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Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate−Phosphate Rearrangement: A Highly Practical Method for Cross-Benzoin Reaction

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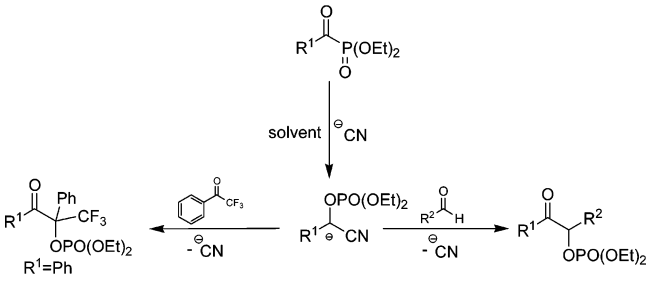

Acylphosphonates are potent acyl anion precursors that generate acyl anion equivalents under the promotion of cyanide anion via phosphonate−phosphate rearrangement. These anions readily react with aldehydes to provide cross-benzoin products. In this way it is possible to synthesize a variety of aromatic−aromatic, aromatic−aliphatic, and aliphatic−aromatic benzoins. Moreover the reaction of benzoylphosphonate with potent electrophile 2,2,2-trifluoroacetophenone provided the corresponding aldehyde−ketone coupling product in high yield.

Polarity reversal (umpolung) of carbonyl group (acyl anion equivalents) provides a powerful alternative to traditional carbon−carbon bond construction methods and adds new dimensions of flexibility to the design of synthetic targets.[1] 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[2] and Stetter[3] reactions. As far as the cross-benzoin and intramolecular Stetter reactions are concerned, the use of acylsilanes[4,5] as acyl anion precursors based on the nucleophile-promoted Brook rearrangement[6] is the most practical and selective method available. However, acylsilanes for use as precursors suffer from tedious preparative operations that often require a stoichiometric strong base or metal nucleophiles, and most of the time they are synthesized from the corresponding acyl anions.[7] Thus, there is always a need for practical and easily accessible acyl anion precursors that can engage in catalytic carbon−carbon bond-forming reactions.

Phosphorus, like silicon, has the ability to migrate from carbon to oxygen and oxygen to carbon.In fact deprotonation of α-hydroxyphosphonates and base-catalyzed addition of dialkyl phosphites to acylphosphonates induce such phosphonate−phosphate rearrangements, which have a close analogy to the 1,2-Brook rearrangement of acylsilanes.[8] We envisioned that the typical nucleophilic catalysis of benzoin and Stetter reactions might promote acylphosphonates to generate an appropriate concentration of the corresponding acyl anion equivalents that are sufficiently nucleophilic in order to participate in the reactions with electrophiles. It is very important to note that Johnson and co-workers very recently reported the viability of this approach in the synthesis of a variety of aromatic−aromatic cross-benzoin products **3** from aromatic acylphosphonates, with [18-crown-6/KCN] complex as catalyst in diethyl ether providing the optimal conditions (Scheme 1).[9] Morover Kurihara reported stoichiometric strong base deprotonation of α-cyanophosphates generating cyano-phosphate anions **1b** that react with a variety of electrophiles including aldehydes to provide **3**.[10] However, they reported that cyano-phosphate anions **1b**

(1) For recent reviews, see: (a) Johnson, J. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 1326−1328. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res*. **2004**, *37*, 534−541. (c) Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J*. **2002**, *8*, 5288−5295.

(2) (a) Enders, D.; Kalfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743−1745 and references therein. (b) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084−12085. (c) Hachisu, Y.; Bode, J. W.; Suzuki, K. J. *J. Am. Chem. Soc.* **2003**, *125*, 8432−8433. (d) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, *346*, 1097−1100. (e) Enders, D.; Oliver, N. *Synlett* **2004**, 2111−2114.

(3) (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc*. **2004**, *126*, 8876−8877. (b) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc*. **2005**, *127*, 6284−6289. (c) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899−1902. (d) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem*. **2004**, *126*, 2025−2035. (e) Mennen, S.; Blank, J.; Tan-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun*. **2005**, 195−197. (f) Murry, J. E.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697.

(4) For examples of acylsilanes in benzoin synthesis, see: (a) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536. (b) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071. (c) Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G. *J. Org. Chem*. **1985**, *50*, 130−133. For application of benzils in benzoin synthesis, see: (d) Kuebrich, J. P.; Schowen, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1220−1223. (e) Demir, A. S.; Reis, Ö. *Tetrahedron* **2004**, *60*, 3803−3811.

(5) Stetter reaction with acylsilanes. For organocatalysis, see: (a) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314−2315. For metallophosphite catalysis, see: (b) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed*. **2005**, *44*, 2377−2379. For cyanide catalysis, see: (c) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital*. **1987**, *117*, 645−648.

(6) (a) Brook, A. G. *Acc. Chem. Res*. **1974**, *7*, 77−84. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084 and references therein.

(7) Clark, C. T.; Milgram, B. C.; Scheidt, K. *Org. Lett.* **2004**, *6*, 3977−3980.

(8) (a) Hammerschmidt, F.; Schneyder, E.; Zbiral, E. *Chem. Ber.* **1980**, *113*, 3891−3897. (b) Fitch, S.; Moedritzer, K. *J. Am. Chem. Soc*. **1962**, *84*, 1876. (c) Ruel, R.; Bouvier, J.-P.; Young, R. N. *J. Org. Chem*. **1995**, *60*, 5209−5213. Cyanide anion promoted phosphonate-phosphate rearrangement of acetylphosphonate in aqueous medium was reported; see: (d) Hall, L. A. R.; Stephens, C. W.; Drysdale, J. J. *J. Am. Chem. Soc*. **1957**, *79*, 1768−1769.

(9) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal*. **2005**, *347*, 1207−1211.

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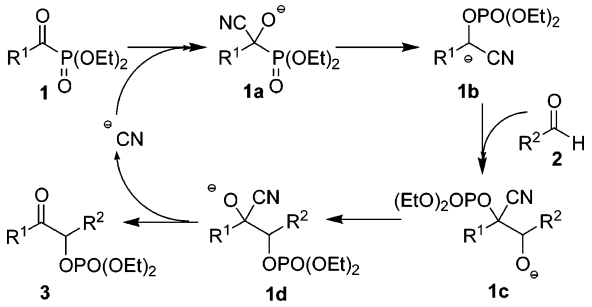
SCHEME 1. Mechanism of Cross-Benzoin Reaction via Cyanide Ion Promoted Generation of Acyl Anions from Acylphosphonates

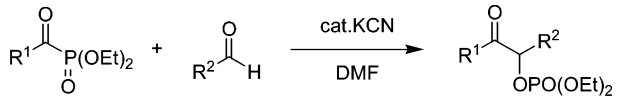


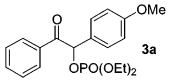
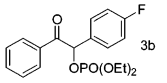
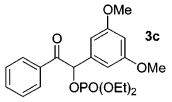
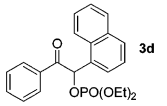
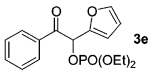
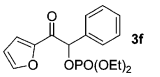
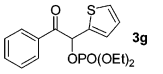
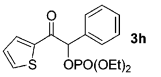
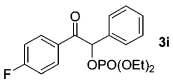
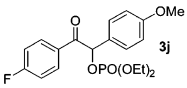
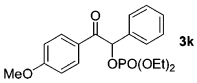
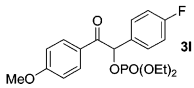
with electron-rich aromatic and aliphatic groups are not useful in this particular transformation. Herein, we report our preliminary results in the realization of this idea utilizing acylphosphonates **1** as the acyl anion precursors and aldehydes **2** as electrophiles in the presence of a cyanide catalyst to provide cross-benzoin products **3** (Scheme 1).[11] Acylphosphonates are readily available on a multigram scale from acyl chlorides and trialkyl phosphites via Arbuzov reaction without need to use any special condition or apparatus.[12]

We initially investigated the reaction of benzoylphosphonate with *p*-anisaldehyde catalyzed by 10% KCN in the presence of phase transfer catalysts (Bu_4NBr or 18-crown-6) in various solvents and observed very slow or no conversion in many solvents at ambient temperature. Although heating provided varying degrees of conversions in different solvents, reaction in DMF provided a smooth and fast transformation into the desired product **3a** in 93% yield at ambient temperature without using a phase transfer catalyst (Table 1, entry 1).

Next, we investigated the scope of this reaction for the synthesis of typical aromatic−aromatic benzoins. Reaction of benzoylphosphonate with various aromatic aldehydes furnished the expected products in good to excellent yields (Table 1, entries 1−8). Heterocyclic aldehydes provided the expected products **3e** and **3g**, albeit contaminated with isomeric benzoins **3f** and **3h** (Table 1, entries 5−8). This concurrent regioisomerization process was also pointed out by Johnson and co-workers.[9] Whereas lowering the temperature (0 °C) provided the expected products without isomer contamination, increasing the catalyst load (30%) quickly furnished the isomeric products. In this way the synthesis of both isomeric benzoins was possible from the same starting materials. Formation of isomeric benzoins is presumably due to the basic cyanide-catalyzed isomerization of the expected benzoins. In fact, the treatment of isolated pure **3g** with catalytic DBU under the same reaction conditions afforded **3h** with complete conversion. To understand the scope of the

TABLE 1. Synthesis of Aromatic−Aromatic Benzoins[a]



entry	R^1	R^2	Product	Yield (%)[b]
1	Ph	4-OMePh	 **3a**	93
2	Ph	4-FPh	 **3b**	83
3	Ph	3,5-$(OMe)_2$Ph	 **3c**	88
4	Ph	1-napthyl	 **3d**	87
5	Ph	2-furyl	 **3e**	81
6	Ph	2-furyl	 **3f**	85
7	Ph	2-thienyl	 **3g**	86
8	Ph	2-thienyl	 **3h**	89
9	4-FPh	Ph	 **3i**	87
10	4-FPh	4-OMePh	 **3j**	93
11	4-OMePh	Ph	 **3k**	91
12	4-OMePh	4-FPh	 **3l**	94

[a] Reactions were carried out on a 1 mmol scale (1.1 equiv of aldehyde) with concentrations of 0.5 M in the presence of 10% KCN at room temperature except for entries 5 and 7 at 0 °C and entries 6, 8, 11, and 12 with 30% KCN. [b] Isolated yields.

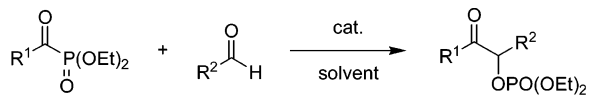
method in synthesizing all of the isomers of a given pair of a donor and acceptor, we examined the reaction of substituted aroylphosphonates. Whereas the reaction of 4-*F*-benzoylphosphonate proceeded smoothly to give disubstituted cross-benzoins **3i** and **3j** in very good yields (Table 1, entries 9−10), electron-rich 4-MeO-benzoylphosphonate reacted very slowly under the usual reaction conditions. Gratifyingly, simply increasing the catalyst load (30% KCN) resulted in a smooth transformation providing **3k** and **3l** in very good yields (Table 1, entries 11 and 12).

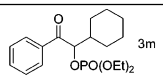
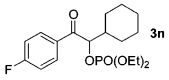
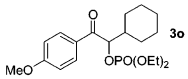
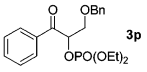
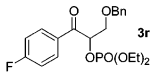
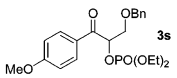
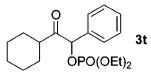
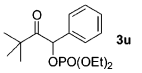
(10) For examples of stoichiometric generation of acyl anion equivalents from α-cyanophosphates and their reactions, see: (a) Kurihara, T.; Santo, K.; Harusawa, S.; Yoneda, R.; *Chem. Pharm. Bull.* **1987**, *35*, 4777−4788. (b) Schrader, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 917−919.

(11) This mechanistic picture is based on the well-known benzoin reaction mechanism and its congeners; see refs 1, 4, and 9.

(12) (a) Berlin, K. D.; Taylor, H. A. *J. Am. Chem. Soc.* **1964**, *86*, 3862−3866. (b) Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron* **1998**, *54*, 12233−12242.

TABLE 2. Synthesis of Aromatic−Aliphatic and Aliphatic−Aromatic Benzoins[a]



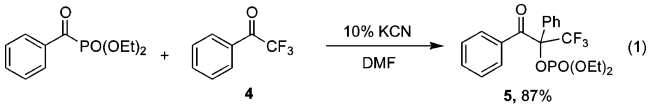
entry	R^1	R^2	Product	Yield (%)[b]
1	Ph	cyclohexyl	 3m	87
2	4-FPh	cyclohexyl	 3n	81
3	4-OMePh	cyclohexyl	 3o	85
4	Ph	benzyloxymethyl	 3p	81
5	4-FPh	benzyloxymethyl	 3r	75
6	4-OMe	benzyloxymethyl	 3s	77
7	cyclohexyl	Ph	 3t	64
8	$(CH_3)_3C$	Ph	 3u	87

[a] For entries 1−6, reactions were carried out in premixed DMF solution of 20% CsF and 30% TMSCN (see Supporting Information for details). For entries 7 and 8, 2 equiv of aldehyde with 30% KCN and 30% 18-crown-6 in toluene (5 mL, 0.2 M) was heated to 100 °C. [b] Isolated yields.

After establishing the utility of acylphosphonates in aromatic−aromatic cross-benzoin synthesis, we investigated their potential in the incorporation of aliphatic moieties into the benzoin structure and started with the reactions of aroylphosphonates with aliphatic aldehydes. Although the initial reactions with the KCN catalyst provided the expected benzoins, yields were low with considerable site product(s) contamination. Later we found that the DMF solution of premixed CsF (20%) and TMSCN (30%) was superior to KCN in terms of conversion rates and product purity. In fact the reaction of aroylphosphonates with cyclohexancarboxaldehdye and benzyloxyacetaldehyde furnished the products in good yields (Table 2, entries 1−6).

The use of both KCN and CsF + TMSCN in DMF failed to give good yields in reactions between aliphatic acylphosphonates and aromatic aldehydes. Presumably the highly enolizable nature of aliphatic acylphosphonates resulted in the protonation of the critical acyl anion equivalent, and hence the presumed catalytic cycle failed (Scheme 1). We found that the use of 30% KCN and 30% 18-crown-6 in refluxing toluene provided better yields (Table 2, entries 7 and 8). Although we examined the reactions of a wide range of aliphatic acylphosphonates **1** (R^1 = cyclohexyl, isopropyl, methyl) and aromatic aldehydes **2** (R^2 = Ph, 4-OMePh, 4-FPh) to obtain aliphatic−aromatic benzoins in the 60−70% yield range, the formation of a protonation product (15−20%) was unavoidable. The separation of this product to obtain pure products proved to be highly problematic. When reaction was carried out with nonenolizable trimethylacetylphosphonate, good yield of the corresponding benzoin was obtained smoothly in toluene (Table 2, entry 8). Last, the syntheses of aliphatic−aliphatic cross-benzoins **3** (R^1 = cyclohexyl, isopropyl, methyl and R^2 = cyclohexyl, isopropyl, methyl) were very sluggish, providing only <20% estimated yields.

Prompted by the success of acylphosphonates as acyl anion precursors in benzoin condensation, we carried out preliminary experiments to further study the potential of these entities. Catalytic intermolecular coupling of aldehydes and ketones has not been realized so far.[2c−e] Thus, we examined the reaction of benzoylphosphonate with potent electrophile 2,2,2-trifluoroacetophenone **4**, which furnished the expected coupling product **5** in 87% yield (eq 1). The same reaction with acetophenone only provided poor yields together with the recovered starting materials.



In conclusion, we have shown that acylphosphonates are a new generation of potent acyl anion precursors that undergo nucleophile-promoted phosphonate−phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. Compared to laborious synthesis of acylsilanes, they are readily available on a multigram scale from the corresponding carboxylic acids or aldehydes, which offers an atom- and time-efficient access to acyl anions. They add a new and highly practical method to the toolbox of synthetic chemists. Current work is directed toward further understanding the nature and reactivity of acylphosphonates as acyl anion precursors in reactions with various electrophiles and development of enantioselective version of the presented reaction.

Experimental Section

General Procedures for Cyanide-Catalyzed Cross-Benzoin Reactions. Reactions were carried out according to different procedures depending on the nature of the substrates. Briefly, reactions between aromatic acylphosphonates were carried out in DMF with 10% KCN catalysis (Method A), and slight modifications in temperature (0 °C, Method B) or catalyst load (30% KCN, Method C) were made to optimize yields. Reactions between aromatic acylphosphonates and aliphatic aldehydes were carried out in DMF with CsF + TMSCN catalysis (Method D), and reactions between aliphatic acylphosphonates and aromatic aldehydes were carried out in toluene with 30% KCN and 30% 18-crown-6 as catalyst system (Method E). Representative procedures are as follows.

Representative Example for Method A: Diethyl 2-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-oxoethyl phosphate (3j). The title compound was prepared according to Method A using 260 mg (1 mmol) of acylphosphonate, 149.8 mg (1.1 mmol) of *p*-methoxybenzaldehyde, 6.5 mg (10%, 0.1 mmol) KCN, and 2 mL of DMF. After 25 min at ambient temperature, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 368 mg (93%) of the product as a

colorless oil: IR (film) 2986, 2839, 1698, 1601, 1512, 1461, 1443, 1257, 1177, 1159, 1044, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, J = 7.0 Hz), 1.33 (3H, t, J = 6.7 Hz), 3.76 (3H, s), 3.88−3.96 (2H, m), 4.14−4.26 (2H, m), 6.58 (1H, d, J = 7.8 Hz), 6.89 (2H, d, J = (8.7 Hz), 7.05 (2H, m), 7.41 (2H, d, J = 8.7 Hz), 7.94−7.98 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J = 6.9 Hz), 16.3 (d, J = 6.9 Hz), 55.6, 64.2 (d, J = 6.3 Hz), 65.0 (d, J = 6.0 Hz), 80.0 (d, J = 4.8 Hz), 114.9, 116.1 (d, J = 22.0 Hz), 127.1, 130.0, 131.1 (d, J = 2.9 Hz), 132 (d, J = 9.2 Hz), 160.8, 166.1 (d, J = 255 Hz), 192.4 (d, J = 4.7 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −1.19. Anal. Calcd for $C_{19}H_{22}FO_6P$: C, 57.58; H, 5.59. Found: C, 57.31; H, 5.32.

Representative Example for Method B: Diethyl 2-oxo-2-phenyl-1-(thiophen-2-yl)ethyl phosphate (3g). The title compound was prepared according to Method B using 242 mg (1 mmol) of acylphosphonate, 123 mg (1.1 mmol) of 2-thiophenecarboxaldehyde, 6.5 mg (10%, 0.1 mmol) KCN, and 2 mL of DMF. After 30 min at 0 °C, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 305 mg (86%) of the product as a pale yellow oil: IR (film) 2968, 1695, 1516, 1443, 1435, 1282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, dt, J = 1, 7 Hz), 1.31 (3H, dt, J = 1, 7.9 Hz), 3,9−4,05 (2H, m), 4.1−4.25 (2H, m), 6.9 (1H, dj, J = 7.9 Hz), 6.96 (1H, dd, J = 3.6, 5.1 Hz), 7.17 (1H, dd, J = 1.1, 3.6 Hz), 7.36 (1H, dd, J = 1.1, 5.1 Hz), 7.4−7.44 (2H, m), 7.51−7.57 (1H, m), 7.95−7.9 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.73 (d, J = 7.3 Hz), 15.85 (d, J = 6,8 Hz), 63.9 (d, J = 6.3 Hz), 64.3 (d, J = 5.9 Hz), 74.7 (d, J = 4.2 Hz), 127.2, 128.2, 128.6, 128.7, 128.9, 133.6, 134.0, 136.6 (d, J = 6.2 Hz), 192.2 (d, J = 4.8 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −2.61. Anal. Calcd for $C_{16}H_{19}O_5PS$: C, 54.23; H, 5.40. Found: C, 54.05; H, 5.26.

Representative Example for Method C: Diethyl 1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-oxoethyl phosphate (3l). The title compound was prepared according to Method C using 272 mg (1 mmol) of acylphosphonate, 136.5 mg (1.1 mmol) of *p*-fluorobenzaldehyde, 19.5 mg KCN (30%, 0.3 mmol), and 2 mL of DMF. After 6 h at ambient temperature, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 372 mg (94%) of the product as a colorless oil: IR (film) 2993, 1693, 1601, 1511, 1261, 1173, 1037, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, t, J = 7.1 Hz), 1.33 (3H, t, J = 7.1 Hz), 3.84 (3H, s), 3.89−3.98 (2H, m), 4.14−4.24 (2H, m), 6.60 (1H, d, J = 8.1 Hz), 6.9 (2H, d, J = 8.8 Hz), 7.06 (2H, m), 7.45−7.55 (2H, m), 7.93 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (d, J = 7.1 Hz), 16.0 (d, J = 7.0 Hz), 55.4, 63.9 (d, J = 6.2 Hz), 63.3 (d, J = 6 Hz), 78.8 (d, J = 4.9 Hz), 114, 116 (d, J = 22.1 Hz), 130 (d, J = 8.2 Hz), 131.3, 163.1 (d, J = 251 Hz), 163.9, 191.7 (d, J = 4.9 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −2.30. Anal. Calcd for $C_{19}H_{22}FO_6P$: C, 57.58; H, 5.59. Found: C, 57.52; H, 5.61.

Representative Example for Method D: 3-(Benzyloxy)-1-oxo-1-phenylpropan-2-yl diethyl phosphate (3p). The title compound was prepared according to Method D using 242 mg (1 mmol) of acylphosphonate, 165 mg (1.1 mmol) of benzyloxyacetaldehyde, 30 mg CsF (20%), 29.7 mg TMSCN (30%), and 2 mL of DMF. After 5−10 min at ambient temperature, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 318 mg (81%) of the product as a colorless oil: IR (film) 2950, 2354, 1692, 1635, 1515, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.1−1.23 (6H, m), 3.8−3.83 (2H, m), 3.96−4.09 (4H, m), 4.43−4.52 (2H, m), 5.74−5.79 (1H, m), 7.14−7.23 (5H, m), 7.36−7.41 (2H, m), 7.49−7.53 (1H, m), 7.86−7.89 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (d, J = 2.76 Hz), 16.0 (d, J = 2.79 Hz), 64.12 (d, J = 6.0 Hz), 64.2 (d, J = 6.0 Hz), 70.4 (d, J = 6.1 Hz), 73.4, 77.9 (d, J = 5.4 Hz), 127.6, 127.8, 128.3, 128.8, (d, J = 3.0 Hz), 133.6, 134.9, 137.3, 194.8 (d, J = 3.0 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −2.27. Anal. Calcd for C20H25O6P: C, 61.22; H, 6.42. Found: C,61.42; H, 6.64.

Representative Example for Method E: 2-Cyclohexyl-2-oxo-1-phenylethyl diethyl phosphate (3t). The title compound was prepared according to Method E using 248 mg (1 mmol) of acylphosphonate, 212.2 mg (2 mmol) of benzaldehyde, 19.5 mg KCN (30%, 0.3 mmol), 79 mg (30%, 0.3 mmol) of 18-crown-6, and 5 mL of toluene. After 6 h at 100 °C, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 227 mg (64%) of the product as a colorless oil: IR (film) 2926, 1692, 1655, 1512, 1450, 1280, 1229, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, dt, J = 0.9, 7.2 Hz), 1.34 (3H, dt, J = 0.9, 6.9 Hz), 1.10−1.45 (5H, m), 1.60−1.83 (5H, m), 2.50 (1H, m), 3.84−3.94 (2H, m), 4.11−4.21 (2H, m), 5.75 (1H, d, J = 8.1 Hz), 7.30−7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (2C, m), 25.2, 25.6, 25.7, 28.0, 29.3, 29.7, 46.7, 64.1 (2C,m), 81.9 (d, J = 5.2 Hz), 127.9, 128.9, 129.3, 134.5, 207.2; ^{31}P NMR (161 MHz, $CDCl_3$) δ −2.44. Anal. Calcd for $C_{18}H_{27}O_5P$: C, 61.01; H, 7.68. Found: C, 61.24; H, 7.52.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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