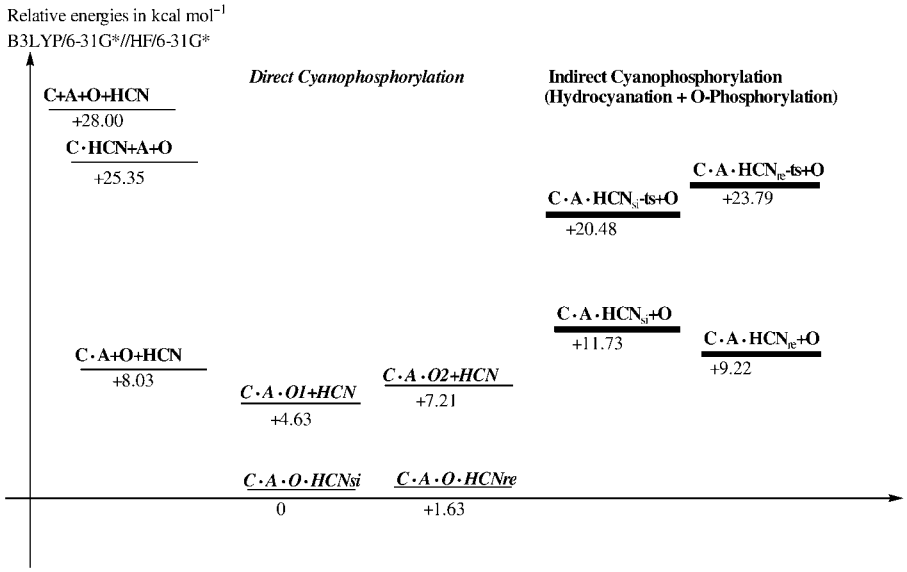


Figure 3.

phosphate **O** (***C·A·O1*** and ***C·A·O2***), and also a ternary complex presumably relevant for the indirect cyanophosphorylation with the aldehyde **A** and **HCN** (**C·A·HCN$_{Si}$** and **C·A·HCN$_{Re}$**). Also shown in Figure 3 are the quaternary complexes **C·A·O·HCN$_{Si}$** and **C·A·O·HCN$_{Re}$**, which are the lowest energy species but nevertheless quite labile. The HF/6-31G*-optimised geometries of all these stationary points are provided as Supporting Information. The competition between the direct and indirect cyanophosphorylations is shown in Figure 3 in two different blocks. In spite of the many attempts (starting from either the ternary or quaternary complexes), we have been unable to find the transition structures corresponding to the so-called direct cyanophosphorylation (Figure 3, left). In sharp contrast, we found the transition structures of the hydrocyanation process (shown in bold-face Figure 3, right), namely **C·A·HCN$_{Si}$-ts** and **C·A·HCN$_{Re}$-ts** separated by $\Delta\Delta E = 3.31$ kcal mol^{-1}, the former being the energy lowest, in excellent agreement with experiment. These data clearly support that the observed cyanophosphorylation might be the result of a two-operation process (indirect cyanophosphorylation) involving initial enantioselective hydrocyanation, followed by *O*-phosphorylation.

Nevertheless, the recent demonstration by Hoveyda and Snapper that the salicylpeptide-catalysed hydrocyanation of imines involved the addition of HNC rather than HCN,[15c] and also the experimental evidence provided by Corey[16] on the HNC versus HCN issue led us to further pursue the hydrocyanation issue in more detail. The results of this analysis initially run at the HF/6-31G* level of calculation are illustrated in Figure 4 (single point B3LYP/6-31G*//HF/6-31G* energies are given). The relevant conclusions being: 1) both the HCN and HNC modes of addition are active, competing routes for the hydrocyanation of aldehydes (see, however, below); 2) the lowest energy barrier for both routes corresponds to *Si* attack, in accordance with experiment.

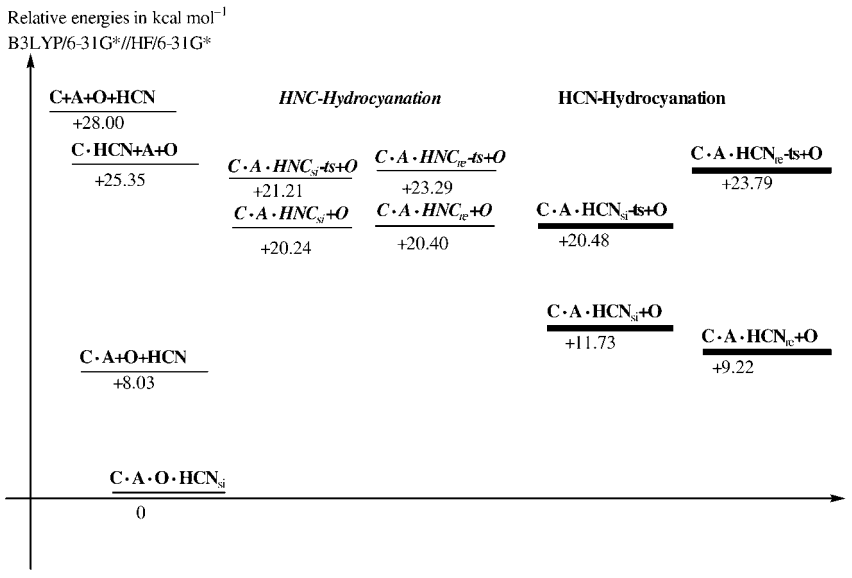


Figure 4.

For a more precise analysis on this issue, we felt necessary to carry out a DFT study at the B3LYP/6-31G* level of calculation (the large molecular size of the species under analysis precluded further upgrading such as post Hartree–Fock MP2 calculations). According to this study (Figure 5) only one mode of addition is actually possible, namely that of addition of HCN, as in no case we were able to find the transition structures for the addition of HNC to the aldehyde. Therefore we conclude that our (*S*)-configured catalyst is in fact capable of performing an LABB dual role in promoting the addition of HCN (not HNC) to the *Si* face of the aldehyde in an enantioselective manner ($\Delta\Delta E^* = 3.31$ kcal mol^{-1}), and thus give rise to the (*R*)-configured cyanohydrin, in agreement with experiment. These data give support to the empirical *RRS*/*SSR* rule mentioned above.

Synthetic applications of enantiopure cyanophosphates 3: Chemoselective ethanolysis of the cyano group of cyanohydrin *O*-phosphates **3** was achieved by treatment with acetyl chloride in anhydrous ethanol at 0 °C, thereby leading to α-*O*-phosphate carboxylate ethyl esters **6**. In this manner, we prepared compounds **6a** and **6o** in excellent chemical yield and almost overall retention of the configuration (Scheme 3a). This methodology, however, failed for allyl phosphate **3j**. In this case, a number of side products, presumably originated by allyl rearrangements, were observed (^{1}H NMR spectra) in the crude reaction product. Double hydrolysis of the phosphoryl and cyano groups, also failed by using TMSI, concentrated or diluted hydrochloric acid at several temperatures or even under microwave irradiation or titanium complexes.[10] In all cases mixtures of racemic, hydrolysed products were obtained. The ester **6a** could be successfully obtained by reaction of the commercially available ethyl (*S*)-mandelate with diethyl cyanophosphonate (1.2 equiv) in the presence of triethylamine (1.2 equiv) at room temperature (Scheme 3b). The reaction proceeded without racemisation thereby yielding compound (*S*)-**6a** in good yield and 99% *ee*. Other bases such as pyridine or *N*-methylimidazole did not improve the reaction and diethyl chlorophosphate was shown not to be a suitable phosphorylating agent for this purpose.

Enantiopure β-amino alcohols are within reach from cyanohydrin *O*-phosphates **3** by simple reduction with lithium aluminium hydride. Thus, for instance, β-amino alcohol (*R*)-**7a**[27] was obtained by reduction of (*R*)-**3a** in good chemical and stereochemical yields (no racemisation observed). For an easier manipulation, (*R*)-**7a** can be conveniently converted in quantitative

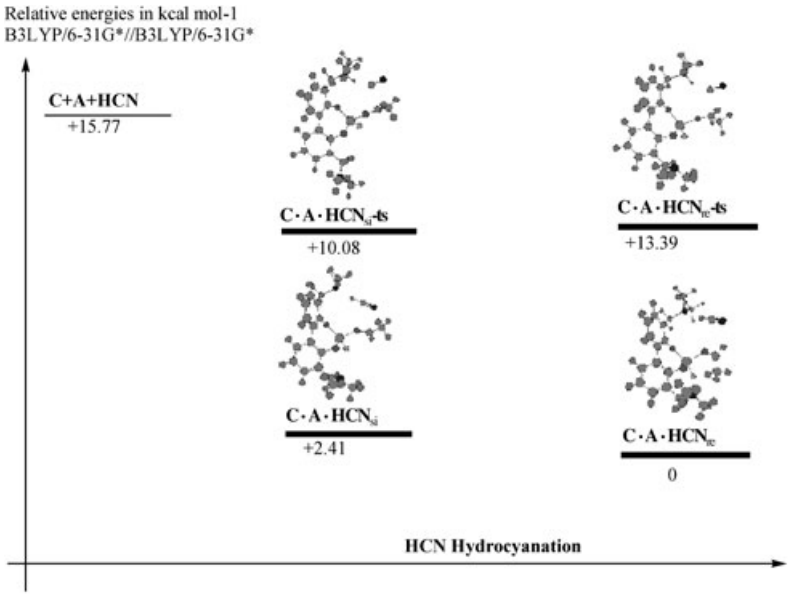
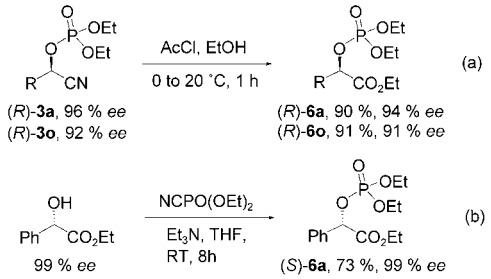
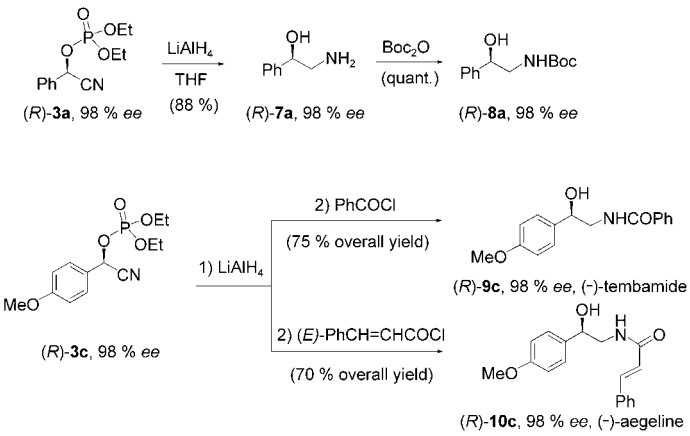


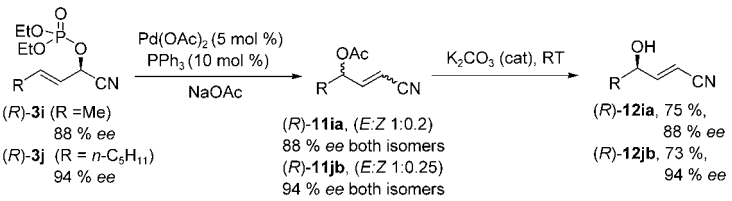
Figure 5.



Scheme 3.



Scheme 4.



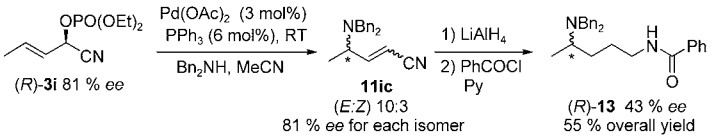
Scheme 5. R = n-C_5H_{11}

yield in its *N*-Boc derivative (*R*)-**8a**[28] (Scheme 4). The optical rotations measured for β-amino alcohols (*R*)-**7a** and (*R*)-**8a** were in agreement with those of the literature, thereby confirming the absolute configuration already assigned to products **3**. With this simple procedure in hand, the direct synthesis of natural products (−)-tembamide and (−)-aegeline[1c,17] was tested. Due to its instability, crude **3c**, obtained in 98% *ee* (Table 2, entry 6), was reduced at room temperature with lithium aluminium hydride in THF and quenched with water. The resulting crude product was treated with cinnamoyl chloride or benzoyl chloride leading to enantioenriched (98% *ee* in both examples) (−)-aegeline and (−)-tembamide in 70 or 75% overall yield, respectively (Scheme 4).

Next we tried to explore the palladium-catalysed nucleophilic substitution upon allyl phosphates **3** as a valuable route to access enantioenriched γ-cyanoallyl alcohols,[29] of which alcohol **12jb** is a useful precursor for the synthesis of coriolic acid as well as D- and L-sphingosines[30,31] (Scheme 5). For this purpose, we subjected cyanohydrin *O*-phosphates **3i** and **3j** to palladium-catalysed allyl rearrangement with sodium acetate at room temperature, in the presence of palladium acetate (5 mol%) and triphenylphosphane (10 mol%). Due to their instability, acetates **11** were not purified but, instead, submitted to a very mild base-catalysed hydrolysis.[30b] After flash chromatography we obtained alcohols **12ia**[30c] and **12ja**[30b] as pure (*E*)-isomers in 75 and 73% overall chemical yield and 88 and 94% *ee*, respectively (Scheme 5). The absolute configuration of the products (*E*)-**12**, was determined by comparison of their optical rotations with those described in the literature.[30,31]

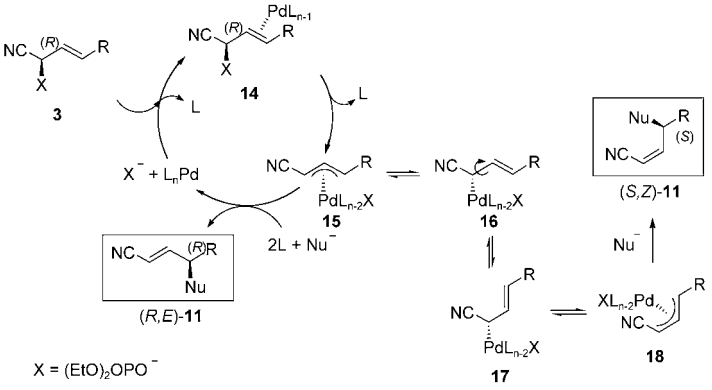
Interestingly, we observed that the newly generated chiral centre at the γ-position of the (*E* and *Z*)-α,β-unsaturated derivatives **11ia** and **11jb** had opposite configurations, though, curiously enough, both were obtained in identical *ee*. This observation is not without precedent as some palladium(0)-catalysed allyl substitution reactions has been previously reported to induce opposite absolute configuration at the newly-created chiral centre of the (*E*)- and (*Z*)-configured product.[32] In addition, we also observed that palladium(0)-catalysed allyl sub-

stitution in the presence of dibenzylamine behaved analogously. Actually, the product of nucleophilic substitution **11ic** was obtained as a 10:3 (*E*:*Z*) mixture, each product having the same enantiomeric purity (81% *ee*) as the starting allyl phosphate **3i**. Reduction of the unsaturated nitrile group of **11ic** followed by protection of the resulting primary amine with benzoyl chloride led to *N*-benzoyl-1,4-diamine **13** (Scheme 6). The final *ee* obtained was in agreement with the reversal of stereochemistry postulated for the chiral centre on the (*E*) and (*Z*)-isomers of **11ic**. The *ee* of unknown compound **13** was determined by chiral HPLC analysis (Daicel Chiralpak AD).



Scheme 6.

The stereochemical outcome described above is consistent with the reaction mechanism reported for allyl carbonates.[32a] The expected double inversion involving intermediate **15** easily explains why the major (*E*)-isomer of **11** should possess the (*R*) configuration. In addition, since η^3-allyl palladium **15** is in equilibrium with η^3-allyl palladium **18**, by means of a η^3–η^1 shift to **16**, bond rotation and η^1–η^3 shift, this species should give rise upon nucleophilic attack to the (*Z*) isomer **11** with the opposite (*S*) configuration (Scheme 7).



Scheme 7.

In summary, C_2-symmetric binolam-derived complexes **1**, having an aluminium atom as the system core and two proximate aminomethyl arms, efficiently catalyse the asymmetric cyanophosphorylation reaction of aldehydes, both in terms of chemical and stereochemical yield. All evidences, including ab initio and DFT calculations support a mechanism where the catalyst works as a true bifunctional Lewis acid/Brønsted base (LABB) system, the aluminium acting as Lewis acid in binding the carbonyl aldehyde, and the amino arm by capturing hydrogen cyanide. The overall enantioselective cyanophosphorylation observed appears to be the consequence of the enchainment of two reactions namely, enantioselective hydrocyanation which is then followed by *O*-phosphorylation. The existence of a strongly positive NLE observed when this reaction is carried out in toluene suggests that the actual catalyst is in equilibrium with some oligomeric species of the aluminium complexes.[33] Most important, the chiral ligand (*S*)-BINOLAM **2** can be easily recovered at the end of the reaction and recycled without loss of efficiency, thus suggesting its possible application in large-scale processes. Direct applications of cyanohydrin *O*-phosphates in the synthesis of *O*-phosphorylated hydroxy esters, β-amino alcohols and γ-cyanoallyl alcohols convert this cyanohydrin derivatives in very interesting chiral building blocks for synthetic organic chemistry.

Computational Details

In most cases structures corresponding to ground state and transition state geometries were fully optimised (no geometrical constraints imposed) using gradients techniques at the HF/6-31G(d) level of theory,[34] that is, by using the set of split-valence, d-polarised 6-31G(d) basis,[35] as implemented in Gaussian98 A11.[36] Single-point energies B3LYP/6-31G*//HF/6-31G* have been also determined. Only for the study of the aggregation (tetramerisation) of modelled species such as phelam–AlCl **D** we had to recourse to HF/STO-3G calculations.

The original input structures were, in most cases, the optimised structures resulting from prior semiempirical work (not shown) carried out with PM3 as implemented in the Spartan package.[37] Electron correlation was incorporated to our studies by means of density functional theory,[38] by using the non-local hybrid three-parameter functional developed by Becke and denoted B3LYP exchange-correlation functional.[39,40] All stationary points were examined by diagonalisation of their Hessian matrices (vibrational analysis).[41] Ground state equilibrium geometries on the potential energy surface were recognised as having real frequencies only, whereas transition structures were recognised as having only one negative eigenvalue (visualised on a screen with the help of an appropriate program). In all cases, the zero-point vibrational energies (ZPVE) were computed at the same level and were not scaled.

Experimental Section

General: All reactions were carried out under argon, including the transfer of solid reagents to the reaction vessel. Anhydrous solvents were freshly distilled under an argon atmosphere. Aldehydes were also distilled prior to use. Molecular sieves were dried at 120 °C for 4 h. (*S*)- and (*R*)-BINOLAM **2** were prepared according to the literature protocol.[5,12,14] Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet 510 P-FT) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained at 25 °C on a Bruker AC-300 by using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. HPLC analyses were performed on a Shimadzu LC-10 AD equipped with a chiral column (detailed for each compound in the main text), by using mixtures of *n*-hexane/isopropyl alcohol as mobile phase, at 25 °C. Chiral GC analysis was performed on a HP-5890 by using a WCOT γ-cyclodextrin column. Low-resolution electron impact (EI) mass spectra were obtained at

70 eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin–Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher and Schuell F1400/LS silica gel plates and the spots were visualised under UV light ($\lambda = 254$ nm). For flash chromatography we employed Merck silica gel 60 (0.040–0.063 mm). The retention time of the major enantiomer is highlighted in italics

General procedure for the preparation of compounds 3: Dimethylaluminium chloride (1 M solution in hexanes, 0.025 mmol, 25 μL) was added under argon to a solution of enantiopure (*S*)-BINOLAM **2** (0.025 mmol, 11.4 mg), in dry toluene (1 mL), and the resulting suspension stirred at room temperature for 1 h. Then, freshly distilled aldehyde (0.25 mmol) and diethyl cyanophosphonate (0.75 mmol, 125 μL) were added in one portion. The reaction was monitored by GC and ^{1}H NMR spectroscopy and, when it was judged complete, 2 M aqueous solution of hydrochloric acid (2 mL) and ethyl acetate (2 mL) were added. The resulting mixture was stirred vigorously for 10 min. The emulsion was filtered and the aqueous phase treated with a 1 M buffer solution of NH_3/NH_4Cl until the pH was basic; then ethyl acetate was added (2×10 mL) and the organic layer was separated, dried ($MgSO_4$) and eventually evaporated, thereby recovering pure ligand **2** (11 mg, 95%). The organic phase from the acidic work up was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography thereby yielding pure cyanohydrin *O*-phosphates **3** (yields shown in Table 2). Spectroscopic and physical data for **3a–n** follows:

(*S*)-2-(Diethylphosphoryloxy)-2-phenylacetonitrile (3a): Colourless oil; $[\alpha]_D^{25} = -20.12$ ($c = 2$, $CHCl_3$); 98% *ee* from HPLC analysis, Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 95:5, 1.0 mL min^{-1}, $t_r = 16.8$ and 19.9 min; $R_f = 0.57$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2240$, 1270, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$–1.23 (dt, $J = 7.1$, 0.9 Hz, 3H, CH_3), 1.34–1.39 (dt, $J = 7.1$, 0.9 Hz, 3H, CH_3), 3.94–4.05, 4.13–4.25 (2×m, 4H, 2×CH_2), 6.05 (d, $J = 8.9$ Hz, 1H, CHCN), 7.44–7.46 (m, 3H, ArH), 7.53–7.56 ppm (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.7$–15.9 (m, 2×CH_3), 64.5–64.7 (m, 2×CH_2), 66.4 (d, $J = 4.4$ Hz, *C*HCN), 116.1 (d, $J = 6.6$ Hz, CN), 127.4, 129.1, 130.5, 132.4 ppm (ArC); MS (EI): *m*/*z*: 269 (4) $[M]^+$, 213 (70), 133 (42), 116 (100), 115 (69), 105 (48), 89 (33); HRMS: *m*/*z*: calcd for $C_{12}H_{16}O_4NP$: 269.0817; found: 269.0820.

(*S*)-2-(4-Chlorophenyl)-2-(diethylphosphoryloxy)acetonitrile (3b): Colourless oil; $[\alpha]_D^{25} = -14.60$ ($c = 2$, $CHCl_3$); 96% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 12.0$ and 14.7 min; $R_f = 0.43$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2354$, 1273, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$, 1.38 (2×t, $J = 7.1$ Hz, 6H, 2×CH_3), 3.98–4.07, 4.14–4.26 (2×m, 4H, 2×CH_2), 6.03 (d, $J = 8.9$ Hz, 1H, CHCN), 7.43 (d, $J = 8.5$ Hz, 2H, ArH), 7.50 ppm (d, $J = 8.5$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$ (m, 2×CH_3), 64.8 (d, $J = 6$ Hz, 2×CH_2), 65.7 (d, $J = 4.4$ Hz, *C*HCN), 115.7 (d, $J = 6.6$ Hz, CN), 128.8, 129.5, 130.9, 136.8 ppm (ArC); MS (EI): *m*/*z*: 303 (15) $[M]^+$, 247 (88), 150 (98), 149 (100), 139 (42), 114 (32); HRMS: *m*/*z*: calcd for $C_{12}H_{15}O_4NPCl$: 303.0427; found: 303.0432.

(*R*)-2-(Diethylphosphoryloxy)-2-(4-methoxyphenyl)acetonitrile (3c): Data of the colourless oily crude product (see text): 98% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 12.0$ and 14.7 min; $R_f = 0.30$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2243$, 1258, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$, 1.38 (2×t, $J = 7.1$ Hz, 6H, 2×CH_3CH_2O), 3.84 (s, 3H, CH_3O), 3.83–4.04, 4.15–4.25 (2×m, 4H, 2×CH_2O), 5.99 (d, $J = 8.6$ Hz, 1H, CHCN), 6.95 (d, $J = 8.6$ Hz, 2H, ArH), 7.48 ppm (d, $J = 8.6$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$ (d, $J = 7.3$ Hz, 2×CH_3CH_2), 55.40 (d, $J = 3.3$ Hz, CH_3O), 64.7 (d, $J = 5.5$ Hz, 2×CH_2O), 66.3 (d, $J = 4.4$ Hz, *C*HCN), 114.5 (ArC), 116.3 (d, $J = 6.6$ Hz, CN), 124.5 (d, $J = 5.5$ Hz, ArC), 161.3 ppm (ArC); MS (IE): *m*/*z*: 299 (8) $[M]^+$, 162 (12), 147 (39), 46 (97), 145 (100), 135 (17); HRMS: *m*/*z*: calcd for $C_{13}H_{18}O_5NP$: 299.0923; found: 299.0928.

(*R*)-2-(Diethylphosphoryloxy)-2-(4-nitrophenyl)acetonitrile (3d): Pale yellow oil; $[\alpha]_D^{25} = -0.9$ ($c = 2$, $CHCl_3$); 26% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 17.9$ and 37.4 min; $R_f = 0.20$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2363$, 1530, 1350, 1271, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$, 1.40 (2×t, $J = 7.1$ Hz, 6H, 2×CH_3), 4.02–4.15, 4.18–4.30 (2×m, 4H, 2×CH_2), 6.17 (d, $J = 9.0$ Hz, 1H, CHCN), 7.76, 8.32 ppm (2×d, $J = 8.7$ Hz, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$ (m, 2×CH_3), 65.1 (d, $J = 4.4$ Hz, *C*HCN), 65.2 (d, $J = 6.3$ Hz, 2×CH_2), 115.2 (d, $J = 6.6$ Hz, CN), 124.4, 128.3, 138.6, 149.0 ppm (ArC); MS (EI): *m*/*z*: 314 (4) $[M]^+$, 258 (100), 161 (28), 125 (26), 114 (44); HRMS: *m*/*z*: calcd for $C_{12}H_{15}O_6N_2P$: 314.0668; found: 314.0669.

(*R*)-2-(Diethylphosphoryloxy)-2-(3-phenoxyphenyl)acetonitrile (3e): Colourless oil; $[\alpha]_D^{25} = +8.9$ ($c = 2$, $CHCl_3$); 97% *ee* from HPLC analysis Daicel Chiralpak AS, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 15$ and 19.7 min; $R_f = 0.44$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2361$, 1268, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$, 1.36 (2×dt, $J = 7.1$, 1.0 Hz, 6H, 2×CH_3), 3.96–4.09, 4.13–4.26 (2×m, 4H, 2×CH_2), 6.01 (d, $J = 8.9$ Hz, 1H, CHCN), 7.00–7.09 (m, 3H, ArH), 7.13–7.17 (m, 2H, ArH), 7.34 (t, $J = 2$ Hz, 1H, ArH), 7.36–7.42 ppm (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$, 16.2 (2×d, $J = 7.5$ Hz, 2×CH_3), 64.5, 64.9 (2×d, $J = 5.7$ Hz, 2×CH_2), 66.0 (d, $J = 4.4$ Hz, *C*HCN), 115.9 (d, $J = 5.5$ Hz, CN), 117.1, 119.3, 120.3, 121.6, 124.1, 129.9, 130.6 (ArC), 134.1 (d, $J = 5.5$ Hz, ArC), 156.2, 158.2 ppm (ArC); MS (EI): *m*/*z*: 361 (84) $[M]^+$, 305 (100), 225 (51), 207 (29), 197 (39), 181 (67), 114 (72); HRMS: *m*/*z*: calcd for $C_{18}H_{20}O_5NP$: 361.1079; found: 361.1079.

(*R*)-2-(2-Chlorophenyl)-2-(diethylphosphoryloxy)acetonitrile (3f): Colourless oil; $[\alpha]_D^{25} = +23.8$ ($c = 2$, $CHCl_3$); 97% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 95:5, 1.0 mL min^{-1}, $t_r = 10.1$ and 12.5 min; $R_f = 0.35$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2358$, 1274, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$, 1.37 (2×dt, $J = 7.1$, 1.1 Hz, 6H, CH_3), 4.05–4.15, 4.17–4.28 (2×m, 4H, 2×CH_2), 6.36 (d, $J = 8.7$ Hz, 1H, CHCN), 7.36–7.47 (m, 3H, ArH), 7.68–7.72 ppm (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.8$, 16.0 (2×d, $J = 4.4$ Hz, 2×CH_3), 63.5 (d, $J = 4.4$ Hz, *C*HCN), 64.6, 65.0 (2×d, $J = 5.5$ Hz, 2×CH_2), 115.4 (d, $J = 4.4$ Hz, CN), 127.7, 128.9 (ArC), 130.1 (d, $J = 4.4$ Hz, ArC), 130.3, 131.7, 132.8 ppm (ArC); MS (EI): *m*/*z*: 268 (59) $[M-Cl]^+$, 240 (18), 212 (31), 185 (100), 150 (57), 122 (19), 114 (18); HRMS calcd for $C_{12}H_{15}O_4NP$: 268.0738; found: 268.0739 $[M-Cl]^+$.

(*R*)-2-(Diethylphosphoryloxy)-2-(6-methoxy-2-naphthyl)acetonitrile (3g): Colourless oil; $[\alpha]_D^{25} = +12.2$ ($c = 2$, $CHCl_3$); 94% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 16.4$ and 24.0 min; $R_f = 0.21$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2357$, 1271, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$, 1.39 (2×t, $J = 7.1$ Hz, 6H, 2×CH_3CH_2), 3.93 (s, 3H, CH_3O), 3.95–4.02, 4.18–4.26 (2×m, 4H, 2×CH_2), 6.18 (d, $J = 8.8$ Hz, 1H, CHCN), 7.16 (brs, 1H, ArH), 7.21 (m, 1H, ArH), 7.58 (d, $J = 8.5$, 1H, ArH), 7.80 (t, $J = 9.5$ Hz, 2H, ArH), 7.96 ppm (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.8$ (m, 2×CH_3), 55.3 (s, CH_3O), 64.4, 64.6 (2×d, $J = 5.5$ Hz, 2×CH_2), 66.8 (d, $J = 5.5$ Hz, *C*HCN), 116.2 (d, $J = 6.6$ Hz, CN), 105.7, 119.9, 124.6, 127.2, 127.3, 127.5, 128.2, 129.9, 135.4, 158.9 ppm (ArC); MS (EI): *m*/*z*: 349 (0.1) $[M]^+$, 321 (10), 265 (10), 212 (17), 196 (91), 195 (100), 180 (10), 166 (14), 153 (27), 125 (17), 91 (28); HRMS: *m*/*z*: calcd for $C_{17}H_{20}NPO_5$: 349.3200; found: 349.3995.

(*R*)-2-(Diethylphosphoryloxy)-2-(3-pyridyl)acetonitrile (3h): Pale yellow oil; 4% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 28.7$ and 29.9 min; $R_f = 0.55$ (ethyl acetate); IR (neat): $\tilde{\nu} = 2254$, 1286, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$, 1.37 (2×m, 6H, 2×CH_3), 4.15, 4.23 (2×m, 4H, 2×CH_2), 6.13 (d, $J = 9.2$ Hz, 1H, CHCN), 7.37 (m, 1H, ArH), 7.60 (d, $J = 8.0$ Hz, 1H, ArH), 7.82 (t, $J = 7.6$ Hz, 1H, ArH), 8.65 ppm (brs, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$, 16.1 (2×d, $J = 4.4$ Hz, 2×CH_3), 64.9 (m, 2×CH_2), 67.2 (d, $J = 5.5$ Hz, *C*HCN), 115.6 (d, $J = 4.4$ Hz, CN), 121.4, 124.8, 137.7, 149.9, 151.5 ppm (ArC); MS (EI): *m*/*z*: 270 (16) $[M]^+$, 214 (37), 133 (60), 118 (100), 117 (69), 108 (42), 98 (48); HRMS: *m*/*z*: calcd for $C_{11}H_{15}O_4N_2P$: 270.0769; found: 270.0773.

(*E*,2*R*)-2-(Diethylphosphoryloxy)pent-3-enenitrile (3i): Colourless oil; $[\alpha]_D^{25} = -17.48$ ($c = 2$, $CHCl_3$); 88% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 210$ nm, *n*-hexane/2-propanol 95:5, 1.0 mL min^{-1}, $t_r = 9.6$ and 12.3 min; $R_f = 0.36$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2247$,

1269, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (m, 6H, 2× CH_3CH_2O), 1.73 (d, $J = 6.6$ Hz, 3H, CH_3CH), 4.07 (m, 4H, 2× CH_2O), 5.37 (t, $J = 7.5$ Hz, 1H, CHCN), 5.55 (m, 1H, C=C*H*CHCN), 6.10 ppm (m, 1H, C=C*H*CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.3$ (CH_3CH), 15.5 (d, $J = 6.6$ Hz, 2× CH_3CH_2O), 64.4 (m, 2× CH_2), 64.7 (d, $J = 4.4$ Hz, *C*HCN), 115.5 (d, $J = 5.5$ Hz, CN), 122.2 (d, $J = 5.5$ Hz, C=*C*HCHCN), 135.3 ppm (CH_3CH=*C*); MS (EI): *m/z*: 233 (1) [*M*], 177 (30), 127 (21), 99 (100), 81 (23); HRMS: *m/z*: calcd for $C_9H_{16}O_4NP$: 233.0817; found: 233.0813.

(*E*,2*R*)-2-(Diethylphosphoryloxy)non-3-enenitrile (3j): Colourless sticky oil; $[\alpha]_D^{25} = -20.81$ ($c = 2$, $CHCl_3$); 94% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 210$ nm, *n*-hexane/2-propanol 98:2, 1.0 mL min^{-1}, $t_r =$ 13.4 and *17.9* min; $R_f = 0.53$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} =$ 2243, 1272, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J =$ 6.5 Hz, 3H, $CH_3CH_2CH_2$), 1.27–1.45 [m, 12H, 2× CH_3CH_2O, $(CH_2)_3CH_3$], 2.11 (m, 2H, CH_2CH=CH), 4.15 (m, 4H, 2× CH_2O), 5.44 (t, $J = 7.5$ Hz, 1H, CHCN), 5.59 (m, 1H, C=C*H*CHCN), 6.14 ppm (m, 1H, C=C*H*CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ [$CH_3(CH_2)_3$], 15.9 (d, $J = 6.6$ Hz, 2× CH_3CH_2O), 22.3 (CH_2CH_3), 27.8 ($CH_2CH_2CH_3$), 31.5 (CH_2CH_2CH=C), 31.8 (CH_2CH=CH), 64.4, 64.8 (2× d, $J = 7.3$ Hz, 2× CH_2O), 65.1 (d, $J = 7.3$ Hz, CH), 115.7 (d, $J = 7.3$ Hz, CN), 121.0 (d, $J =$ 5.5 Hz, C=*C*HCHCN), 140.6 ppm (CH_2CH=CH); MS (EI): *m/z*: 289 (1) $[M]^+$, 155 (53), 127 (62), 99 (100), 81 (20); HRMS: *m/z*: calcd for $C_{13}H_{24}O_4NP$: 289.1443; found: 289.1451.

(*E*,2*R*)-2-(Diethylphosphoryloxy)-4-phenylbut-3-enenitrile (3k): Pale yellow oil; $[\alpha]_D^{25} = -19.1$ ($c = 1.5$, $CHCl_3$); 95% *ee* from HPLC analysis Daicel Chiralpak AS, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 18.8$ and 20.9 min; $R_f = 0.29$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} =$ 2230, 1270, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$, 1.40 (2× dt, $J = 7.1$, 0.9 Hz, 6H, 2× CH_3), 4.09–4.27 (m, 4H, 2× CH_2), 5.68 (dt, $J = 7.2$, 0.9 Hz, 1H, CHCN), 6.25 (dd, $J = 15.8$, 6.7 Hz, 1H, C=C*H*CHCN), 6.97 (d, $J = 15.8$ Hz, 1H, C*H*=CHCN), 7.36–7.40 (m, 3H, ArH), 7.42–7.46 ppm (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 15.7, 15.9 (2× d, $J = 5.6$ Hz, 2× CH_3), 64.5, 64.7 (2× d, $J = 6.6$ Hz, 2× CH_2), 65.1 (d, $J = 4.4$ Hz, *C*HCN), 115.4 (d, $J = 6.6$ Hz, CN), 119.2 (d, $J = 4.4$ Hz, *C*HCHCN), 127.2, 128.4, 129.5, 134.2 (ArC), 137.6 ppm (Ph*C*H); MS (EI): *m/z*: 295 (34) $[M]^+$, 221 (15), 159 (70), 141 (100), 140 (94), 127 (33), 115 (36), 99 (78); HRMS: *m/z*: calcd for $C_{14}H_{18}O_4NP$: 295.0973; found: 295.0971.

(*E*,2*R*)-2-(Diethylphosphoryloxy)-3-methyl-4-(2-methyl-4-thiazolyl)but-3-enenitrile (3l): Pale yellow oil; $[\alpha]_D^{25} = -18.5$ ($c = 1$; $CHCl_3$); 90% *ee* from HPLC Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 80:20, 1 mL min^{-1}. $t_r = 19.9$ and *26.8* min; $R_f = 0.20$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2227$, 1269, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$, 1.39 (2× dt, $J = 7.1$, 0.9 Hz, 6H, 2× CH_3CH_2O), 2.31 (d, $J =$ 1.1 Hz, 3H, CH_3C=CH), 2.72 (s, 3H, CH_3CS), 4.08–4.26 (m, 4H, 2× CH_2), 5.51 (d, $J = 8.4$ Hz, 1H, CHCN), 6.73 (s, 1H, CH=C), 7.12 ppm (s, 1H, CHS); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$ (CH_3C=CH), 15.9 (m, 2× CH_3CH_2), 19.3 (CH_3CS), 64.7 (m, 2× CH_2), 70.4 (d, $J = 5.5$ Hz, *C*HCN), 115.5 (d, $J = 5.5$ Hz, CN), 119.5 (*C*=CN), 125.1 (CN), 129.7 (d, $J = 5.5$ Hz, *C*=CHCN), 150.9 (*C*H=C), 165.5 ppm (C=N); MS (EI): *m/z*: 330 (2) $[M]^+$, 193 (38), 177 (100), 176 (92), 151 (39), 135 (57); HRMS: *m/z*: calcd for $C_{13}H_{19}O_4N_2PS$: 330.0803; found: 330.0798.

(*S*)-2-(Diethylphosphoryloxy)octanenitrile (3m): Colourless sticky oil; $[\alpha]_D^{25} = +20.19$ ($c = 2$, $CHCl_3$); 98% *ee* from CG analysis WCOT γ-CD (0.25 nm section, FS-Lipodex-E), $T_{inject} = 250$ °C, $T_{detect} = 260$ °C, $T_{column} =$ 90 °C (5 min) and 180 °C (2 °C min^{-1}), $p = 100$ kPa, $t_r = 70.7$ and 71.1 min; $R_f = 0.40$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2240$, 1276, 1032 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$): $\delta = 0.86$ (t, $J = 6.7$ Hz, 3H, CH_3CH_2), 1.28–1.38 [m, 12H, 2× CH_3CH_2O, $(CH_2)_3CH_3$], 1.49 (m, 2H, CH_2CH_2CH), 1.91 (m, 2H, CH_2CH), 4.15 (m, 4H, 2× CH_2O), 4.96 ppm (m, 1H, CHCN); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ ($CH_3CH_2CH_2$), 15.9 (d, $J = 6.6$ Hz, 2× CH_3CH_2O), 22.3 (CH_2CH_3), 24.1 (CH_2CH_2CH), 28.3, 31.3 [$(CH_2)_2CH_2CH_3$], 34.1 (d, $J = 5.5$ Hz, CH_2CH), 64.5, 64.7 (2× d, $J = 4.4$ Hz, 2× CH_2O), 64.8 (d, $J = 6.0$ Hz, CH), 116.8 ppm (d, $J = 6.7$ Hz, CN); MS (EI): *m/z*: 276 (0.4) $[M]^+$, 155 (66), 127 (73), 99 (100), 81 (37); HRMS: *m/z*: calcd for $C_{12}H_{24}O_4NP$: 277.1443; found: 277.1441.

(*R*)-2-(Diethylphosphoryloxy)-3-phenylpropanenitrile (3n): Colourless oil; $[\alpha]_D^{25} = +15.9$ ($c = 2$, $CHCl_3$); 36% *ee* from HPLC Daicel Chiralcel OD-H, $\lambda = 254$ nm, *n*-hexane/2-propanol 95:5, 1.0 mL min^{-1}, $t_r = 9.2$ and *12.3* min; $R_f = 0.50$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2240$, 1269, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$–1.34 (m, 6H, 2× CH_3), 3.23 (d, $J = 7.0$ Hz, 2H, CH_2CH), 3.92–4.17 (m, 4H, 2× CH_2O), 5.15 (m, 1H, CHCN), 7.28–7.36 ppm (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.8$ (d, $J = 6.6$ Hz, 2× CH_3), 40.4 (d, $J = 5.5$ Hz, CH_2CH), 64.6 (m, 2× CH_2O), 65.4 (d, $J = 6.6$ Hz, *C*HCN), 116.4 (d, $J = 3.3$ Hz, CN), 127.9, 128.8, 129.6, 132.9 ppm (ArC); MS (EI): *m/z*: 283 (0.02) [*M*], 155 (5), 130 (15), 129 (100), 103 (6); HRMS: *m/z*: calcd for $C_{13}H_{18}O_4NP$: 283.0993; found: 283.1000.

(*S*)-2-(Diethylphosphoryloxy)-4-phenylbutanenitrile (3o): Colourless oil; $[\alpha]_D^{25} = -9.79$ ($c = 2$, $CHCl_3$); 92% *ee* from HPLC Daicel Chiralpak AS, $\lambda =$ 254 nm, *n*-hexane/2-propanol 90:10, 1 mL min^{-1}, $t_r = 11.6$ and 13.9 min; $R_f = 0.33$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} = 2334$, 1266, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (t, $J = 7.1$ Hz, 6H, 2× CH_3), 2.26 (m, 2H, CH_2CH), 2.85 (m, 2H, CH_2CH_2), 4.11–4.23 (m, 4H, 2× CH_2O), 4.93–5.00 (m, 1H, CHCN), 7.19–7.25 (m, 3H, ArH), 7.29–7.34 ppm (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$ (m, 2× CH_3), 30.3 (CH_2CH_2), 35.8 (d, $J = 6.6$ Hz, CH_2CH), 64.1 (d, $J = 6.1$ Hz, *C*HCN), 64.6, 64.8 (2× d, $J = 2.2$ Hz, 2× CH_2O), 116.6 (d, $J = 3.3$ Hz, CN), 126.6, 128.3, 128.71, 138.9 ppm (ArC); MS (EI): *m/z*: 298 (0.4) $[M+H]^+$, 155 (97), 143 (48), 127 (80), 116 (33), 99 (100); HRMS: *m/z*: calcd for $C_{14}H_{20}O_4NP$: 297.1130; found: 298.1205 $[M+H]^+$.

General procedure for the phosphorylation of enantiomerically enriched cyanohydrins 4: To a solution of the cyanohydrin **4** (0.5 mmol) and diethyl chlorophosphate, or diethyl cyanophosphonate, (0.6 mmol) in THF (4 mL) was added the corresponding base (0.6 mmol for both phosphorylating agents or 0.05 mmol when diethyl cyanophosphonate was used, see text). When the reaction was judged complete water (5 mL) and ethyl acetate (5 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. The residue obtained was purified as described above. The optical purity of compounds **3** were then analysed by chiral HPLC (see above).

General procedure for the synthesis of 3 through the corresponding phosphites 5: This procedure was performed following the literature.[20]

General procedure for the synthesis of the α-hydroxyesters *O*-phosphates 6: *Method A*: A solution of the compound **3** (0.25 mmol) in ethanol (10 mL) was cooled at 0 °C and acetyl chloride was added (3 mL). The reaction was stirred for 1 h at the same temperature and the solvent evaporated under vacuo. A dilute solution of sodium bicarbonate was added until the pH was slightly basic and ethyl acetate was added (5 mL) for extraction. The collected organic phases were treated with brine (5 mL), separated and then dried ($MgSO_4$) and evaporated under vacuo thereby yielding the corresponding esters **6** as pure compounds (no further purification being required).

Method B: To a solution of ethyl (*S*)-mandelate (0.5 mmol, 81 μL) and diethyl cyanophosphonate (0.6 mmol, 100 μL) in THF (4 mL), was added at room temperature triethylamine (0.6 mmol, 84 μL). The reaction was stirred at room temperature for 8 h and the organic solvent was evaporated, adding water (5 mL) and ethyl acetate (5 mL). The organic phase was separated, dried ($MgSO_4$) and evaporated giving the pure compound **6a** in 72% yield without any racemisation.

Ethyl (*R*)-2-(diethylphosphoryloxy)-2-phenylacetate (6a): Colourless liquid; $[\alpha]_D^{25} = +56.9$ ($c = 2$, $CHCl_3$); 97% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 98:2, 1 mL min^{-1}, $t_r =$ *32.8* and 38.0 min; $R_f = 0.39$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu} =$ 1755, 1268, 1181, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$–1.22 (m, 6H, CH_3CH_2OP, CH_3CH_2OC), 1.31 (dt, $J = 7.0$, 1.0 Hz, 3H, CH_3CH_2OP), 3.91 (m, 2H, CH_2OP), 4.17 (m, 4H, CH_2OP, CH_2OC), 5.71 (d, $J = 8.4$ Hz, 1H, CH), 7.33–7.38 (m, 3H, ArH), 7.43–7.47 ppm (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9$ (CH_3CH_2OC), 15.8 (m, 2× CH_3CH_2OP), 61.7 (CH_2OC), 63.9, 64.1 (2× d, $J = 6.1$ Hz, 2× CH_2OP), 76.6 (CH), 127.1, 128.6, 129.1 (ArC), 135 (d, $J = 6.6$ Hz, ArC), 168.7 ppm (d, $J = 6.6$ Hz, CO); MS (EI): *m/z*: 298 (10) $[M]^+$, 270 (14), 243 (100), 215 (13), 109 (52), 107 (49), 105 (43), 91 (48); HRMS: *m/z*: calcd for $C_{14}H_{21}O_6P$: 316.1076; found: 316.1071.

Ethyl (*R*)-2-(diethylphosphoryloxy)-4-phenylbutanoate (6o): Colourless liquid; $[\alpha]_D^{25}=+4.5$ ($c=1.5$, $CHCl_3$); 90% *ee* from HPLC analysis Daicel Chiralpak AD, $\lambda=254$ nm, *n*-hexane/2-propanol 98:2, 1 mL min^{-1}, $t_r=$ 31.5 and *36.0* min; $R_f=0.22$ (*n*-hexane/ethyl acetate 3:2); IR (neat): $\tilde{\nu}=$ 1754, 1234, 1168, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.26$–1.37 (m, 9H, 2×CH_3CH$_2$OP, CH$_3$CH$_2$OC), 2.17–2.22 (m, 2H, CH_2CH), 2.77 (t, $J=7.9$ Hz, 2H, PhCH_2,), 4.11–4.26 (m, 6H, 2×CH$_2$OP, CH$_2$OC), 4.79–4.88 (m, 1H, CH), 7.18–7.21 (m, 3H, ArH), 7.25–7.29 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=14.1$ (*C*H$_3$CH$_2$OC), 16.0 (m, 2× *C*H$_3$CH$_2$OP), 30.8 (*C*H$_2$Ph), 34.7 (*C*H$_2$CH), 61.5 (*C*H$_2$OC), 64.1 (m, 2× *C*H$_2$OP), 74.8 (CH), 126.2, 128.4, 128.5, 140.5 (ArC), 169.9 ppm (d, $J=$ 3.3 Hz, CO); MS (EI): *m*/*z*: 345 (0.1) $[M+H]^+$, 197 (48), 155 (29), 144 (28), 117 (100), 115 (27), 99 (25), 91 (54); HRMS: *m*/*z*: calcd for $C_{16}H_{25}O_6P$: 344.1389; found: 344.1379.

General procedure for the synthesis of aminoalcohol derivative 8a:[28] To a suspension of $LiAlH_4$ (2.5 mmol, 95 mg) in THF (5 mL) at 0°C, a solution of **3a** (0.5 mmol, 135 mg) in THF (2 mL) was slowly added. After stirring (4 h), the reaction was quenched with water (0.5 mL), and di-*tert*-butyl dicarbonate (0.6 mmol, 131 mg) was added in one portion, stirring the reaction at room temperature overnight. THF was evaporated, water (5 mL) and ethyl acetate (5 mL) were added and the organic phase separated, dried ($MgSO_4$) and evaporated. The residue was purified thereby yielding **8a** as an optically pure enantiomer. Colourless oil; $[\alpha]_D^{25}=-3.4°$ ($c=1.0$, EtOH) (98% *ee*); {lit.[28] $[\alpha]_D^{25}=+3.5$ ($c=1.0$, EtOH), (99% *ee*) for the (*S*)-enantiomer}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.42$ [s, 9H, C-(CH$_3$)$_3$], 3.14–3.26, 3.40–3.45 (2×m, 3H, CH$_2$, OH), 4.75–4.79 (m, 1H, C*H*OH), 7.24–7.33 ppm (m, 5H, Ar).

General procedure for the synthesis of naturally occurring (−)-tembamide and (−)-aegeline:[1c,17] A solution of the crude product **3c** (0.25 mmol, 75 mg) in THF (2 mL) was slowly added to a suspension of $LiAlH_4$ (1.25 mmol, 49 mg) in THF (5 mL) at 0°C. After stirring the mixture for 12 h the reaction was quenched with an aqueous 1 M solution of NaOH (0.375 mmol, 0.375 mL) and benzoyl chloride (0.38 mmol, 44 μL for the synthesis of tembamide) or cinnamoyl chloride (0.38 mmol, 64 mg for the synthesis of aegeline) poured into the flask, the reaction being stirred for an additional 6 h time. THF was evaporated, water (5 mL) and ethyl acetate (5 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. The residue was purified by recrystallisation, thus obtaining (−)-tembamide **9c** or (−)-aegeline **10c** as optically pure enantiomers.

(−)-Tembamide (9c):[17] Colourless prisms; m.p. 149°C (*n*-hexane) {lit[17] m.p. 147–148°C)}, $[\alpha]_D^{25}=-58°$ ($c=0.4$, $CHCl_3$) (98% *ee*); {lit.[17] $[\alpha]_D^{24}=-59.8$, ($c=0.4$, $CHCl_3$), (99% *ee*)]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 3.46–3.55 (m, 1H, CH$_2$N), 3.80 (s, 3H, CH$_3$O), 3.80–3.91 (m, 1H, CH$_2$N), 4.87–4.91 (m, 1H, CHO), 6.66 (brs, 1H, OH), 6.89 (d, 2H, $J=8.6$ Hz, ArH), 7.32 (d, 2H, $J=8.6$ Hz, ArH), 7.39–7.50 (m, 3H, ArH), 7.73–7.76 ppm (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=47.7$ (CH$_2$N), 55.3 (CH$_3$O), 73.3 (CHOH), 113.9, 126.9, 127.1, 128.6, 131.6, 133.8, 134.1, 159.3 (ArC), 168.5 ppm (C=O).

(−)-Aegeline (10c):[17] Pale yellow oil; $[\alpha]_D^{25}=-34.5°$ ($c=0.5$, $CHCl_3$) (98% *ee*); {lit.[17] $[\alpha]_D^{24}=-35.6$, ($c=0.4$, $CHCl_3$) (99% *ee*)]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.41$–3.50 (m, 1H, CH$_2$N), 3.78–3.86 (m, 1H, CH$_2$N), 3.80 (s, 3H, CH$_3$O), 4.87 (dd, $J=8.0$, 1H, 3.3 Hz, CHO), 6.08 (brs, 1H, OH), 6.40 (d, $J=15.6$ Hz, 2H, ArC*H*=CH), 6.89 (d, $J=8.6$ Hz, 2H, ArH), 7.31 (d, $J=8.6$ Hz, 2H, ArH), 7.35–7.38 (m, 3H, ArH), 7.48–7.51 (m, 2H, ArH), 7.65 ppm (d, $J=15.6$ Hz, 2H, C=CHC=O); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=47.6$ (CH$_2$N), 55.3 (CH$_3$O), 73.4 (CHOH), 113.9 (ArC), 120.00 (OC*C*H=CH), 127.1, 127.9, 128.8, 129.8, 133.8, 134.1, 141.77, 159.3 (CH=*C*HAr, ArC), 167.1 ppm (CO).

General procedure for the synthesis of unsaturated cyanoacetates 11: Compound **3** (1 mmol), sodium acetate (4 mmol, 256 mg) and acetic acid (4 mmol, 230 μL) were added to a suspension of $Pd(OAc)_2$ (0.05 mmol, 11.7 mg) and PPh_3 (0.1 mmol, 25 mg) in acetonitrile (5 mL). The reaction was stirred at room temperature for 24 h, the solvent evaporated and water (5 mL) added. The aqueous phase was treated with ethyl acetate (2×5 mL) and the combined organic portions dried ($MgSO_4$) and evaporated.). Spectroscopic and physical data of the major compounds **11** of the crude mixtures (see text and Scheme 5) follows:

(*E*,4*R*)-4-Acetoxypent-2-enenitrile (11ia):[30c] 88% *ee* from HPLC analysis Daicel Chiralcel OD-H, $\lambda=210$ nm, *n*-hexane/2-propanol 97:3, 0.6 mL min^{-1}, t_r (*Z* isomer) = 17.5 and *19.6* min, t_r (*E* isomer) = *20.7* and 27.7 min.^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.36$ (d, $J=6.7$ Hz, 3H, CH_3CH), 2.09 (s, 3H, CH$_3$CO), 5.39–5.49 (m, 1H, CH$_3$C*H*), 5.54 (d, $J=$ 16.3 Hz, 1H, C*H*=CHCN), 6.65 ppm (dd, $J=16.3$, 4.9 Hz, 1H, CH= C*H*CN).

(*E*,4*R*)-4-Acetoxynon-2-enenitrile (11jb):[30b] 94% *ee* from HPLC Daicel Chiralcel OD-H, $\lambda=210$ nm, *n*-hexane/2-propanol 99:1, 1.5 mL min^{-1}, t_r (*Z* isomer) = 7.3 and *9.3* min, t_r (*E* isomer) = *7.9* and 12.8 min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.86$–0.90 (m, 3H, CH_3CH$_2$), 1.25–1.32 (m, 6H, 3×CH$_2$), 1.61–1.65 (m, 2H, CH$_2$), 2.10 (s, 3H, COCH$_3$), 5.36 (q, $J=$ 5.3 Hz, 1H, CH$_2$C*H*), 5.50 (d, $J=17.7$ Hz, 1H, CH=C*H*CN), 6.63 ppm (dd, $J=17.7$, 5.3 Hz, 1H, C*H*=CHCN); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 13.9 (*C*H$_3$CH$_2$), 20.8 (CH$_3$*C*H$_2$), 22.4, 24.4, 31.3, 33.4 (3×CH$_2$, *C*H$_3$CO), 72.2 (*C*HO), 100.5 (CH=*C*HCN), 116.6 (CN), 151.4 (CH=*C*HCH), 169.8 ppm (CO); MS (EI): *m*/*z*: 180 (0.5) $[M-CH_3]^+$, 166 (15), 153 (32), 124 (20), 96 (100).

General procedure for the synthesis of cyanoallyl alcohols 12: Anhydrous potassium carbonate (0.2 mmol, 28 mg) was added to a solution of **11** (0.8 mmol) in dry methyl alcohol (5 mL), and the resulting suspension stirred overnight. Then, silica gel (100 mg) was added and the mixture stirred for another additional 5 min. The solvent was evaporated, the resulting crude being then purified by flash chromatography, which yielded pure compounds **12**.

(*E*,4*S*)-4-Hydroxypent-2-enenitrile (12ia):[30c] Colourless oil; $[\alpha]_D^{25}=-51.5$ ($c=0.9$, $CHCl_3$), 98% *ee*; {lit.[30c] for the (*S*)-enantiomer $[\alpha]_D^{24}=25.2$ ($c=$ 0.74, $CHCl_3$), 46% *ee*}; ^{1}H NMR (300 MHz, $CHCl_3$) $\delta=1.33$ (d, $J=$ 7.0 Hz, 3H, CH$_3$), 3.4 (brs, 1H, OH), 4.50 (ddq, $J=7.0$, 3.9, 0.9, Hz, 1H, CHO), 5.65 (dd, $J=16.3$, 0.9 Hz, 1H, CHCN), 6.75 (dd, $J=16.3$, 3.9 Hz, 1H, C*H*=CHCN); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta=22.3$ (CH$_3$), 66.8 (CHO), 97.9 (*C*HCN), 117.3 (CN), 157.8 (*C*H=CHCN).

(*E*,4*R*)-4-Hydroxynon-2-enenitrile (12jb):[30b] Colourless oil; $[\alpha]_D^{25}=-37.0$ ($c=1.0$, $CHCl_3$), 94% *ee*) {lit.[30b] for the (*S*)-enantiomer $[\alpha]_D^{25}=+37.4$ ($c=1.12$, $CHCl_3$), 99% *ee*}; IR (neat): $\tilde{\nu}=$ 3439, 2225, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$): $\delta=0.87$–0.91 (t, $J=6.6$, 3H, CH_3CH$_2$), 1.23–1.61 (m, 8H, 4×CH$_2$), 4.31 (m, 1H, C*H*OH), 5.07 (brs, 1H, OH), 5.67 (d, $J=16.4$ Hz, 1H, CH=C*H*CN), 6.75 ppm (dd, $J=16.4$, 4.0 Hz, 1H, C*H*=CHCN); ^{13}C NMR (75 MHz, $CHCl_3$) $\delta=13.9$ (*C*H$_3$CH$_2$), 22.4, 24.7, 31.5, 36.4 (4×CH$_2$), 71.0 (*C*HOH), 98.7 (CH=*C*HCN), 117.3 (CN), 156.6 ppm (CH=*C*HCH); MS (EI): *m*/*z*: 166 (2) $[M]^+$, 153 (32), 124 (28), 96 (100), 83 (83).

(*E*,4*R*)-4-(*N*,*N*-Dibenzylamino)pent-2-enenitrile (11ic): To a suspension of $Pd(OAc)_2$ (0.02 mmol, 4 mg) and PPh_3 (0.04 mmol, 9.5 mg) in acetonitrile (2 mL), compound **3i** (0.40 mmol, 94 mg) and dibenzylamine (0.80 mmol, 160 μL) were added in this order. The mixture was stirred for 12 h and then the solvent evaporated under vacuo. Water was added (5 mL) and the aqueous phase extracted with ethyl acetate (2×5 mL). The organic phase was dried ($MgSO_4$) and evaporated under vacuo. The resulting residue was purified by flash chromatography thus obtaining a colourless oily compound **11ic** as a mixture *Z*:*E* 0.3:1. $[\alpha]_D^{25}=+153.5°$ ($c=2.0$, $CHCl_3$), 88% *ee* from HPLC analysis (for each enantiomer) Daicel Chiralcel OD-H, $\lambda=254$ nm, *n*-hexane/2-propanol 95:5, 1.0 mL min^{-1}. $t_r=$ *8.1* and 13.9 (*Z*), *10.3* and 11.8 (*E*) min; $R_f=0.53$ (*Z*) and 0.60 (*E*) (*n*-hexane/ethyl acetate 4:1); IR (neat): $\tilde{\nu}=$ 2222, 1636 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$): $\delta=1.21$ (d, $J=6.9$ Hz, 3H, CH$_3$, *E*), 1.29 (d, $J=6.9$ Hz, CH$_3$, *Z*), 3.50 (m, 1H, CHCH$_3$, *E* and d, $J=$ 14.4 Hz, CH$_2$N, *Z*), 3.58 (s, 4H, CH$_2$, *E*), 3.77 (d, $J=14.4$ Hz, CH$_2$N, *Z*), 5.41 (d, $J=11.2$ Hz, CHCN, *Z*), 5.48 (d, $J=16.5$ Hz, 1H, CHCN, *E*), 6.54 (m, C*H*=CH, C*H*=CH, *Z*), 6.78 (dd, $J=16.5$, 5.3 Hz, 1H, C*H*=CH, *E*), 7.22–7.37 ppm (m, 13H, ArH, *Z*+*E*); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta=$ 13.1 (CH$_3$, *E*), 17.4 (CH$_3$, *Z*), 53.7 (CH$_2$, *E*), 54.2 (CH$_2$, *Z*), 54.4 (*C*HCH$_3$, *E*), 55.3 (*C*HCH$_3$, *Z*), 100.1 (*C*HCN, *Z*), 100.2 (*C*HCN, *Z*), 117.4 (CN), 127.1, 127.2, 128.3, 128.3, 128.4, 139.2, 139.3 (ArC, *Z*+*E*), 155.5 (*C*H=CH,*Z*), 157.4 ppm (*C*H=CH,*E*); MS (IE): *m*/*z*: 276 (2) $[M]^+$, 261 (21), 91 (100). HRMS: *m*/*z*: calcd for $C_{19}H_{20}N_2$: 276.3801; found: 276.3805.

***N*-[4-(*N*′,*N*′-Dibenzylamino)pentyl]benzamide 13**: To a suspension of lithium aluminium hydride (1 mmol, 38 mg) in anhydrous THF (3 mL)

was slowly added, at 0 °C, a solution of **11ic** (0.25 mmol, 69 mg). The reaction mixture was stirred at room temperature overnight and quenched with cold water (3 mL). The aqueous phase was extracted with ethyl acetate (2×5 mL) and the organic phase dried ($MgSO_4$) and evaporated under vacuo. The residue, dissolved in dichloromethane (3 mL), was treated with benzoyl chloride (0.55 mmol, 78 μL) and pyridine (0.75 mmol, 75 μL) at 0 °C, and the reaction was further stirred at room temperature for 6 h. The organic solution was washed with water, dried ($MgSO_4$) and evaporated. The resulting residue was purified by flash chromatography (silica gel) thus yielding pure amide **13** as a pale yellow oil; 42% *ee* from HPLC, Daicel Chiralcel AD, $\lambda = 254$ nm, *n*-hexane/2-propanol 90:10, 1.0 mL min^{-1}, $t_r = 16.7$ and *21.4* min; $R_f = 0.57$ (*n*-hexane/ethyl acetate 3:2). IR (neat): $\tilde{\nu} = 3120$, 1737 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$): $\delta = 0.88$ (d, $J = 7.6$ Hz, 3H, $CHCH_3$), 1.25–1.31 (m, 2H, $CH_2CH_2CH_2$), 1.56–1.72 (m, 2H, $CHCH_2$), 2.74 (m, 1H, $CHCH_3$), 3.24–3.31 (m, 2H, CH_2NH), 3.35, 3.72 (2×d, $J = 14.0$ Hz, 4H, 2×CH_2Ph), 7.20–7.70 (m, 15H, ArH); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta = 13.2$ (CH_3), 26.9, 31.2 ($CHCH_2CH_2$), 39.9 (CH_2NH), 51.5, 53.2 (2×CH_2Ph, $CHCH_3$), 126.7, 127.8, 128.5, 128.6, 128.9, 131.3, 134.8, 140.5 (Ar), 167.4 (C=O); MS (EI): *m*/*z*: 385 (3) $[M-H]^+$, 295 (14), 224 (59), 105 (26), 91 (100), 77 (10); HRMS: *m*/*z*: calcd for $C_{26}H_{30}N_2O$: 386.2358; found: 386.2361.

Acknowledgements

This work has been supported by DGES of the Spanish Ministerio de Ciencia y Tecnología (BQU2001-0724-C02), by Generalitat Valenciana (CTIOIB/2002/320 and GRUPOS03/134) and by the University of Alicante. Thanks are also due to CESCA (Centre de Supercomputació de Catalunya), and the UIB (Universitat de les Illes Balears) for their generous allocation of computation time. A. Baeza also thanks Generalitat Valenciana for a pre-doctoral fellowship (CTBPRB/2002/107).

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Received: December 16, 2004
Published online: March 17, 2005