JOC*Note*

Preparation of Asymmetric α-Ketophosphonates by [3,3]-Sigmatropic Shift of Enolphosphonates

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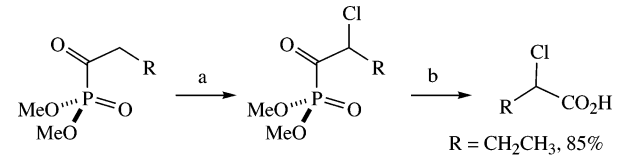
Abstract: α-Ketophosphonates are prepared by a [3,3]-sigmatropic shift of enolphosphonates.

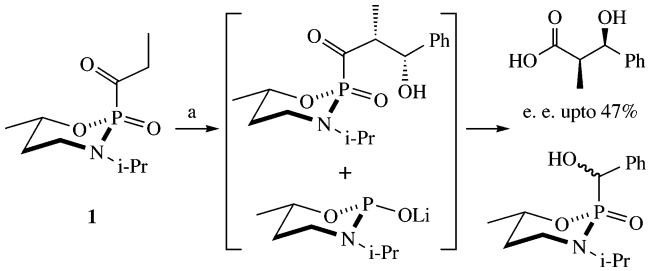
α-Ketophosphonates are one of the most interesting and versatile classes of organophosphorus compounds. α-Ketophosphonates undergo a diverse range of reactions and therefore, have found many useful synthetic applications toward both the preparation of other organophosphorus compounds and the synthesis of non-phosphorus-containing molecules.[1] For instance, the reduction of α-ketophosphonates affords the corresponding α-hydroxyphosphonates;[2] treatment of α-ketophosphonates with a Wittig reagent affords the corresponding vinylphosphonates;[3] the corresponding oximes[4] and hydrazones[5] can be obtained from the reactions of α-ketophosphonates with hydroxylamine and hydrazine; β,γ-unsaturated-α-ketophosphonates can be epoxidized[6] and also undergo a very facile Diels−Alder cycloaddition both as diene[7] and hetero-dienophile.[8] Finally, the C−P bond in α-ketophosphonates is susceptible to facile cleavage under nucleophilic attack, for instance during acidic and basic hydrolysis,[9] and therefore, α-ketophosphonates can be considered as synthetic equivalents to acid chlorides. More recently, asymmetric α-ketophosphonates containing a chiral phosphorus atom are prepared which provide exciting opportunities for introducing an asymmetric dimension in one or all of these reactions.[10]

SCHEME 1[a]



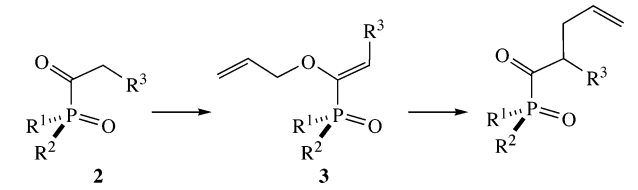
[a] Reagents and conditions: (a) SO_2Cl_2 (1.3 equiv), 7 h, dark, rt; (b) H_2O_2 (4 equiv), $NaHCO_3$ (4 equiv), CH_2Cl_2.

SCHEME 2[a]



[a] Reagents and conditions: (a) LHMDS, THF, −78 °C, then benzaldehyde.

SCHEME 3



One of the reactions of α-ketophosphonates which has as yet remained unexplored is their C-alkylation at the adjacent position to the C=O. Indeed, there are very few examples in the literature pertaining to derivatization at the β-carbon of α-ketophosphonates. Two examples of halogenation of α-ketophosphonates are reported with use of either elemental bromine or chlorine,[11] or sulfuryl chloride (Scheme 1).[12] No base is required for either reaction and it is not certain if the reactions proceed through enolization of α-ketophosphonates or whether they are radical initiated. Evans reported isolation of an aldol product from the reaction of α-ketophosphonates **1** (Scheme 2) although the reaction affords substantial quantities of a byproduct and its mechanism is unclear.[10]

Here, we report on a methodology for the C-allylation of α-ketophosphonates **2** via a [3,3]-sigmatropic shift of the corresponding allylenolphosphonates, **3** (Scheme 3). Furthermore, we will show that asymmetric α-ketophosphonates undergo this reaction with diastereoselectivity and that the selectivity in these reactions is influenced by chirality at the phosphorus.

We had previously demonstrated that the enol tautomers of α-ketophosphonates are thermodynamically

(1) (a) Afarinkia, K.; Vinader, M. V. The Synthesis of Acyl Phosphorus, -Arsenic, -Antimony or -Bismuth Functions. In *Comprehensive Organic Functional Group Transformations*; Moody, C. J., Ed.; Pergamon: London, 1995; Vol. 5, p 393. (b) Savignac, P.; Igora, B. Ketophosphonates. In *Modern Phosphonate Chemistry*; CRC Press: New York, 2003; p 319. (c) Afarinkia, K. The Synthesis of Acyl Phosphorus, -Arsenic, -Antimony or -Bismuth Functions. In *Comprehensive Organic Functional Group Transformations II*; Jones, R. C. F., Ed.; Elsevier: London, 2004; Vol. 5, in press.

(2) (a) Oshikawa, T.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2728. (b) Karaman, R.; Goldblum, A.; Breuer E.; Leader, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 765.

(3) Yamashita, M.; Kojima, M.; Yoshida, H.; Ogata T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1625.

(4) (a) Breuer, E.; Schlossman, A.; Safadi, M.; Gibson, D.; Chorev M.; Leader, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3263. (b) Breuer, E.; Zaher H.; Tashma, Z. *Tetrahedron Lett.* **1992**, 2067.

(5) Scherer, H.; Hartmann, A.; Regitz, M.; Tunggal, B. D.; Günther, H. *Chem. Ber.* **1972**, *105*, 3357.

(6) (a) Öhler, E.; Zbiral, E.; El-Badawi, M. *Tetrahedron Lett.* **1983**, *24*, 5599. (b) Hammerschmidt F.; Zbirol, E. *Ann. Chem.* **1979**, 492.

(7) (a) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (b) Telan, L. A.; Poon, C.-D.; Evans, S. A., Jr. *J. Org. Chem.* **1996**, *61*, 7455.

(8) S. Hanessian, P.; Compain *Tetrahedron* **2002**, *58*, 6521.

(9) (a) Kume, A.; Fujii, M.; Sekine M.; Hata, T. *J. Org. Chem.* **1984**, *49*, 2139. (b) Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980**, *45*, 4162. (c) Fujii, M.; Ozaki, K.; Sekine, M.; Hata, T. *Tetrahedron* **1987**, *43*, 3395. (d) Breuer, E.; Karaman, R.; Goldblum, A.; Leader, H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 2029. (e) Karaman, R.; Goldblum, A.; Breuer, E.; Leader, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 765.

(10) (a) Gordon, N. J.; Evans, S. A. *J. Org. Chem.* **1993**, *58*, 5293. (b) Gordon, N. J.; Evans, S. A. *Phosphorus Sulfur Silicon Relat. Elem.* **1995**, *75(1−4)*, 47.

(11) Öhler, E.; El-Badawi, M.; Zbiral, E. *Chem. Ber.* **1984**, *117*, 3034.

(12) Stevens, C.; De Buyck, L.; De Kimpe, N. *Tetrahedron Lett.* **1998**, *39*, 8739.

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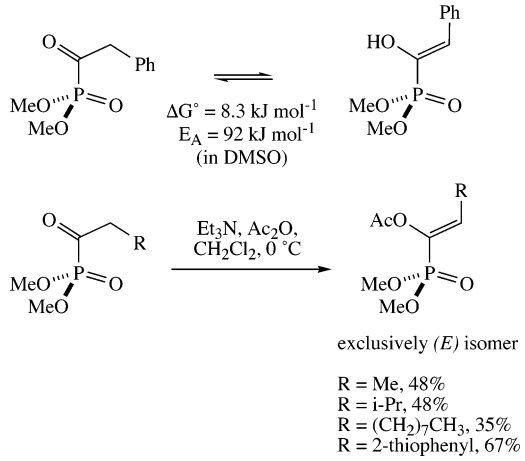
SCHEME 4



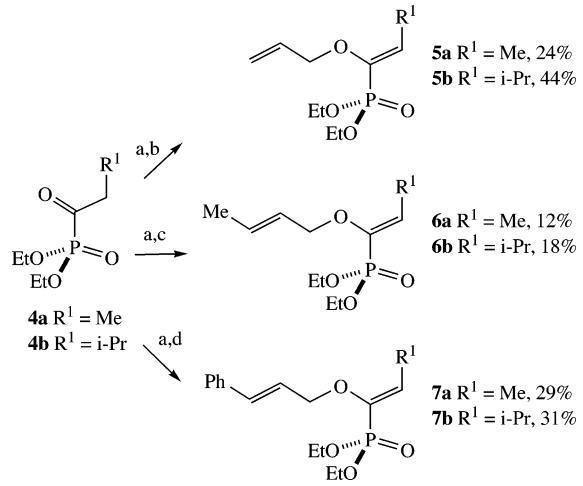
quite stable. Indeed, simple α-ketophosphonates undergo very facile tautomerization to the extent that at room temperature in polar solvents, significant quantities of the enol tautomer can be spectroscopically observed (Scheme 4).[13] The enol tautomers can be "trapped" as vinyl acetates,[13] silylenol ethers,[13] and sulfonates[14] which have in all cases been isolated as the *E* isomer. Although a study of the relative stability of the enolate anions of α-ketophosphonates has not been carried out, it can be assumed that they are also thermodynamically quite stable and that their formation is facile. Therefore, it was doubtful from the outset if the enolates derived from α-ketophosphonates would be reactive enough to undergo C-alkylation. Indeed, enolate formation by treatment of α-ketophosphonates **4a** and **4b** with organolithium bases such as LDA and BuLi and attempted C-alkylation with various electrophiles failed to give any desired product, affording instead mainly unreacted α-ketophosphonates. During the subsequent extensive studies with various additives and reaction conditions, we failed to obtain any C-alkylation products. Careful examination of some reaction mixtures, however, revealed the presence of small quantities of O-alkylation products. After further exploration, it became possible to isolate phosphoenols **5a**−**7a** and **5b**−**7b** by treatment of α-ketophosphonates **4a** and **4b** with organopotassium bases such as t-BuOK and KHMDS, followed by an excess of electrophiles such as allyl bromide, crotyl chloride, and cinnamyl bromide (Scheme 5). The enol configuration in all compounds was found to be exclusively trans as determined by large $^3J_{PH}$ couplings of 10−12 Hz, indicative of a cis arrangement between the phosphorus atom and the olefinic hydrogen. This is consistent with the previous observations on the O-acylation, O-silylation, and O-sulfonation of enolphosphonates.[13,14]

When heated at reflux in toluene, phosphoenols **5a**−**7a** and **5b**−**7b** underwent a clean and facile [3,3]-sigmatropic rearrangement to the corresponding α-ketophosphonates **8a**−**10a** and **8b**−**10b** (Scheme 6). Interestingly, all six phosphoenols showed trace amounts of the corresponding rearranged α-ketophosphonates when stored at room temperature for a period of days suggesting the rearrangement is a facile reaction.

Compounds **9a**−**10a** and **9b**−**10b** were obtained as a single diastereomer as determined by ^{31}P NMR spectroscopy. The relative configuration of the rearranged products was deduced from a proposed chair transition state for the sigmatropic shift (Scheme 7).

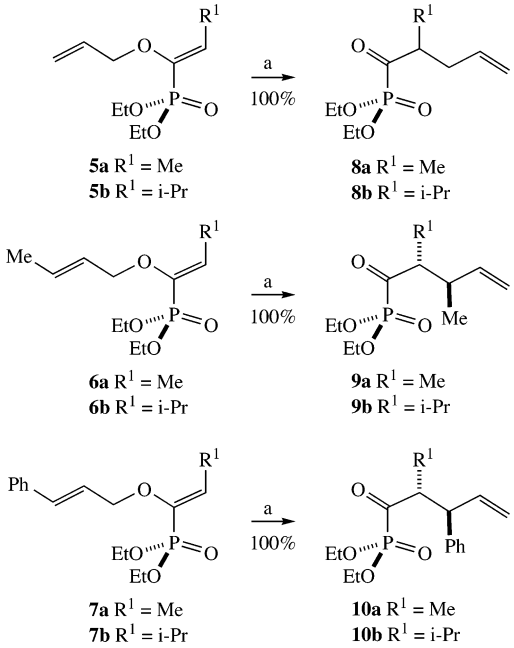
Having shown that the [3,3]-sigmatropic shift is a viable method for the synthesis of C_β-alkylated nonasymmetric α-ketophosphonates, we next prepared asym-

SCHEME 5[a]



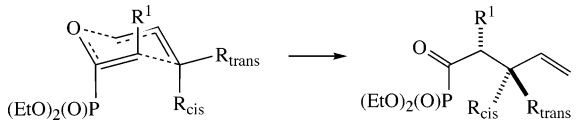
[a] Reagents and conditions: (a) KHMDS, THF, −78 °C, 3 h; (b) allyl bromide, 25 °C, 15 h; (c) crotyl chloride, 25 °C, 15 h; (d) cinnamyl bromide, 25 °C, 15 h.

SCHEME 6[a]



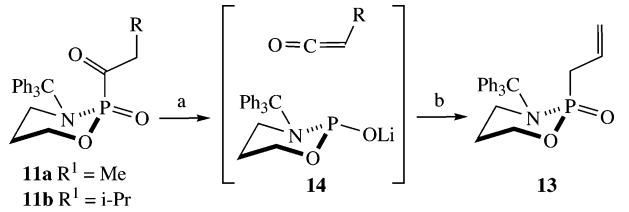
[a] Reagents and conditions: (a) toluene, reflux, 4 h.

SCHEME 7



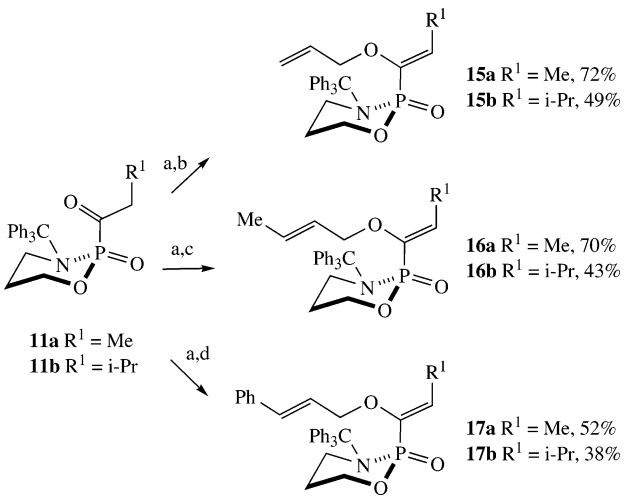
(13) Afarinkia, K.; Echenique J.; Nyburg, S. C. *Tetrahedron Lett.* **1997**, *38*, 1663.
(14) Okauchi, T.; Yano, T.; Fukomachi, T.; Ichikawa, J.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 5337.

SCHEME 8[a]



[a] Reagents and conditions: (a) BuLi, THF, −72 °C[a]; (b) allyl bromide (excess), warm to rt.

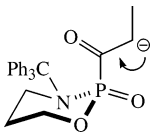
SCHEME 9[a]



[a] Reagents and conditions: (a) KHMDS, THF, −78 °C, 3 h; (b) allyl bromide, 25 °C, 15 h; (c) crotyl chloride, 25 °C, 15 h; (d) cinnamyl bromide, 25 °C, 15 h.

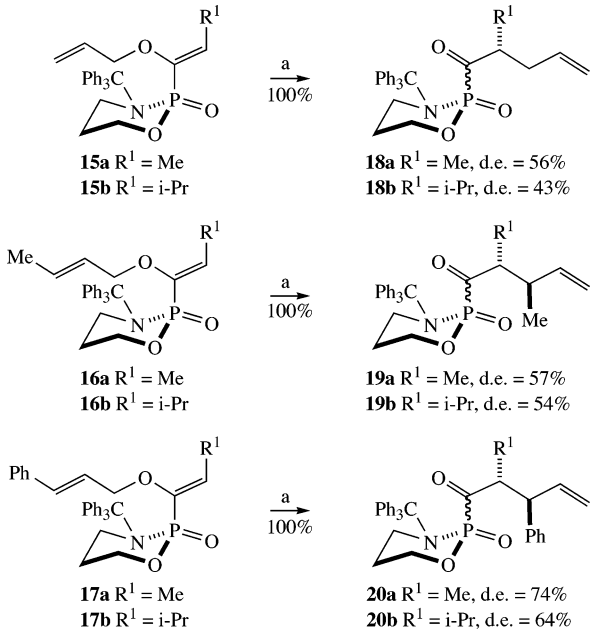
metric α-ketophosphonates **11a** and **11b**.[15] It is expected that the chiral phosphorus atom will induce asymmetry in the C−C bond formation resulting in the formation of asymmetric α-ketophosphonates.

Treatment of α-ketophosphonates **11a** and **11b** with organolithium bases such as LDA and BuLi followed by addition of allyl bromide failed to afford the expected product. However, allylphosphonamidate **13**[16] was obtained in moderate yield, presumably through the formation of phosphite anion **14** (Scheme 8). This result was entirely consistent with the observations by Evans during the attempted aldol reactions of **1** (Scheme 1).



Nevertheless, using an organopotassium base, we were able to obtain reasonable yields of **15a**−**17a** and **15b**−**17b** (Scheme 9). As before, phosphoenols **15a**−**17a** and **15b**−**17b** underwent a clean and facile [3,3]-sigmatropic (Claisen) rearrangement when heated at reflux in toluene to the corresponding α-ketophosphonates **18a**−**20a** and **18b**−**20b** (Scheme 10). Again there was evidence that

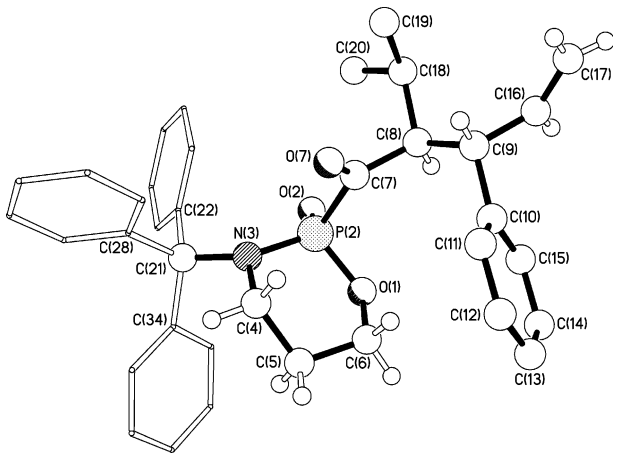
SCHEME 10[a]



[a] Reagents and conditions: (a) toluene, reflux, 5 h.

all six phosphoenols undergo an exceptionally facile rearrangement even at room temperature.

All six α-ketophosphonates **18a**−**20a** and **18b**−**20b** were obtained as diastereomeric mixtures as determined by integration of the corresponding signals in ^{31}P NMR spectra. Compounds **18a** (R^1 = Me) and **18b** (R^1 = i-Pr) were obtained as 78:22 and 72:28 ratio of diastereomers, respectively. Best selectivities were observed for compounds **20a** (R^1 = Me) and **20b** (R^1 = i-Pr) with ratio of diastereomers being 87:13 and 82:18, respectively. The relative configuration of the major diastereomer in **20b** was confirmed by X-ray crystallography to be the (R_P,*S*,*S*)/(S_P,*R*,*R*) enantiomeric pair.

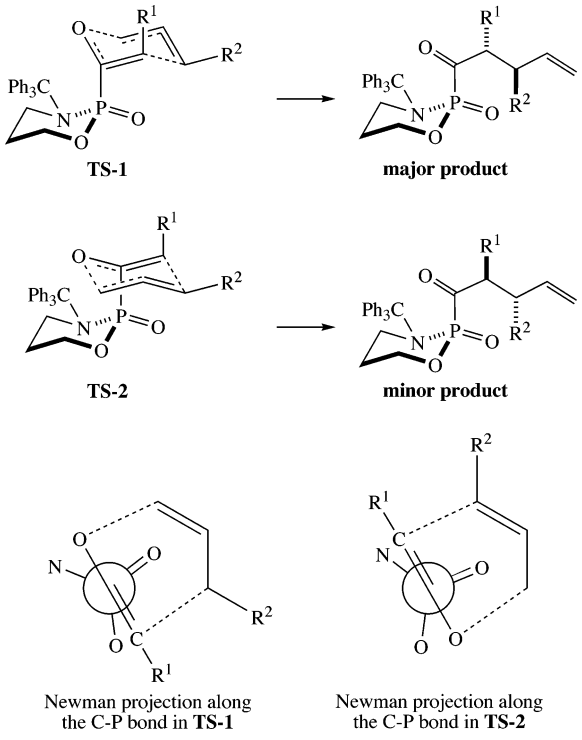


Although the difference between distereoselectivities is fairly modest, two trends are discernible. First, the distereoselectivity in the rearrangements of **15a**, **16a**, and **17a**, where R^1 is Me, is better than the corresponding distereoselectivity in **15b**, **16b**, and **17b**, where R^1 is i-Pr. This means that steric bulk in the R^1 group disfavors the formation of the major diastereomer. On the other hand, distereoselectivity increases from **15a** to **16a** to **17a**, and

(15) Afarinkia, K.; Angell, R.; Jones, C. L.; Lowman, J. *Tetrahedron Lett.* **2001**, *42*, 743.

(16) (a) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1995**, *117*, 11879. (b) Denmark, S. E.; Chen, C.-T. *J. Org. Chem.* **1994**, *59*, 2922. (c) Denmark, S. E.; Darrow, R. L. *J. Org. Chem.* **1990**, *55*, 5926.

SCHEME 11



also from **15b** to **16b** to **17b**, where R^2 (Scheme 11) changes from hydrogen atom to methyl and then phenyl groups.

On the basis of these observations, we can rationalize the diastereoselectivity in the [3,3]-sigmatropic shifts (Claisen rearrangements) by proposing two competing transition states: **TS-1** (which leads to the major diastereomer) and **TS-2** (which leads to the minor diastereomer) for the migration (Scheme 11). The axial placement of the P−C bond is consistent with the previous observations of the preference for this conformation in 1,3,2-oxazaphosphorinane-2-ones.[15] Furthermore, we propose that a near periplanar arrangement between ring P−X (where X is a nitrogen or oxygen atom) and the C−O bond is preferred. The previous successful models for alkylations of 2-alkyl-1,3,2-oxazaphosphorinanes[16] and nucleophilic addition to 2-alkenyl-1,3,2-oxazaphosphorinanes[17] are based on similar conformational preferences. According to this model, **TS-1** is the preferred transition state because the steric repulsion arising from the nitrogen substituent can be accommodated at the expense of the steric repulsion arising from the ring oxygen lone pair.

In summary, we have shown that α-ketophosphonates can be alkylated at the position adjacent to the C=O function through a two-step process of O-allylation followed by a [3,3]-sigmatropic shift. The reaction is stereospecific affording exclusively the anti (*threo*) product. Alkylation of asymmetric α-ketophosphonates is stereoselective affording the *unlike*[18] enantiomeric pair (R_P,*S*,*S*)/(S_P,*R*,*R*) as the major diastereomer.

(17) Afarinkia, K.; Binch, H. M.; De Pascale, M. E. *Synlett* **2000**, 1769.

(18) For the use of the *like* and *unlike* nomenclature see ref 16b and: Prelog, V.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

Experimental Section

General Procedure for Preparation of Phosphoenols. The corresponding alkyl halide (10 mmol) was added to a stirred solution of α-ketophosphonate or α-ketophosphonamidate (0.5 mmol) in THF (25 mL) maintained under an argon atmosphere at −78 °C. A 0.5 M solution of KHMDS in toluene (1.0 mL, 0.5 mmol) was added and the resulting solution was stirred at −78 °C for 3 h. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by addition of 10% aqueous ammonium acetate (10 mL) and the organic products were extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and water (20 mL) and were dried over $MgSO_4$. The solvent was removed in vacuo to give the crude product. The product was purified by column chromatography, using 50% ethyl acetate in petroleum ether as eluent.

***N*-Trityl[3-methyl(3-phenyl-2-propenyloxy)but-1-ene]-1,3,2-oxazaphophorinane-2-one, 17b:** δ_H ($CDCl_3$, 400 MHz) 0.55 and 1.33 (2H, m, $CH_2CH_2CH_2$), 0.96 and 1.03 [2 × 3H, d, J_H = 7 Hz, $CH(CH_3)_2$], 2.89 (1H, m, $CHMe_2$), 3.06 and 3.54 (2H, m, NCH_2), 3.92 (2H, m, OCH_2), 4.50 and 4.64 (2H, m, OCH_2-CH=), 5.72 (1H, m, CH=CHPh), 6.40 (1H, m, PC=$CHCH_3$), 6.72 (1H, m, CH=CHPh), 7.08−7.51 (15H, m, Ar*H*); δ_C {H} ($CDCl_3$, 100 MHz) 21.0 and 22.7 [$CH(CH_3)_2$], 25.9 (d, J_P = 12 Hz, $CHMe_2$), 26.1 (d, J_P = 6 Hz, $CH_2CH_2CH_2$), 46.5 (d, J_P = 25 Hz, NCH_2), 63.1 (d, J_P = 8 Hz, OCH_2), 73.8 (CH_2CH=CHPh), 77.8 (d, J_P = 3 Hz, CPh_3), 125.3 (CH_2CH=*C*HPh), 127.0 (aromatic *C*H), 127.8 (aromatic *C*H), 130.8 (aromatic *C*H), 133.6 (CH_2*C*H=CHPh), 134.7 141.4 (d, J_P = 31 Hz, PC=*C*H), 143.4 (d, J_P = 215 Hz, P*C*=CH), 144.2 (aromatic *C*); δ_P {H} ($CDCl_3$, 162 MHz) 16.7; IR (liquid) 3060, 2968, 2912 (C−H str), 1638 (C=C str), 1255 (P=O str), 1050, 1024 (P−O str), 996 (P−O bnd), 918 (P−N bnd) cm^{-1}; *m*/*z* 563 (M^+, 3), 363 (52), 243 (100, Ph_3C^+), 165 (22), 117 (18); found $[M + Na]^+$ 586.2193, calcd for $C_{36}H_{38}NO_3PNa$ 586.2481.

General Procedure for the Thermal [3,3]-Sigmatropic Rearrangement of Phosphoenols. A toluene (5 mL) solution of phosphoenols (2 mmol) was refluxed for 5 h under an atmosphere of argon. The solvent was removed in vacuo to give the products.

***N*-Trityl-2-[1-oxo-4-(2-propyl)-3-phenylpent-4-enyl]-1,3,2-oxazaphophorinane-2-one, 20b:** δ_H ($CDCl_3$, 400 MHz) 0.47 and 1.00 (2H, m, $CH_2CH_2CH_2$), 0.95 and 1.02 [2 × 3H, d, J_H = 7 Hz, $CH(CH_3)_2$], 2.16 (1H, m, $CHMe_2$), 2.71 and 3.44 (2H, m, NCH_2), 2.53 (1H, m, CHPh), 2.91 [2H, m, C(O)C*H*], 3.75 (2H, m, OCH_2), 5.05 (2H, m, $CH=CH_2$), 5.94 (1H, m, $CH=CH_2$), 7.01−7.46 (20H, m, aromatic *H*); δ_C {H} ($CDCl_3$, 100 MHz) 19.2 and 20.7 [$CH(CH_3)_2$], 25.6 ($CH_2CH_2CH_2$), 28.9 ($CHMe_2$), 46.4 (NCH_2), 49.9 (*C*HPh), 60.9 [d, J_P = 48 Hz, C(O)*C*H], 66.5 (d, J_P = 9 Hz, OCH_2), 78.0 (d, J_P = 3 Hz, CPh_3), 116.1 ($CH=CH_2$), 126.7−144.4 (aromatic *C* and *C*H), 140.0 ($CH=CH_2$), 217.6 [d, J_P = 156 Hz, PC(O)]; δ_P {H} ($CDCl_3$, 162 MHz) 2.7 (major), −0.3 (minor); IR (CCl_4) 3060, 2964, 2932 (C−H str), 1681 (C=O str), 1636 (C=C str), 1263 (P=O str), 1046, 1028 (P−O str), 998 (P−O bnd), 912 (P−N bnd) cm^{-1}; *m*/*z* 563 (M^+, 6), 363 (100), 243 (100, Ph_3C^+), 165 (26), 117 (27); found $[(2M + Na)]^+$ 1149.4901, calcd for $C_{72}H_{76}N_2O_6P_2Na$ 1149.5071. Anal. Calcd for $C_{36}H_{38}NO_3P$: C, 76.71; H, 6.80; N, 2.48. Found: C, 76.68; H, 6.85; N, 2.37.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of all new compounds and crystal data for compound **20b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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