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A recyclable chiral auxiliary for the asymmetric syntheses of α-aminonitriles and α-aminophosphinic derivatives

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Abstract—Optically active α-aminonitriles and α-aminophosphinic derivatives have been prepared in high yield and high ee using an easy route by extending our previously developed method involving the following sequence: (i) stereoselective Strecker condensation of a chiral ketone with HCN and NH_3 followed by (ii) condensation with RCHO, an HCN donor or a phosphinate and (iii) regioselective decomposition of the intermediate to release the target compound. The third step enables the easy regeneration of the initial chiral ketonic auxiliary.

1. Introduction

The Strecker reaction[1] represents one of the simplest and most economical methods for the preparation of α-amino acids on a laboratory scale as well as on a larger scale. There has also been considerable interest in extending the scope of this reaction to asymmetric processes for the synthesis of optically active amino acids and in particular of non-proteinogenic α-amino acids.[2] α-Aminophosphonic and α-aminophosphinic acids, in which the carboxyl group of the α-amino acids is replaced by a phosphorus-derived functionality, have attracted significant attention because of their structural analogy allowing some of their derivatives to behave as transition state analogues in hydrolytic reactions. The corresponding enzyme inhibitor properties have been exploited in the design of herbicides, neuroactive agents, HIV protease antagonists, etc.[3] Although numerous examples of the stereoselective syntheses of α-amino-acids and α-aminophosphonic[4] derivatives can be found in the literature, there are only few examples dealing with the stereoselective synthesis of α-aminophosphinic derivatives. Recently, Haruki et al.[5] proposed a synthesis based on the control of chirality of both C and P centres starting from a chiral phoshinate. The latter was obtained by the resolution of two diastereoisomers. The originality of this concept is based on the use of a chiral phosphorus auxiliary. However, this process implies the separation of diastereoisomers at an intermediary stage and many subsequent steps to afford the α-aminophosphinate product.

A popular asymmetric concept in stereoselective synthesis is the use of a preformed N-substituted chiral imine and the subsequent addition of a nucleophile HX (X = CN, PO_3H, PO_2H, PO_2Et, etc.) in the absence or presence of a catalyst.[6] It is also possible to add a chiral nucleophile such as 2-hydrogeno-2oxo-1,4,2-oxazaphosphinane onto a prochiral imine as recently described by Pirat et al.[7] The level of asymmetric induction at the α-carbon depends both on the nature of the substituents (steric hindrance, hydrophilic/hydrophobic interactions) and/or the possible interaction of the nucleophile with the substrate that could be otherwise enhanced in the organocatalytic versions of these reactions.[2]

According to Harada's principle,[8] and following our previous investigations on the Strecker reaction, we have already outlined a promising synthesis involving a tertiary

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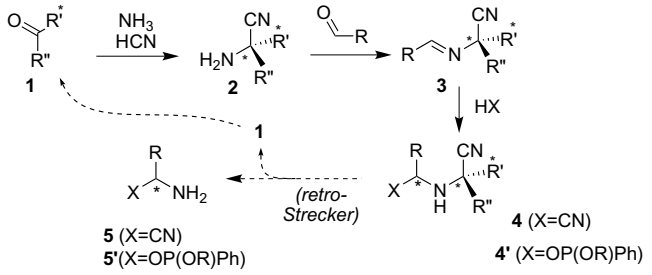
α-aminonitrile **2** derived from the Strecker reaction between a chiral ketone **1** with HCN and NH_3[9]. The subsequent condensation of this tertiary α-aminonitrile with an aldehyde affords the N-substituted chiral imine **3**. Imines **3** with a cyano group closely attached to the nitrogen atom display an increased stability as shown, for example, by a good resistance to the hydrolysis that make the use of stabilizing aromatic substituents useless in these cases. The subsequent addition of HCN leads to iminodinitrile **4**. The selective decomposition of **4** (X = CN) gave the enantiomerically enriched aminonitrile **5** with the recovery of the starting chiral ketone **1**. In this synthesis, the chirality of product **5** is the result of two consecutive 1–3 transfer of chirality in the steps of formation of aminonitrile **2** and of iminodinitrile **4** (Scheme 1).



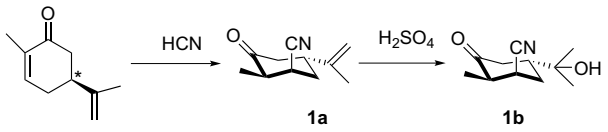
Scheme 1.

We have already demonstrated that the immobilization of the ketonic auxiliary offers opportunities in the synthesis of chiral amino acids on solid supports.[10] Taking into account the availability of various hydrocyanating agents, such as cyanohydrins $Me_2C(CN)OH$, diethyl aluminium cyanide $(C_2H_5)_2AlCN$,[11] or trimethylsilyl cyanide (TMSCN),[12,13] we decided to investigate the effects of hydrocyanating agents on the stereoselectivity of the asymmetric synthesis of α-aminonitriles. Herein, we report the generalization of this synthetic methodology to the asymmetric synthesis of α-aminophosphinate **5′** via a N-substituted α-aminophosphinate **4′** (X = OP(OR)Ph). This methodology allows in principle chiral auxiliary **2** to be regenerated from the recycled ketone **1**.

2. Results and discussion

The chiral ketonic precursors **1a** and **1b** were prepared from enantiopure (−)-carvone.[10] (1*R*,2*R*,3*R*,5*R*)-(−)-3-Cyanodihydrocarvone **1a** was obtained by the straightforward stereoselective hydrocyanation of the cyclic double bond. Subsequent hydroxylation of **1a** afforded (−)-(1*R*,2*R*,5*R*)-2-methyl-5-(1-hydroxy-1-methylethenyl)-3-oxocyclohexane carbonitrile **1b** (Scheme 2).

Starting from compounds **1a** or **1b,** α-aminonitriles **2a** and **2b** (Scheme 3) were prepared according to a procedure previously described by us[10] in convenient yields. The 1–3 asymmetric induction from the initial stereogenic centre of carvone gives high diastereoselectivity (up to 90%) and good yield starting from (*R*)-cyanocarvone. The subsequent step consisted of the selective reaction of the major diastereoisomer of α-aminonitriles **2a** and **2b** from the diastereoisomeric mixture with RCHO. As described previously, chiral imines **3a** and **3b** are obtained with a preferential *anti* configuration.[14] The corresponding imines **3a** and **3b**, are obtained in good yields (89% in the case of R = Bn).



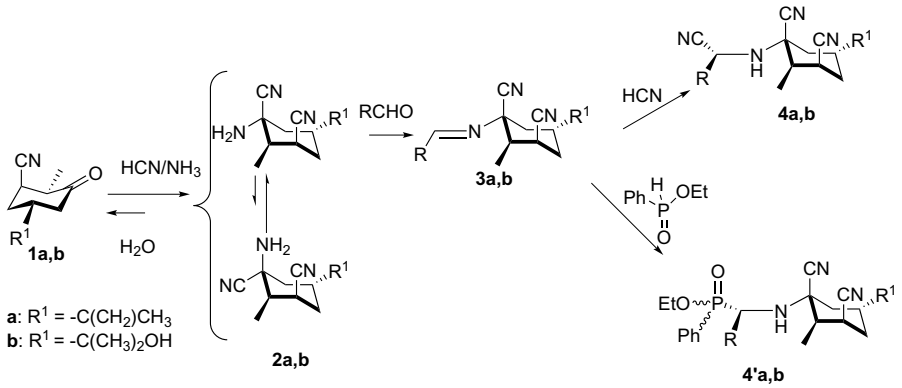
Scheme 2.

2.1. α-Aminonitrile synthesis

Hydrogen cyanide can be generated directly in the reaction mixture by neutralization of cyanide salts, or obtained from a donor such as acetone cyanohydrin. The addition of hydrogen cyanide to imines **3a** and **3b** leads to α-iminodinitriles, **4a** and **4b**, respectively. The (*R*)-configuration observed on the formed tetrahedral centre corresponds to an attack on the less bulky *Si* side of the imine. In the case of the precursor of the valine, R = Pr^i, prepared either by the addition of HCN or by using $(CH_3)_2C(CN)OH$ as a HCN donor, the observed diastereoselectivities (*R*/*S*) were quite similar (about 70:30, Table 1). This result is in agreement with a dissociation of the acetone cyanohydrin leading to the formation of trace amounts of HCN in methanol. However, it should be noted that these yields and diastereoselectivities are considerably higher than those obtained by the one pot reaction between aminonitrile **2** and aldehyde **1′** in the form of cyanohydrin RCH(CN)OH (R = Pr^i, yield 10%, *R*/*S* = 55:45).

In Table 1 are shown the main results obtained using diethylaluminium cyanide or trimethylsilyl cyanide as hydrocyanating reagents. With diethylaluminium cyanide, the diastereoselectivity (*R*/*S* = 70:30) remains unchanged when compared to the direct hydrocyanation in spite of the fact that a complexation of the alkoxide $EtAl(OPr^i)CN$ (generated by previous treatment of Et_2AlCN with 2-PrOH) on the *Si* face of the chiral imine is highly probable. With trimethylsilyl cyanide, the experimental conditions proposed by Kunz et al.[13] (2-PrOH/20 °C/$ZnCl_2$ or THF/−40 °C/$SnCl_4$) led to a strong increase in the reaction rate for the hydrocyanation of imine **3a** although the diastereoselectivity is often reduced when compared with the direct use of HCN.

In a less dissociating solvent, such as chloroform and in the presence of zinc chloride, the same diastereoselectivity (*R*/*S* = 75:25) was observed using chiral auxiliary **1a**, whereas **1b** induces a significant improvement (*R*/*S* = 85:15). These results suggest that the presence of the 1-hydroxy-1-methylethyl group in the chiral auxiliary **1b** allows the complexation of $ZnCl_2$ on the *Si* face of the imine and then facilitates the cyanide attack generated by the interaction of Me_3SiCN with the Lewis acid.



Scheme 3.

Table 1. Yields and diastereoselectivities of the synthesis of α-aminodinitriles **4a** and **4b** (R = Pr^i) by hydrocyanation of the imines **3a** and **3b** (R = Pr^i)

HCN donor	Conditions	Chiral auxiliary	Yield (%)	Diastereoisomers **4** (R = Pr^i) ratio (*R*/*S*)
$Me_2C(OH)CN$	MeOH/reflux	**1a**	68	70:30
		1b	75	75:25
HCN	MeOH/20 °C	**1a**	54	75:25
		1b	50	75:25
Et_2AlCN/2-PrOH (1.5:1)	THF/−78 °C	**1a**	85	70:30
Me_3SiCN	(1) $HCCl_3$/20 °C	**1a**	0	
	(2) $HCCl_3$/20 °C/$ZnCl_2$	**1a**	75	70:30
	(3) 2-PrOH/20 °C/$ZnCl_2$	**1a**	54	60:40
	(4) THF/−40 °C/$SnCl_4$	**1a**	63	70:30
	(5) THF/20 °C/$SnCl_4$	**1a**		60:40
	(6) $HCCl_3$/20 °C/$ZnCl_2$	**1b**	73	85:15

For the hydrocyanation by Me_3SiCN, the experimental conditions are given below: (imine weight g, solvent volume mL, Me_3SiCN volume mL, Lewis acid weight g, reaction time h.) 1 (1, 20, 0.5, 0, 2); 2 (0.5, 20, 0.5, 0.53, 2); 3 (1, 40, 1, 0.5, 6); 4 (1, 20, 1, 0.6, 6); 5 (1, 20, 1, 0.6, 4); 6 (0.3, 20, 0.3, 0.15, 4).

As we have shown previously,[10] the formation of the chiral α-aminonitrile **5** can be achieved by the treatment of α-aminodinitrile **4** with silver nitrate in nitric acid, without racemization. This regioselective decomposition in high yield and high ee of the tertiary aminonitrile present in **4** leads to an acceptable recovery of the chiral ketone **1**.

2.2. α-Aminophosphinate synthesis

Chiral imines **3a** and **3b** obtained by the addition of benzaldehyde (R = Ph) onto α-aminonitriles **2a** and **2b**, were chosen as substrates for the hydrophosphinylation reaction using ethyl phenyl phosphinate as a model compound. Chiral imines **3a** and **3b** were heated with 1.2 equiv of racemic ethylphenylphosphinate at 60–70 °C either in chloroform or without solvent according to the classical procedure[15] and the reaction was run until the imine was entirely consumed. The diastereoisomeric ratios for N-protected α-aminophosphinates **4′a** and **4′b** were determined by ^{31}P NMR in the reaction mixture. From a stereochemical point of view, the addition step induces the formation of two new stereogenic centres (the reactive carbon atom and the phosphorus atom) leading, in principle, to four diastereoisomers, which could be detected by ^{31}P NMR. The results are reported in Table 2. Elimination of the solvent followed by crystallization in EtOAc afforded the two major diastereoisomers of **4′b**. The best yields (Table 2) were obtained starting from **3b**, when the reaction was performed in $CHCl_3$. The diastereoisomeric ratios were almost independent of changes in the experimental conditions used.

Suitable crystals of one of the major diastereoisomers of **4′b** (δ 40.4 ppm, ^{31}P NMR) were obtained by repeated crystallization from ethyl acetate. Figure 1 shows the molecular structure as determined by X-ray diffraction analysis performed on a single crystal. All NMR data could be assigned and are in good agreement with the chair-like conformation characteristic of the crystal. Coupling constants are given in Section 4.

The major diastereoisomer **4′b** has an (*S*)-configuration at C_α indicating that the diastereoselectivity of this first step is clearly under kinetic control. The (*S*)-configuration at the α-carbon is the result of the preferential formation of

Table 2. Diastereoisomeric ratio and the yield of N-protected aminophosphinate **4′a** and **4′b** with or without solvent

N-Protected aminophosphinate	Solvent	Diastereoisomeric ratio (%) ^{31}P NMR	Yield (%)
4′b	$CHCl_3$	8:46:3:43	96
4′b	No solvent	9:51:8:32	55
4′a	$CHCl_3$	7:51:5:37	80
4′a	No solvent	9:47:6:38	71

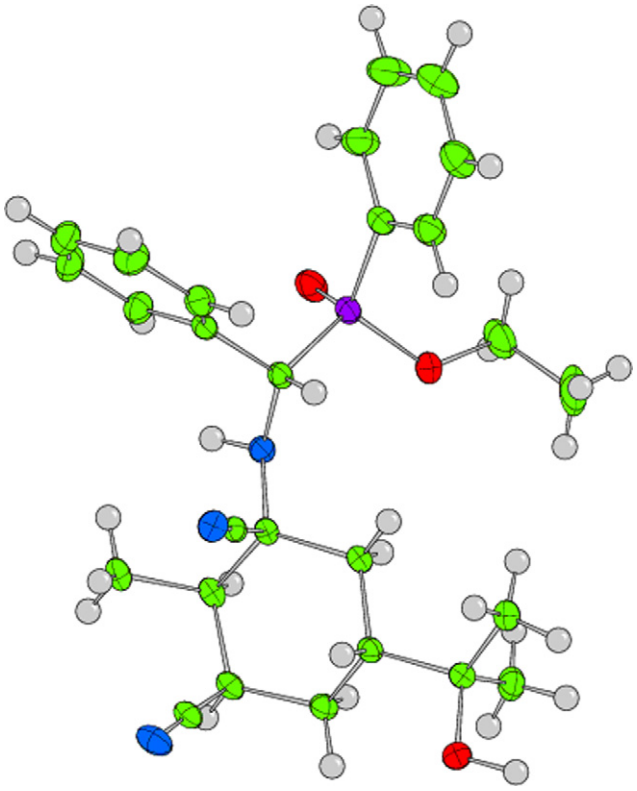
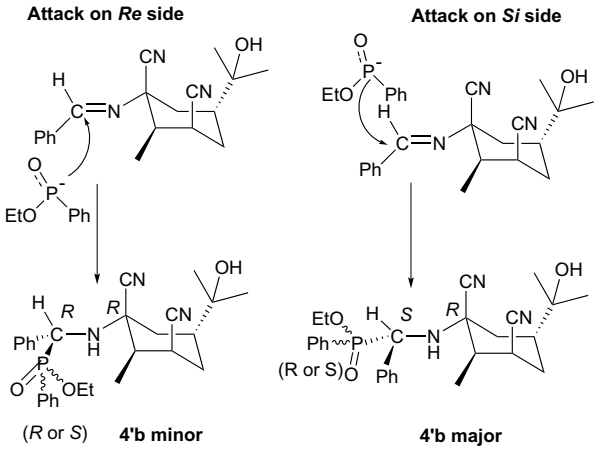


Figure 1. The X-ray structure of a molecule of **4′b** showing displacement ellipsoids drawn at the 30% probability level. Hydrogen atom spheres are drawn with an arbitrary radius.

a transition state corresponding to the addition of ethylphenylphosphinate onto the *Si* face of the imine **3b** in an *anti*-configuration, as shown in Scheme 4.



Scheme 4. Possible explanation for the preferential (*S*)-configuration at the α-carbon by attack on the *anti*-conformer of imines **3a** and **3b**.

In order to confirm our hypothesis and to validate the recovery of the ketonic auxiliary, the deprotection of **4′b** (Scheme 5) was achieved by using aqueous $AgNO_3$/HNO_3 as previously described.[9]

The resulting α-aminophosphinate **5′b** [two majors diastereoisomers were identified as C(*S*)P(*R*) and C(*S*)P(*S*)] was obtained in high yield (90%) and with a P(*R*)/P(*S*) ratio equal to 78:22. Treatment of **5′b** with HBr in glacial acetic acid according the Belov[16] procedure afforded pure (*S*)-α-aminobenzyl phenylphosphinic acid. The specific rotation {$[\alpha]^{20}$ (λ, nm) = +29 (589)} was opposite to that of the known compound[16] thus confirming our hypothesis and indicating that the diastereoisomeric excess exceeds 9:1 in the hydrophosphinylation step. The starting ketone was also recovered in good yield (89%) and without substantial racemization.

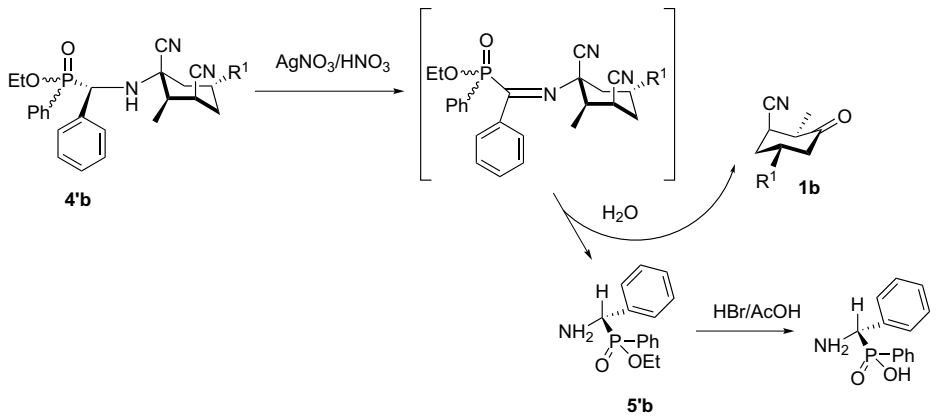
3. Conclusion

In conclusion, we have developed a concise five step enantioselective synthesis of α-aminophosphinic acids by extending our original asymmetric synthetic route to α-aminonitriles or aminoacids using a chiral recyclable auxiliary. This synthetic pathway corresponds to 1–5 chirality transfer. The specific structure of the cyclanic starting chiral ketone allows the easy regeneration of the chiral auxiliary. The key step of the process involves the addition of HX (X = CN or PO(OEt)(Ph)) onto the *Si* face of a prochiral imine. In the first case (HCN), we showed that the stereoselectivity could be enhanced by the use of $ZnCl_2$. Excellent stereoselectivity is observed for the hydrophosphinylation reaction. *C*(*S*)-α-aminophosphinates are obtained in good yield through an easy work-up. Application of the synthesis of chiral α,α′-diaminophosphinate is currently on going.

4. Experimental

^{1}H NMR spectra were recorded with a Bruker AC200 (200 MHz) or a Bruker AM400 (400 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from TMS, which was used as an internal standard. ^{31}P NMR spectra were recorded with a Bruker AC200 (81.01 MHz). Chemical shifts are expressed in parts per million downfield from H_3PO_4 85%. ^{13}C NMR spectra were recorded with a Bruker AM400 spectrometer (100.61 MHz) using broadband decoupling. Chemical shifts are expressed in parts per million downfield from TMS, using the middle resonance of $CDCl_3$ (δ 77 ppm) as an internal standard. Infrared spectra were recorded with a Thermo Nicolet Avatar 320 FT-IR spectrophotometer. Mass spectra were obtained with a Jeol SX 102 spectrometer and on Micromass Q-Tof by electrospray ionization. Elemental analyses were performed with a Perkin–Elmer 2400 CHN recorder.

The collection of the diffraction data was performed at 173 K on an Oxford-Diffraction GEMINI-S single crystal diffractometer using graphite-monochromatized Cu-Kα radiation (λ = 1.5418 Å) in order to maximize the difference between Friedel intensities as to facilitate the determination of the absolute configuration. A total of 9367 frames were collected using ω and ϕ scans mode. The three-dimensional structure was solved in the monoclinic space group *C2* (no. 5) by using ab initio methods with the recently discovered charge-flipping algorithm.[17] The



Scheme 5.

absence of the inversion centre was established by an analysis of the resulting electron density map yielding $R_{sym} = 0.62$, where R_{sym} is the normalized averaged weighted square phase error between symmetry equivalent structure factor phases. The final Flack parameter, 0.015(18), shows that the right absolute configuration was chosen. The hydrogen atoms were found from difference Fourier maps, and their positions were optimized using an initial refinement with soft restraints on the bonds and angles to regularize their geometry. The H_2O molecule was found to be disordered with respect to its protons over two positions with equal occupation probabilities. The structural refinements were performed with the CRYSTALS package[18] on F_{obs} using reflections with $I > 2\sigma(I)$. CCDC 677069 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Optical rotations were measured at 589 nm (Na) and 365, 436, 546, 578 nm (Hg) with a digital polarimeter Perkin–Elmer 341 using a 1 mL cell. Melting points (uncorrected) were measured with a Totoli instrument. TLC were performed with Silica 60 F254 (Merck) plates and revealed with iodine and/or UV-ray.

(−)-(1*R*,2*R*,5*R*)-2-Methyl-5-(1-methylethenyl)-3-oxocyclohexane carbonitrile **2a** and (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-methylethenyl)cyclohexane-1,3-dicarbonitrile **3a** (R = Pr^i) were prepared according to our previously described procedures.[9,10]

4.1. (1*R*,2*R*,3*R*,5*R*)-1-Amino-2-methyl-5-(1-hydroxy-1-methyl-ethyl)cyclohexane-1,3-dicarbonitrile 2b

A solution of sodium cyanide (5.98 g, 122.04 mmol) and ammonium chloride (7.75 g, 144.86 mmol) in 96 mL of 28% ammonia solution was added dropwise to a solution of **2b** (10 g, 51.21 mmol) in methanol (7 mL). The reaction mixture was then stirred at room temperature. After 24 h, ammonia was removed in vacuo. The solution was saturated with sodium chloride and extracted with dichloromethane. The organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Yield: 80%. mp = 121.4–122 °C; $[\alpha]_D^{20} = -14.9$ (*c* 0.32, CH_3OH); IR (CH_2Cl_2, cm^{-1}) *v* 3603 (OH), 3391 (NH_2), 2304 (CN), 1389–1372 (*gem* dimethyl); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (6H, d, CH_3, $J_{H-H} = 8.52$ Hz), 1.31 (3H, d, CH_3, $J_{H\text{-}2ax} = 6.82$ Hz,), 1.30 (1H, t, H-6ax, $J_{6ax-6eq} = 12.88$ Hz,), 1.41 (1H, td, H-4ax, $J_{4ax-4eq} = 13.42$ Hz, $J_{4ax-5ax} = 4.85$ Hz,), 1.63 (1H, m, H-2ax), 1.80 (1H, br s, OH), 1.94 (1H, m, H-5ax), 2 (2H, br s, NH_2), 2.18 (1H, m, H-4eq, $J_{4eq-4ax} = 13.52$ Hz, $J_{4eq-3eq} = 2.57$ Hz,), 2.26 (1H, m, H-6eq, $J_{6eq-6ax} = 13.08$ Hz, $J_{6eq-5ax} = 2.51$ Hz,), 3.04 (1H, m, H-3eq, $J_{3eq-2ax} = 4.97$ Hz, $J_{3eq-4eq} = 2.62$ Hz,); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 14.7 (CH3), 26.86 (CH_3), 27.4 (C-4), 29.8 (C-3), 40.12 (C-6), 42.44 (C-2), 53.93 (C-1), 71.4 (*C*–OH), 118.71 (*C*N–C-3), 121.63 (*C*N–C-1).

4.2. (1*R*,2*R*,3*R*,5*R*)-1-Benzylideneamino-2-methyl-5-(1-hydroxy-1-methyl-ethyl)cyclohexane-1,3-dicarbonitrile 3b (R = Ph)

A mixture of α-aminonitrile **2b** (3.92 g, 17.73 mmol), benzaldehyde (2.80 g, 26.38 mmol) and anhydrous Na_2SO_4 in 35 mL of anhydrous chloroform was refluxed with a water-separative funnel. During the reaction, the mixture was filtered twice after which more anhydrous Na_2SO_4 was added. After 18 h, the mixture was cooled to room temperature and filtered. The filtrate was concentrated under vacuum to give the crude iminodinitrile. Yield: 89%. The residue was purified by chromatography (silica gel column) by using diethyl ether/methanol (98:2) as eluent. Yield: 47%. Mp = 72.4–76.8 °C; $[\alpha]_D^{20} = -32.0$ (*c* 0.11, CH_3OH); IR (KBr, cm^{-1}) *v* 3395 (N–H), 2251 (CN), 1707 (C=N), 1646 (C=$C_{aromatic}$), 1384, 1368 (*gem* dimethyl), 1225 (C–O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, d, $J_{H\text{-}2ax} = 6.9$ Hz, CH_3), 1.17 (6H, m, CH_3), 1.55 (1H, m, H_{4ax}), 1.73 (1H, m, H_{6ax}), 2.02 (1H, m, H_{6eq}), 2.11 (1H, m, H_{2ax}), 2.29 (1H, m, H_{4eq}), 2.49 (1H, m, H_{5ax}), 3.16 (1H, m, H-3eq), 7.43–7.74 (5H, m, $H_{aromatic}$), 8.55 (1H, s, H_{imine}).

4.3. (1*R*,2*R*,3*R*,5*R*)-1-Isobutylidene-amino-2-methyl-5-(1-hydroxy-1-methylethyl)cyclohexane-1,3-dicarbonitrile 3b (R = Pr^i)

A mixture of α-aminonitrile **2b** (1.6 g, 7.24 mmol), isobutyraldehyde (7.78 g, 10.86 mmol) and anhydrous Na_2SO_4 in 35 mL of anhydrous chloroform was heated at reflux

in the presence of a water-separative funnel. During the reaction, wet sulfate was removed by filtration and a new amount of anhydrous Na_2SO_4 was introduced in the reaction medium. After 6 h, the mixture was cooled to room temperature and filtered. Evaporation of the solvent in vacuo afforded slightly yellow crystals. Yield: 90%. IR ($CHCl_3$, cm^{-1}) ν 3600, 3400–3500 (br) (O–H), 2240 (CN), 1660 (C=N), 1390, 1370 (*gem* dimethyl); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.1–1.26 (15H, CH_3, Pr^i), 3.16 (1H, m, H-3eq), 7.9 (1H, s, H_{imine}).

4.4. Hydrocyanation of (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-methylethenyl)cyclohexane-1,3-dicarbonitrile 3a (R = Pr^i) by acetone cyanohydrin

Acetone cyanohydrin (7.5 mL, 79 mmol) was added to **3a** (R = Pr^i) (1.9 g, 7.4 mmol) in methanol (50 mL). After 4 h at reflux, methanol was eliminated in vacuo. The remaining acetone cyanohydrin was distilled in vacuo (0.1 mm Hg) to afford a mixture of (*R*)-**4a** and (*S*)-**4a**. Diastereoisomeric excess (de) (*R*/*S*) = 7:3 was determined by ^1H NMR 250 MHz. Silica gel chromatography (acetone/$CHCl_3$: 3:97) of the mixture gave the two iminodinitriles (*R*)-**4a** (R = Pr^i) and (*S*)-**4a**, (R = Pr^i) Yield: 68%. Compound (*R*)-**4a**, (R = Pr^i) mp = 163 °C; $[\alpha]_D^{20} = +60.8$ (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν 3305–3340 (NH), 3080 (CH_2=CH), 2240 (CN), 1640 (C=C); NMR ^1H ($CDCl_3$, 250 MHz) δ 1.13 (d, 6H, Pr^i, $J = 6.78$ Hz), 1.3 (m, 1H, H-6ax), 1.43 (d, 3H, CH_3, $J = 6.78$ Hz), 1.55 (m, 1H, H_{4ax}), 1.79 (m, 4H, CH_3, H_{2ax}), 2.04 (m, 1H), 2.20 (m, 1H, H_{4eq}), 2.53 (m, 2H, H_{6eq}, H_{5ax}), 3.15 (m, 1H, H_{3eq}), 3.65 (t, 1H), 4.85 (d, 2H, CH_2).

Compound (*S*)-**4a** (R = Pr^i): Mp = 185 °C; $[\alpha]_D^{20} = -102.2$ (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν 3305–3340 (NH), 3080 (CH_2=CH), 2240 (CN), 1640 (C=C); NMR ^1H (250 MHz, $CDCl_3$) δ 1.03 (d, 6H, Pr^i), 1.23 (m, 1H, H-6ax), 1.37 (d, 3H, CH_3, $J = 6.78$ Hz), 1.50 (m, 1H, H-4ax), 1.73 (m, 4H, CH_3, H-2ax), 1.90 (m, 1H, H), 2.14 (m, 1H, H-4eq), 2.26 (m, 1H, H-6eq), 2.69 (m, 1H, H-5ax), 3.08 (m, 1H, H-3eq), 3.45 (t, 1H, H), 4.76 (d, 2H, CH_2).

4.5. Hydrocyanation of (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-hydroxy-1-methylethyl)cyclohexane-1,3-dicarbonitrile 3b (R = Pr^i) by acetone cyanohydrin

Acetone cyanohydrin (6.9 mL, 76 mmol) was added to **3b** (R = Pr^i) (2.1 g, 7.6 mmol) in methanol (50 mL). The mixture is heated at reflux for 5 h. Methanol was then evaporated in vacuo. The remaining acetone cyanohydrin was distilled in vacuo (0.1 mm Hg) to afford a mixture of (*R*)-**4b** and (*S*)-**4b**. Yield: 75%. de (*R*/*S*) = 7.5:2.5 by ^1H NMR 250 MHz. The two iminodinitriles (*R*)-**4b** (R = Pr^i) and (*S*)-**4b** (R = Pr^i) were separated by silica gel chromatography (MeOH/$CHCl_3$ 1:9).

Compound (*R*)-**4b** (R = Pr^i): mp = 168–170 °C; $[\alpha]_D^{20} = +57.2$ (*c* 1, MeOH); IR ($CHCl_3$, cm^{-1}) ν 3600 (OH), 3300–3500 (NH), 2240 (CN), 1370–1390 (CH_{3gem}); NMR ^1H (250 MHz, $CDCl_3$) δ 1.05 (d, 6H, CH_{3gem}, $J = 6.7$ Hz), 1.2 (s, 3H, CH_{3b}), 1.34 (d, 3H, CH_{3a}, $J = 6.8$ Hz), 1.38 (t, 1H, H_{6ax}), 1.44 (m, 1H, H_{4ax}), 1.70 (m, 1H, H_{2ax}), 1.95 (m, 1H), 2.21 (m, 1H, H_{4eq}), 2.67 (m, 1H, H_{6eq}), 3.09 (m, 1H, H_{3eq}), 3.65 (t, 1H).

Compound (*R*)-**4a** (R = Pr^i): IR ($CHCl_3$, cm^{-1}) ν 3600 (OH), 3300–3500 (NH), 2240 (CN), 1370–1390 (CH_{3gem}); NMR ^1H (250 MHz, $CDCl_3$) δ 1.05 (d, 6H, CH_{3gem}, $J = 6.7$ Hz), 1.2 (s, 3H, CH_{3b}), 1.34 (d, 3H, CH_{3a}, $J = 6.8$ Hz), 1.38 (t, 1H, H_{6ax}), 1.44 (m, 1H, H_{4ax}), 1.70 (m, 1H, H_{2ax}), 1.95 (m, 1H), 2.21 (m, 1H, H_{4eq}), 2.5 (m, 1H, H_{6eq}), 3.09 (m, 1H, H_{3eq}), 3.57 (m, 1H).

4.6. Hydrocyanation of (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-methylethenyl)cyclohexane-1,3-dicarbonitriles 3a and 3b (R = Pr^i) by hydrogen cyanide

Potassium cyanide (0.252 g, 3.9 mmol) in 15 mL of methyl alcohol was added dropwise to 5 mL of an HCl solution (0.79 M) in methyl alcohol in a 100 mL flask equipped with a condenser thermostated at 0 °C. A solution of **3a** (1 g, 3.9 mmol) in 10 mL of methyl alcohol was then added dropwise at room temperature. After 4 h, the mixture was filtered and the solvent was evaporated in vacuo. The reaction mixture was treated by chloroform. Salts were eliminated by filtration and the solvent was removed. Yield: 54%. de (*R*/*S*) = 7.5:2.5 by ^1H NMR 250 MHz. The same protocol was used for **3b** (R = Pr^i); Yield: 50%. de (*R*/*S*) = 7.5:2.5.

4.7. Hydrocyanation of (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-methylethenyl)cyclohexane-1,3-dicarbonitriles 3a and 3b (R = Pr^i) by diethylaluminium cyanide

Under nitrogen, propan-2-ol (0.06 g, 1 mmol) was added to a toluene (1.5 mL, 1.5 mmol) solution (1 M) of diethylaluminium cyanide. This mixture was added quickly to a solution of **3a** (0.257 g, 1 mmol) in 2.5 mL of THF at −78 °C. The mixture was allowed to return to room temperature and stirred for 2 h, cooled to −78 °C, neutralized by 1 mL of HCl (0.05 M) and diluted by 5 mL of EtOAc. After elimination of the aluminium salts by filtration on Celite, the solvent was evaporated in vacuo to afford a crystalline white product. Yield: 85%. de (*R*/*S*) = 7:3 by ^1H NMR 250 MHz. Compound **3b** (R = Pr^i) Yield: 75%; de (*R*/*S*) = 7:3.

4.8. Hydrocyanation of (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-methylethenyl)cyclohexane-1,3-dicarbonitrile 3a (R = Pr^i) by trimethylsilylcyanide

The hydrocyanation was performed under nitrogen and the solutions of trimethylsilylcyanide and imine were mixed under the conditions described in Table 1. At the end of the reaction, the remaining trimethylcyanide was hydrolyzed by the addition of water (ca 50 mL). The reaction medium was washed with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The yield and de (*R*/*S*) of the reaction were reported in Table 1.

4.9. Hydrocyanation of (1*R*,2*R*,3*R*,5*R*)-1-isobutylideneamino-2-methyl-5-(1-hydroxy-1-methylethyl)cyclohexane-1,3-dicarbonitrile 3b (R = Pr^i) by trimethylsilylcyanide

Under nitrogen, a solution of trimethylsilylcyanide (0.29 mL, 2.2 mmol) in $CHCl_3$ (10 mL) and anhydrous $NiCl_2$ (0.15 g, 1.1 mmol) were added to **3b** (0.3 g, 1.1 mmol) in $CHCl_3$ (10 mL). The mixture was stirred during 4 h at room temperature. At this time, the trimethylsilylcyanide excess was hydrolyzed by the addition of 40 mL of water. The aqueous layer was extracted twice with $CHCl_3$. Organic layers were joined, dried over Na_2SO_4 and the solvent was removed in vacuo. Yield: 73%. De (*R*/*S*) = 8.5:1.5 by ^{1}H NMR 250 MHz.

4.10. Ethyl{[(1*R*,2*R*,3*R*,5*R*)-1,3-dicyano-5-(1-hydroxy-1-methylethyl)-2-methylcyclohexylamino]-phenyl-methyl}-phenylphosphinate 4′b (R = Ph)

A mixture of imine **3b** (R = Ph) (352 mg, 1.14 mmol) and ethylphenylphosphinate (242 mg, 1.42 mmol) in chloroform (5 mL) was refluxed (50–70 °C) for 18 h. After completion (monitored by ^{31}P NMR 81.01 MHz) the removal of the solvent in vacuo gave a mixture of four diastereoisomers in an 8:46:3:43 ratio. The addition of 10 mL of hot ethyl acetate and crystallization at room temperature affords white crystals of **4′b** as two major isomers [^{31}P NMR ($CDCl_3$, 81.01 MHz) δ 40.4, 37.9; de = 6:4]. Yield: 96%. mp = 165–170 °C; $[\alpha]_D^{20} = -7.7$ (*c* 0.013, CH_3OH); ^{31}P NMR ($CDCl_3$, 81.01 MHz) δ 40.9, 40.4, 38.5, 37.9; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1 (3H, d, $J_{H-H\text{-}2ax}$ = 7.04 Hz, CH_3), 1.09 (6H, d, J_{H-H} = 8.96 Hz, CH_3), 1.26 (3H, t, J_{H-H} = 7.03 Hz, $CH_{3(EtO)}$), 1.30 (1H, m, H-6ax), 1.54 (1H, m, H-4ax), 1.68 (1H, m, H-2ax), 1.88 (1H, m, H-5ax), 2 (1H, m, H-4eq), 2.12 (1H, m, H-6eq), 2.5 (2H, br s, NH, OH), 3 (1H, m, H-3eq), 4.05 (2H, m, CH_2), 4.18 (1H, d, J_{H-P} = 15.02 Hz, CH minor), 4.31 (1H, d, J_{H-P} = 18.74 Hz, CH major), 7.11–7.39 (10H, m, $H_{aromatic}$); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 15.17 (O–CH_2–*C*H_3), 16.59 (CH–*C*H_3), 26.83, 27.58 (*C*H_3–C–OH), 29.52 (C-4), 33.03 (C-3), 37.71 (C-6), 38.93 (C-2), 41.98 (C-5), 57.85 and 58.94 (*C*H–P), 61.90 (O-*C*H_2–CH_3), 71.39 (C-1), 76.72 (CH_3–*C*–OH), 118.38 and 118.57 (CN), 127.53–132.60 ($CH_{aromatic}$=$CH_{aromatic}$), 135.57 ($C_{aromatic}$–P and $C_{aromatic}$–CH).

Repeated crystallization from ethyl acetate afforded one of the two major diastereoisomers (^{31}P NMR ($CDCl_3$, 81.01 MHz) δ 40.4). Mp = 165 °C. $[\alpha]_D^{20} = -30.6$ (*c* 0.01, CH_3OH). HRMS: (MH^+) calcd for $C_{27}H_{35}N_3O_3P$, 480.2403; found, 480.2416.

4.11. Ethyl{[(1*R*,2*R*,3*R*,5*R*)-1,3-dicyano-5-(1-hydroxy-1-methylethyl)-2-methyl-cyclohexylamino]-phenyl-methyl}-phenylphosphinate 4′b (R = Ph) solvent free

A mixture of imine **3b** (R = Ph) (130 mg, 0.43 mmol) and ethylphenylphosphinate (89.6 mg, 0.53 mmol) was refluxed (50–70 °C) for 20 h to give a mixture of 4 diastereoisomers. NMR yield: 55%. Diastereoisomeric ratio determined by ^{31}P NMR 81.01 MHz: 9:51:8:32.

4.12. Ethyl{[(1*R*,2*R*,3*R*,5*R*)-1,3-dicyano-5-(1-methylethenyl)-2-methyl-cyclohexylamino]-phenyl-methyl}-phenylphosphinate 4′a (R = Ph) in chloroform

A mixture of imine **3a** (R = Ph) (237 mg, 0.81 mmol) and ethylphenylphosphinate (166 mg, 0.98 mmol) in 2.5 mL of chloroform was refluxed (50–70 °C) for 18 h. The removal of the solvent in vacuo gave a mixture of four diastereoisomers. Yield: 85%. Diastereoisomeric ratio determined by ^{31}P NMR 81.01 MHz: 7:51:5:37.

4.13. Ethyl{[(1*R*,2*R*,3*R*,5*R*)-1,3-dicyano-5-(1-methylethenyl)-2-methyl-cyclohexylamino]-phenyl-methyl}-phenylphosphinate 4′a (R = Ph) solvent free

A mixture of imine **3a** (R = Ph) (243 mg, 0.83 mmol) and ethylphenylphosphinate (170 mg, 1 mmol) was refluxed (50–70 °C) for 20 h to gave a mixture of four diastereoisomers. Yield: 96%. Diastereoisomeric ratio determined by ^{31}P NMR 81.01 MHz: 9:47:6:38.

4.14. Cleavage of ethyl{[(1*R*,2*R*,3*R*,5*R*)-1,3-dicyano-5-(1-hydroxy-1-methylethyl)-2-methyl-cyclohexylamino]-phenyl-methyl}-phenylphosphinate 4′b (R = Ph) by $AgNO_3$

In a 50 mL flask containing **4′b** (111 mg, 0.231 mmol) in 3 mL of methanol was added 4.6 mL of $AgNO_3$ 0.1 M. The pH of the solution was adjusted to 1 with dilute nitric acid. The mixture was stirred at 50 °C. After completion of the reaction (monitored by ^{31}P NMR), silver cyanide salts were removed by filtration. The NaCl was added to the filtrate to precipitate the excess Ag^+ and the suspension was filtered. The reaction medium was extracted with 5 mL of CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate. Starting chiral ketone **1b** was recovered after removal of the solvent in vacuo. Yield = 89% and $[\alpha]_D^{20} = -17.5$ (*c* 1, EtOH 100) The aqueous layer was neutralized by NaOH 0.1 M and extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate. Crude ethyl α-aminobenzylphenylphosphinate **5′b** was obtained after removal of the solvent (yield: 63%, 2 diastereoisomers). Diastereoisomeric ratio: 78:22 (by ^{31}P NMR, 81.01 MHz). $[\alpha]_D^{20} = +36.5$ (*c* 0.02, CH_3OH); ^{31}P NMR (DMSO-d_6, 81.01 MHz), δ 37.6, 35.9; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.1 (3H, t, J_{H-H} = 7.11 Hz, CH_3 minor), 1.28 (3H, t, J_{H-H} = 6.99 Hz, CH_3 major), 3.26 (2H, br s, NH_2), 3.83 (2H, q, J_{H-H} = 7,14 Hz, CH_2 minor), 4.06 (2H, q, J_{H-H} = 6.99 Hz, CH_2 major), 4.95 (1H, d, J_{H-P} = 11.96 Hz, CH minor), 5.06 (1H, d, J_{H-P} = 12.33 Hz, CH major), 7.47 (10H, m, $H_{aromatic}$); FAB-MS: *m*/*z* 276 $[M+1]^+$ (calcd 275.3).

4.15. Hydrolysis of ethyl α-aminobenzylphenylphosphinate 5′b

Compound **5′b** (40 mg, 0.146 mmol) was treated with 33% HBr in glacial acetic acid (0.7 mL) at room temperature according to Belov's procedure.[16] After completion of the reaction (monitored by TLC) the volatile products were removed in vacuo. The residue was dissolved in 1 mL of methanol and propylene oxide was added to eliminate the

excess of Br^-. Diethyl ether (5 mL) was added to initiate the precipitation and the mixture was placed in the refrigerator. Filtration and washing with Et_2O gave the desired compound **6′b**. Mp = 205 °C; $[\alpha]^{20}$ (λ, nm) = +29 (589), +30 (578), +34 (546), +67 (436), +121 (365), (*c* 0.02, HCl/EtOH 1:1); ^{31}P NMR (D_2O, 81.01 MHz) δ 35.7; ^1H NMR (D_2O, 200 MHz) δ 3.6 (1H, d, $J_{H-P} = 11.96$ Hz, CH), 7.47 (10H, m, $H_{aromatic}$).

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