Solvent-free synthesis of racemic cyanohydrin *O*-phosphates

Alejandro Baeza, Carmen Nájera,* and José M. Sansano

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
E-mail: cnajera@ua.es

Dedicated to Prof. José Elguero on the occasion of his 70th birthday
Dedicated to Prof. Pedro Molina on the occasion of his 60th birthday 3
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Abstract
Aldehydes and ketones are transformed into racemic cyanohydrin *O*-phosphates by reaction with stoichiometric amounts of diethyl cyanophosphonate and sub-stoichiometric amounts of triethylamine (10 mol. %), at room temperature in the absence of solvent. This green process takes place in excellent yield and with very short reaction time.

Keywords: Green chemistry, aldehydes, ketones, catalysis, cyanohydrin derivatives, cyanophosphates

Introduction

When a chemical reaction has to be performed selectively at one reactive site in a multifunctional compound, other reactive groups must be temporarily blocked. The protective group must form a highly stable derivative, which can be manipulated without any significant decomposition.[1] The cyanohydrins are very important organic intermediates [2] and are clear examples of unstable molecules that require a suitable hydroxy-protecting group. This desirable protection can be performed in a two-step sequence, starting from the aldehyde or ketone, through the corresponding cyanohydrin, followed by *O*-protection—although a one-pot procedure, starting from aldehydes or ketones, became synthetically more advantageous. The syntheses of racemic [3,4,5] *O*-alkoxycarbonyl cyanohydrins,[6–12] *O*-aroyl- or *O*-acyl- cyanohydrins, [9,13,14] and cyanohydrin *O*-phosphates have been developed using a number of different strategies. Particularly, for the synthesis of racemic cyanohydrin *O*-phosphates from ketones and aldehydes employing 1.5 equivalents of lithium cyanide and diethyl chlorophosphate,[15] a three-fold excess of both lithium cyanide and diethyl cyanophosphonate [16] and an excess of diethyl cyanophosphonate in combination with a sub-stoichiometric amount of lithium

diisopropylamine,[17] have been used in the presence of solvents. Among these, the first method required lower amounts of reagents—especially of the toxic lithium cyanide. The interest in cyanophosphates concerns their use in the synthesis of very interesting chiral building blocks as β-amino alcohols and γ-cyano-allylic alcohols [5a] and several racemic unsaturated intermediates.[15]

In our search for syntheses of non-racemic cyanohydrin *O*-phosphates from aldehydes, employing diethyl cyanophosphonate and the chiral 3,3'-bis-(diethylaminomethyl)-1,1'-binaphthol–AlCl (BINOLAM–AlCl) complex as bifunctional catalyst,[5a] we needed to prepare the same compounds in racemic form. However, we could not use the first method mentioned above because lithium cyanide is not now commercially available.[18] Moreover, it is crucial to avoid the use of large amounts of cyanide-ion surrogates. It is well documented that the exclusion of volatile organic solvents is the most important aim in synthetic organic, "green" chemistry. These solvent-free organic reactions, with the minimum amount of reagents, make synthesis simpler, save energy, and prevent solvent wastes, hazards, and toxicity. For these reasons, the study of these environmentally friendly protecting groups has become an important and popular research area.[19]

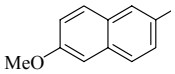
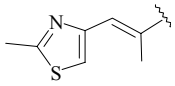
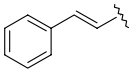
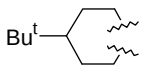
In this work, we present an alternative synthesis of cyanohydrin *O*-phosphates by means of a solvent-free process involving a triethylamine-catalyzed addition of diethyl cyanophosphonate onto aldehydes and ketones, which thus avoids the use of lithium cyanide.

Results and Discussion

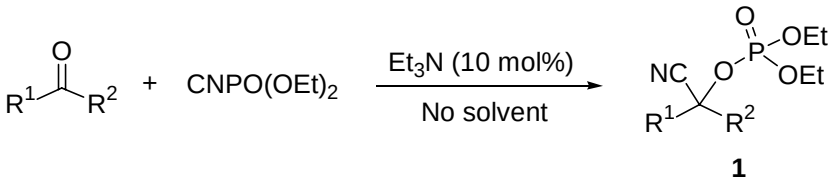
The reaction of aldehydes and ketones with diethyl cyanophosphonate, in the presence of sub-stoichiometric amounts of triethylamine (10 mol. %), afforded cyanohydrin *O*-phosphates **1** as very clean reaction products (Scheme 1 and Table 1). Initially we tested DABCO as catalyst but triethylamine was finally selected because it gave similar chemical results and purification benefits. The reaction was monitored by GC and when it was judged complete the triethylamine was evaporated. The aldehydes required 1.1 equivalents of diethyl cyanophosphonate to complete the reaction in very short reaction times (5 min), furnishing compounds **1** in excellent chemical yields (Table 1, entries 1–17). There was no apparent difference between electron-rich and electron-deficient aromatic aldehydes, and the rate of the reaction was similar, irrespective of the aromatic-, α,β-unsaturated-, or aliphatic aldehyde used. Many of these examples have been chosen because parts of their structures are contained in very interesting compounds: for example, **1a** is a part of the new cyanogenic glycosides isolated from the leaves and roots of *Phyllagatis rotundifolia*;[20] product **1c** is considered to be a precursor of the natural products (–)-tembamide and (–)-aegeline,[2,21] and the cyanohydrin derivative **1d** is an intermediate in the industrial production of pyrethroid insecticides.[22] In addition, compound **1e** is an intermediate in the synthesis of the anti-thrombotic agent clopidogrel,[23] cyanohydrin **1h** is a direct precursor of 2-amino-1-(3-pyridinyl)ethanol,[24] product **1l** is employed in the preparation of sphingosines [25]

and coriolic acid,[26] and **1j** can be applied for the elaboration of a key intermediate in the synthesis of epothilone A.[27]

Table 1. Solvent-free synthesis of racemic cyanohydrin *O*-phosphates **1**

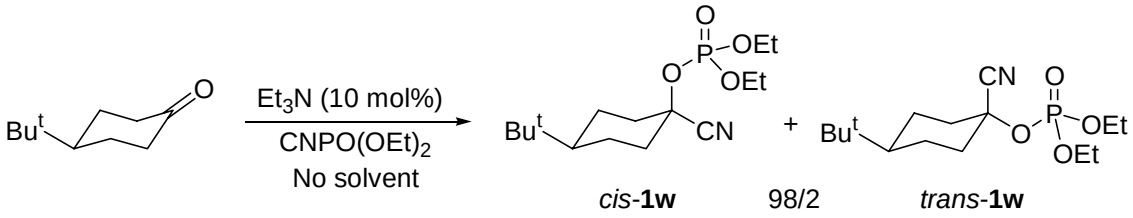
E	R^1	R	$CNPO(OEt)_2$	time		Yield
1	Ph	H	1.1	< 5		98
2	4-	H	1.1	< 5		93
3	4-	H	1.1	5		93
4	3-	H	1.1	< 5		95
5	2-ClC_6H_4	H	1.1	< 5		97
6	4-ClC_6H_4	H	1.1	< 5		97
7		H	1.1	< 5	**g**	95
8		H	1.1	< 5	**h**	98
9		H	1.1	5	**i**	91
10		H	1.1	5	**j**	92
11	(*E*)-	H	1.1	< 5		95
11	(*E*)-	H	1.1	5		91
13		H	1.1	< 5	**m**	97
11	$(CH_3)_3C$	H	1.1	10		93
11	*n*-C_6H_{13}	H	1.1	< 5		98
11	$PhCH_2$	H	1.1	5		96
11	$PhCH_2CH_2$	H	1.1	5		97
11	Ph	M	1.2	30		89[b]
11	4-ClC_6H_4	M	1.2	180		70[b]
12	CH_2=CH	M	1.2	35		87[b]
12	*n*-C_5H_{11}	M	2.0	240		88[b]
12	$PhCH_2CH_2$	M	2.0	300		72[b]
12			1.2	30[c]	**w**	90[c]
13						

[a] Crude compounds (>95 % purity). [b] Isolated after flash chromatography. [c] Isolated as a 98/2 *cis/trans* mixture.



Scheme 1

The cyanophosphorylation of the less reactive ketones took longer times to proceed under the standard reaction conditions (Table 1, entries 18–23), requiring 1.2 or 2.0 equivalents of diethyl cyanophosphonate. The chemical yields were high, but somewhat lower than those obtained for the aldehydes. The presence of an electron-withdrawing group in the aromatic ring of the corresponding acetophenone led to a noticeable effect: thus the chloro-substituted compound reacted six times slower than the unsubstituted one (Table 1, entries 18 and 19). In the case of methyl vinyl ketone (Table 1, entry 20) the reaction was not so slow, and only the corresponding 1,2-addition product **1t** was observed in the ^{1}H- NMR spectra of the crude material. However, 2-cyclohexenone gave a very complex mixture of addition products in very low yield, possibly originates from 1,4-additions of the cyanide anion.[15] By contrast, methyl vinyl ketone furnished a very good yield of product **1t** without any of the corresponding isomerized α,β-unsaturated nitrile as was previously reported.[15] 4-*tert*-Butylcyclohexanone reacted as fast as acetophenone or methyl vinyl ketone, from the equatorial direction. The crude product **1w** was finally isolated, in 90% yield, as a 98/2 *cis/trans*- mixture according to NMR experiments (COSY and NOESY), as shown in Scheme 2.



Scheme 2

The presumed mechanism, based on *ab initio* calculations and experimental results, would involve a hydrocyanation addition followed by *O*-phosphorylation, such as was suggested for the synthesis of non-racemic cyanophosphonates [28] and *O*-methoxycarbonyl [29] cyanohydrins. This process would be initially promoted by traces of hydrogen cyanide, which exist in commercial diethyl cyanophosphonate, and the resulting cyanohydrin would finally be *O*-phosphorylated by diethyl cyanophosphonate, an excellent phosphorylating agent as was revealed in asymmetric processes.[28,29]

Thus, we have described a very simple process for obtaining cyanohydrin *O*-phosphates from aldehydes and ketones in very short reaction times, in excellent yields, and with high purity. This protocol is very attractive, in comparison with other procedures described, because the use of

lithium cyanide is avoided. Other remarkable aspects are the absence of solvent, the operational temperature, the small amount of the inexpensive triethylamine, and the easy workup. All these features make this transformation a "green" process which is able to be scaled-up to an industrial level.

Experimental Section

General Procedures. IR spectra were recorded on a Nicolet 510 P-FT and only the structurally most important peaks are listed. ^{1}H- NMR (300 MHz) and ^{13}C- NMR (75 MHz) spectra were obtained at 25ºC on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. COSY and NOESY experiments were run in a Bruker DRX500 using $CDCl_3$ as solvent. GC analysis was performed on a HP-5890 using a Chirasil column WCOT-1. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on a Shimadzu QP-5000, and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were also recorded on a Finnigan MAT 95S. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040–0.063 mm).

General procedure

In a round bottomed flask was stirred, at room temperature, a mixture of the carbonyl compound (0.5 mmol) and Et_3N (10 mol.%, 7 μL), and diethyl cyanophosphonate (1.1–2.0 eq., see Table) was added. When the reaction was complete (GC monitoring), the Et_3N was evaporated *in vacuo* to yield the desired cyanophosphates **1** as pure crude compounds. Compounds **1a**–**1q** did not require any further purification (>95 % purity), but products **1r**–**w** were purified by flash chromatography, eluting with mixtures of *n*-hexane/ethyl acetate.

2-(Diethylphosphoryloxy)-2-phenylacetonitrile (1a).[15] Colorless oil; R_f 0.57 (*n*-hexane/ethyl acetate, 3/2); IR (neat): υ 2240, 1270, 1024 cm^{-1}; ^{1}H- NMR: δ 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 x m, 4H, 2 x 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: δ 15.7–15.9 (m, 2 x CH_3), 64.5–64.7 (m, 2 x 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 (M^+, 4%), 213 (70), 133 (42), 116 (100), 115 (69), 105 (48), 89 (33); HRMS calcd for $C_{12}H_{16}O_4NP$: 269.0817; found: 269.0820.

2-(Diethylphosphoryloxy)-2-(4-nitrophenyl)acetonitrile (1b). Pale yellow oil; R_f 0.20 (*n*-hexane/ethyl acetate 3/2); IR (neat): υ 2363, 1530, 1350, 1271, 1032 cm^{-1}; ^{1}H- NMR: δ = 1.28, 1.40 (2 x t, *J* 7.1 Hz, 6H, 2 x CH_3), 4.02–4.15, 4.18–4.30 (2 x m, 4H, 2 x CH_2), 6.17 (d, *J* 9.0 Hz, 1H, CHCN), 7.76, 8.32 ppm (2 x d, *J* 8.7 Hz, 4H, ArH); ^{13}C- NMR: δ 15.9 (m, 2 x CH_3), 65.1 (d, *J* 4.4 Hz, *C*HCN), 65.2 (d, *J* 6.3 Hz, 2 x 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 (M^+, 4%), 258 (100), 161 (28), 125 (26), 114 (44); HRMS calcd for $C_{12}H_{15}O_6N_2P$: 314.0668; found: 314.0669.

2-(Diethylphosphoryloxy)-2-(4-methoxyphenyl)acetonitrile (1c). Colorless oil; R_f 0.30 (*n*-hexane/ethyl acetate 3/2); IR (neat): υ 2243, 1258, 1028 cm^{-1}; ^{1}H- NMR: δ = 1.22, 1.38 (2 x t, *J* 7.1 Hz, 6H, 2 x *CH*$_3$CH$_2$O), 3.84 (s, 3H, CH$_3$O), 3.83–4.04, 4.15–4.25 (2 x m, 4H, 2 x CH$_2$O), 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: δ 15.9 (d, *J* 7.3 Hz, 2 x *C*H$_3$CH$_2$), 55.40 (d, *J* 3.3 Hz, CH$_3$O), 64.7 (d, *J* 5.5 Hz, 2 x CH$_2$O), 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 (EI): *m/z* 299 (M^+, 8%), 162 (12), 147 (39), 46 (97), 145 (100), 135 (17); HRMS calcd for $C_{13}H_{18}O_5NP$: 299.0923; found: 299.0928.

2-(Diethylphosphoryloxy)-2-(3-phenoxyphenyl)acetonitrile (1d). Colorless oil; R_f 0.44 (*n*-hexane/ethyl acetate 3/2); IR (neat): υ 2361, 1268, 1024 cm^{-1}; ^{1}H- NMR: δ = 1.28, 1.36 (2 x dt, *J* 7.1, 1.0 Hz, 6H, 2 x CH$_3$), 3.96–4.09, 4.13–4.26 (2 x m, 4H, 2 x 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: δ 15.9, 16.2 (2 x d, *J* 7.5 Hz, 2 x CH$_3$), 64.5, 64.9 (2 x d, *J* 5.7 Hz, 2 x 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 (M^+, 84%), 305 (100), 225 (51), 207 (29), 197 (39), 181 (67), 114 (72); HRMS calcd for $C_{18}H_{20}O_5NP$: 361.1079; found: 361.1079.

2-(2-Chlorophenyl)-2-(diethylphosphoryloxy)acetonitrile (1e). Colorless oil; R_f 0.35 (*n*-hexane/ethyl acetate 3/2); IR (neat): υ 2358, 1274, 1027 cm^{-1}; ^{1}H- NMR: δ = 1.29, 1.37 (2 x dt, *J* 7.1, 1.1 Hz, 6H, CH$_3$), 4.05–4.15, 4.17–4.28 (2 x m, 4H, 2 x 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: δ = 15.8, 16.0 (2 x d, *J* 4.4 Hz, 2 x CH$_3$), 63.5 (d, *J* 4.4 Hz, *C*HCN), 64.6, 65.0 (2 x d, *J* 5.5 Hz, 2 x 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 (M^+-Cl, 59%), 240 (18), 212 (31), 185 (100), 150 (57), 122 (19), 114 (18); HRMS calcd for $C_{12}H_{15}O_4NP$ (M^+-Cl): 268.0738; found: 268.0739.

2-(4-Chlorophenyl)-2-(diethylphosphoryloxy)acetonitrile (1f). Colorless oil; R_f 0.43 (*n*-hexane/ethyl acetate 3/2); IR (neat): υ 2354, 1273, 1032 cm^{-1}; ^{1}H- NMR: δ = 1.24, 1.38 (2t, *J* 7.1 Hz, 6H, 2 x CH$_3$), 3.98–4.07, 4.14–4.26 (2 x m, 4H, 2 x 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: δ 15.9 (m, 2 x CH$_3$), 64.8 (d, *J* 6 Hz, 2 x 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 (M^+, 15%), 247 (88), 150 (98), 149 (100), 139 (42), 114 (32); HRMS calcd for $C_{12}H_{15}O_4NPCl$: 303.0427; found: 303.0432.

2-(Diethylphosphoryloxy)-2-(6-methoxy-2-naphthyl)acetonitrile (1g). Colorless oil; R_f 0.21 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2357, 1271, 1029 cm^{-1}; ^{1}H- NMR: δ = 1.19, 1.39 (2 x t, *J* 7.1 Hz, 6H, 2 x C*H*$_3$CH$_2$), 3.93 (s, 3H, CH$_3$O), 3.95–4.02, 4.18–4.26 (2 x m, 4H, 2 x CH$_2$), 6.18 (d, *J* 8.8 Hz, 1H, CHCN), 7.16 (br. s, 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: δ 15.8 (m, 2 x CH$_3$), 55.3 (s, CH$_3$O), 64.4, 64.6 (2 x d, *J* 5.5 Hz, 2 x 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 (M^+, 0.1%), 321 (10), 265 (10), 212 (17), 196 (91), 195 (100), 180 (10), 166 (14), 153 (27), 125 (17), 91 (28); HRMS calcd for $C_{17}H_{20}NPO_5$: 349.3200; found: 349.3995.

(*R*)-2-(Diethylphosphoryloxy)-2-(3-pyridyl)acetonitrile (1h). Pale yellow oil; R_f 0.55 (ethyl acetate); IR (neat): ν 2254, 1286, 1016 cm^{-1}; ^{1}H- NMR: δ = 1.30, 1.37 (2 x m, 6H, 2 x CH_3), 4.15, 4.23 (2 x m, 4H, 2 x 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 (br. s, 1H, ArH); ^{13}C- NMR: δ 15.9, 16.1 (2 x d, *J* 4.4 Hz, 2 x CH_3), 64.9 (m, 2 x 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 (M^+, 16%), 214 (37), 133 (60), 118 (100), 117 (69), 108 (42), 98 (48); HRMS calcd for $C_{11}H_{15}O_4N_2P$: 270.0769; found: 270.0773.

2-(Diethylphosphoryloxy)-2-(2-furyl)acetonitrile (1i). Pale yellow liquid; R_f 0.19 (*n*-hexane/ ethyl acetate: 3/2); IR (liq.): ν 2221, 1271, 1004, 1153 cm^{-1}; ^{1}H- NMR: δ = 1.25 (dt, *J* 7.1, 1.1 Hz, 3H, CH_3CH_2O), 1.36 (dt, *J* 7.1, 1.1 Hz, 3H, CH_3CH_2O), 4.01–4.11 (m, 2H, CH_2), 4.13–4.26 (m, 2H, CH_2), 6.09 (d, *J* 8.6 Hz, 1H, CH-CN), 6.43 (dd, *J* 3.3, 1.8 Hz, 1H, C*H*=CH-O), 6.71 (d, *J* 3.3 Hz, 1H, C=CH-O), 7.51 ppm (dd, *J* 1.8, 0.8 Hz, 1H, CH=C); ^{13}C- NMR: δ_C =15.9 (dd, *J* 6.6, 4.4 Hz, OCH_2CH_3), 59.4 (d, *J* 4.4 Hz, CH_2), 64.9 (m, CH_2O), 111.1 (*C*H=CH-O), 112.6 (*C*H=C), 114.1 (d, *J* 6.6 Hz, CN), 144.6 (d, *J* 5.5 Hz, OC=*C*), 145.2 ppm (C=*C*H-O); MS (EI): *m/z* 259 (M^+ 13 %), 203 (60), 122 (24), 106 (100), 105 (95), 99 (30); HRMS calcd for $C_{10}H_{14}O_5NP$ 259.0610, found: 259.0594.

(*E*)-2-(Diethylphosphoryloxy)-3-methyl-4-(2-methyl-4-thiazolyl)but-3-enenitrile (1j). Pale yellow oil; R_f 0.20 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2227, 1269, 1031 cm^{-1}; ^{1}H- NMR: δ = 1.33, 1.39 (2 x dt, *J* 7.1, 0.9 Hz, 6H, 2 x 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 x 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: δ 14.3 (CH_3C=CH), 15.9 (m, 2 x CH_3CH_2), 19.3 (CH_3CS), 64.7 (m, 2 x 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 (M^+, 2%), 193 (38), 177 (100), 176 (92), 151 (39), 135 (57); HRMS calcd for $C_{13}H_{19}O_4N_2PS$: 330.0803; found: 330.0798.

(*E*)-2-(Diethylphosphoryloxy)pent-3-enenitrile (1k).[15] Colorless oil; R_f 0.36 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2247, 1269, 1028 cm^{-1}; ^{1}H- NMR: δ = 1.27 (m, 6H, 2 x CH_3CH_2O), 1.73 (d, *J* 6.6 Hz, 3H, CH_3CH), 4.07 (m, 4H, 2 x 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: δ 13.3 (CH_3CH), 15.5 (d, *J* 6.6 Hz, 2 x CH_3CH_2O), 64.4 (m, 2 x 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 (M^+, 1%), 177 (30), 127 (21), 99 (100), 81 (23); HRMS calcd for $C_9H_{16}O_4NP$: 233.0817; found: 233.0813.

(*E*)-2-(Diethylphosphoryloxy)non-3-enenitrile (1l). Colorless sticky oil; R_f 0.53 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2243, 1272, 1032 cm^{-1}; ^{1}H- NMR: δ = 0.87 (t, *J* 6.5 Hz, 3H, $CH_3CH_2CH_2$), 1.27–1.45 [m, 12H, 2 x CH_3CH_2O, $(CH_2)_3CH_3$], 2.11 (m, 2H, CH_2CH=CH), 4.15 (m, 4H, 2 x 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: δ 13.8 [$CH_3(CH_2)_3$], 15.9 (d, *J* 6.6 Hz, 2 x CH_3CH_2O), 22.3

(*C*H_2CH$_3$), 27.8 (*C*H_2CH$_2$CH$_3$), 31.5 (*C*H_2CH$_2$CH=C), 31.8 (*C*H_2CH=CH), 64.4, 64.8 (2 x d, *J* 7.3 Hz, 2 x *C*H_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$_2$*C*H=CH); MS (EI): *m/z* 289 (M^+, 1%), 155 (53), 127 (62), 99 (100), 81 (20); HRMS calcd for $C_{13}H_{24}O_4NP$: 289.1443; found: 289.1451.

(*E*)-2-(Diethylphosphoryloxy)-4-phenylbut-3-enenitrile (1m). Pale yellow oil; R_f 0.29 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2230, 1270, 1029 cm^{-1}; ^{1}H- NMR: δ = 1.34, 1.40 (2 x dt, *J* 7.1, 0.9 Hz, 6H, 2 x CH$_3$), 4.09–4.27 (m, 4H, 2 x 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: δ 15.7, 15.9 (2 x d, *J* 5.6 Hz, 2 x CH$_3$), 64.5, 64.7 (2 x d, *J* 6.6 Hz, 2 x 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 (M^+, 34%), 221 (15), 159 (70), 141 (100), 140 (94), 127 (33), 115 (36), 99 (78); HRMS calcd for $C_{14}H_{18}O_4NP$: 295.0973; found: 295.0971.

2-(Diethylphosphoryloxy)-3,3-dimethylbutanenitrile (1n).[15] Pale yellow oil; R_f 0.37 (*n*-hexane / ethyl acetate: 3/2); IR (liq.): ν 2246 (CN), 1274 (P=O) 1023, 980 (P-O), 1166 (C-O) cm^{-1}; ^{1}H-NMR: δ_H =1.10 (s, 9H, 3 x CH$_3$), 1.35–1.40 (m, 6H, 2 x CH$_3$), 4.10–4.24 (m, 4H, 2 x CH$_2$), 4.63 ppm (d, *J* 8.2 Hz, 1H, CHCN); ^{13}C- NMR: δ_C 15.9 (dd, *J* 6.6, 2.2 Hz, OCH$_2$*C*H$_3$), 24.0 (CH$_3$), 35.6 [d, *J* 5.5 Hz, *C*(CH$_3$)$_3$], 64.6 (d, *J* 5.5 Hz, CH$_2$), 73.4 (d, *J* 6.6 Hz, CH), 116.0 ppm (CN); MS (EI): *m/z* 250 (M^+ + 1, 0.2 %), 193 (25), 178 (15), 165 (32), 155 (30), 153 (16), 137 (100), 127 (60), 125 (18), 99 (63); HRMS calcd for $C_{10}H_{20}O_4NP$: 249.1130, found: 249.1141.

2-(Diethylphosphoryloxy)octanenitrile (1o). Colorless sticky oil; R_f 0.40 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2240, 1276, 1032 cm^{-1}; ^{1}H- NMR: δ = 0.86 (t, *J* 6.7 Hz, 3H, *CH*$_3$CH$_2$), 1.28–1.38 [m, 12H, 2 x *CH*$_3$CH$_2$O, (*CH*$_2$)$_3$CH$_3$], 1.49 (m, 2H, C*H*$_2$CH$_2$CH), 1.91 (m, 2H, C*H*$_2$CH), 4.15 (m, 4H, 2 x CH$_2$O), 4.96 ppm (m, 1H, CHCN); ^{13}C- NMR: δ 13.8 (*C*H$_3$CH$_2$CH$_2$), 15.9 (d, *J* 6.6 Hz, 2 x *C*H$_3$CH$_2$O), 22.3 (*C*H$_2$CH$_3$), 24.1 (*C*H$_2$CH$_2$CH), 28.3, 31.3 [(*C*H$_2$)$_2$CH$_2$CH$_3$], 34.1 (d, *J* 5.5 Hz, *C*H$_2$CH), 64.5, 64.7 (2 x d, *J* 4.4 Hz, 2 x CH$_2$O), 64.8 (d, *J* 6.0 Hz, CH), 116.8 ppm (d, *J* 6.7 Hz, CN); MS (EI): *m/z* 276 (M^+, 0.4%), 155 (66), 127 (73), 99 (100), 81 (37); HRMS calcd for $C_{12}H_{24}O_4NP$: 277.1443; found: 277.1441.

2-(Diethylphosphoryloxy)-2-phenylpropanenitrile (1p).[15] Colorless oil; R_f 0.41 (*n*-hexane/ ethyl acetate: 3/2); IR (liq.): ν 2220, 1270, 1030, 980, 1096 cm^{-1}; ^{1}H- NMR: δ_H 1.28 (dt, *J* 7.1, 1.1 Hz, 3H, CH$_3$CH$_2$O), 1.32 (dt, *J* 7.1, 1.1 Hz, 3H, CH$_3$CH$_2$O), 2.14 (s, 3H, CH$_3$), 4.01–4.08 (m, 2H, CH$_2$), 4.11–4.20 (m, 2H, CH$_2$), 7.46 (m, 3H, ArH), 7.64 ppm (m, 2H, ArH); ^{13}C- NMR: δ_C 15.9 (d, *J* =6.6 Hz, OCH$_2$*C*H$_3$), 30.1 (d, *J* 5.0 Hz, CH$_3$), 64.3 (m, CH$_2$O), 75.4 (d, *J* 7.7 Hz, *C*CN), 118.1 (d, *J* 3.3 Hz, CN), 125, 128.7, 129.5, 137.7 ppm (ArC); MS (EI): *m/z* 283 (M^+ 17 %), 147 (100), 130 (55), 129 (70), 127 (20), 105 (21), 103 (46), 99 (32); HRMS calcd for $C_{13}H_{18}O_4NP$ 283.0973; found: 283.0963.

2-(Diethylphosphoryloxy)-4-phenylbutanenitrile (1q). Colorless oil; R_f 0.33 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2334, 1266, 1032 cm^{-1}; ^{1}H- NMR: δ = 1.37 (t, *J* 7.1 Hz, 6H, 2 x CH$_3$), 2.26 (m, 2H, *CH*$_2$CH), 2.85 (m, 2H, *CH*$_2$CH$_2$), 4.11–4.23 (m, 4H, 2 x CH$_2$O), 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: δ 15.9 (m, 2 x CH$_3$),

30.3 (*C*H_2CH_2), 35.8 (d, *J* 6.6 Hz, *C*H_2CH), 64.1 (d, *J* 6.1 Hz, *C*HCN), 64.6, 64.8 (2 x d, *J* 2.2 Hz, 2 x 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 (M^++1, 0.4%), 155 (97), 143 (48), 127 (80), 116 (33), 99 (100); HRMS calcd for $C_{14}H_{20}O_4NP$: 297.1130; found: 298.1205 (M^++1).

2-(Diethylphosphoryloxy)-2-methyl-2-phenylacetonitrile (1r).[15,16b] Colorless oil; R_f 0.40 (*n*-hexane/ethyl acetate 3/2); IR (neat): ν 2220, 1270, 1024 cm^{-1}; ^{1}H- NMR: δ 1.28, 1.32 (2 x t, *J* 7.1 Hz, 6H, 2 x CH_3CH_2), 2.14 (s, 3H, CH_3CO), 4.09 (m, 4H, 2 x CH_2); 7.46, 7.64 ppm (2 x m, 5H, Ar*H*); ^{13}C- NMR: δ 15.7, 15.7 (2 x d, *J* 7.0 Hz, 2 x CH_3CH_2), 30.13 (d, *J* 5.0 Hz, CH_3CO), 64.2, 64.4 (2 x d, *J* 6.5 Hz, 2 x CH_2), 77.5 (d, *J* 8.0 Hz, *C*HCN), 118.1 (CN), 124.9, 128.7, 129.5, 137.8 ppm (ArC); MS (EI): *m/z* 284 (M^++1, 1%), 283 (M^+, 14), 155 (15), 147 (70), 130 (54), 129 (100), 127 (32), 103 (52), 99 (58), 77 (48).

2-(Diethylphosphoryloxy)-2-(4-chlorophenyl)-2-methylacetonitrile (1s). Colorless oil; R_f 0.26 (*n*-hexane/ethyl acetate 3/2); IR (liq.): ν 2238, 1274, 1029, 985, 1097 cm^{-1}; ^{1}H- NMR: δ_H = 1.28, 1.32 (2 x dt, *J* 7.1, 1.1 Hz, 3H, 2 x C*H*$_3$CH$_2$O), 2.10 (s, 3H, CH_3C), 4.01–4.18 (m, 4H, 2 x CH_2O), 7.39 (d, *J* 8.7 Hz, 2H, ArH), 7.55 ppm (d, *J* 8.7 Hz, 2H, ArH); ^{13}C- NMR: δ_C 15.9 (d, *J* 6.6 Hz, OCH_2CH_3), 30.3 (d, *J* 4.4 Hz, CH_3), 64.6 (t, *J* 6.6 Hz, CH_2), 75.0 (d, *J* 7.7 Hz, *C*CN), 118.0 (d, *J* 3.3 Hz, CN), 126.6, 129.0, 135.7 (ArC), 136.5 ppm (d, *J* 5.5 Hz, ArC); MS (EI): *m/z* 317 (M^+ 17 %), 183 (22), 181 (47), 166 (27), 165 (44), 164 (79), 163 (100), 139 (38), 137 (26), 128 (46), 127 (34); HRMS calcd for $C_{13}H_{17}O_4NPCl$: 317.0584, found: 317.0597.

2-(Diethylphosphoryloxy)-2-methylbut-3-enenitrile (1t).[15] Pale yellow oil; R_f 0.63 (*n*-hexane/ethyl acetate 3/2); IR (liq.): ν 2256, 1273, 1028, 981, 1165 cm^{-1}; ^{1}H- NMR: δ_H =1.33–1.39 (m, 6H, 2 x C*H*$_3$CH$_2$O), 1.90 (s, 3H, CH_3C), 4.11–4.22 (m, 4H, 2 x CH_2O), 5.46 (d, *J* 10.3 Hz, 1H, CH_{2cis}=CH), 5.75 (d, *J* 17.0 Hz, 1H, CH_{2trans}=CH), 6.05 ppm (dd, *J* 17.0, 10.3 Hz, 1H, C=CH); ^{13}C- NMR: δ_C 15.9 (d, *J* =6.6 Hz, 2 x OCH_2CH_3), 28.0 (d, *J* 4.4 Hz, CH_3), 64.5 (dd, *J* 6.5, 3.3 Hz, 2 x CH_2), 74.7 (d, *J* 7.7 Hz, *C*CN), 117.2 (d, *J* 3.3 Hz, CN), 118.9 (CH_2=*C*H), 134.7 ppm (d, *J* 4.4 Hz, *C*H_2=CH); MS (EI): *m/z* 233 (M^+ 0.1 %), 177 (21), 127 (47), 125 (27), 109 (20), 99 (100), 97 (47); HRMS calcd for $C_9H_{16}O_4NP$: 249.0817, found: 233.0782.

2-(Diethylphosphoryloxy)-2-methylheptanenitrile (1u). Colorless oil; R_f 0.23 (*n*-hexane/ethyl acetate: 3/2); IR (liq.): ν 2218, 1294, 1029, 1166 cm^{-1}; ^{1}H- NMR: δ_H = 0.89 (t, *J* 7 Hz, 3H, C*H*$_3$(CH$_2$)$_4$), 1.30–1.39 (m, 10H, 2 x CH_3CH_2O + 2 x CH_2), 1.51–1.58 (m, 2H, CH_2), 1.82 (s, 3H, CH_3-C), 1.85–1.91 (m, 1H, CH_2-C), 1.97–2.02 (m, 1H, CH_2C) 4.08–4.22 ppm (m, 4H, CH_2O); ^{13}C- NMR: δ_C 13.9 (*C*H_3CH_2), 15.9 (d, *J* 6.6 Hz, OCH_2CH_3), 22.3, 23.7 (CH_2), 26.3 (d, *J* 2.2 Hz, *C*H_3-C), 31.2 (CH_2), 41.3 (d, *J* 6.6 Hz, *C*H_2C), 64.4 (t, *J* 5.5 Hz, CH_2), 74.9 (d, *J* 7.7 Hz, *C*-CN), 118.8 ppm (d, *J* 4.4 Hz, CN); MS (EI): *m/z* 277 (M^+ + 1, 0.5 %), 164 (21), 155 (75), 127 (91), 99 (100); HRMS calcd for $C_{11}H_{21}O_4NP$ (M^+- Me): 262.1208, found: 262.1187.

2-(Diethylphosphoryloxy)-2-methyl-4-phenylbutanenitrile (1v). Colorless oil; R_f 0.29 (*n*-hexane/ethyl acetate: 3/2); IR (liq.): ν 2242, 1272, 1027, 981, 1100 cm^{-1}; ^{1}H- NMR: δ_H = 1.35–1.41 (m, 6H, 2 x C*H*$_3$CH$_2$O), 1.89 (s, 3H, CH_3), 2.11–2.20 (m, 1H, CH_2C), 2.22–2.38 (m, 1H, CH_2C), 2.80–2.98 (m, 2H, $PhCH_2$), 4.13–4.26 (m, 4H, 2 x CH_2O), 7.22 (m, 3H, ArH), 7.28–7.33 ppm (m, 2H, ArH); ^{13}C- NMR: δ_C 16.0 (d, *J* 6.6 Hz, 2 x OCH_2CH_3), 26.4 (d, *J* 2.2 Hz, CH_3),

30.4 (Ph*C*H_2), 43.3 (d, *J* 6.6 Hz, CH_2CCH) 64.5 (t, *J* 5.5 Hz, 2 x CH_2), 74.5 (d, *J* 7.6 Hz, *C*CN), 118.5 (d, *J* 4.4 Hz, CN), 126.4, 128.3, 128.6, 139.6 ppm (ArC); MS (EI): *m/z* 312 (M^+ + 1, 0.1 %), 156 (59), 155 (100), 127 (72), 99 (82); HRMS calcd for $C_{15}H_{22}O_4NP$: 311.1286, found: 311.1291.

1-(Diethylphosphoryloxy)-4-*tert*-butylcyclohexanecarbonitrile (1w). Colorless sticky oil; R_f 0.40 (*n*-hexane/ethyl acetate: 3/2); IR (liq.): ν 2241, 1275, 1032, 985, 1102 cm^{-1}; ^{1}H- NMR: δ_H = 0.86 [s, 9H, C(CH_3)$_3$], 0.98–1.07 (m, 1H, CH), 1.32–1.42 (m, 8H, 2 x CH_3CH_2O + CH_2), 1.76–1.80 (m, 2H, CH_2), 1.85–1.90 (m, 2H, CH_2), 2.46–2.50 (m, 2H, CH_2), 4.10–4.20 ppm (m, 4H, 2 x CH_2O); ^{13}C- NMR: δ_C 15.9 (d, *J* 6.6 Hz, OCH_2*C*H_3), 24.3 (CH_2), 27.4 [C(*C*H_3)$_3$], 32.1 [*C*(CH_3)$_3$], 37.3 (d, *J* 4.4 Hz, CH_2C), 46.3 (CH), 64.3 (d, *J* 5.5 Hz, *C*H_2O), 76.6 (d, *J* 7.7 Hz, *C*CN), 118.2 ppm (d, *J* 3.3 Hz, CN); MS (EI): *m/z* 317 (M^+ + 1, 0.2 %), 155 (100), 127 (49), 99 (49); HRMS calcd for $C_{15}H_{28}O_4NP$ (M^+- Me): 317.1756, found: 317.1802.

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References and Footnotes

1. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc.: New York, 1999.
2. (a) North, M., Ed.; *Synthesis and Applications of Non-racemic Cyanohydrins and α-Amino Acids*, *Tetrahedron Symposium in Print* 2004, *60*, 10371. (b) Brunel, J.-M. ; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752. (c) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147.
3. For the synthesis of non-racemic O-alkoxycarbonyl cyanohydrins: (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636. (c) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197. (d) Belokon', Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett*. **2003**, *5*, 4505. (e) Belokon' Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433.
4. For the synthesis of non-racemic O-acyl or *O*-benzoyl cyanohydrins, see: (a) Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* **2004**, *45*, 4763. (b) Belokon', Y. N.; Carta, P.; North, M. *Lett. Org. Chem.* **2004**, *1*, 81. (c) Belokon' Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A. Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.;

Khrustalev, V. N.; North, M. *Helv. Chim. Acta* **2002**, *85*, 3301. (d) Belokon', Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun.* **2002**, 244.

5. For the synthesis of non-racemic cyanohydrin *O*-phosphates, see: (a) Baeza, A.; Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3143. (b) Abiko, Y.; Yamagiwa, N.; Sugita, M.; Tian, J.; Matsunaga, S.; Shibasaki, M. *Synlett* **2004**, 2434.
6. Au, A. T. *Synth. Commun.* **1984**, *14*, 743.
7. Thasana, N.; Prachyawarakorn, V.; Tontoolarug, S.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1019.
8. Shin, D.-S.; Jung, Y.-S.; Kim, J.-J.; Ahn, C. *Bull. Korean Chem. Soc.* **1998**, *19*, 119.
9. Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229.
10. Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191.
11. Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995.
12. Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.
13. Okimoto, M.; Chiba, T. *Synthesis* **1996**, 1188.
14. Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807.
15. Micó, I.; Nájera, C. *Tetrahedron* **1993**, *49*, 4327.
16. (a) Yoneda, R.; Harusawa, S.; Kurihara, T. *J. Org. Chem.* **1991**, *56*, 1827. (b) Yoneda, R.; Osaki, T.; Harusawa, S.; Kurihara, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 607 and references cited therein.
17. Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1983**, *31*, 3932.
18. Recently, an *in situ* generation of lithium cyanide from acetone cyanohydrin has been described: Ciaccio, J. A.; Smrtka, M.; Maio, W. A.; Rucando, D. *Tetrahedron Lett.* **2004**, *45*, 7201.
19. Tanaka, K. In *Solvent-Free Organic Synthesis*, Wiley-VCH: Weinheim, 2003.
20. Ling, S.-K.; Tanaka, T.; Kouno, I. *J. Nat. Prod.* **2002**, *65*, 131.
21. (a) Cho, B. T.; Kang, S. K.; Shin, S. H. *Tetrahedron: Asymmetry* **2002**, *13*, 1209. (b) Brown, R. F. C.; Donohue, A. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron* **1994**, *50*, 13739. (c) Brown, R. F. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron: Asymmetry* **1993**, *4*, 205.
22. (a) Beckmann, M.; Haack, K.-J. *Chem. Unserer Zeit* **2003**, *37*, 88. (b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.
23. van Langen, L. M.; van Rantwijk, F.; Sheldon, R. A. *Org. Process Res. Dev.* **2003**, *7*, 828.
24. Duquette, J.; Zhang, M.; Zhu, L.; Reeves, R. S. *Org. Process Res. Devel.* **2003**, *7*, 285.
25. Johnson, D. V.; Felfer, U.; Griengl, H. *Tetrahedron* **2000**, *56*, 781.
26. Johnson, D. V.; Griengl, H. *Tetrahedron* **1997**, *53*, 617.
27. (a) Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 209. (b) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521.
28. Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M., in preparation.
29. Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M., in preparation.