Inter- and Intramolecular Pathways for the Formation of Tetrahydrofurans from β-(Phosphatoxy)alkyl Radicals. Evidence for a Dissociative Mechanism

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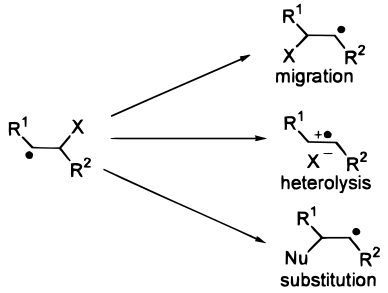
β-(Phosphatoxy)alkyl radicals generated by photolysis of Barton PTOC esters in the presence of allyl alcohol and *tert*-butyl mercaptan undergo nucleophilic substitution followed by 5-*exo*-*trig* radical ring closure leading to tetrahydrofurans in good yield and with high trans selectivity. β-(Phosphatoxy)alkyl radicals obtained by intramolecular hydrogen 1,5-abstraction with an alkoxyl radical undergo nucleophilic displacement providing tetrahydrofurans. The ensemble of results, including the effects of leaving groups and substituents, strongly support a dissociative mechanism for these radical nucleophilic displacement reactions.

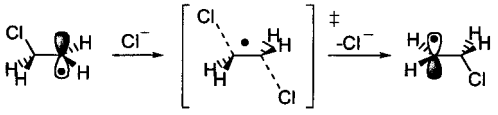
Introduction

The vicinal displacement of a phosphate group from a β-(phosphatoxy)alkyl radical by a nucleophile constitutes a new and interesting class of reaction with potential for incorporation into radical/polar crossover tandem sequences; it is the most recent addition to the reaction manifold of β-ester-substituted radicals that also includes rearrangements and heterolyses (Scheme 1).[1] This general class of nucleophilic substitutions was first recognized by Zipse, who predicted that the degenerate, vicinal displacement of chloride from the β-chloroethyl radical by chloride anion would be a concerted process involving backside attack (Scheme 2).[2−4] The first actual example of this class of reactions was realized in these laboratories and involved the reaction of octanol with the 1-(diphenylphosphatoxy)-2-methyl-1-phenyl-2-propyl radical (**2**) under laser flash photolytic conditions with an apparent bimolecular rate constant of 2×10^6 $M^{-1}\cdot s^{-1}$ at 20 °C (Scheme 3).[5] In a preparative experiment conducted in the presence of *tert*-butyl thiol, the ether **4** could be isolated in 60% yield.[5] No evidence was found for the formation of the regioisomeric product octyl 1-phenyl-2-methylpropyl ether, which provided some support for a concerted vicinal displacement. First generation stereochemical probes revealed the substitution to be only moderately stereoselective.[6] This low stereoselectivity raised the possibility of either a Zipse-type concerted process with attack on either lobe of the initial, singly occupied orbital in **2** or a dissociative mechanism with attack on a contact ion pair.[6] Very recent work from our laboratories has provided strong evidence in favor of the companion reaction, the β-(phosphatoxy)alkyl rearrangement[1] being dissociative in nature with the precise outcome being dependent on the partitioning between contact and solvent separated ion pairs.[7,8]

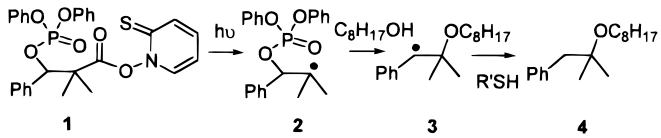
Scheme 1



Scheme 2



Scheme 3



In this paper, we describe in full our initial studies aimed at exploring the preparative potential of this class of reactions, especially with respect to the formation of tetrahydrofurans,[9] from which we also deduce strong support for the dissociative pathway.

Results and Discussion

We reasoned that an elementary radical/polar crossover sequence could be set up by the use of allyl alcohol

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(1) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273.
(2) Zipse, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1985.
(3) Zipse, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2691.
(4) Zipse, H. *Acc. Chem. Res.* **1999**, *32*, 571.
(5) Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Martinez, F. N.; Newcomb, M.; Wink, D. J.; Yao, Q. *J. Am. Chem. Soc.* **1998**, *120*, 211.
(6) Crich, D.; Gastaldi, S. *Tetrahedron Lett.* **1998**, *39*, 9377.
(7) Whitted, P. O.; Horner, J. H.; Newcomb, M.; Huang, X.; Crich, D. *Org. Lett.* **1999**, *1*, 153.
(8) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H. *J. Am. Chem. Soc.* **1999**, *121*, 10685.
(9) Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* **1999**, *1*, 225.

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Scheme 4

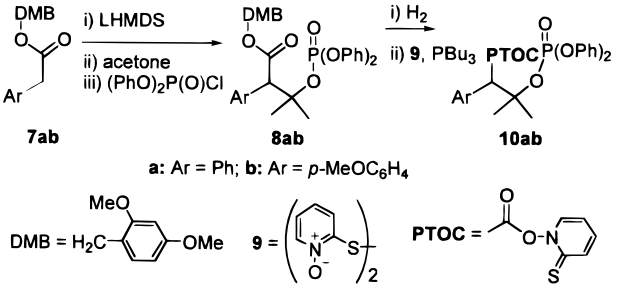
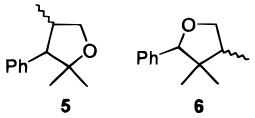


Table 1. Intermolecular Reaction of *β*-(Phosphatoxy)alkyl Radicals with Allyl Alcohol

substrate	product (% yield)[a]	substrate	product (% yield)[a]
1	**5** (82) t/c = 90/10	**17**c	**18c** (92) t/c = 85/15
10a	**5** (85) t/c = 90/10	**10**b	**19** (67)
17a	**18a** (78) t/c = 94/6	**17**d	**20a** (90)
17b	**18b** (75) t/c = 88/12	**17**e	**20b** (85)

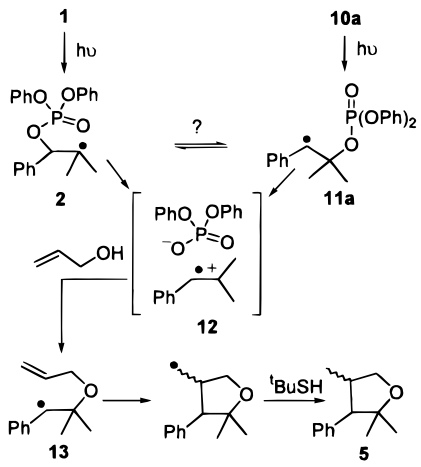
[a] Yields refer to isolated mixtures of diastereomers with the ratios established by NMR.

as nucleophile in the vicinal displacement sequence. In the anticipated sequence the *β*-(phosphatoxy)alkyl radical undergoes vicinal nucleophilic substitution leading to a 1-phenyl-3-oxa-5-hexenyl radical, which should undergo rapid, 5-exo-cyclization with formation of a (tetrahydrofuranyl)methyl radical. Allyl alcohol had previously been used in a similar context to trap the radical cation arising from fragmentation of a nucleotide C4′ radical by the Giese group.[10] In the event, white light photolysis of the *O*-acyl thiohydroxamate **1** in allyl alcohol, in the presence of *tert*-butyl thiol as chain-transfer agent, led to the isolation of two stereoisomeric tetrahydrofurans (**5**) in 82% combined yield and a 9/1 ratio. It was readily apparent from the ^{1}H-spectral data that the two tetrahydrofurans had the indicated regiochemistry; NOE studies led to the assignment of the major isomer as the trans diastereomer. No evidence was found for the formation of the regioisomeric products (**6**). Given the high regioselectivity of the reaction set out in Scheme 3 and the known trans selectivity of the 1-phenyl-5-hexenyl radical itself,[11] this particular result was unexceptional.

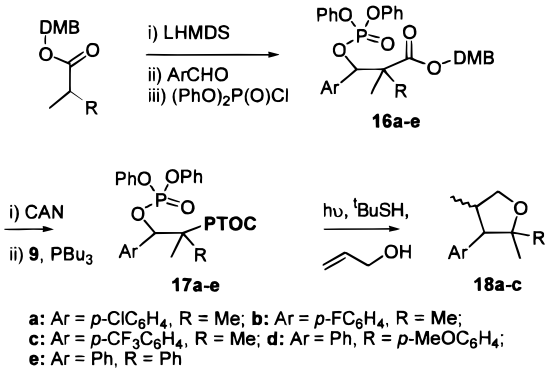


The regioisomeric *O*-acyl thiohydroxamate (**10a**) was prepared, as outlined in Scheme 4,[8] in the expectation that a concerted vicinal displacement on the derived radical by allyl alcohol would lead to the tetrahydrofuran **6**. However, it soon became apparent that the only cyclic products, isolated in 85% yield, were a 9/1 trans/cis mixture of the stereoisomers of **5**. Hence, both regioisomeric substrates **1** and **10a** led to the same product in comparable yield and with comparable stereoselectivity (Table 1). It is therefore highly likely that both reactions proceed via common intermediates and that these intermediates are the radical cation/phosphate anion pair **12** and the benzylic oxahexenyl radical **13** (Scheme 5). We cannot exclude the possibility that radicals **2** and **11a**

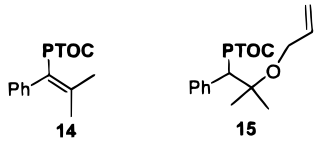
Scheme 5



Scheme 6

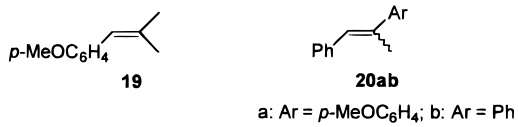


are in equilibrium via a *β*-(phosphatoxy)alkyl migration and that such a migration precedes the substitution process in the case of radical **2**.[12] The remote possibility that **5** could be formed from **10a**, via elimination of diphenyl phosphate to give **14**, Michael addition of allyl alcohol, affording **15**, and eventual decarboxylative cyclization, was eliminated from consideration when an authentic sample of **14** failed to yield any **5** under the standard reaction conditions. Presumably, the highly regioselective nature of the capture of radical cation **12** reflects the considerably higher (~8 kcal·mol^{-1}) radical stabilization energy of a secondary benzyl radical over of a *tert*-alkyl radical.[13]



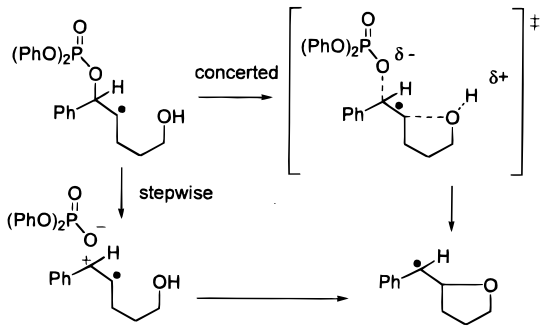
A series of experiments were conducted with para-substituted analogues of **1**, prepared as illustrated in Scheme 6, leading to the results set out in Table 1. Electron-withdrawing substituents generally resulted in clean reactions, good to excellent yields, and high trans selectivity for the ring closure in excellent agreement with the observations from the parent compound (**1**). It was not possible to make a direct comparison with the

(10) Giese, B.; Beyrich-Graf, X.; Burger, J.; Kesselheim, C.; Senn, M.; Schafer, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1742.
(11) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064.
(12) The rate constant for the rearrangement of **2** to **11a** in benzene at 20 °C is 1.2 × 10^6 s^{-1} (see ref 21).
(13) Brocks, J. J.; Beckhaus, H.-D.; Beckwith, A. L. J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935.



corresponding *p*-methoxy-substituted system owing to the instability of the diphenyl phosphate. However, we were able to synthesize the regioisomer (**10b**) by the method of Scheme 4; on photolysis in the presence of allyl alcohol and *tert*-butyl thiol it provided only β,β-dimethyl-4-methoxystyrene (**19**). Two further substrates (**17d** and **e**) also led only to alkene formation on photolysis in the presence of allyl alcohol and the thiol. Given the reasonable expectation that **17d** and **17e** do provide the alkene radical cation on fragmentation of the derived β-(phosphatoxy)alkyl radicals,[7,8] it is clear that significant extra stabilization of these radical cations, afforded by conjugation with a second aryl ring, enables other pathways to compete with trapping by the alcohol nucleophile. This observation is consistent with the report by Johnston and Schepp who noted that methanol addition to the styrene radical cation is 6×10^3 times faster than to the more stabilized *p*-methoxystyrene radical cation.[14] Various possibilites exist for the formation of **19** and **20a**,**b** from the radical cations resulting from the fragmentation of **10b** and **17d**,**e**, respectively. These include electron transfer from the thiol or other donor; indeed, Giese has proposed a similar pathway for the formation of alkene from nucleoside-based radical cations.[15] A second possibility is trapping by the thiol, to give a β-(alkylthio)-alkyl radical, followed by elimination of the thiyl radical. Yet a third possibility involves deprotonation to an allyl radical followed by hydrogen transfer from the thiol. At the present time we have not attempted to differentiate between these alternatives.

Scheme 7

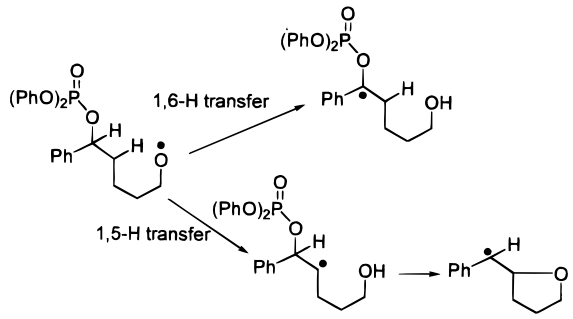


We next turned our attention to intramolecular nucleophilic attack on β-(phosphatoxy)alkyl radicals by suitably disposed alcohols. As in the intermolecular case, we anticipated two mechanistic pathways; one a Zipse-like concerted displacement and the other stepwise and dissociative with the intermediacy of a radical cation (Scheme 7). We further anticipated that if the concerted mechanism exists at all it is most likely to manifest itself in such an intramolecular example where it, unlike the dissociative pathway, benefits from the high effective molarity.

(14) Johnston, L. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1993**, *115*, 6564.

(15) Giese, B.; Burger, J.; Kang, T. W.; Kesselheim, C.; Wittmer, T. *J. Am. Chem. Soc.* **1992**, *114*, 7322.

Scheme 8



The problem with realizing such a scheme lay in the correct choice of precursor for the β-(phosphatoxy)alkyl radical. Barton esters, as used in the intermolecular case, did not seem like a wise choice as these active esters might reasonably have been expected to condense with the intramolecular alcohol resulting in the formation of lactones.[16] Similarly, β-bromoalkyl phosphates were discounted owing to the evident complication of the bromide being displaced by the nucleophile prior to the radical step. The β-(arylselenyl)alkyl phosphates do not suffer from this complication, but experience has taught us that they are unstable with respect to epi-seleninium ion formation and eventual elimination to the alkene. Ultimately, we opted for the C−H bond as the ideal radical precursor requiring no protecting group chemistry and with generation of the β-(phosphatoxy)alkyl radical by hydrogen atom abstraction by an alkoxyl radical (Scheme 8). The main question with this approach was the potential for 1,6-hydrogen atom abstraction from the benzylic position, rather than 1,5-abstraction to give the desired β-(phosphatoxy)alkyl radical. Early studies on the Barton reaction indicated that the 5-phenyl-1-pentyloxyl radical did not abstract hydrogen from the benzylic site, giving instead only products of 1,5-hydrogen abstraction.[17] However, the influence of the additional C−H bond weakening effect of the benzylic phosphate group in the intended sequence remained an unknown that could only be reliably probed by experiment. We selected the reaction of triphenylstannane with *N*-alkoxyphthalimides, recently described by the Kim group,[18] as the means of generating the alkoxyl radical such that eventual chain propagation would be assured by the presence of the stannane.

A series of three radical precursors with leaving groups of different abilities was prepared uneventfully from known 5-hydroxy-1-phenylpentanone,[19] as outlined in Scheme 9, via the common alcohol **27** using routine techniques. Several methyl-substituted analogues (**31**−**36**), for the most part as mixtures of diastereomers, were obtained by variations on this theme as outlined in the Supporting Information.

The cyclization reactions were conducted by dropwise addition of triphenylstannane and AIBN, in benzene or acetonitrile, to the substrate at reflux in the same solvent followed by heating to reflux for a further 2 h and leading

(16) Barton esters have been formed in the presence of alcohols (for some examples, see: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413); however, it was felt that lactonization would be a serious problem if such a strategy were applied to the present system.

(17) Kabasakalian, P.; Townley, E. R.; Yudis, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2716.

(18) Kim, S.; Lee, T. A.; Song, Y. *Synlett.* **1998**, 501.

(19) Descotes, G.; Soula, J.-C. *Bull. Soc. Chim. Fr.* **1964**, 2636.

Scheme 9

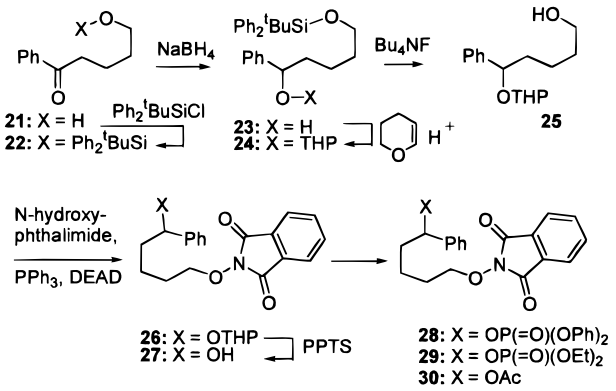


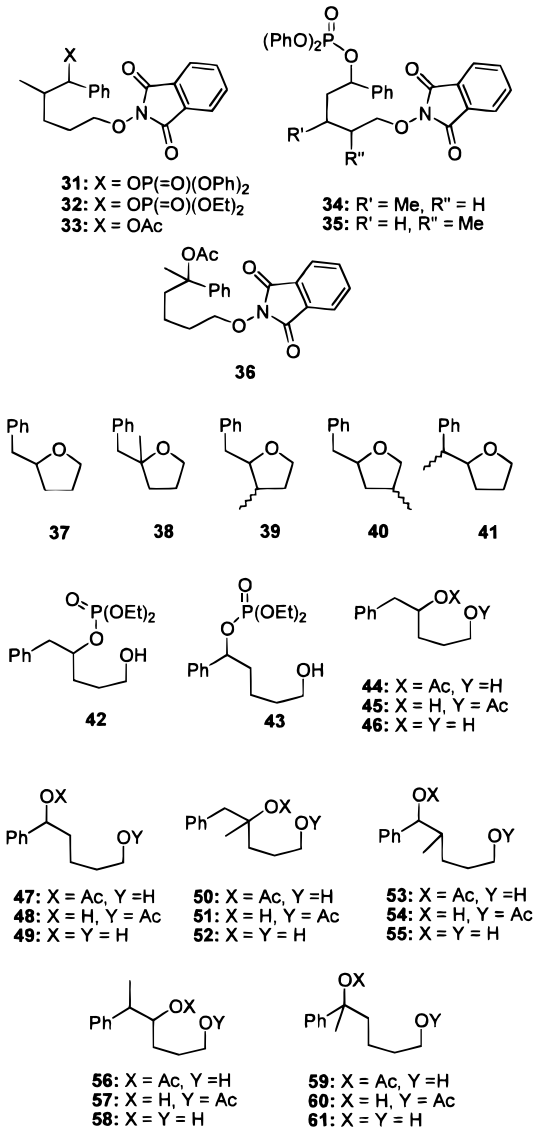
Table 2. Hydrogen Abstraction/Cyclizations

substrate	solvent	tetrahydrofuran (% yield)[a]	migration (% yield)[b]	reduction (% yield)[b]
28	benzene	**37** (95)		
29	benzene	**37** (60)	**42** (25)	**43** (15)
30	benzene	**37** (0)	**44** + **45** (74)	**47** + **48** (26)
31	benzene	**38** (90)		
32	benzene	**38** (85)		
33	benzene	**38** (0)	**50** + **51** (35)	**53** + **54** (65)
34	benzene	**39** (90), ~1/1		
35	benzene	**40** (92), ~~55/45		
36	benzene	**41** (0)	**56** + **57** (80)	**59** + **60** (20)
28	benzene/ ~acetonitrile 1/1	**37** (98)		
30	benzene/ ~acetonitrile 1/1	**37** (0)	**44** + **45** (64)	**47** + **48** (36)
31	benzene/ ~acetonitrile 1/1	**38** (92)		

[a] Yields of tetrahydrofurans refer to isolated materials. [b] Yields of migration and reduction products were determined by integration of the NMR spectra of the crude reaction mixtures.

to the results collected in Table 2. Several conclusions are apparent from Table 2. First, any fears about the regioselectivity of the hydrogen atom abstraction process were misplaced. Second, the efficiency of the cyclization reaction is a function of the leaving group with diphenyl phosphate being optimal and acetate ineffective. Third, a relatively inefficient cyclization of a diethyl phosphate may be rescued by inclusion of a methyl group at the site of nucleophilic attack. Fourth, little or no stereoselectivity is observed under the present conditions.

Taken as a whole, the above series of observations support very strongly the notion that vicinal nucleophilic displacement of β-ester-substituted radicals occurs by a dissociative mechanism involving initial fragmentation of the radical to give a radical cation/ester anion pair with subsequent capture by the nucleophile. The strongest evidence for this mechanism is derived from the two diethyl phosphates **29** and **32** from which it is seen that additional substitution at the site of nucleophilic eventual attack increases the yield, most likely through stabilization of the intermediate radical cation. With less potent leaving groups migration is a competing reaction as is readily seen by the contrast between the diethyl and diphenyl phosphates. This phenomenon is best attributed to collapse of the radical cation/anion pair being competitive with capture by the external nucleophile. In the case of the acetates this collapse is much faster than nucleophilic attack and completely dominates the chemistry.



At this stage, however, we cannot completely rule out the possibility that the acetate migration is taking place through a concerted mechanism. From a practical point of view, the acetate examples are complicated by an intramolecular scrambling of the acetate group itself between the two hydroxyls of the monoacetylated diol products. This is evidently a post radical step and has no bearing on the above discussion of mechanism; the product mixtures may be simplified for analysis by simple saponification.

In conclusion, it has been demonstrated that β-(phosphatoxy)alkyl radicals may be displaced by inter- or intramolecular alcohols giving rise to β-(alkoxy)alkyl radicals. These displacements may be engineered so as to permit the formation of tetrahydrofurans. The majority of evidence supports a dissociative mechanism involving initial fragmentation of the β-(phosphatoxy)alkyl radical to a radical cation/anion pair, even in the nonpolar solvent benzene, which undergoes subsequent nucleophilic capture by the alcohol.

Experimental Section

General Methods.[20] Compounds **1**[21] and **7a**−**10a**[8] were prepared as previously described. Compounds prefixed by an **S** are to be found in the Supporting Information.

(20) For general experimental details see ref 21.

General Protocol A. One-Pot Aldol Condensation/Phosphorylation. 2,4-Dimethoxybenzyl 3-(Diphenylphosphatoxy)-3-methyl-2-(4-methoxyphenyl)butanoate (8b). LHMDS was prepared in situ by adding *n*-BuLi (1.70 mL, 4.25 mmol) to a solution of hexamethyldisilamine (1.08 mL, 4.68 mmol) in THF (8.0 mL) at −78 °C. After the mixture was stirred for 20 min, **7b** (0.893 g, 2.83 mmol) was added in THF (2.0 mL). Dry acetone (0.31 mL, 4.25 mmol) was then added at −78 °C over 30 min. After the mixture was stirred for 30 min, diphenyl chlorophosphate (1.14 g, 4.25 mmol) was added in THF (2.0 mL). The reaction temperature was allowed to warm slowly to −20 °C before the addition of saturated NH_4Cl solution and EtOAc. The water layer was extracted with EtOAc, and the combined organic phases were washed with water and brine and then dried (Na_2SO_4). Removal of the solvent under vacuum and flash chromatography on silica gel (hexane/EtOAc 3/1) afforded **8b** as an oil (0.79 g, 46%): ^{1}H NMR ($CDCl_3$) δ 7.35−7.09 (m, 13 H), 6.38 (d, J = 7.7 Hz, 2 H), 6.39−6.37 (m, 2 H), 5.05 (AB quart, J = 33.0, 12.0 Hz, 2 H), 3.97 (s, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 1.70 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR δ 171.1, 161.4, 159.4, 159.0, 150.8 (t), 131.4, 129.8, 129.7, 126.2, 125.2 (d), 120.4 (d), 116.5, 113.6, 104.1, 98.6, 87.8, 87.7, 62.4, 60.8, 60.7, 55.5, 55.4, 25.8, 25.4; ^{31}P NMR δ −16.65. Anal. Calcd for $C_{33}H_{35}O_9P$: C, 65.34; H, 5.82. Found: C, 64.93; H, 5.72.

General Protocol B. (1*H*)-2-Thioxo-1-pyridyl 3-(Diphenylphosphatoxy)-3-methyl-2-(4-methoxyphenyl)butanoate (10b). A solution of **8b** (0.264 g, 0.456 mmol) in EtOAc (20 mL) was stirred under 1 atm of H_2 over Pd/C (0.152 g, 50 wt %) overnight and then filtered. Removal of the solvent under vacuum afforded 3-(diphenylphosphatoxy)-3-methyl-2-(4-methoxyphenyl)butanoic acid, as an oil, quantitatively. No further purification of this acid was attempted: ^{1}H NMR ($CDCl_3$) δ 9.38 (br s, 1 H), 7.29−7.11 (m, 12 H), 6.79 (d, J = 8.8 Hz, 2 H), 3.96 (s, 1 H), 3.78 (s, 3 H), 1.69 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR δ 175.8, 159.6, 150.7 (t), 131.4, 129.8, 129.4, 125.8, 125.3, 120.4, 120.3, 113.9, 87.8, 87.7, 60.6, 60.5, 55.4, 26.1, 25.2; ^{31}P NMR δ −16.89. To a solution of this acid (0.17 g, 0.375 mmol) and **9** (0.103 g, 0.410 mmol) in CH_2Cl_2 (8.0 mL) in a flask covered with aluminum foil was added n-Bu_3P (0.091 mL, 0.573 mmol) at 0 °C under Ar. The reaction mixture was stirred at room temperature for 3 h before aqueous Na_2CO_3 was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried (Na_2SO_4), and concentrated to dryness. Flash chromatography on silica gel (within 10 min on a ca. 10 cm column, hexane/EtOAc 2:1) in the dark gave **10b** (0.161 g, 76%) as a yellowish syrup: ^{1}H NMR ($CDCl_3$) δ 7.58 (dd, J = 8.1, 1.6 Hz, 1 H), 7.33−7.07 (m, 13 H), 6.82 (d, J = 8.8 Hz, 2 H), 6.43 (dt, J = 6.9, 1.8 Hz, 1 H), 4.35 (s, 1 H), 3.77 (s, 3 H), 1.77 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR δ 175.5, 166.7, 159.8, 150.6 (q), 137.6, 137.2, 133.5, 131.3, 129.8, 125.4, 123.8, 120.3, 120.2, 120.1, 114.1, 112.6, 87.3 (d), 60.4, 58.0, 57.9, 55.3, 26.4, 25.2; ^{31}P NMR δ −16.63. No further characterization was attempted on this hydrolytically and photolytically unstable compound.

General Protocol C. Photolysis of Barton Esters in the Presence of *tert*-Butylthiol and Allyl Alcohol. *cis/trans*-2,2,4-Trimethyl-3-phenyltetrahydrofuran (5). A solution of **1** (0.107 g, 0.2 mmol) and *tert*-butylthiol (45.3 μL, 0.4 mmol) in allyl alcohol (4.0 mL) in a Pyrex flask was photolyzed at room temperature with a 250 W Philips' Krypton lamp for 1 h. After removal of the volatiles under vacuun, ^{1}H and ^{31}P NMR spectra indicated a clean reaction and complete conversion of **1** with essentially quantitative formation of diphenyl phosphate (^{31}P NMR δ −10.36 in $CDCl_3$). Purification by preparative TLC (hexane/EtOAc 20:1) gave **5** (32 mg, 82%) as the major product. ***trans*-5:** ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.31 (s, 3 H), 2.62 (d, J = 11.5 Hz, 1 H), 2.79 (m, 1 H), 3.50 (dd, J = 9.3, 8.0 Hz, 1 H), 4.14 (t, J = 8.0 Hz, 1 H), 7.20−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.7, 24.5, 28.5, 38.0, 63.2, 72.7, 83.9, 127.0, 128.5, 128.9, 139.0. ***cis*-5:** δ 0.68 (d, J = 7.0 Hz, 3 H), 1.02 (s, 3 H), 1.36 (s, 3 H), 2.92 (d, J = 11.5 Hz, 1 H), 3.10 (m, 1 H), 3.66 (t, J = 9.0 Hz, 1 H), 4.19 (t, J = 9.0 Hz, 1 H), 7.20−7.36 (m, 5 H); HRMS calcd for $C_{13}H_{18}O$ 190.1358, found 190.1360.

(1*H*)-2-Thioxo-1-pyridyl 3-Methyl-2-phenyl-2-butenoate (14). This compound was obtained from **8a**[8] by the exact method used for the formation of **10a**[8] with the exception that the final purification/elimination was carried out by chromatography on silica gel basified with Et_3N: ^{1}H NMR δ 7.61 (dd, J = 8.0, 1.8 Hz, 1 H), 7.40−7.31 (m, 6 H), 7.10 (m, 1 H), 6.53 (dt, J = 6.9, 1.3 Hz, 1 H), 2.37 (s, 3 H), 1.78 (s, 3 H); ^{13}C NMR δ 138.0, 137.3, 136.2, 133.4, 130.4, 126.5, 127.9, 112.6, 25.2, 23.6. No further characterization was attempted on this hydrolytically and photolytically unstable compound.

2,4-Dimethoxybenzyl 3-(diphenylphosphatoxy)-2,2-dimethyl-3-(4-chlorophenyl)propanoate (16a) was prepared from 2,4-dimethoxybenzyl 2-methylpropanoate[21] and 4-chlorobenzaldehyde by general protocol A: ^{1}H NMR δ 7.30−7.11 (m, 13 H), 6.94 (d, J = 8.3 Hz, 2 H), 6.44 (m, 2 H), 5.83 (d, J = 8.2 Hz, 1 H), 4.99 (AB quart, J = 54.6, 12.0 Hz, 2 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 1.26 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR δ 174.6, 161.4, 159.1, 150.6 (t), 134.7, 134.4, 131.6, 129.9, 129.8, 129.3, 128.2, 125.5, 125.3, 120.3 (d), 120.0 (d), 116.5, 104.1, 98.6, 85.0, 84.9, 62.6, 55.5, 21.3, 20.5; ^{31}P NMR δ −12.24. Anal. Calcd for $C_{32}H_{32}ClO_8P$: C, 62.90; H, 5.28. Found: C, 62.84; H, 5.41.

General Protocol D. Conversion of 2,4-Dimethoxybenzyl Esters to Barton Esters via Oxidative Cleavage with CAN. (1*H*)-2-Thioxo-1-pyridyl 3-(Diphenylphosphatoxy)-2,2-dimethyl-3-(4-chlorophenyl)-propanoate (17a). A solution of **16a** (0.803 g, 1.51 mmol) in a mixture of acetonitrile and water (10:1 v/v, 26 mL) was treated with ceric ammonium nitrate (1.59 g, 2.91 mmol), and the resulting mixture was stirred at room temperature for 1 h. Water was then added and the mixture extracted with EtOAc. The combined extracts were concentrated to dryness, and the residue was taken up in EtOAc, washed repeatedly with a freshly prepared 15% aqueous solution of $NaHSO_3$, water, and brine, and then dried (Na_2SO_4). Removal of the solvent gave 3-(diphenylphosphatoxy)-2,2-dimethyl-3-(4-chlorophenyl)propanoic acid as an oil quantitatively. Without further purification this acid was converted to the title compound, exactly according to the method described in general protocol B, in 57% yield: ^{1}H NMR δ 7.79 (dd, 1 H), 7.60 (dd, 1 H), 7.30−7.10 (m, 12 H), 6.89 (d, 2 H), 6.38 (dt, 1 H), 5.95 (d, J = 8.4 Hz, 1 H), 1.38 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR δ 175.8, 170.2, 150.2 (t), 138.6, 137.1, 135.2, 133.8, 132.8, 130.0, 129.8, 129.4, 128.4, 125.9, 125.4, 120.4 (d), 119.7, 119.6, 112.7, 84.1, 84.0, 48.6, 48.5, 23.1, 17.6; ^{31}P NMR δ −11.79. Anal. Calcd for $C_{28}H_{25}ClNO_6PS\cdot 0.5H_2O$: C, 58.08; H, 4.52. Found: C, 57.93; H, 4.29.

***cis/trans*-2,2,4-Trimethyl-3-(4-chlorophenyl)tetrahydrofuran (18a).** Application of general protocol C to **17a** gave the title compound: ^{1}H NMR δ trans 7.30 (d, J = 8.5 Hz, 2 H), 7.14 (d, J = 8.5 Hz, 2 H), 4.13 (t, J = 8.0 Hz, 1 H), 3.48 (t, J = 8.4 Hz, 1 H), 2.75 (m, 1 H), 2.59 (d, J = 11.5 Hz, 1 H), 1.29 (s, 3 H), 0.96 (d, J = 8.1 Hz, 3 H), 0.84 (s, 3 H); cis 7.27 (d, J = 8.5 Hz, 2 H), 7.06 (d, J = 8.5 Hz, 2 H), 4.18 (t, J = 8.9 Hz, 1 H), 3.59 (t, J = 9.0 Hz, 1 H), 3.09 (m, 1 H), 2.88 (d, J = 7.7 Hz, 1 H), 1.35 (s, 3 H), 1.01 (s, 3 H), 0.67 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 137.2, 135.8, 132.8, 131.6, 130.1, 128.7, 128.3, 127.8, 84.4, 83.4, 73.0, 72.6, 62.6, 58.4, 38.2, 37.5, 29.0, 28.4, 25.6, 24.4, 15.6, 14.4. Anal. Calcd for $C_{13}H_{17}ClO$: C, 69.48; H, 7.62. Found: C, 68.97; H, 7.71.

4-Methoxy-β,β-dimethylstyrene (19).[22] Application of general protocol C to **10b** gave the title compound: ^{1}H NMR δ 7.16 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.21 (s, 1 H), 3.81 (s, 3 H), 1.89 (d, J = 1.1 Hz, 3 H), 1.85 (d, J = 1.0 Hz, 3 H).

β-4-Methoxyphenyl-β-methylstyrene (20a).[23] Application of general protocol C to **17d** gave the title compound: ^{1}H NMR δ 7.48 (d, J = 8.5 Hz, 2 H), 7.26−7.05 (m, 5 H), 6.90 (d, J = 8.5 Hz, 2 H), 3.82 (s, 3 H), 2.28 (d, J = 1.1 Hz, 3 H).

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α-Methylstilbene (20b).[24] Application of general protocol C to **17e** gave the title compound: ^{1}H NMR δ 7.55−7.26 (m, 10 H), 6.85 (s, 1 H), 2.29 (d, J = 1.3 Hz, 3 H).

General Protocol E. Phosphorylation. 1-(Diethylphosphatoxy)-1-phenyl-5-(*N*-phthalimidoxy)pentane (29). Diethyl chlorophosphate (0.112 g, 0.651 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of **27** (0.141 g, 0.434 mmol) and DMAP (0.08 g, 0.651 mmol) in CH_2Cl_2 (8.0 mL). The resulting reaction mixture was stirred at room temperature for 24 h before it was diluted with EtOAc. The organic layer was washed with saturated NH_4Cl solution, water, and brine, dried (Na_2SO_4), and concentrated to dryness. Column chromatography on silica gel eluting with hexane/EtOAc (1/1) gave **29** (0.104 g, 52%, 100% based on recovered **27**) as a colorless oil: ^{1}H NMR δ 7.80 (dd, 2 H), 7.73 (dd, 2 H), 7.37−7.26 (m, 5 H), 5.27 (dd, J = 13.7, 7.3 Hz, 1 H), 4.14 (t, J = 6.6 Hz, 2 H), 4.08 (m, 1 H), 3.96 (m, 1 H), 3.85 (m, 2 H), 2.03 (m, 1 H), 1.89 (m, 1 H), 1.79 (m, 2 H), 1.62 (m, 1 H), 1.47 (m, 1 H), 1.22 (dt, J = 7.1, 0.8 Hz, 3 H), 1.11 (dt, J = 7.1, 0.8 Hz, 3 H); ^{13}C NMR δ 163.7, 140.6, 134.6, 132.3, 132.2, 129.1, 128.6, 128.4, 126.6, 123.6, 80.5 (d), 78.3, 63.7 (t), 37.7 (d), 27.9, 21.6, 16.1 (t); ^{31}P NMR δ −1.08. Anal. Calcd for $C_{23}H_{28}NO_7P\cdot{}^1/_4H_2O$: C, 59.29; H, 6.16. Found: C, 59.02; H, 6.08.

1-Phenyl-1-(diphenylphosphatoxy)-5-(*N*-phthalimidoxy)pentane (28). This compound was prepared by general protocol E, with replacement of diethyl chlorophosphate by diphenyl chlorophosphate, in 63% yield: ^{1}H NMR δ 7.81 (dd, 2 H), 7.72 (dd, 2 H), 7.33−7.06 (m, 13 H), 6.97 (dd, 2 H), 5.54 (dd, J = 13.5, 7.3 Hz, 1 H), 4.09 (t, J = 6.6 Hz, 2 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.74 (m, 2 H), 1.47 (m, 2 H); ^{13}C NMR δ 163.7, 150.7 (t), 139.6, 134.6, 129.8, 129.7, 129.1, 128.6, 126.7, 125.4, 125.2, 123.6, 120.4, 120.3, 120.2, 120.1, 82.6 (d), 78.1, 37.4 (d), 27.8, 21.4; ^{31}P NMR δ −11.89. Anal. Calcd for $C_{31}H_{28}NO_7P$: C, 66.78; H, 5.06. Found: C, 66.64; H, 5.08.

1-(Acetoxy)-1-phenyl-5-(*N*-phthalimidoxy)pentane (30). 4-(1-Pyrrolidinyl)pyridine (0.16 g, 1.07 mmol) was added at room temperature to a solution of **27** (0.692 g, 2.13 mmol) and Ac_2O (0.613 mL, 8.52 mmol) in NEt_3 (15.0 mL). The resulting reaction mixture was stirred at room temperature overnight before it was diluted with EtOAc and saturated NH_4Cl solution. The organic layer was washed with 2 N HCl to pH 6−7, washed subsequently with water, saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and concentrated to dryness. Column chromatography on silica gel (hexane/EtOAc 1/1) gave **30** (0.704 g, 90%) as a white solid: mp 92−94 °C; ^{1}H NMR δ 7.83 (dd, 2 H), 7.73 (dd, 2 H), 7.34−7.26 (m, 5 H), 5.75 (dd, J = 7.6, 6.1 Hz, 1 H), 4.17 (t, J = 6.6 Hz, 2 H), 2.08 (s, 3 H), 2.00 (m, 1 H), 1.90−1.76 (m, 3 H), 1.54 (m, 2 H); ^{13}C NMR δ 170.6, 163.8, 140.7, 134.6, 129.1, 128.6, 128.1, 126.7, 123.7, 78.3, 76.0, 36.1, 28.0, 21.8, 21.5. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76. Found: C, 68.75; H, 5.80.

2-Methyl-1-phenyl-1-(diphenylphosphatoxy)-5-(*N*-phthalimidoxy)pentane (31). Phosphorylation of **S5** with diphenyl chlorophosphate according to general protocol E gave **31** in 77% yield: ^{1}H NMR δ 7.82−7.79 (m, 2 H), 7.74−7.71 (m, 2 H), 7.32−7.07 (m, 13 H), 6.93 (m, 2 H), 5.40 (dd, J = 7.8, 6.2 Hz), 5.28 (t, J = 7.5 Hz) (1 H), 4.05 (m, 2 H), 2.06 (m, 1 H), 1.88−1.63 (m, 2 H), 1.48 (m), 1.26 (m) (2 H), 0.96 (d, J = 6.7 Hz), 0.77 (d, J = 6.8 Hz) (3 H); ^{13}C NMR δ 163.8, 150.8, 150.7, 150.6, 138.5, 138.3, 134.6, 129.8, 129.7, 129.0 (d), 128.5, 128.4, 127.4, 127.1, 125.3, 125.2, 123.6, 120.4, 120.3, 120.2, 120.1, 86.7, 86.6, 86.3, 86.2, 78.6, 78.5, 39.8, 39.7, 39.5, 39.4, 28.3, 28.1, 25.8, 25.6, 15.2, 14.8; ^{31}P NMR δ −11.65, −11.83. Anal. Calcd for $C_{32}H_{30}NO_7P\cdot{}^1/_4H_2O$: C, 66.72; H, 5.34. Found: C, 66.71; H, 5.33.

1-(Diethylphosphatoxy)-2-methyl-1-phenyl-5-(*N*-phthalimidoxy)pentane (32). Phosphorylation of **S5** with diethyl chlorophosphate according to general protocol E gave **32** in 60% yield: ^{1}H NMR δ 7.81 (m, 2 H), 7.72 (m, 2 H), 7.32−7.22 (m, 5 H), 5.12 (dd, J = 8.0, 6.2 Hz), 5.03 (t, J = 7.6 Hz) (1 H), 4.18 (t, J = 6.5 Hz), 4.11 (t, J = 6.6 Hz) (2 H), 4.09 (m, 1 H), 3.93 (m, 1 H), 3.80 (m, 2 H), 2.10−1.65 (m), 1.52 (m), 1.34 (m) (5 H), 1.20 (dt, J = 7.0, 0.8 Hz), 1.09 (dt, J = 6.9, 0.9 Hz) (3 H), 1.00 (d, J = 6.7 Hz), 0.79 (d, J = 6.8 Hz) (3 H); ^{13}C NMR δ 163.7, 139.6, 139.4, 134.6, 129.1, 128.3, 128.1, 127.3, 127.1, 123.6, 84.6 (d), 84.3 (d), 78.8, 78.6, 63.7 (t), 39.8 (d), 39.6 (d), 28.5, 28.2, 25.9, 25.7, 16.1 (d), 15.3, 14.9; ^{31}P NMR δ −0.86, −1.02. Anal. Calcd for $C_{24}H_{30}NO_7P$: C, 60.06; H, 6.40. Found: C, 59.91; H, 6.42.

1-(Acetoxy)-2-methyl-1-phenyl-5-(*N*-phthalimidoxy)pentane (33). Acetylation of **S5** gave **33** quantitatively: ^{1}H NMR δ 7.82 (m, 2 H), 7.73 (m, 2 H), 7.31−7.23 (m, 5 H), 5.64 (d, J = 6.3 Hz), 5.53 (d, J = 7.7 Hz) (1 H), 4.18 (t, J = 6.4 Hz), 4.11 (t, J = 6.6 Hz) (2 H), 2.09 (s), 2.07 (s) (3 H), 2.04 (m), 1.95−1.66 (m), 1.59−1.18 (m) (5 H), 0.95 (d, J = 6.7 Hz), 0.80 (d, J = 6.8 Hz) (3 H); ^{13}C NMR δ 170.5, 163.8, 139.6, 134.6, 129.1, 128.4, 127.9, 127.8, 127.2, 126.9, 123.6, 80.0, 79.3, 78.7, 78.6, 38.4, 38.2, 28.8, 28.4, 25.9, 21.3, 15.7, 15.0. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08. Found: C, 69.13; H, 6.04.

3-Methyl-1-phenyl-1-(diphenylphosphatoxy)-5-(*N*-phthalimidoxy)pentane (34). Phosphorylation of **S14** with diphenyl chlorophosphate according to general protocol E gave **34** in 91% yield: ^{1}H NMR δ 7.82 (m, 2 H), 7.74 (m, 2 H), 7.36−7.15 (m, 13 H), 5.60 (m, 1 H), 4.14 (m, 2 H), 2.17 (m), 1.95 (m), 1.81 (m) (3 H), 1.65 (m, 2 H), 0.98 (d, J = 5.4 Hz, 3 H); ^{13}C NMR δ 163.7, 150.7 (t), 140.2, 139.3, 134.6, 129.8, 129.7, 129.1 (d), 128.7 (d), 127.1, 126.8, 125.3, 125.1, 123.6, 120.3, 120.2, 120.1, 81.5, 81.4, 80.9, 80.8, 76.8, 76.6, 45.5, 45.4, 44.5, 44.4, 35.3, 34.8, 26.7, 26.5, 19.6, 19.0; ^{31}P NMR δ −11.82, −12.00. Anal. Calcd for $C_{32}H_{30}NO_7P$: C, 67.24; H, 5.29. Found: C, 67.66; H, 5.70.

4-Methyl-1-phenyl-1-(diphenylphosphatoxy)-5-(*N*-phthalimidoxy)pentane (35). Phosphorylation of **S23** with diphenyl chlorophosphate according to general protocol E gave **35** 97% yield: ^{1}H NMR δ 7.80 (m, 2 H), 7.72 (m, 2 H), 7.35−7.05 (13 H), 6.97 (d, 2 H), 5.52 (dd, J = 13.1, 5.8 Hz, 1 H), 3.96 (ddd, J = 10.0, 7.7, 1.5 Hz, 1 H), 3.88 (t, J = 7.7 Hz, 1 H), 2.18−1.88 (m, 3 H), 1.61−1.40 (m, 1 H), 1.35−1.12 (m, 1 H), 1.00 (dd, J = 6.7, 2.1 Hz, 3 H); ^{13}C NMR δ 163.6, 150.8, 150.7, 150.6, 139.6, 134.6, 129.8, 129.7, 129.1, 128.6, 126.7, 125.4, 125.2, 123.6, 120.4, 120.3, 120.2, 83.2, 35.1 (q), 32.3 (d), 28.8, 28.7, 16.8. Anal. Calcd for $C_{32}H_{30}NO_7P1/2H_2O$: C, 66.20; H, 5.38. Found: C, 66.36; H, 5.22.

General Protocol F. Mitsunobu Reaction for the Introduction of the Phthalimidoxy Group. 1-(Acetoxy)-1-methyl-1-phenyl-5-(*N*-phthalimidoxy)pentane (36). Diethyl azodicarboxylate (0.128 mL, 0.794 mmol) was added dropwise at room temperature to a solution of **59** (0.104 g, 0.44 mmol), *N*-hydroxyphthalimide (0.102 g, 0.66 mmol), and PPh_3 (0.177 g, 0.66 mmol) in THF (7.0 mL). The resulting reaction mixture was stirred at room temperature for 24 h before it was diluted with EtOAc and water. The aqueous layer was further extracted with EtOAc, and the combined organic phases were washed with saturated aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated to dryness. Column chromatography on silica gel (hexane/EtOAc 1/1) gave **36** (88 mg, 52%) as a white solid: mp 119−121 °C; ^{1}H NMR δ 7.82 (dd, 2 H), 7.74 (dd, 2 H), 7.32−7.19 (m, 5 H), 4.14 (t, J = 6.6 Hz, 2 H), 2.07 (s, 3 H), 2.04 (m, 2 H), 1.85 (s, 3 H), 1.74 (m, 2 H), 1.41 (m, 2 H); ^{13}C NMR δ 169.9, 163.8, 145.1, 134.6, 129.1, 128.4, 127.0, 124.7, 123.7, 84.0, 78.4, 42.3, 28.4, 25.0, 22.5, 20.1. Anal. Calcd for $C_{22}H_{23}NO_5\cdot{}^1/_4H_2O$: C, 68.47; H, 6.14. Found: C, 68.68; H, 6.10.

General Protocol G. Hydrogen Abstraction/Cyclization. A solution of Ph_3SnH (1.3 equiv) and AIBN (50 mol %) in degassed benzene (0.002 M in Ph_3SnH) or in degassed CH_3CN and PhH (v/v 1/1) (0.002 M in Ph_3SnH) was added with a syringe pump (0.49 mL/h) under Ar to a refluxing solution of the phosphate in degassed benzene (0.001 M in phosphate). Stirring was continued for another 2 h after the addition finished before the solvent was removed under vacuum. In each case the crude reaction mixture was inspected by ^{1}H NMR spectroscopy before it was subjected to preparative TLC (hexane/EtOAc 10/1) to afford the product.

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2-Benzyltetrahydrofuran (37):[25] 95% from **28** and 60% from **29**; ^{1}H NMR δ 7.34−7.22 (m, 5 H), 4.09 (m, 1 H), 3.91 (q, J = 8.0 Hz, 1 H), 3.77 (dt, J = 8.0, 6.5 Hz, 1 H), 2.95 (dd, J = 13.6, 6.4 Hz, 1 H), 2.77 (dd, J = 13.6, 6.5 Hz, 1 H), 1.88 (m, 3 H), 1.58 (m, 1 H); ^{13}C NMR δ 139.1, 129.4, 128.4, 126.3, 80.2, 68.0, 42.1, 31.1, 25.7.

2-Benzyl-2-methyltetrahydrofuran (38):[26] 90% from **31** and 85% from **32**: ^{1}H NMR δ 7.31−7.21 (m, 5 H), 3.85 (m, 1 H), 3.79 (m, 1 H), 2.80 (s, 2 H), 1.97−1.60 (m, 4 H), 1.19 (s, 3 H); ^{13}C NMR δ 138.6, 130.5, 128.0, 126.2, 82.9, 67.5, 47.0, 36.3, 26.5, 26.1.

***cis/trans*-2-Benzyl-3-methyltetrahydrofuran (39):** 90%; ^{1}H NMR δ 7.27 (m, 5 H), 4.04 (dt, J = 8.1, 5.5 Hz), 3.97 (dt, J = 14.7, 8.0 Hz) (1 H), 3.83 (m), 3.74 (ddd, J = 14.1, 8.5, 5.6 Hz), 3.59 (dt, J = 7.3, 5.0 Hz) (2 H), 2.90−2.70 (m, 2 H), 2.27 (m), 2.08 (m), 1.89 (m), 1.67−1.47 (m) (3 H), 1.03 (d, J = 7.0 Hz), 0.97 (d, J = 6.5 Hz), (3 H); ^{13}C NMR δ 139.9, 139.3, 129.5, 129.2, 128.5 (d), 126.3, 126.2, 86.5, 82.5, 67.0, 66.4, 40.7, 38.8, 37.1, 35.7, 34.8, 34.1, 17.5, 14.7. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.52; H, 9.23.

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***cis/trans*-2-Benzyl-4-methyltetrahydrofuran (40):** 92%; ^{1}H NMR δ 7.24 (m, 5 H), 4.21 (m), 4.10 (m) (1 H), 4.02 (dd, J = 8.2, 6.9 Hz), 3.90 (t, J = 7.8 Hz) (1 H), 3.38 (t, J = 8.0 Hz), 3.28 (dd, J = 8.2, 7.0 Hz) (1 H), 3.00 (dd, J = 9.9, 4.8 Hz), 2.94 (dd, J = 10.2, 4.8 Hz) (1 H), 2.80 (dd, J = 10.2, 5.1 Hz), 2.74 (dd, J = 9.9, 4.8 Hz) (1 H), 2.30 (m), 2.08 (m) (1 H), 1.81 (m), 1.54 (m) (1 H), 1.26−1.10 (m, 1 H), 1.03 (d, J = 6.6 Hz), 1.00 (d, J = 6.8 Hz) (3 H); ^{13}C NMR δ 139.2, 129.4 (d), 128.5, 126.3, 81.0, 79.7, 75.3, 74.8, 42.5, 40.8, 39.3, 34.5, 33.3, 18.2, 18.0. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.04; H, 9.19.

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Supporting Information Available: Experimental parts and characterization data for all substrates, their precursors, and all minor products not included in the above Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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