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Protonation of acyl anion equivalents generated from acylphosphonates: nonhydride access to the aldehyde oxidation state from the carboxylic acid oxidation state

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Abstract—Acylphosphonates, which are easily available from carboxylic acids, are potent acyl anion precursors and undergo cyanide ion promoted phosphonate–phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. The protonation of these acyl anion equivalents furnished cyanohydrin *O*-phosphates in good yields. For the high yield formation of cyanohydrin *O*-phosphates from arylphosphonates THF should be used and from alkylphosphonates DME was used.

1. Introduction

Acyl anion equivalents provide a powerful alternative to traditional carbon–carbon bond construction methods, and adds new dimensions of flexibility to the design of synthetic targets.[1a–h] These useful entities have been traditionally obtained by functional group manipulation and stoichiometric strong base deprotonation of the corresponding carbonyl compounds. Recently, impressive progress has been made in the catalytic generation of acyl anion equivalents, especially in the benzoin and Stetter reactions. As far as the cross-benzoin and intramolecular Stetter reactions are concerned, the use of acylsilanes as acyl anion precursors based on the nucleophile-promoted Brook rearrangement are the most practical and selective methods available.[1i–n]

Cyanohydrins are very important synthetic 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, has become synthetically more advantageous. Cyanophosphates are interesting building blocks for the synthesis of β-amino alcohols and γ-cyano-allylic alcohols[3] and several intermediates.[4] A number of different strategies are known[5] for the synthesis of cyanohydrin *O*-phosphates. The synthesis of racemic cyanohydrin *O*-phosphates from ketones and aldehydes starting from lithium cyanide and diethyl chlorophosphate, lithium cyanide, and diethyl cyanophosphonate,[6] diethyl cyanophosphonate in combination with lithium diisopropylamine,[7] cyanophosphonate and triethylamine at room temperature in the absence of a solvent and nonracemic cyanohydrin *O*-phosphates from aldehydes, employing diethyl cyanophosphonate and the chiral 3,3′-bis-(diethylaminomethyl)-1,1′-binaphthol–AlCl (BINOLAM–AlCl) complex as a bifunctional catalyst.[3] Recently, Aoyama et al.[8] described a method for the cyano-phosphorylation of aldehydes with diethyl cyanophosphonate in the presence of *N*-heterocyclic carbenes, and Shibasaki et al.[9] described the catalytic asymmetric cyano-phosphorylation of aldehydes using a YLi_3 tris (binaphthoxide) complex.

The complexity and difficult availability of the reagents for the above-mentioned methods prompted us to develop simple, generally applicable methods for the synthesis of these important compounds.

2. Results and discussion

Recently, we have shown that acylphosphonates are potent acyl anion precursors and undergo nucleophile-promoted phosphonate–phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. Acylphosphonates **1** as the acyl anion precursors and aldehydes **2** as electrophiles in the presence of a cyanide catalyst provides cross-benzoin products. Aromatic–aromatic

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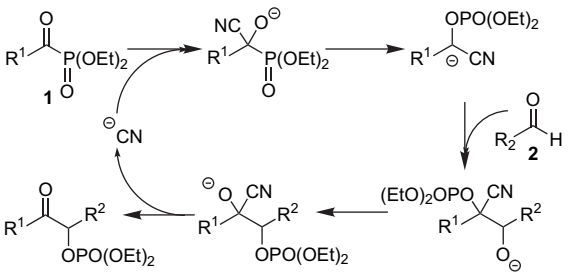
cross-benzoin synthesis, aroylphosphonates with aliphatic aldehydes, aliphatic acylphosphonates, and aromatic aldehydes furnished the acyloin products in good yields (Scheme 1).[10]



Scheme 1.

Protonation of acyl anion equivalents generated from acylphosphonates has twofold potential. First, the protonation of these intermediates not only provides a practical nonhydride reduction of carboxylic acids but also provides products that can be used as synthons for a variety of targets. Second, they gave us the opportunity to identify the side products of their reactions with aldehydes to be a proton abstraction from the environment or from reactants.[10a,11] This was the case in the reaction when utilizing aliphatic acylphosphonates.

As depicted in Scheme 2, the protonation of **3** would lead to **4**, which is equivalent to an aldehyde under the appropriate hydrolysis conditions. Therefore, this protonation strategy has the advantage of the direct reduction of carboxylic acids to aldehydes under aqueous conditions. The same transformation is known for the corresponding acylsilanes.[12] However, this is not a feasible approach because the synthesis of acylsilanes is laborious and generally obtained from aldehydes from which cyanohydrins are already available.

Acylphosphonates are easily available from carboxylic acids and the protonation of their cyanide promoted rearrangement intermediates would lead to a common intermediate for the synthesis of α-amino aldehydes, α-hydroxy-β-amino acids, and diols.

Acylphosphonates were synthesized according to the literature procedures starting from the triethylphosphite and acylchloride (82–89% yields).[10] The phosphonates **1k–n** were obtained from thionyl chloride and the protected amino acid by refluxing in benzene.

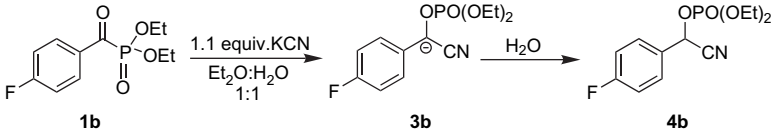
We examined the protonation of **3b** under two-phase conditions. Briefly, an organic solution (1 M DMF, toluene, or ether) of **1b** was mixed with an aqueous solution of KCN. All reactions were complete in a few minutes by TLC monitoring. Subsequent examination by NMR spectroscopy showed that reactions in toluene and ether provided the expected **4b** in pure form, however, yields were just 51 and 66%, respectively. We examined the protonation of **3b** under various conditions. A high yield formation of the product was achieved when mixing an ethereal solution of **1b** with KCN and then adding water to the mixture. This furnished the product in 90% yield after the work-up procedure (Scheme 2).

When the reaction was carried out in ether, quenched, and extracted with 1 N HCl, the crude products showed the presence of both **4b** and 4-*F*-benzoic acid **5**. The generation of **5** most likely results from the hydrolysis of **1b** but it was not obvious if **5** was formed directly by the action of water, or if cyanide ion promotion has a role. In order to shed light onto the hydrolysis, to DMF and ether solutions of **1a** was added water (pH=7 and 10, without KCN). TLC monitoring of these mixtures for several hours showed that **1a** is stable in the absence of cyanide anion and only traces of the corresponding acids were observable. When **1a** was stirred in MeOH, only traces of methyl benzoate were observed. However, the same mixture in the presence of KCN instantaneously provided methyl benzoate. These are strong indications of a cyanide ion catalyzed hydrolysis pathway.

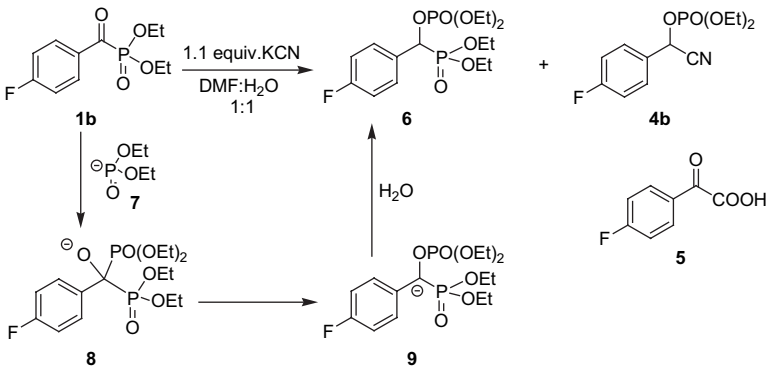
In DMF, crude product recovery was higher but contaminated with a side product. Upon closer examination of the side product, a comparison with the literature values revealed the side product as **6**. This product probably arises from the reaction of **7** with **1b**. Addition of **7** to **1b** promotes a phosphonate–phosphate rearrangement via **8** forming **9**, which subsequently abstracts the proton to provide **6** (Scheme 3). Phosphonate–phosphate rearrangement promoted by **7** is, however, already well known.[13]

Next, we investigated the scope of this reaction for the synthesis of typical cyanophosphates. Reaction with various aryl- and alkylphosphonates furnished the expected products. Surprisingly the first example (**1b**) furnished the highest yield (90%). This result prompted us to carry out solvent screening and we found that THF was a choice of the solvent for arylphosphonates (Table 1, entries 1–6) and the products were obtained in good to excellent yields (79–95%). For alkylphosphonates, DME furnished the best results and the products were obtained in 71–79% yields (entries 7–10). The phosphonate–phosphate rearrangement and protonation reaction of **1b** was also carried out in Et_2O–D_2O and the corresponding deuterated product **4o** was obtained in 78% yield. This also indicated that water is the source of the proton and this method could be used for the synthesis of deuterated benzaldehyde derivatives.

α-Amino aldehydes and α-hydroxy-β-amino acids are highly important compounds. The former is a valuable synthon for the synthesis of interesting targets. The latter can be found in



Scheme 2.



Scheme 3.

Table 1. Cyanophosphate synthesized

Entry	Acylphosphonate **1**	Product **4**[a]	Yield (%) (solvent)
1	**a**	**a**[3a,5b,8,9]	88 (Et_2O), 91 (THF)
2	**b**	**b**	90 (Et_2O), 92 (THF)
3	**c**	**c**[3a,5b,8]	81 (Et_2O), 83 (THF)
4	**d**	**d**[5e]	65 (Et_2O), 80 (THF)
5	**e**	**e**	66 (Et_2O), 79 (THF)
6	**f**	**f**	64 (Et_2O), 95 (THF)
7	**g**	**g**[5b,8]	77 (Et_2O), 79 (DME)
8	**h**	**h**[9]	64 (Et_2O), 77 (DME)

(*continued*)

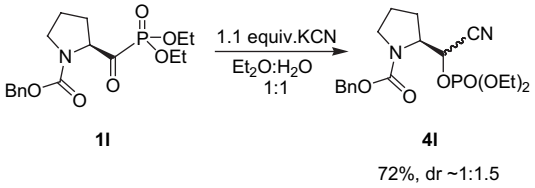
Table 1. (*continued*)

Entry	Acylphosphonate **1**	Product **4**[a]	Yield (%) (solvent)
9	**i**	**i**[11]	55 (Et_2O), 71 (DME)[b]
10	**j**	**j**[3b,8,9]	54 (Et_2O), 73 (DME)
11	**k**	**k**	62 (Et_2O)[c]
12	**l**	**l**	72 (Et_2O)
13	**m**	**m**	66 (Et_2O)
14	**n**	**n**	71 (Et_2O)
15	**b**	**O**	78 (Et_2O)

[a] All the products are colorless oil and the data of the known compounds are in agreement with the literature values.
[b] The reaction is carried out at 0 °C.
[c] Cat. amount of $Zn(OTf)_2$ (5 mol %) is used.

the structure of many biologically active compounds. The anticancer drug Taxol's side chain, *N*-benzoyl-phenylisoserine, bestatin, and amprenavir is just three of the many important compounds in this class. Acylphosphonates are easily available from carboxylic acids, in which the protonation of their cyanide promoted rearrangement intermediates would lead to a common intermediate for the synthesis of α-amino aldehydes and α-hydroxy-β-amino acids.

Therefore, we carried out a preliminary experiment to test the feasibility of this approach. When proloylphosphonate **1l** was subjected to KCN in aqueous ether, product **4l** was obtained in a few minutes with complete consumption of **1l**. The reaction also afforded pure **4l** in 72% yield (Scheme 4).



1l **4l**

72%, dr ~1:1.5

Scheme 4.

The reaction of phenylalanine derived phosphonate **1m** and phenylglycine derived phosphonate **1n** furnished the cyanophosphate **4m** and **4n** in 66–71% yields with 1:1.2 and 1:1.3 diastereomeric ratios, respectively. The same reaction with the phosphonate of methylmandelic acid **1k** afforded the cyanophosphate derivative **4k** in 62% yield with a 1:1.3 diastereomeric ratio. These products are also valuable synthon for the synthesis of interesting targets.

In general, the arylcyanophosphates are obtained in a higher yield than the alkylcyanophosphates and alkylcyanophosphates with α-CH furnished even lower yields.

3. Conclusions

We have shown that acylphosphonates that are easily available from carboxylic acids are potent acyl anion precursors and undergo cyanide ion promoted phosphonate–phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. The protonation of these acyl anion equivalents furnished cyanohydrin *O*-phosphates in good yields. The cyanophosphates are very interesting building blocks for the synthesis of various interesting compounds such as α-amino aldehydes, α-hydroxy-β-amino acids, and diols. Compared to the laborious synthesis of acylsilanes, the acylphosphonates are readily available in multigram scale from the corresponding carboxylic acids that offer an access to acyl anions. Thus, the generation of acyl anion equivalents from the phosphonate–phosphate rearrangement adds a new strategy to the toolbox of synthetic chemists. Moreover, the proven metal coordination ability of the phosphonate moiety makes acylphosphonates a particularly interesting platform for the diastereoselective and enantioselective variants of the presented reactions, which is the subject of current research.

4. Experimental

4.1. General

All reactions sensitive to air or moisture were conducted in flame-dried glassware under an atmosphere of dry Argon. THF and Et_2O were distilled from purple sodium benzophenone. KCN was dried at 100 °C under vacuum. DMF was distilled under reduced pressure and stored under nitrogen. Thin-layer chromatography (TLC) was performed on glass-supported Merck silica gel 60 F_{254} plates. Spots were visualized by UV light and by heat staining with 2% molybdophosphoric acid in ethanol. Flash column chromatography was performed on Merck silica gel 60 (63–200 μm). ^{1}H and ^{13}C NMR spectra were obtained on Bruker Avance 300 MHz and DPX 400 spectrometers. All resonances are referenced to residual solvent signals. Elemental analyses: Leco CHNS 932 Analysator. IR spectra were obtained on Bruker IFS 66/s. Acylphosphonates are synthesized according to the literature procedures.[10]

4.2. General procedure for protonation of acyl anion equivalents

KCN (0.55 mmol) was added to the solution of 0.5 mmol acylphosphonate in 2 mL diethyl ether (or appropriate solvent). After 5 min stirring 1 mL water was added to the mixture. After completion of the reaction (<15 min) (if solvent DME or THF reaction time is 1–2 h), the mixture was diluted with 5 mL ether and 5 mL water. Organic phase was separated and dried with $MgSO_4$ and evaporated under reduced pressure. The products are purified by using flash column chromatography (EtOAC–hexane).

4.2.1. (*S*)-Diethyl 2-methoxy-1-oxo-2-phenylethylphosphonate 1k. Viscous yellow oil. Yield 2.37 g (83%), IR ($CHCl_3$): ν=1692, 1259, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J=7.1 Hz, 3H), 1.37 (t, J=7.1 Hz, 3H), 3.35 (s, 3H), 4.06–4.26 (m, 4H), 4.74 (s, 1H), 7.19–7.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.28, 57.5, 58.2, 62.1, 62.4, 82.0, 96.1, 127.2, 128.1, 128.2, 129.5, 204.5 (low intensity d, J=170 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 8.91. $C_{13}H_{19}O_5P$ (286.26): Calcd C 54.54, H 6.69; found C 54.36, H 6.41.

4.2.2. Diethyl ((*S*)-1-((benzyloxy)carbonyl)pyrrolidin-2-yl)oxomethylphosphonate 1l. Yellow oil. Yield 3.00 g (81%). IR ($CHCl_3$): ν=1692, 1417, 1355, 1259, 1079, 1024 cm^{-1}. ^{1}H NMR (400 MHz, DMSO, 90 °C): δ 1.23 (m, 6H), 1.67–1.85 (m, 1H), 1.88–1.96 (m, 1H), 1.99–2.04 (m, 1H), 2.15–2.28 (m, 1H), 3.34–3.52 (m, 2H), 4.00–4.13 (m, 4H), 4.80–4.83 (m, 1H), 5.02–5.10 (m, 2H), 7.28–7.37 (m, 5H). ^{13}C NMR (100 MHz, DMSO, 90 °C): δ 15.8, 15.9, 23.2, 28.4, 46.7, 63.3 (d, J=7.2 Hz), 63.5 (d, J=7.3 Hz), 65.7 (d, J=6.5 Hz), 66.3, 127.4, 127.6, 128.2, 128.4, 136.7, 209.1 (d, J=159 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 12.03. $C_{17}H_{24}NO_6P$ (369.35): Calcd C 55.28, H 6.55, N 3.79; found C 55.33, H 6.41, N 3.51.

4.2.3. (*S*)-Diethyl 1-oxo-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropylphosphonate 1m. Yellow oil. Yield 3.56 g (86%). IR ($CHCl_3$): ν=1690, 1425, 1355, 1266, 1085, 1021 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.32 (m,

5H), 3.38 (dd, J=3.4, 10.8 Hz, 1H), 3.67 (dd, J=4.7, 9.6 Hz, 1H), 4.08–4.17 (m, 4H), 5.30–5.38 (m, 1H), 7.04–7.19 (m, 5H), 7.61–7.70 (m, 2H), 7.73–7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7 (d, J=6.3 Hz), 15.8 (d, J=6.1 Hz), 32.2, 52.6, 63.6 (d, J=7.5 Hz), 63.8 (d, J=7.2 Hz), 122.9, 126.3, 128.0, 128.4, 131.3, 133.4, 135.6, 166.5, 203.8 (d, J=169 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 8.91. $C_{21}H_{22}NO_6P$ (415.38): Calcd C 60.72, H 5.34, N 3.37; found C 60.56, H 5.21, N 3.18.

4.2.4. (*S*)-Diethyl 1-oxo-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethylphosphonate 1n. Yellow oil. Yield 2.84 g (71%). IR ($CHCl_3$): ν=1728, 1382, 1218, 1014 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (m, 6H), 4.08 (m, 4H), 7.24–7.30 (m, 3H), 7.43 (m, 1H), 7.56 (d, J=7.6 Hz, 2H), 7.64–7.66 (m, 1H), 7.70–7.72 (m, 1H), 7.76–7.81 (m, 1H), 7.83–7.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 15.8, 63.7, 63.8, 96.2, 123.5, 127.4, 128.3, 128.4, 130.5, 132.4, 134.1, 167.5, 204.1 (d, J=169 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 12.20 ppm. $C_{20}H_{20}NO_6P$ (401.35): Calcd C 59.85, H 5.02, N 3.49; found C 59.61, H 5.28, N 3.21.

4.2.5. Cyano(4-fluorophenyl)methyl diethyl phosphate 4b. Yellow oil. Yield 132 mg (92%). IR ($CHCl_3$): ν=2360, 1699, 1653, 1559, 1541, 1508, 1268, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (J=7.1 Hz, 3H), 1.38 (t, J=7.1 Hz, 3H), 3.94–4.01 (m, 2H), 4.15–4.25 (m, 2H), 6.04 (d, J=8.9 Hz, 1H), 7.11–7.17 (m, 2H), 7.53–7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8 (d, J=6.5 Hz), 15.9 (d, J=6.6 Hz), 64.6 (d, J=6.1 Hz), 64.9 (d, J=6.1 Hz), 65.7 (d, J=4.4 Hz), 116.0 (d, J=6.2 Hz), 116.4 (d, J=22 Hz), 128.6 (m), 129.7 (d, J=8.8 Hz), 163.8 (d, J=251.6 Hz). ^{31}P NMR (161 MHz, $CDCl_3$) δ −2.17. $C_{12}H_{15}FNO_4P$ (287.22): Calcd C 50.18, H 5.26, N 4.88; found C 50.42, H 5.33, N 5.23. Deuterated derivative **4o**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, J=6.7 Hz, 3H), 1.38 (t, J=6.7 Hz, 3H), 3.94–4.01 (m, 2H), 4.15–4.25 (m, 2H), 7.11–7.17 (m, 2H), 7.53–7.58 (m, 2H).

4.2.6. Cyano(2-methylphenyl)methyl diethyl phosphate 4e. Yellow oil. Yield 112 mg (79%). IR ($CHCl_3$): ν=2360, 1653, 1559, 1271, 1030 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, J=7.1 Hz, 3H), 1.38 (t, J=7.1 Hz, 3H), 2.50 (s, 3H), 3.98–4.10 (m, 2H), 4.12–4.31 (m, 2H), 6.16 (d, J=8.7 Hz, 1H), 7.24–7.39 (m, 3H), 7.56 (d, J=7.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.9 (d, J=6.9 Hz), 16.0 (d, J=6.8 Hz), 18.9, 64.6 (d, J=6.2 Hz), 64.7 (d, J=4.9 Hz), 64.8 (d, J=6.0 Hz), 116.1 (d, J=5.6 Hz), 126.8, 128.3, 130.6, 130.7, 131.4, 136.6. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ −2.10. $C_{13}H_{18}NO_4P$ (283.26): Calcd C 55.12, H 6.41, N 4.94; found C 55.41, H 6.33, N 4.73.

4.2.7. Cyano(3-chlorophenyl)methyl diethyl phosphate 4f. Yellow oil. Yield 144 mg (95%). IR ($CHCl_3$): ν=2360, 1559, 1474, 1271, 1028 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.1 Hz, 3H), 1.31 (t, J=7.1 Hz, 3H), 3.95–4.12 (m, 2H), 4.18–4.30 (m, 2H), 6.02 (d, J=8.9 Hz, 1H), 7.36–7.47 (m, 3H), 7.56 (d, J=1.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.9 (d, J=6.9 Hz), 16.0 (d, J=6.9 Hz), 64.6 (d, J=6.1 Hz), 64.7 (d, J=4.9 Hz), 64.8 (d, J=6.0 Hz), 116.1 (d, J=5.6 Hz), 126.8, 128.3, 130.6, 130.7, 131.4, 136.6. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ −2.10. $C_{12}H_{15}ClNO_4P$ (303.68): Calcd C 47.46, H 4.98, N 4.61; found C 47.21, H 4.62, N 4.35.

4.2.8. (2*S*)-1-Cyano-2-methoxy-2-phenylethyl diethyl phosphate 4k. Yellow oil. Yield 97 mg (62%). IR ($CHCl_3$): ν=2362, 1220, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.38 (m, 6H), 3.34 and 3.38 (2s, 3H), 3.77–4.19 (m, 4H), 4.47 (m, 1H), 4.96 and 5.12 (dd, J=2.8, 6.2 Hz and dd, J=2.8, 6.2 Hz, 1H), 7.25–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9 (d, J=6.9 Hz), 16.0 (d, J=6.8 Hz), 18.9, 64.6 (d, J=6.2 Hz), 64.7 (d, J=4.9 Hz), 64.8 (d, J=6.0 Hz), 116.1 (d, J=5.6 Hz), 126.8, 128.3, 130.6, 130.7, 131.4, 136.6. ^{31}P NMR (161 MHz, $CDCl_3$): δ −2.86, −2.58. $C_{14}H_{20}NO_5P$ (313.29): Calcd C 53.67, H 6.43, N 4.47; found C 53.81, H 6.51, N 4.21.

4.2.9. ((*S*)-1-((Benzyloxy)carbonyl)pyrrolidin-2yl)(cyano)methyl diethyl phosphate 4l. Yellow oil. Yield 143 mg (72%). IR ($CHCl_3$): ν=2360, 1700, 1559, 1541, 1507, 1418, 1280, 1026 cm^{-1}. ^{1}H NMR (400 MHz, DMSO, 60 °C): δ 1.21–1.32 (m, 6H), 1.84–2.09 (m, 4H), 3.23–3.64 (m, 2H), 4.05–4.11 (m, 4H), 4.20–4.30 (m, 1H), 5.05–5.16 (m, 2H), 5.42–5.58 (m, 1H), 7.32–7.39 (m, 5H). ^{13}C NMR (100 MHz, DMSO, 60 °C): δ 17.5, 32.3, 49.0, 62.9, 66.1, 66.2, 66.3, 66.3, 66.4, 68.3, 68.5, 117.9, 129.4, 129.7, 130.2, 130.2, 138.3, 138.4. ^{31}P NMR (161 MHz, DMSO, 60 °C): δ −2.54, −2.32, −1.44. $C_{18}H_{25}N_2O_6P$ (396.37): Calcd C 54.54, H 6.36, N 7.07; found C 54.32, H 6.67, N 6.83.

4.2.10. (2*S*)-1-Cyano-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropyl diethyl phosphate 4m. Yellow oil. Yield 145 mg (66%). IR ($CHCl_3$): ν=2370, 1720, 1651, 1560, 1545, 1510, 1452, 1260, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.30 and 1.32–1.42 (m, 6H), 3.34–3.59 (m, 2H), 3.85–3.93 (m, 1H), 4.14–4.01 (m, 1H), 4.18–4.31 (m, 2H), 4.86–4.95 (m, 1H), 5.67–5.76 (m, 1H), 7.10–7.18 (m, 5H), 7.68–7.71 (m, 2H), 7.74–7.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 16.1, 34.0, 54.1 (d, J=8.8 Hz), 65.0, 65.1, 65.2, 115.0, 123.7, 127.2, 128.7, 128.8, 131.1, 134.4, 135.5. ^{31}P NMR (161 MHz, $CDCl_3$): δ −2.86, −2.78. $C_{22}H_{23}N_2O_6P$ (442.4): Calcd C 59.73, H 5.24, N 6.33; found C 59.54, H 5.43, N 6.21.

4.2.11. (2*S*)-1-Cyano-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl diethyl phosphate 4n. Yellow oil. Yield 151 mg (71%). IR ($CHCl_3$): ν=2360, 1717, 1653, 1559, 1541, 1507, 1457, 1260, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (t, J=7.1 Hz, 3H), 1.25 (t, J=7.1 Hz, 3H), 3.44–3.54 (m, 1H), 3.56–3.65 (m, 1H), 3.87–3.97 (m, 1H), 4.01–4.06 (m, 1H), 5.52 (d, J=10.7 Hz, 1H), 6.34 (dd, J=1.8, 8.8 Hz, 1H), 7.23–7.32 (m, 3H), 7.56 (d, J=7.1 Hz, 2H), 7.65–7.68 (m, 2H), 7.78–7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7 (d, J=7.2 Hz), 16.0 (d, J=7.2 Hz), 56.7 (d, J=9.3 Hz), 64.0 (d, J=4.9 Hz), 64.2 (d, J=5.9 Hz), 64.6 (d, J=5.6 Hz), 96.2, 115.2, 123.9, 129.0, 129.1, 129.2, 131.6, 134.2, 134.3, 167.0. ^{31}P NMR (161 MHz, $CDCl_3$) δ −3.20. $C_{21}H_{21}N_2O_6P$ (428.38): Calcd C 58.88, H 4.94, N 6.54; found C 58.66, H 4.81, N 6.33.

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