Dephosphonylation of β-Carbonyl Phosphonates

Shi Yong Lee, Chi-Wan Lee, and Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1 Kusong Dong, Yusong Gu, Taejon 305-701, Korea

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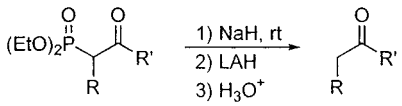
A new methodology has been developed for the P−C bond cleavage of β-carbonyl phosphonates. The α,α-disubstituted β-keto phosphonates and the α-carbamoyl phosphonates have been shown to undergo dephosphonylation by reaction of their lithium enolate with $LiAlH_4$, followed by quenching with aqueous H_2SO_4, affording regioselectively α,α-disubstituted ketone and α-substituted and α,α-disubstituted secondary amides.

Introduction

There are a number of applications of β-keto esters[1] and β-keto sulfones[2] as synthetically useful intermediates for preparation of regioselectively α-alkylated ketones by alkylation with subsequent defunctionalization. On the contrary, the method employing phosphonate as a temporary activating group in the same manner has not been studied yet due to the fact that dephosphonylation[3] of β-keto phosphonate is less known. Although various methods or reagents[4,5] have been used to reduce a $C-P^V$ bond into a C−H bond, the known chemical methods for $C-P^V$ bond cleavage are of limited generality due to the unique substrate requirements. Moreover, there is only one literature reference[6] involving the C−P bond reduction of β-keto-1-phosphonato esters analogous to β-keto phosphonates. Recently, we have reported a new utility of β-keto phosphonate as a precursor to α-alkylated ketones through dephosphonylation.[7] The dephosphonylation could be accomplished by reaction of β-keto phosphonate sodium enolate with $LiAlH_4$, followed by quenching with aqueous H_2SO_4 (Scheme 1).

To expand the scope and utility of this dephosphonylation, we have examined various phosphonates including β-enamino[8] and β-carbamoyl phosphonates. In this paper,

Scheme 1



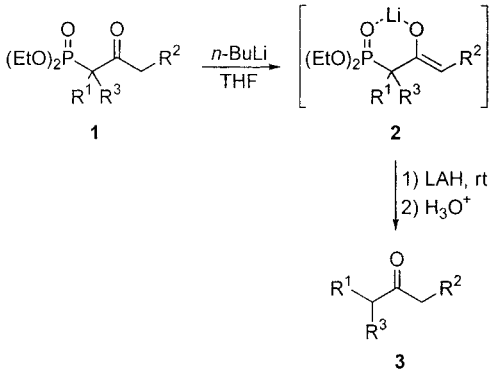
we present our efforts to generalize a new method for the P−C bond cleavage of β-carbonyl phosphonates.

Results and Discussion

In our previous paper, β-keto phosphonates were dephosphonylated by successive treatment with NaH and $LiAlH_4$ to give the corresponding ketones in good yields, after acidic quenching. To gain insight into the mechanism of this reductive P−C bond cleavage, some experiments were carried out side by side. Their results suggested that dephosphonylation with $LiAlH_4$ could occur via metal enolate of β-keto phosphonate. Therein at least one hydrogen atom at the α-position of β-keto phosphonates was left unsubstituted for the enolate formation.

We attempted dephosphonylation for a different kind of β-keto phosphonates, which involve two substituents at the α-position. These α,α-disubstituted β-keto phosphonates **1** under the reaction conditions similar to those of the previous work were assumed to provide the corresponding dephosphonylated ketones **3** via metal enolate **2** utilizing a γ-hydrogen (Scheme 2).[9]

Scheme 2



If successful, this approach would be well suited to the synthesis of substituted ketones of the type **3** from the α,α-disubstituted β-keto phosphonates **1** by $LiAlH_4$-mediated reduction of presumed metal enolates **2**, which

* To whom correspondence should be addressed. Phone: 82-42-869-2819. Fax: 82-42-869-2810. E-mail: dyoh@sorak.kaist.ac.kr.

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(6) In this case, it was reported as a notable result that, during attempted reductions of 2-oxo-1-phosphonato ester to corresponding 2-hydroxy-1-phosphonato ester with various reductants, only Li(*t*-BuO)$_3$AlH among them cleaved the P−C bond selectively to give the corresponding β-keto ester. However, the mechanism and any application of the dephosphonylation were not reported. Durrant, G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2582.

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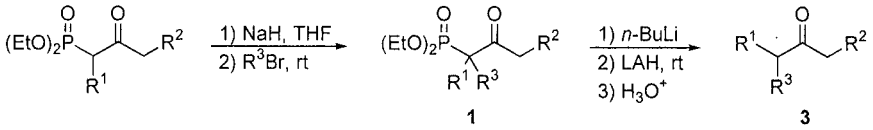
Table 1. Alkylation and Dephosphonylation of Substituted *β*-Keto Phosphonates



entry	R^1	R^2	R^3	product **1**, yield (%)[a]	product **3**, yield (%)[a,b]
a	$-(CH_2)_2-$		cinnamyl	**1a**, 84	**3a**, 53 (62)
b	$-(CH_2)_3-$		cinnamyl	**1b**, 74	**3b**, 46 (72)
c	$-(CH_2)_3-$		allyl	**1c**, 67	**3c**, 58 (66)
d	$-CH_2CH(CH_3)CH_2-$		cinnamyl	**1d**, 72	**3d**, 88
e	Me	Et	crotyl	**1e**, 87	**3e**, 71
f	Me	Et	cinnamyl	**1f**, 81	**3f**, (73)
g	Me	H	crotyl	**1g**, 71	**3g**, 74
h	Me	H	cinnamyl	**1h**, 80	**3h**, 84
i	cinnamyl	Me	cinnamyl	**1i**, 74	**3i**, 77

[a] Yield of isolated product. [b] Solvent was evaporated below 0 °C, and in parentheses is the yield using LDA instead of *n*-BuLi as a base.

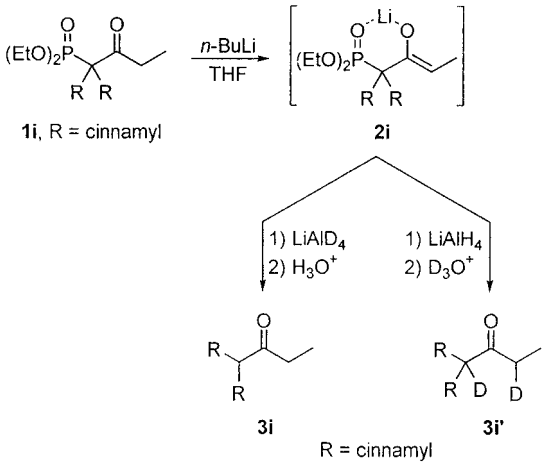
in turn could be generated by treatment of **1** with *n*-BuLi. The whole procedure including preparation of *β*-keto phosphonates represents the use of phosphonate as a temporary activating group for regioselective alkylation of ketones. A test reaction with a representative α,α-disubstituted *β*-keto phosphonate proved to be successful.

First, we performed alkylation of substituted *β*-keto phosphonates[10] at the α-position for preparation of α,α-disubstituted *β*-keto phosphonates **1**. The reaction of sodium enolates of *β*-keto phosphonates, generated by treatment with NaH, with excessive alkyl halides at room temperature for 2−5 h gave the corresponding α-fully substituted *β*-keto phosphonates in good yields, without side products as shown in Table 1. Cyclic *β*-keto phosphonates required longer reaction time than acyclic ones. Use of excessive alkyl halides is thought to bring about short reaction times and high yields, which offers an advantage over two literature examples[11] reported until now to our knowledge.

The prepared α,α-disubstituted *β*-keto phosphonates **1** were dephosphonylated to afford ketones **3**. After **1** was treated with *n*-BuLi or LDA, the reaction of the lithium enolates with $LiAlH_4$ at room temperature for 0.5−1 h and then quenching with 5 N H_2SO_4 aqueous solution provided the corresponding ketones in good yields along with a small amount of alcohols resulting from overreduction as side products. In some cases, a small improvement of yields was realized by the use of LDA in place of *n*-BuLi as a base. Usually 3 equiv of $LiAlH_4$ was used, and use of less than 3 equiv necessitated longer reaction times, leading to lower yields. In addition, using more dilute H_2SO_4 in quenching caused increasing amounts of alcohols as side products, which also resulted in lower yields.

To make the mechanism of dephosphonylation clear, we carried out deuterium experiments as follows. When the reaction of lithium enolate of *β*-keto phosphonate **1i** with $LiAlD_4$ was followed by quenching with a diluted H_2SO_4, the ketone product **3i** did not contain any deuterium. On the other hand, in the case of using $LiAlH_4$ and deuterated acid, the reaction afforded the ketone **3i′** containing two deuteriums at the α- and α′-positions, respectively, as shown in Scheme 3. To investigate a

Scheme 3



possibility of H−D exchange reaction between D_3O^+ and ketone, a blank experiment was carried out in the following manner. Product **3b** was treated with 5 N AcOD/D_2O at room temperature for 1 h. As a result, no deuterated ketone was observed, which makes it likely that the proton exchange reaction of the product ketones does not take place under our quenching conditions.

These results suggest that the cleavage of the P−C bond is not caused by direct attack of hydride on the α-carbon atom linked with the phosphorus atom as an S_N2 type reaction or the *γ*-carbon atom as an S_N2' type reaction, and a possibility that acid might play a significant role in dephosphonylation.

As another extension of dephosphonylation, we also turned our attention to the question of whether α-carbamoyl phosphonates[12,13] could be dephosphonylated. If the dephosphonylation of α-carbamoyl phosphonates could be accomplished by successive treatment with *n*-BuLi and $LiAlH_4$, then the corresponding secondary

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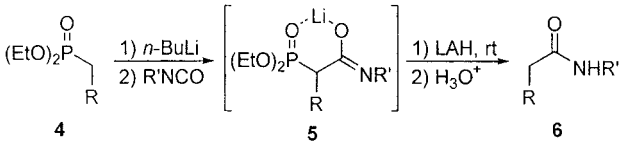
Scheme 4



4 5 6

Table 2. Dephosphonylation of β-Carbonyl Phosphonates

compound	R	R′	yield (%)[a]
6a	Me	benzyl	66
6b	Me	Ph	52
6c	Me	cyclohexyl	70
6d	allyl	4-ClPh	83
6e	PhS	benzyl	72
6f	PhS	Ph	81
6g	PhS	cyclohexyl	79
6h	Ph	cyclohexyl	56
6i	H	benzyl	47[b]

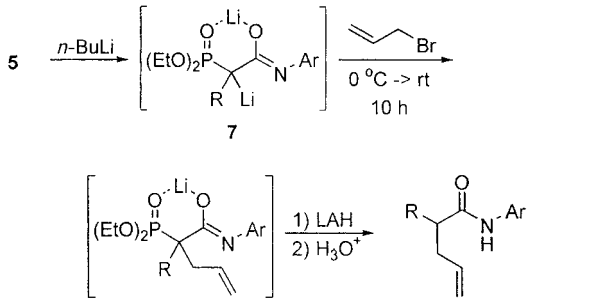
[a] Yield of isolated products. [b] Not to be isolated, the yield was determined by NMR analysis.

amides[14] would be obtained in good yields. To this end, when we examined the reaction of α-lithio alkylphosphonates, derived from diethyl alkylphosphonates **4**, with isocyanates followed by addition of $LiAlH_4$ and quenching with aqueous H_2SO_4, dephosphonylation proved successful. A variety of secondary amide products could be obtained as solids (Scheme 4, Table 2).

Although α-carbamoyl phosphonates could be readily prepared by quenching the metal complexes **5** with aqueous acid solution,[13] we carried out the whole procedure without a stop in one pot.

Finally, to examine a possibility of geminal alkylation of substituted secondary amides through this scheme, we attempted to make dianion species. Treatment of lithio complex **5** with 1 equiv of *n*-BuLi produced the presumed dianion species **7,** which then were alkylated with allyl bromide and underwent subsequent dephosphonylation with $LiAlH_4$, affording the α,α-disubstituted secondary amides **8** (Scheme 5). All the steps have proceeded not

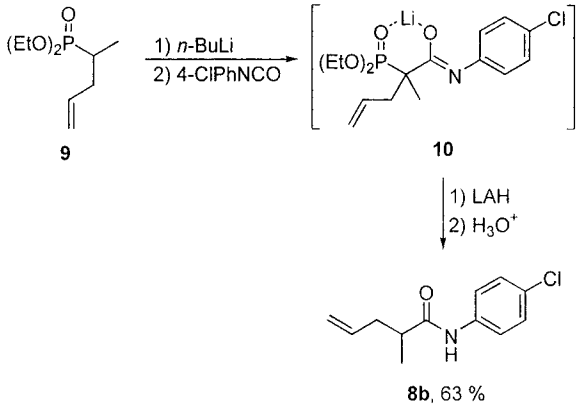
Scheme 5



8a, R = PhS, Ar = Ph, 65 %
8b, R = Me, Ar = 4-ClPh, 61 %

only in one pot but also in high yields from readily available phosphonates and isocyanates.

Scheme 6



8b, 63 %

Also, compound **8b** could be synthesized from α-methyl homoallylphosphonate **9**,[15] prepared by allylation of diethyl ethylphosphonate, through reaction of its anion with isocyanate and dephosphonylation of the resulting lithio complex **10** with $LiAlH_4$ (Scheme 6). The strategy using dephosphonylations like these is thought to be the unique pathway accessible to α,α-disubstituted secondary amides.

Conclusion

These studies have shown that the α,α-disubstituted β-keto phosphonates and the α-carbamoyl phosphonates undergo dephosphonylation by successive treatment with *n*-BuLi and $LiAlH_4$, yielding regioselectively α,α-disubstituted ketone and α-substituted and α,α-disubstituted secondary amides. Also these results suggest that the use of β-carbonyl phosphonates as precursors to α-alkylated ketones and amides would be a complement of existing methods to alkylate ketones regioselectively employing β-keto esters and β-keto sulfones. In some cases isolated yields were modest, and dephosphonylation has been demonstrated to require rather severe conditions. Nevertheless, this dephosphonylation offers a reasonable route to geminal dialkylation of ketones and secondary amides.

Experimental Section

General Procedures. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. THF was dried over and distilled from sodium metal with benzophenone as the indicator. Melting points were recorded in open capillary tubes and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS (0 ppm), residual $CHCl_3$ (7.24 ppm), or solvent resonance (77.0 ppm) as a standard. Some starting materials were synthesized as described in the literature with minor modification.[10]

General Procedure for the Alkylation of β-Keto Phosphonates. To a suspension of sodium hydride (0.060 g, 80%, 2.0 mmol) in dry THF (5 mL) at 0 °C was added the proper β-keto phosphonate (2.0 mmol) in dry THF (5 mL) slowly, and the mixture was allowed to warm to room temperature. After the mixture was stirred for 1 h, alkyl bromide (4.0 mmol) in dry THF (5 mL) was added, and the resulting reaction mixture was stirred for 2−5 h at the same temperature. Aqueous H_2SO_4 solution (3.5 N, 5 mL) was added, and the resulting solution extracted with diethyl ether (50 mL × 2). The combined organic layers were washed with aqueous $NaHCO_3$ solution (5%, 5 mL × 1) and distilled water (5 mL × 2), and

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dried over $MgSO_4$. After evaporation of ether, the residue was chromatographed on a silica gel column using an EtOAc−hexane mixture as eluent to provide the pure α-fully substituted *β*-keto phosphonate **1** as a colorless oil.

Diethyl 1-Cinnamyl-2-oxocyclopentylphosphonate (1a). Using the general procedure described above, the title compound was obtained as a colorless oil (0.565 g, 84%) from diethyl 2-oxocyclopentylphosphonate[10b] (0.44 g, 2.0 mmol) and cinnamyl bromide (0.788 g, 4.0 mmol) under a reaction time of 4 h after chromatography (EtOAc/hexane, 50/50): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 1.34 (dt, *J* = 1.6, 7.0 Hz, 6H), 1.75−1.99 (m, 1H), 2.07−2.21 (m, 3H), 2.43−2.66 (m, 3H), 2.70−2.91 (m, 1H), 4.08−4.24 (m, 4H), 5.95−6.11 (m, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 7.18−7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 16.3−16.4 (m), 19.7, 29.6, 36.0, 39.2, 54.4 (d, *J* = 133.2 Hz), 62.5−62.9 (m), 124.1 (d, *J* = 12.0 Hz), 126.1, 127.4, 128.5, 134.1, 136.9, 215.4; HRMS calcd for $C_{18}H_{25}O_4P$ 336.1491, found 336.1478.

Diethyl 1-Cinnamyl-2-oxocyclohexylphosphonate (1b). Using the general procedure described above, the title compound was obtained as a colorless oil (0.259 g, 74%) from diethyl 2-oxocyclohexylphosphonate[10b] (0.234 g, 1.0 mmol) and cinnamyl bromide (0.394 g, 2.0 mmol) under a reaction time of 4 h after chromatography (EtOAc/hexane, 50/50): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 1.28−1.37 (m, 6H), 1.66−1.79 (m, 2H), 1.96−2.53 (m, 6H), 2.85−3.03 (m, 2H), 4.04−4.21 (m, 4H), 6.04−6.19 (m, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 7.17−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 16.3−16.5 (m), 21.5, 25.7, 31.8 (d, *J* = 4.3 Hz), 36.6 (d, *J* = 3.7 Hz), 41.2, 55.7 (d, *J* = 125.2 Hz), 62.7 (d, *J* = 7.1 Hz), 125.3 (d, *J* = 9.9 Hz), 126.1, 127.2, 128.4, 133.7, 137.2, 208.4.

Diethyl 1-Allyl-2-oxocyclohexylphosphonate (1c).[11b] Using the general procedure described above, the title compound was obtained as a colorless oil (0.368 g, 67%) from 2-oxocyclohexylphosphonate (0.468 g, 2.0 mmol) and allyl bromide (0.484 g, 4.0 mmol) under a reaction time of 5 h after chromatography (EtOAc/hexane, 70/30): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 1.22−1.32 (m, 6H), 1.58−1.71 (m, 2H), 1.92−2.39 (m, 6H), 2.68−2.92 (m, 2H), 3.97−4.18 (m, 4H), 4.96−5.05 (m, 2H), 5.55−5.71 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 16.2−16.4 (m), 21.4 (d, *J* = 2.4 Hz), 25.6, 31.5 (d, *J* = 4.3 Hz), 37.3 (d, *J* = 4.0 Hz), 41.1, 55.2 (d, *J* = 125.4 Hz), 62.5−62.7 (m), 118.6, 133.6 (d, *J* = 9.8 Hz), 208.2.

Diethyl 1-Cinnamyl-5-methyl-2-oxocyclohexylphosphonate (1d). Using the general procedure described above, the title compound was obtained as a colorless oil (0.262 g, 72%) from 5-methyl-2-oxocyclohexylphosphonate[10b] (0.248 g, 1.0 mmol) and cinnamyl bromide (0.394 g, 2.0 mmol) under a reaction time of 5 h after chromatography (EtOAc/hexane, 50/50): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 0.92 (d, *J* = 6.6 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 6H), 1.18−1.59 (m, 2H), 1.88−1.99 (m, 1H), 2.13−2.29 (m, 1H), 2.35−2.52 (m, 3H), 2.90−3.05 (m, 2H), 3.99−4.23 (m, 4H), 5.99−6.13 (m, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 7.17−7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 16.4 (t, *J* = 5.6 Hz), 21.6, 27.8, 34.1, 36.8 (d, *J* = 3.4 Hz), 40.3, 41.2, 55.4 (d, *J* = 122.2 Hz), 62.8 (d, *J* = 7.2 Hz), 125.4 (d, *J* = 10.6 Hz), 126.1, 127.2, 128.5, 133.8, 137.3, 208.3.

Diethyl 1-Crotyl-1-methyl-2-oxopentylphosphonate (1e). Using the general procedure described above, the title compound was obtained as a colorless oil (0.505 g, 87%) from diethyl 1-methyl-2-oxopentylphosphonate[10a] (0.452 g, 2.0 mmol) and crotyl bromide (0.635 g, 85%, 4.0 mmol) under a reaction time of 2 h after chromatography (EtOAc/hexane, 80/20): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 0.83 (t, *J* = 7.4 Hz, 3H), 1.21−1.36 (m, 9H), 1.43−1.60 (m, 2H), 1.56 (d, *J* = 7.2 Hz, 3H), 2.21−2.47 (m, 1H), 2.52−2.63 (m, 2H), 2.74−2.93 (m, 1H), 3.97−4.12 (m, 4H), 5.04−5.20 (m, 1H), 5.38−5.54 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 13.5, 16.3−16.5 (m), 17.0, 17.8, 30.4, 36.4, 41.7, 54.2 (d, *J* = 127.2 Hz), 62.4−62.7 (m), 124.5 (d, *J* = 14.5 Hz), 129.7, 207.9.

Diethyl 1-Cinnamyl-1-methyl-2-oxopentylphosphonate (1f). Using the general procedure described above, the title compound was obtained as a colorless oil (0.570 g, 81%) from diethyl 1-methyl-2-oxopentylphosphonate (0.452 g, 2.0 mmol) and cinnamyl bromide (0.788 g, 4.0 mmol) under a reaction time of 2 h after chromatography (EtOAc/hexane, 75/25): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 0.87 (t, *J* = 7.4 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 6H), 1.42 (d, *J* = 16.7 Hz, 3H), 1.48−1.64 (m, 2H), 2.51−2.64 (m, 1H), 2.65 (t, *J* = 7.1 Hz, 2H), 3.01−3.13 (m, 1H), 4.03−4.18 (m, 4H), 5.92−6.07 (m, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 7.15−7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 13.6, 16.4 (d, *J* = 5.7 Hz), 16.8 (d, *J* = 4.8 Hz), 17.0, 36.9 (d, *J* = 3.9 Hz), 41.8, 54.4 (d, *J* = 127.1 Hz), 62.4−62.8 (m), 124.1 (d, *J* = 13.7 Hz), 126.1, 127.3, 128.4, 133.9, 136.9, 207.8. Anal. Calcd for $C_{19}H_{29}O_4P$: C, 64.76; H, 8.29. Found: C, 64.35; H, 8.49.

Diethyl 1-Crotyl-1-methyl-2-oxopropylphosphonate (1g). Using the general procedure described above, the title compound was obtained as a colorless oil (0.279 g, 71%) from diethyl 1-methyl-2-oxopropylphosphonate[10a] (0.313 g, 1.5 mmol) and crotyl bromide (0.477 g, 85%, 3.0 mmol) under a reaction time of 3 h after chromatography (only EtOAc): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 1.23−1.36 (m, 9H), 1.57 (d, *J* = 6.4 Hz, 3H), 2.26 (s, 3H), 2.31−2.55 (m, 1H), 2.76−2.91 (m, 1H), 3.99−4.14 (m, 4H), 5.06−5.22 (m, 1H), 5.38−5.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 16.3−16.5 (m), 17.9, 28.1, 36.4 (d, *J* = 4.2 Hz), 54.6 (d, *J* = 127.3 Hz), 62.5−62.7 (m), 124.3 (d, *J* = 14.4 Hz), 129.9, 206.0.

Diethyl 1-Cinnamyl-1-methyl-2-oxopropylphosphonate (1h). Using the general procedure described above, the title compound was obtained as a colorless oil (0.259 g, 80%) from diethyl 1-methyl-2-oxopropylphosphonate (0.208 g, 1.0 mmol) and cinnamyl bromide (0.394 g, 2.0 mmol) under a reaction time of 3 h after chromatography (only EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 1.34 (t, *J* = 7.0 Hz, 6H), 1.45 (d, *J* = 17.5 Hz, 3H), 2.36 (s, 3H), 2.55−2.66 (m, 1H), 3.05−3.15 (m, 1H), 4.10−4.20 (m, 4H), 5.95−6.06 (m, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 7.20−7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 16.4 (d, *J* = 5.6 Hz), 16.9 (d, *J* = 5.0 Hz), 28.2, 36.9 (d, *J* = 3.8 Hz), 54.7 (d, *J* = 127.3 Hz), 62.7−62.9 (m), 123.9 (d, *J* = 13.7 Hz), 126.2, 127.4, 128.5, 134.1, 136.9, 205.9.

Diethyl 1,1-Dicinnamyl-2-oxobutylphosphonate (1i). Using the general procedure described above, the title compound was obtained as a colorless oil (0.652 g, 74%) from diethyl 1-cinnamyl-2-oxobutylphosphonate[11a] (0.649 g, 2.0 mmol) and cinnamyl bromide (0.788 g, 4.0 mmol) under a reaction time of 3 h after chromatography (EtOAc/hexane, 50/50): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 1.08 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 6H), 2.77−2.96 (m, 6H), 4.06−4.21 (m, 4H), 6.14−6.28 (m, 2H), 6.47 (d, *J* = 14.8 Hz, 2H), 7.15−7.32 (m, 10H).

General Procedure for the Dephosphonylation of α-Fully Substituted *β*-Keto Phosphonates. *n*-BuLi (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) or LDA (0.55 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 1.1 mmol) was added dropwise by syringe to a stirred solution of α-fully substituted *β*-keto phosphonate (**1**, 1.0 mmol) in dry THF (4 mL) under N_2 at −78 °C. The mixture was allowed to warm slowly to room temperature, and transferred into a stirred solution of $LiAlH_4$ (0.114 g, 3 mmol) in dry THF (6 mL) at the same temperature. After the mixture was stirred for 30 min, aqueous H_2SO_4 solution (5 N, 5 mL) was added, and the resulting solution extracted with diethyl ether (50 mL × 2). The combined organic layers were washed with aqueous $NaHCO_3$ solution (5%, 5 mL × 1) and distilled water (5 mL × 2), and dried over $MgSO_4$. After evaporation of ether, the residue was chromatographed on a silica gel column using an EtOAc−hexane mixture as eluent to provide the pure α,α-disubstituted ketone **3** as a colorless oil. The solvent was evaporated below 0 °C in vacuo.

2-Cinnamylcyclopentanone (3a). Using the general procedure described above, the title compound was obtained as a colorless oil (0.107 g, 53% for using *n*-BuLi as a base; 0.124 g, 62% for using LDA as a base) from diethyl 1-cinnamyl-2-oxocyclopentylphosphonate (**1a**; 0.336 g, 1.00 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 1.52−1.85 (m, 2H), 1.88−2.06 (m, 2H), 2.14−2.30 (m, 4H), 2.57−2.73 (m, 1H), 6.14 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 7.15−7.36 (m, 5H); ^{13}C NMR (50 MHz,

$CDCl_3$) δ 20.6, 28.9, 33.0, 38.1, 48.9, 126.0, 127.0, 127.6, 128.4, 131.7, 137.3, 220.3; HRMS calcd for $C_{14}H_{16}O$ 200.1201, found 200.1206.

2-Cinnamylcyclohexanone (3b). Using the general procedure described above, the title compound was obtained as a colorless oil (0.049 g, 46% for using *n*-BuLi as a base; 0.077 g, 72% for using LDA as a base) from diethyl 1-cinnamyl-2-oxocyclohexylphosphonate (**1b**; 0.175 g, 0.50 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−1.47 (m, 1H), 1.58−1.75 (m, 2H), 1.77−1.92 (m, 1H), 1.98−2.21 (m, 3H), 2.25−2.51 (m, 3H), 2.61−2.72 (m, 1H), 6.13−6.23 (m, 1H), 6.37 (d, J = 15.8 Hz, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 27.9, 33.0, 33.5, 42.1, 50.7, 126.0, 126.9, 128.3, 128.4, 131.6, 137.5, 212.4.

2-Allylcyclohexanone (3c).[16] Using the general procedure described above, the title compound was obtained as a colorless oil (0.080 g, 58% for using *n*-BuLi as a base; 0.091 g, 66% for using LDA as a base) from diethyl 1-allyl-2-oxocyclohexylphosphonate (**1c**; 0.274 g, 1.0 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24−1.39 (m, 1H), 1.53−2.13 (m, 6H), 2.21−2.37 (m, 3H), 2.43−2.55 (m, 1H), 4.90−5.01 (m, 2H), 5.61−5.81 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.9, 27.8, 33.3, 33.7, 41.9, 50.1, 116.1, 136.4, 212.3.

2-Cinnamyl-4-methylcyclohexanone (3d). Using the general procedure described above, the title compound was obtained as a colorless oil (0.100 g, 88% for using *n*-BuLi as a base) from diethyl 1-cinnamyl-5-methyl-2-oxocyclohexylphosphonate (**1d**; 0.182 g, 0.50 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, J = 6.3 Hz, 3H), 1.06−1.26 (m, 1H), 1.29−1.46 (m, 1H), 1.80−2.18 (m, 4H), 2.33−2.58 (m, 3H), 2.61−2.77 (m, 1H), 6.11−6.26 (m, 1H), 6.38 (d, J = 15.9 Hz, 1H), 7.17−7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 32.0, 32.7, 35.8, 41.5, 41.7, 49.5, 125.9, 126.0, 126.9, 128.4, 131.5, 137.5, 212.4.

2-Crotylhexan-3-one (3e). Using the general procedure described above, the title compound was obtained as a colorless oil (0.110 g, 71% for using *n*-BuLi as a base) from diethyl 1-crotyl-1-methyl-2-oxopentylphosphonate (**1e**; 0.290 g, 1.0 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.50−1.63 (m, 5H), 1.95−2.02 (m, 2H), 2.34−2.41 (t, J = 7.1 Hz, 2H), 2.51 (q, J = 6.9 Hz, 1H), 5.22−5.56 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 16.0, 17.0, 17.8, 36.0, 43.3, 46.4, 127.3, 128.2, 214.3.

2-Cinnamylhexan-3-one (3f). Using the general procedure described above, the title compound was obtained as a colorless oil (0.157 g, 73% for using LDA as a base) from diethyl 1-cinnamyl-1-methyl-2-oxopentylphosphonate (**1f**; 0.352 g, 1.0 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.50−1.68 (m, 2H), 2.14−2.28 (m, 1H), 2.42 (t, J = 7.6 Hz, 2H), 2.47−2.57 (m, 1H), 2.57−2.73 (m, 1H), 6.11 (dt, J = 15.8, 6.9 Hz, 1H), 6.39 (d, J = 15.9 Hz, 1H), 7.15−7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 16.1, 16.9, 36.1, 43.2, 46.1, 125.9, 127.0, 127.4, 128.4, 131.9, 137.2, 213.7. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.24; H, 9.30.

3-Crotylbutan-2-one (3g). Using the general procedure described above, the title compound was obtained as a colorless oil (0.093 g, 74% for using *n*-BuLi as a base) from diethyl 1-crotyl-1-methyl-2-oxopropylphosphonate (**1g**; 0.262 g, 1.0 mmol) after chromatography (EtOAc/hexane, 10/90): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, J = 6.9 Hz, 3H), 1.58−1.63 (m, 3H), 1.95−2.07 (m, 1H), 2.11 (s, 3H), 2.18−2.32 (m, 1H), 2.43−2.58 (m, 1H), 5.24−5.52 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8, 17.0, 23.3, 35.9, 47.2, 127.4, 127.9, 211.8.

3-Cinnamylbutan-2-one (3h).[17] Using the general procedure described above, the title compound was obtained as a colorless oil (0.079 g, 84% for using *n*-BuLi as a base) from diethyl 1-cinnamyl-1-methyl-2-oxopropylphosphonate (**1h**; 0.162 g, 0.50 mmol) after chromatography (EtOAc/hexane, 20/80): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 7.0 Hz, 3H), 2.18 (s, 3H), 2.22−2.32 (m, 1H), 2.52−2.62 (m, 1H), 2.63−2.73 (m, 1H), 6.09−6.19 (m, 1H), 6.42 (d, J = 15.8 Hz, 1H), 7.20−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 28.4, 36.1, 47.1, 126.0, 127.2, 127.3, 128.5, 132.1, 137.3, 211.8.

1,1-Dicinnamylbutan-2-one (3i). Using the general procedure described above, the title compound was obtained as a colorless oil (0.117 g, 77% for using *n*-BuLi as a base) from diethyl 1,1-dicinnamyl-2-oxobutylphosphonate (**1i**; 0.220 g, 0.50 mmol) employing $LiAlD_4$ (0.063 g, 1.5 mmol) in place of $LiAlH_4$ after chromatography (EtOAc/hexane, 20/80): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3H), 2.30−2.60 (m, 6H), 2.80 (quintet, J = 7.1 Hz, 1H), 6.03−6.18 (m, 2H), 6.40 (d, J = 15.9 Hz, 2H), 7.16−7.34 (m, 10H).

α,α′-d_2-1,1-Dicinnamylbutan-2-one (3i′). Using the general procedure described above, the title compound was obtained as a colorless oil from **1i** employing AcOD/D_2O (5 N, 5 mL) in place of aqueous H_2SO_4 solution as a quenching agent: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (d, J = 7.2 Hz, 3H), 2.35−2.52 (m, 5H), 6.11 (dt, J = 15.8, 7.2 Hz, 2H), 6.41 (d, J = 15.9 Hz, 2H), 7.18−7.35 (m, 10H).

General Procedure for the Dephosphonylation of α-Carbamoyl Phosphonates. To a stirred solution of the proper phosphonate (**4**; 1.0 mmol) in dry THF (5 mL) under N_2 at −78 °C was added *n*-BuLi (0.66 mL of a 1.6 M solution in hexanes, 1.05 mmol) dropwise, and the mixture was allowed to warm slowly to −30 °C. Addition of the proper isocyanate (1.0 mmol) was followed by warming slowly to room temperature, and $LiAlH_4$ (3.0 mL of a 1.0 M solution in THF) was added. After the mixture was stirred for 1 h, aqueous H_2SO_4 solution (5 N, 5 mL) was added, and the resulting solution extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with aqueous $NaHCO_3$ solution (5%, 5 mL × 1) and distilled water (5 mL × 2), and dried over $MgSO_4$. After evaporation of ether, the residue was chromatographed on a silica gel column using an EtOAc−hexane mixture as eluent to provide the pure amide **6** as a white solid.

***N*-Benzylpropanamide (6a).**[18] Using the general procedure described above, the title compound was obtained as a white solid (0.108 g, 66%) from diethyl ethylphosphonate (0.166 g, 1.0 mmol) and benzyl isocyanate (0.14 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 50/50): mp 49−50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 7.6 Hz, 3H), 2.22 (q, J = 7.6 Hz, 2H), 4.40 (d, J = 0.5.7 Hz, 2H), 5.86 (br s, 1H), 7.22−7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8, 29.6, 43.5, 127.4, 127.8, 128.6, 138.4, 173.6. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.52; H, 8.16; N, 8.43.

***N*-Phenylpropanamide (6b).** Using the general procedure described above, the title compound was obtained as a white solid (0.078 g, 52%) from diethyl ethylphosphonate (0.166 g, 1.0 mmol) and phenyl isocyanate (0.12 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 30/70): mp 103−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3H), 2.37 (q, J = 7.5 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 7.24−7.51 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.7, 30.7, 119.7, 124.1, 129.0, 137.9, 172.0.

***N*-Cyclohexylpropanamide (6c).**[19] Using the general procedure described above, the title compound was obtained as a white solid (0.109 g, 70%) from diethyl ethylphosphonate (0.166 g, 1.0 mmol) and cyclohexyl isocyanate (0.14 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 50/50): mp 89−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99−1.17 (m, 3H), 1.13 (t, J = 7.5 Hz, 3H), 1.26−1.40 (m, 2H), 1.53−1.70 (m, 3H), 1.64−1.90 (m, 2H), 2.14 (q, J = 7.5 Hz, 2H), 3.66−3.79 (m, 1H), 5.35 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.0, 24.6, 25.5, 29.9, 33.2, 48.0, 172.7. Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.62; H, 10.95; N, 9.02.

***N*-(4-Chlorophenyl)-4-pentenamide (6d).** Using the general procedure described above, the title compound was obtained as a white solid (0.174 g, 83%) from diethyl 3-butenylphosphonate (0.166 g, 1.0 mmol) and 4-chlorophenyl iso-

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cyanate (0.169 g, 1.1 mmol) after chromatography (EtOAc/hexane, 25/75): mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40−2.47 (m, 4H), 5.01−5.12 (m, 2H), 5.77−5.90 (m, 1H), 7.22−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 36.7, 116.0, 121.1, 128.9, 129.2, 136.3, 136.6, 170. 6.

***N*-Benzyl-2-phenylthioacetamide (6e).** Using the general procedure described above, the title compound was obtained as a white solid (0.185 g, 72%) from diethyl phenylthiomethylphosphonate (0.260 g, 1.0 mmol) and benzyl isocyanate (0.14 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 25/75): mp 56−57 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.62 (s, 2H), 4.38 (d, J = 5.8 Hz, 2H), 7.03−7.29 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.1, 43.5, 126.4, 127.2, 127.3, 128.1, 128.4, 129.1, 134.4, 137.6, 167.6.

***N*-Phenyl-2-phenylthioacetamide (6f).**[20] Using the general procedure described above, the title compound was obtained as a white solid (0.197 g, 81%) from diethyl phenylthiomethylphosphonate (0.260 g, 1.0 mmol) and phenyl isocyanate (0.12 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 25/75): mp 73−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 2H), 7.10 (t, J = 7.4 Hz, 1H), 7.17−7.47 (m, 10H), 8.56 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.4, 119.9, 124.8, 127.1, 128.4, 129.0, 129.5, 134.1, 137.2, 165.9. Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.10; H, 5.39; N, 5.76. Found: C, 69.45; H, 5.51; N, 5.77.

***N*-Cyclohexyl-2-phenylthioacetamide (6g).** Using the general procedure described above, the title compound was obtained as a white solid (0.197 g, 79%) from diethyl phenylthiomethylphosphonate (0.260 g, 1.0 mmol) and cyclohexyl isocyanate (0.14 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 25/75): mp 86−88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92−1.37 (m, 5H), 1.47−1.62 (m, 3H), 1.69−1.77 (m, 2H), 3.55 (s, 2H), 3.60−3.76 (m, 1H), 6.67 (br s, 1H), 7.12−7.25 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.4, 25.2, 32.5, 37.4, 48.2, 126.5, 128.1, 129.1, 134.6, 166.5.

***N*-Cyclohexyl-2-phenylacetamide (6h).** Using the general procedure described above, the title compound was obtained as a white solid (0.122 g, 56%) from diethyl benzylphosphonate (0.228 g, 1.0 mmol) and cyclohexyl isocyanate (0.14 mL, 1.1 mmol) after chromatography (EtOAc/hexane, 30/70): mp 124−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92−1.14 (m, 3H), 1.23−1.36 (m, 2H), 1.48−1.63 (m, 3H), 1.78−1.84 (m, 2H), 3.52 (s, 2H), 3.65−3.76 (m, 1H), 5.22 (br s, 1H), 7.20−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 25.4, 32.9, 44.0, 48.1, 127.2, 128.9, 129.3, 135.1, 169.9.

***N*-Benzylaectamide (6i).**[18b] Using the general procedure described above, the title compound was obtained from diethyl methylphosphonate (0.152 g, 1.0 mmol) and benzyl isocyanate (0.14 mL, 1.1 mmol), but cannot be isolated purely even after chromatography (EtOAc/hexane, 50/50). The yield was determined by ^{1}H NMR analysis (47%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3H), 4.54 (d, J = 5.6 Hz, 2H) 7.17−7.38 (m, 5H), 9.71 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.4, 44.5, 127.2, 127.4, 128.6, 137.3, 175.2.

***N*-Phenyl-2-phenylthio-4-pentenamide (8a).** To a stirred solution of diethyl phenylthiomethylphosphonate (0.260 g, 1.0 mmol) in dry THF (5 mL) under N_2 at −78 °C was added *n*-BuLi (0.66 mL of a 1.6 M solution in hexanes, 1.05 mmol) dropwise, and the solution was stirred for 1 h. Phenyl isocyanate (0.12 mL, 1.1 mmol) was added, and the mixture was warmed slowly to −30 °C. *n*-BuLi (0.66 mL of a 1.6 M solution in hexanes, 1.05 mmol) was added dropwise, and the mixture was warmed to 0 °C. After the mixture was stirred for 1 h at the same temperature, allyl bromide (0.087 mL, 1.0 mmol) was added. The mixture was warmed to room temperature, and $LiAlH_4$ (3.0 mL of a 1.0 M solution in THF) was added. After the mixture was stirred for 1 h, aqueous H_2SO_4 solution (5 N, 5 mL) was added, and the resulting solution extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with aqueous $NaHCO_3$ solution (5%, 5 mL × 1) and distilled water (5 mL × 2), and dried over $MgSO_4$. After evaporation of ether, the residue was chromatographed on a silica gel column (EtOAc/hexane, 15/85) to provide the pure amide product as a white solid (0.184 g, 65%): mp 59−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60−2.87 (m, 2H), 3.82−3.86 (m, 2H), 5.13−5.22 (m, 2H), 5.83−5.94 (m, 1H), 7.07−7.45 (m, 10H), 8.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.5, 53.4, 115.1, 118.5, 119.9, 124.6, 127.7, 129.0, 129.4, 130.8, 133.2, 137.3, 166.8; HRMS calcd for $C_{17}H_{17}NOS$ 283.1031, found 283.1049. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.09; H, 6.07; N, 4.94.

***N*-(4-Chlorophenyl)-2-methyl-4-pentenamide (8b). Method A.** Using a procedure similar to that described above for the synthesis of **8a** except that diethyl ethylphosphonate (0.166 g, 1.0 mmol) and 4-chlorophenyl isocyanate (0.169 g, 1.1 mmol) were used, the title compound was obtained as a white solid (0.136 g, 61%) after purification by chromatography (EtOAc/hexane, 15/85).

Method B. Using the general procedure described above for the synthesis of **7**, the title compound was obtained as a white solid (0.141 g, 63%) from diethyl α-allylethylphosphonate **9** (206 g, 1.0 mmol) and 4-chlorophenyl isocyanate (0.169 g, 1.1 mmol) after chromatography: mp 79−82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6.7 Hz, 2H), 2.17−2.25 (m, 1H), 2.36−2.50 (m, 2H), 5.03−5.12 (m, 2H), 5.71−5.84 (m, 1H), 7.22−7.27 (m, 2H), 7.32 (s, 1H), 7.43−7.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 38.3, 42.0, 117.3, 121.3, 128.9, 129.2, 135.4, 136.4, 174.3; HRMS calcd for $C_{12}H_{14}ClNO$ 223.0764, found 223.0775. Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.36; H, 6.42; N, 6.34.

Diethyl 2-Methyl-3-butenylphosphonate (9).[15] To a stirred solution of diethyl ethylphosphonate (0.332 g, 2.0 mmol) in dry THF (6 mL) under N_2 at −78 °C was added *n*-BuLi (1.31 mL of a 1.6 M solution in hexanes, 2.10 mmol) dropwise, and the solution was stirred for 1 h. Allyl bromide (0.190 mL, 2.2 mmol) was added, and the mixture was warmed to room temperature. After the mixture was stirred for 3 h, saturated NH_4Cl solution (2 mL) was added, and the resulting solution extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with distilled water (3 mL × 2), dried over $MgSO_4$, and evaporated. The crude product was purified by chromatography (EtOAc/hexane, 75/25) to afford the title compound as a colorless oil (0.379 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (dd, J = 7.1, 18.5 Hz, 3H), 1.73−1.90 (m, 1H), 1.96−2.07 (m, 1H), 2.46−2.56 (m, 1H), 4.01−4.11 (m, 4H), 4.99−5.06 (m, 2H), 5.64−5.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 16.4 (d, J = 5.8 Hz), 30.6 (d, J = 140.6 Hz), 61.5 (d, J = 7.3 Hz), 116.9, 135.7 (d, J = 15.4 Hz).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all compounds described in the Experimental Section and HRMS data for compounds **1a**, **3a**, **8a**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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