Synthesis and Synthetic Utilization of α-Functionalized Vinylphosphonates Bearing *β*-Oxy or *β*-Thio Substituents

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The *β*-hetero-substituted vinylphosphonates **1a**−**c** on treatment with LDA or LTMP were readily lithiated at the α-position of the phosphono group, and the resulting α-lithiovinylphosphonates were trapped with various electrophiles to afford the corresponding α-functionalized vinylphosphonates **2**−**14** in 55−96% yields. The Friedel−Crafts reaction of α-(silyl)- or α-(germyl)-phosphonoketene dithioacetals **2**, **9**, or **4** with acid chlorides gave α-acylated phosphonoketene dithioacetals **15**−**19** in 53−91% yields. The palladium-catalyzed cross-coupling reaction of *β*-ethoxy-α-(tributylstannyl)vinylphosphonate **13** with a variety of organic halides (R = acyl, allyl, aryl, etc.) provided *β*-ethoxy-α-substituted vinylphosphonates **21**−**26** in good to moderate yields. The palladium-mediated cross-coupling reaction of α-(iodo)vinylphosphonates **7** and **14** with terminal acetylenes afforded α-alkynylated vinylphosphonates **41**−**44** in 69−83% yields. Several α-functionalized *β*-hetero-substituted vinylphosphonates were applied to the synthesis of pyrazoles and an isoxazole possessing a phosphono function.

Vinylphosphonates containing various functional groups have been widely studied due to their synthetic and biological usefulness.[1] We have recently reported the generation of α-carbanions of phosphonoketene dithioacetals and their synthetic application to dithioallenes.[2] These results have intrigued us to develop α-functionalization of vinylphosphonates via α-phosphono-stabilized vinyl anions, which have not, to our knowledge, been explored so far despite their potential usefulness and wide applicability.[3,4] We report here a new convenient synthesis of various vinylphosphonates containing synthetically useful substituents such as organometallic groups and halogens on the α-carbon. They are new homologues of vinylphosphonates and expected to show various reactivities similar to those of vinylphosphonates, vinyl ethers, heteroatom-substituted olefins, etc. We also describe the synthesis of a new class of vinylphosphonates, which are not readily accessible, via functional group transformation of the resulting α-functionalized vinylphosphonates and synthetic applications of several new vinylphosphonates for the preparation of heterocycles.

Table 1. Synthesis of α-Functionalized Vinylphosphonates[a]

Entry	Starting Materials		Reaction Time / h	Product[b] (yield , %)
	Vinylphosphonate	EX (equiv)		
1	**1a**	Me_3SiCl (1.5)	1.0	**2** (81)
2	**1a**	Ph_3SiCl (2.0)	2.0	**3** (69)
3	**1a**	Me_3GeCl (1.0)	1.0	**4** (78)
4	**1a**	Ph_3SnCl (2.2)	3.0	**5** (69)
5	**1a**	MeSSMe (1.0)	1.0	**6** (76)
6	**1a**	I_2 (1.0)	1.0	**7** (72 , 83[c])
7	**1a**	Br_2 (2.0)	1.5	**8** (55)
8	**1b**	Me_3SiCl (1.5)	1.5	**9** (64)
9	**1b**	Bu_3SnCl (1.5)	1.5	**10** (83)
10	**1c**	Me_3SiCl (3.0)	3.0	**11** (96)
11	**1c**	*t*-$BuMe_2SiCl$ (1.5)	13.0	**12** (75)
12	**1c**	Bu_3SnCl (1.5)	5.0	**13** (80)
13	**1c**	I_2 (1.1)	1.5	**14** (91[d])

[a] All reactions were carried out in THF. [b] Isolated yield. [c] CuBr•SMe_2 (1.5 equiv) was used. [d] CuBr•SMe_2 (0.5 equiv) was used.

Results and Discussion

Synthesis of α-Functionalized Vinylphosphonates. To synthesize α-functionalized vinylphosphonates which serve as versatile synthetic intermediates, we examined the reaction of α-phosphonovinyl anions with various electrophiles. The 2,2-(ethylenedithio)-1-phosphonovinyl anion was generated by addition of a THF solution of lithium 2,2,6,6-tetramethylpiperidide (LTMP) to phosphonoketene dithioacetal **1a** at −78 °C for 1.0 h[5] and was subsequently treated with chlorotrimethylsilane (1.5 equiv) to give an α-silylated phosphonoketene dithioacetal **2** in 81% yield (eq 1) (entry 1 in Table 1). Similar treatment of the α-phosphonovinyl anion with chlorotriphenylsilane, chlorotrimethylgermane, or chlorotriphenyltin also produced the corresponding α-triorgano-

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(1) For a review on synthetic uses of vinylphosphonates, see, (a) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333. For biological uses, see, for example: (b) Kawamoto, A. P.; Campbell, M. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1249. (c) Gao, J.; Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 9538.

(2) For the synthesis and synthetic application of phosphonoketene dithioacetals, see: Minami, T.; Okauchi, T.; Matsuki, H.; Nakamura, M.; Ichikawa, J.; Ishida, M. *J. Org. Chem.* **1996**, *61*, 8132.

(3) *β*-Alkyl-α-phosphonio- or phosphonovinyl anion easily isomerizes to the corresponding allyl anion. See: (a) Minami, T.; Shikita, S.; So, S.; Nakayama, M.; Yamamoto, I. *J. Org. Chem.* **1988**, *53*, 2937. (b) Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572.

(4) For the synthesis and synthetic application of α-phosphonoallenyl anion, see: (a) Macomber, R. S.; Hemling, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 343. For *β*-aryl-α-phosphonovinyl anion, see: (b) Mimouni, N.; About-Jaudet, E.; Collignon, N.; Savignac, Ph. *Phosphorus, Sulfur Silicon* **1993**, *75*, 99.

(5) A related 1-lithio ketene dithioacetal has been reported to be generated by halogen/Li exchange of the corresponding bromoketene dithioacetal with *t*-BuLi at much lower temperature (at −120 °C), see: Chamberlin, A. R.; Nguyen, H. *J. Org. Chem.* **1986**, *51*, 940.

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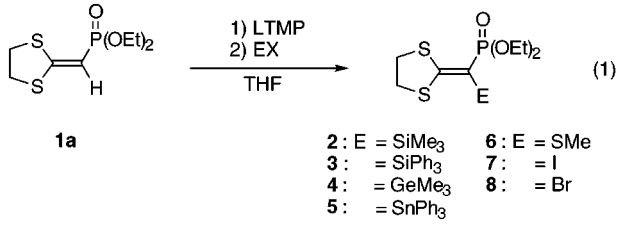
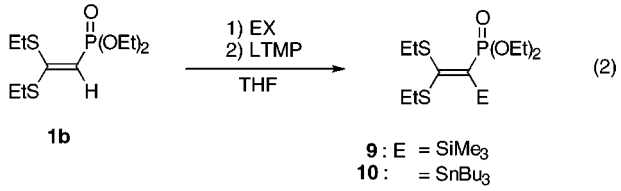


(1)

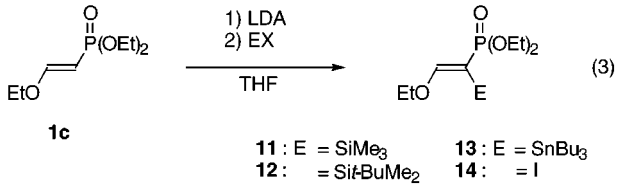
metal-substituted phosphonoketene dithioacetals **3**, **4**, or **5** in 69−78% yields (entries 2−4). In addition, the α-phosphonovinyl anion was similarly trapped with electrophiles such as dimethyl disulfide and halogens (I_2, Br_2) to lead to the desired phosphonoketene dithioacetals bearing the methylthio and halogeno group on the α-carbon in good to moderate yields (entries 5−7).

In the case of acyclic dithioacetal **1b** instead of the cyclic dithioacetal **1a**, a THF solution of LTMP was inversely added dropwise to the mixture of **1b** and an electrophile (Me_3SiCl or Bu_3SnCl) at −78 °C to prevent elimination of a thiolate anion.[6] As expected, α-trimethylsilyl- and α-tributyltin-substituted phosphonoketene dithioacetals **9** and **10** were provided in 64% and 83% yields, respectively (eq 2) (entries 8 and 9).



(2)

Furthermore, we examined the generation of *β*-ethoxy-α-phosphonovinyl anion from *β*-(ethoxy)vinylphosphonate **1c**[7] and its reactivities toward electrophiles.[8] Treatment of **1c** with lithium diisopropylamide (LDA) in THF at −78 °C followed by addition of an electrophile such as chlorotrimethylsilane, *tert*-butylchlorodimethylsilane, chlorotributyltin, or iodine led to the successful formation of α-substituted-*β*-(ethoxy)vinylphosphonates **11**, **12**, **13**, or **14**, respectively, in 75−96% yields (eq 3) (entries 10−13). All compounds **11**−**14** have the *trans*-configuration



(3)

between the ethoxy and the phosphono group, which was determined on the basis of the phosphorus−*cis*-vinyl proton NMR coupling constants ($^3J_{P-H}$ = 7.6−17.1 Hz).[9]

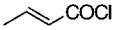
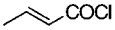
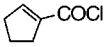
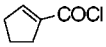
(6) 1,2-Migration of the ethylthio group has been found to take place when acyclic dithioacetal **1b** is added to a LTMP solution. See ref 2.

(7) For the addition of phosphorus dithio acid to **1c**, see: Kutyrev, G. A.; Kashina, N. V.; Ishmaeva, E. A.; Cherkasov, R. A.; Pudovic, A. N. *Zh. Obshch. Khim.* **1977**, *47*, 2460; *Chem. Abstr.* **1978**, *88*, 445.

(8) For the preparation of (*Z*)-2-(ethoxy)vinyllithium via halogen/metal exchange between (*Z*)-2-(ethoxy)vinyl bromide and butyllithium, and reaction with carbonyl compounds, see: Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.

(9) For the effects of stereochemistry on ^{1}H NMR parameters in substituted vinylphosphonates, see: (a) Xu, Y.; Flavin, M. T.; Xu, Z.-Q. *J. Org. Chem.* **1996**, *61*, 7697 and references therein. (b) Galvez-Ruano, E.; Bellanato, J.; Fernandez-Ibanez, M.; Sainz-Diaz, C. I.; Arias-Perez, M. S. *J. Mol. Struct.* **1986**, *142*, 397. (c) Williamson, M. P.; Castellano, S.; Griffin, C. E. *J. Phys. Chem.* **1968**, *72*, 175. Also see ref 2.

Table 2. Friedel−Crafts Acylation of Vinylphosphonates 1a, 2, 4, and 9 with Acid Chlorides[a]

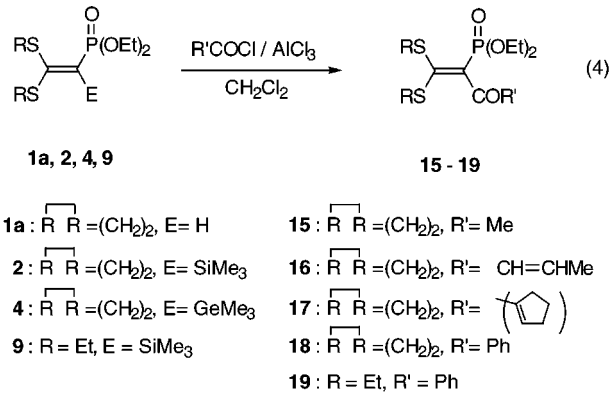
Entry	Starting Materials		Reaction Time / h	Product[b] (yield , %)
	Vinylphosphonate	Acid Chloride		
1[c]	**1a**	MeCOCl	3.0	**15** (38)
2	**2**	MeCOCl	2.0	**15** (89)
3	**4**	MeCOCl	1.0	**15** (55)
4	**2**		1.0	**16** (89)
5	**4**		1.0	**16** (91)
6	**2**		1.0	**17** (68)
7	**4**		1.0	**17** (91)
8	**2**	PhCOCl	1.0	**18** (83)
9	**4**	PhCOCl	1.0	**18** (89)
10[d]	**9**	PhCOCl	1.0	**19** (53)

[a] All reactions were carried out with $AlCl_3$ (2 equiv) and acid chloride (2 equiv) in CH_2Cl_2 at 0 °C unless otherwise noted. [b] Isolated yield. [c] $AlCl_3$ (4 equiv) and MeCOCl (4 equiv) were used. [d] $AlCl_3$ (4 equiv) and PhCOCl (4 equiv) were used.

These results have indicated that α-phosphonovinyl anions as well as various α-hetero-substituted vinyl anions can serve as important intermediates in organic synthesis.[10]

Functional Group Transformations at the α-Position of α-Functionalized Vinylphosphonates. The vinylphosphonates bearing electron-withdrawing substituents, such as ester and cyano groups at the α-position, have been widely used in organic synthesis.[1] These studies prompted us to develop multipurpose vinylphosphonates via the above prepared α-functionalized vinylphosphonates.

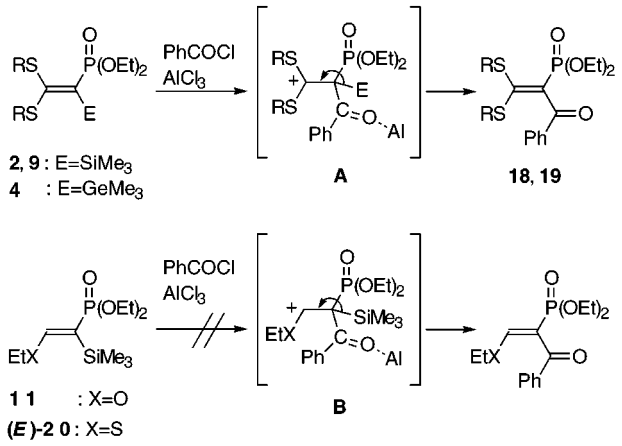
Our first attempt was to introduce an acyl group at the α-position of the phosphonoketene dithioacetals. The Friedel−Crafts reaction of **1a** with acetyl chloride (4 equiv)/$AlCl_3$ (4 equiv) in CH_2Cl_2 at 0 °C for 3.0 h gave the desired α-(acetyl)phosphonoketene dithioacetal **15** in modest yield (38%) (eq 4) (entry 1 in Table 2). To



(4)

(10) For the preparation of α-hetero (B, Si, O, S, Se, Te)-substituted vinyl carbanions and their synthetic application, for R_2B, see: (a) Pelter, A.; Smith, K.; Jones, K. D. *J. Chem. Soc. Perkin Trans. 1* **1992**, 747. For R_3Si: (b) Grobel, B.-Th.; Seebach, D. *Chem. Ber.* **1977**. *110*, 867. For RO (c) see ref 8. For RS, see: (d) Takeda, T.; Furukawa, H.; Fujimori, M.; Suzuki, K.; Fujiwara, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1863. For a review of synthesis and synthetic application of α-seleno and α-telluro vinyl carbanions, see: (e) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 410.

Scheme 1

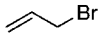


circumvent the low reactivity of **1a** toward an acetyl cation, α-silylated phosphonoketene dithioacetal **2** was used in this reaction instead of **1a**. This modification improved the yield of **15** up to 89% (entry 2). Similar treatment of **2** with various acid chlorides (2 equiv)/$AlCl_3$ (2 equiv) also led to the corresponding α-acylated phosphonoketene dithioacetals **16**−**18** in satisfactory yields (68−89%) (entries 4, 6, and 8).[11] The α-silylated acyclic dithioacetal **9** was also treated with benzoyl chloride (4 equiv)/$AlCl_3$ (4 equiv) to afford the expected benzoylated derivative **19** in a rather low yield (53%) (entry 10). To investigate an effect of α- and *β*-substituents of vinylphosphonates, the reaction of α-germylated dithioacetal, *β*-ethoxy- or *β*-ethylthio-α-silylated vinylphosphonates **4**, **11**, or **20** with acid chlorides was carried out. The dithioacetal **4**, as well as **2** and **9**, was treated with various acid chlorides under the conditions similar to those above to afford the corresponding α-acylated phosphonoketene dithioacetals **15**−**18** in comparably good yields (entries 3, 5, 7, and 9). On the other hand, the reaction of **11** or **20** with acid chlorides (acetyl or benzoyl chlorides) did not give the corresponding acylated products and starting **11** and **20** were recovered in all cases.

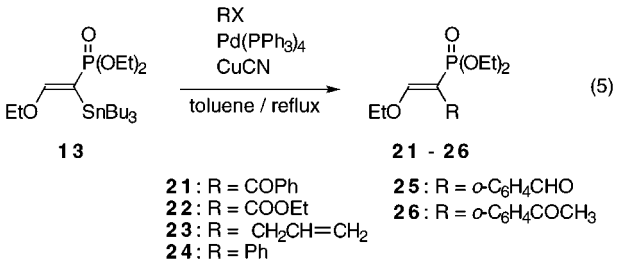
On the basis of these results, we have found that an α-silyl (or α-germyl) substituent and *β*,*β*-dithio substituents were required to achieve reasonable yields in the acylation of vinylphosphonates. This could be rationalized by the stability of the intermediates in these reactions. Cations **A**, arising from α-(silyl)- or α-(germyl)-phosphoketene dithioacetals **2**, **9**, or **4**, have higher stability than cations **B** from *β*-oxy (or *β*-thio) vinyl derivatives **11** (or **20**), because of *β*-silyl[12] (or germyl) and two α-thio[13] cation-stabilizing effects (Scheme 1).

To achieve the synthesis of α-acylated *β*-(ethoxy)-vinylphosphonates, which are not accessible by the Friedel−Crafts reaction or direct acylation of the α-carbanion from **1c** with acid chlorides,[14] we next applied the Stille cross-coupling[15] to *β*-ethoxy-α-(tributylstannyl)-vinylphosphonate **13**. The reaction of **13** with benzoyl chloride in the presence of $Pd(PPh_3)_4$ (4 mol %) and CuCN (9 mol %)[16] gave the desired α-benzoylated *β*-(ethoxy)-vinylphosphonate **21** in 87% yield (eq 5) (entry 1 in Table 3). Similar treatment of **13** with a wide variety of organic

Table 3. Palladium-Catalyzed Cross-Coupling Reaction of Vinylphosphonate 13 with Organic Halides[a]

Entry	RX	Molar ratio of RX / **13**	Reaction Time / h	Product[b] (yield , %)
1	PhCOCl	3.0	1.5	**21** (87)
2	EtOCOCl	3.0	1.5	**22** (76)
3		1.0	24.0	**23** (47)
4	PhI	1.2	2.5	**24** (35)
5	PhBr	1.4	5.0	**24** (79)
6	*o*-IC_6H_4CHO	1.2	4.0	**25** (97)
7	*o*-$IC_6H_4COCH_3$	1.2	10.0	**26** (62)

[a] All reactions were carried out with $Pd(PPh_3)_4$ (4 mol %) / CuCN (9 mol%) in toluene under reflux. [b] Isolated yield.



(5)

halides such as ethyl chloroformate, allyl bromide, and aryl halides successfully produced the corresponding cross-coupling products **22**−**26** in 47−97% yields (entries 2−7).[17] Thus, a new class of α-triorganometal-substituted vinylphosphonates was found to be utilized as a powerful tool for the synthesis of α-acyl-, aryl-, and ester-substituted vinylphosphonates.

Functional Group Transformations at the *β*-Position of α-Silylated Vinylphosphonate. Next, we examined the functional group transformation at the *β*-position of the α-silylated vinylphosphonate **11**. The Michael addition of an ethanethiolate anion with **11** followed by elimination of an ethoxide anion gave a 3.8:1 mixture of (*E*)- and (*Z*)-*β*-ethylthio-α-(trimethylsilyl)-vinylphosphonate (*E*)-**20** and (*Z*)-**20** in 96% yield (Scheme 2).[18] The structures of (*E*)-**20** and (*Z*)-**20** are assignable from their phosphorus−*cis*- and *trans*-vinyl proton coupling constant (see Experimental Section).[9a] Furthermore, α-(trimethylsilyl)vinylphosphonate **28**,[19] which is a versatile synthetic reagent serving as not only vinylphosphonate but also vinylsilane, was readily pre-

(11) Compound **18** was alternatively produced by direct acylation of the vinyl carbanion, generated from **1a** and LTMP in THF at −78 °C, with benzoyl chloride (2.0 equiv) in rather low yield (43%).

(12) See, for examples: (a) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. (b) Jarview, A. W. P. *Organomet. Chem. Rev., Sect. A* **1970**, *6*, 153. (c) Colvin, W. E. *Silicon in Organic Synthesis*; Butterworth: London, 1981; Chapter 3.

(13) See, for example; Price, C. C.; Oae, S. *Sulfur Bonding*; The Ronald Press Company: New York, 1962; Chapter 2.

(14) A direct acylation of the α-carbanion from **1c** with benzoyl chloride in THF at −78 °C were unsuccessful to give the compound **21**, since the product **21** underwent the Michael addition of the α-carbanion.

(15) For reviews, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803.

(16) For the effect of the Cu(I) salt cocatalyst on Stille cross-coupling reactions, see: Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.

(17) Compound **23** was alternatively produced in 94% yield by the reaction of α-carbanion from **1c** with allyl bromide in the presence of $CuBr-SMe_2$ (1.2 equiv) in THF at −78 °C to room temperature.

(18) A direct synthesis of **20** by the reaction of an α-carbanion of *β*-(ethylthio)vinylphosphonate with chlorotrimethylsilane cannot be achieved, since treatment of the vinylphosphonate with LDA generates a *β*-carbanion, but not the α-carbanion. See ref 2.

(19) For an alternative synthesis of **28**, see: Hong, S.; Chang, K.; Ku, B.; Oh, D. Y. *Tetrahedron Lett.* **1989**, *30*, 3307.

Scheme 2

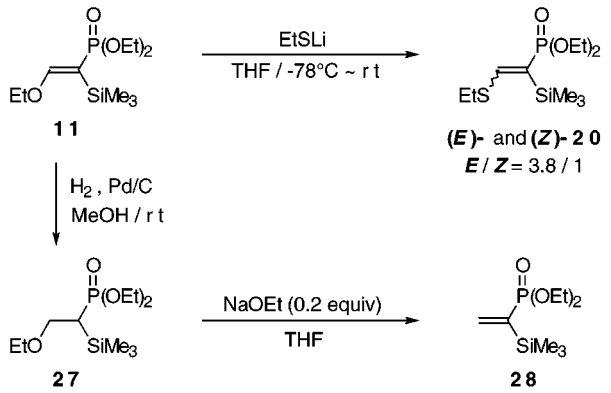


Table 4. Synthesis of β-Functionalized Vinylphosphonates[a]

Entry	Starting Materials		Reaction Time / h	Product [b] (yield , %)
	Vinylphosphonate	EX		
1[c]	**29**	PhCOCl	4.0	**31** (44)
2[c]	**30**	PhCOCl	4.0	**32** (36)
3	**30**	Me_3SiOTf	0.17	**33** (30)
4	**30**	Bu_3SnCl	3.0	**34** (64)

[a] All reactions were carried out at -78 °C in THF. [b] Isolated yield.

[c] $CuBr{\bullet}SMe_2$ (1.1 equiv) was used.

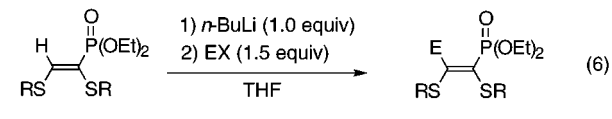
Table 5. Palladium-Catalyzed Cross-Coupling Reaction of Vinylphosphonate 34 with Organic Halides[a]

Entry	EX	Reaction Time / h	Product [b] (yield , %)
1	PhCOCl	1.0	**32** (74)
2	$CH_3CH{=}CHCOCl$	1.5	**35** (66)
3	$CH_2{=}CHCH_2Cl$	1.5	**36** (86)

[a] All reactions were carried out with $Cl_2Pd(PPh_3)_2$ (4 mol%) / CuCN (14 mol %) at 50 °C in toluene. [b] Isolated yield.

pared via **11**. Hydrogenation of **11** over Pd/C at atmospheric pressure gave **27**, followed by treatment of **27** with NaOEt (0.2 equiv) producing the desired **28** in 80% yield.

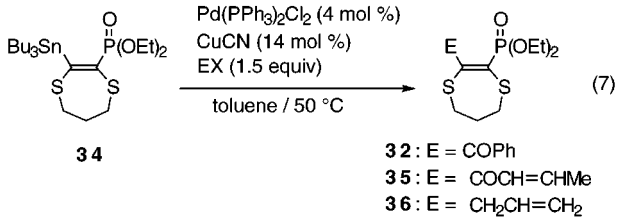
Synthesis of β-Functionalized Vinylphosphonates. We have also explored the possibility of functionalization at the β-position of 1,2-dithio-substituted vinylphosphonates **29** and **30**.[2] The β-(phosphono)vinyl anion,[2] generated from 1,2-bis(ethylthio)vinylphosphonate **29** and *n*-butyllithium at −78 °C, reacted with benzoyl chloride to give the expected β-benzoylated vinylphosphonate **31** in modest yield (44%)(eq 6) (entry 1 in Table 4). Similar treatment of the 1,2-(trimethyl-



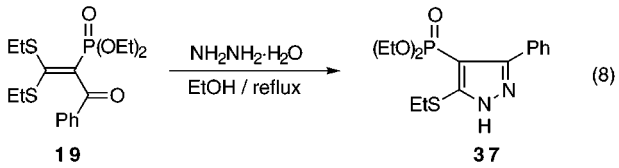
29: R = Et
30: R R = $(CH_2)_3$

31: R = Et , E = PhCO
32: R R = $(CH_2)_3$, E = COPh
33: R R = $(CH_2)_3$, E = $SiMe_3$
34: R R = $(CH_2)_3$, E = $SnBu_3$

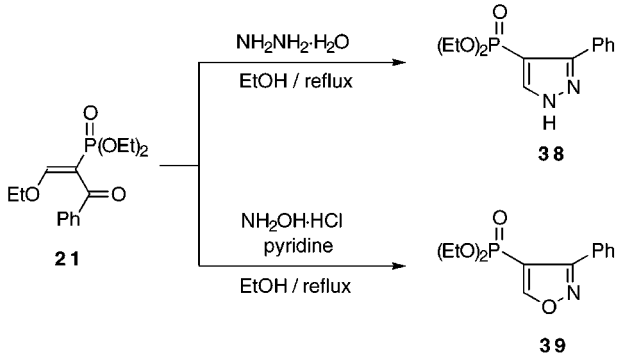
enedithio)-2-phosphonovinyl anion with electrophiles such as benzoyl chloride, trimethylsilyl triflate, and tributyltin chloride led to the corresponding β-functionalized vinylphosphonates **32**−**34** in low to moderate yields (30−64%) (entries 2−4). To test the synthetic usefulness of the functionalized vinylphosphonates, the 2-stannylated 1,2-(dithio)vinylphosphonate **34** analogous to the 1-stannylated vinylphosphonate **13** was subjected to the palladium-catalyzed cross-coupling reaction with several organic halides to give the corresponding 2-substituted 1,2-(dithio)vinylphosphonates **32**, **35**, and **36** in 66−86% yields (eq 7) (Table 5).



Synthesis of Heterocyclic Compounds. Some of α-acyl-β-hetero-substituted vinylphosphonates prepared above were tried to be utilized for the synthesis of phosphono group-containing heterocyclic compounds. α-Acylated vinylphosphonates **19** and **21** were transformed into phosphono-containing pyrazoles **37**[20] and **38**[21] in 82% and 83% yields, respectively, by refluxing with hydrazine monohydrate in EtOH (eq 8 and Scheme 3).



Scheme 3

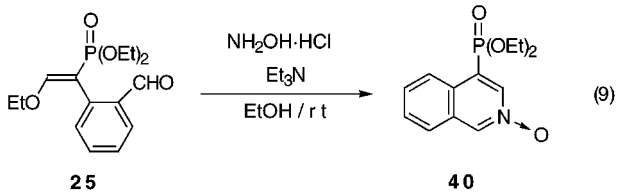


The reaction of **21** with hydroxylamine proceeded under reflux to give 4-(phosphono)isoxazole **39** in 61% yield (Scheme 3). Interestingly, the use of **25** in the reaction with hydroxylamine under mild conditions (room temperature, 60 h) resulted in 4-(phosphono)isoquinoline *N*-oxide **40** in 85% yield (eq 9).[22] These results have shown that α-keto-β-hetero-substituted vinylphosphonates can be utilized for the synthesis of phosphono-containing heterocyclic compounds.

(20) For the cyclization of ketene dithioacetals to thiopyrazoles, see: (a) Taylor, E. C.; Purdum, W. R. *Heterocycles* **1977**, *6*, 1865. (b) Singh, G.; Deb, B.; Ila, H.; Junjappa, H. *Synthesis* **1987**, 286.

(21) For an alternative synthesis of **38**, see: Aboujaoude, E. E.; Collignon, N.; Savignac, P. *Tetrahedron* **1985**, *41*, 427.

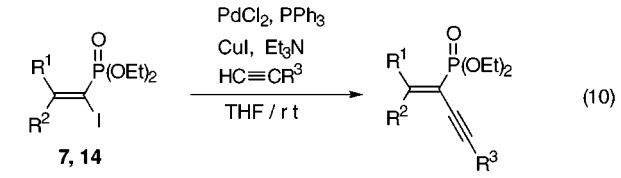
(22) It is well-known that oximes undergo intramolecular Michael addition to electronegative olefins to give cyclic nitrones, see, for example; Minami, T.; Isonaka, T.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1993**, *58*, 7009 and references therein. The spectral data of **40** were consistent with the structure described for eq 9 (see Experimental Section).



(9)

25 **40**

Synthesis of α-Alkynylvinylphosphonates. The development of new classes of enyne systems has attracted considerable attention from organic chemists because the enynes show interesting chemical reactivities[23] and biological reactivities.[24] From this point of view, we have proposed the synthesis a novel kind of enyne compound containing phosphorus and hetero functional groups. The palladium-mediated cross-coupling reaction[25] of iodo-substituted vinylphosphonates **7** and **14** with phenylacetylene in THF at room temperature afforded the desired enyne compounds **41** and **44** in 73% and 79% yields, respectively (eq 10) (entries 1 and 4 in Table 6).



(10)

7, 14

7: R^1 R^2 = $S(CH_2)_2S$
14: R^1 = H, R^2 = OEt

41: R^1 R^2 = $S(CH_2)_2S$, R^3 = Ph
42: R^1 R^2 = $S(CH_2)_2S$, R^3 = TMS
43: R^1 R^2 = $S(CH_2)_2S$, R^3 = CH_2OTHP
44: R^1 = H, R^2 = OEt, R^3 = Ph

Similar palladium-mediated reaction of **7** with (trimethylsilyl)acetylene or 3-(tetrahydro-2-pyranyloxy)propyne at room temperature also produced the corresponding enyne products **42** or **43**, respectively, in good yields (entries 2 and 3). Furthermore, oxidative homo-coupling of terminal alkyne **45** derived from **42** produced the expected diene−diyne derivative **46** in excellent yield (93%) (Scheme 4).[26]

Conclusion. We note the following results from this investigation: (1) α- and β-(phosphono)vinyl anions were successfully trapped with various electrophiles to give α- and β-functionalized vinylphosphonates in good yields; (2) a new class of α- and β-(triorganometal)-substituted vinylphosphonates were applied to the Friedel−Crafts acylation, palladium-mediated cross-coupling reaction, etc., to lead to versatile functional group-containing vinylphosphonates which are not easily accessible; (3) functionalized heterocyclic compounds bearing the phosphono group were synthesized.

Experimental Section

Materials. Dichloromethane was distilled from P_2O_5. THF was distilled from sodium benzophenone ketyl in a recycling still. Diisopropylamine (DIA), 2,2,6,6-tetramethylpiperidine (TMP), and triethylamine (Et_3N) were refluxed with CaH_2 and then distilled. A commercial solution of *n*-BuLi (3.04, 1.68, 1.64, or 1.60 M in hexane) was used. The starting materials **1a**, **1b**, **29**, and **30** were prepared according to the established procedures.[2] Diethyl phosphonoacetaldehyde diethyl acetal was prepared in 89% yield by the Arbuzov reaction of bromoacetaldehyde diethyl acetal with triethyl phosphite at 160−165 °C.

General. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, operating ^{1}H NMR at 59.8 or 500.00 MHz, and ^{13}C NMR at 15.0 or 125.65 MHz, with Me_4Si as an internal standard. Melting points were measured in open capillary tubes and are uncorrected.

Preparation of Diethyl (*E*)-2-(Ethoxy)vinylphosphonate (1c). To a solution of LDA, generated in situ from DIA (2.7 g, 27 mmol) and *n*-BuLi (3.04 M in hexane, 7.8 mL, 24 mmol) in THF (50 mL) at −78 °C for 45 min, was added dropwise diethyl phosphonoacetaldehyde diethyl acetal (6.0 g, 24 mmol) in THF (10 mL), and the reaction mixture was stirred at this temperature for 1.0 h. The reaction was quenched by the addition of phosphate buffer (pH = 7), and the organic layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was distilled under reduced pressure (bp 100 °C/1 mmHg) to give **1c** (4.8 g, 97%) as a colorless oil; IR (neat) 1610, 1240 cm^{-1}; ^{1}H NMR δ 1.33 (6 H, t, J = 7.0 Hz), 1.34 (3 H, t, J = 7.0 Hz), 3.91 (2 H, q, J = 7.0 Hz), 4.08 (4 H, dq, $^3J_{P-H}$ = 2.5 Hz, J = 7.0 Hz), 4.71 (1 H, dd, J = 13.7 Hz, $^2J_{P-H}$ = 10.1 Hz), 7.21 (1 H, dd, J = 13.7 Hz, $^3J_{P-H}$ = 11.6 Hz); ^{13}C NMR δ 14.4, 16.4 (d, $^3J_{P-C}$ = 6.2 Hz), 61.5 (d, $^2J_{P-C}$ = 5.2 Hz), 66.3, 88.0 (d, $^1J_{P-C}$ = 201.5 Hz), 163.3 (d, $^2J_{P-C}$ = 21.6 Hz); MS *m*/*z* 208 (M^+). Anal. Calcd for $C_8H_{17}O_4P$: C, 46.15; H, 8.23. Found: C, 46.27; H, 8.34.

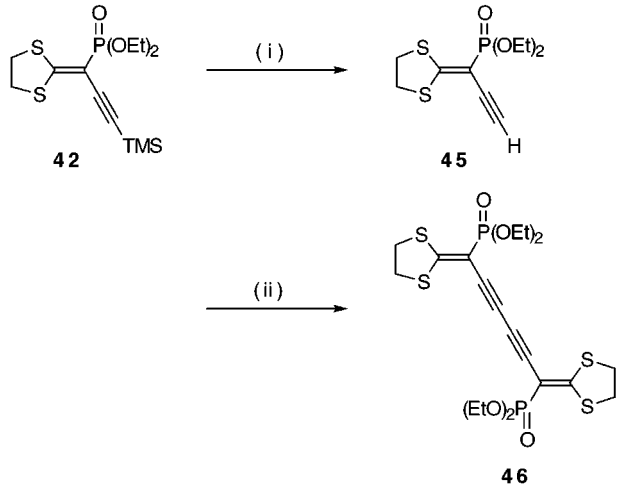
General Procedure for the Synthesis of α-Functionalized Phosphonoketene Dithioacetals 2−8. To a solution

Table 6. Palladium-Mediated Cross-Coupling Reaction of 7 and 14 with Terminal Acetylenes[a]

Entry[b]	Starting Material		Time / h	Product[c]
	Vinylphosphonate	R^3		(Yield , %)
1	**7**	Ph	4 8	**4 1** (73)
2	**7**	$SiMe_3$	6 0	**4 2** (83)
3	**7**	CH_2OTHP	2 4	**4 3** (69)
4[d]	**14**	Ph	1 2	**4 4** (79)

[a] All reactions were carried out in THF at room temperature. [b] $PdCl_2$ (18 mo l%), PPh_3 (46 mol %) and CuI (1.2 equiv) were used unless otherwise noted. [c] Isolated yield. [d] $Pd(PPh_3)_4$ (2 mol %) and CuCN (6 mol%) were used.

Scheme 4



(i) TBAF (0.2 equiv), THF, 50 °C, 10 min, 98%. (ii) $Cu(OAc)_2$ (4.4 equiv), THF-pyridine-EtOH, 70 °C, 30 min, 93 %.

(23) See, for examples, (a) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

(24) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68.

(25) For palladium-mediated cross-coupling reactions between alkenyl halides and terminal alkynes, see, for example; Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.

(26) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.4, p 521.

of LTMP, generated in situ from TMP (0.18 g, 1.3 mmol) and *n*-BuLi (1.64 M in hexane, 0.73 mL, 1.2 mmol) in THF (3 mL) at −78 °C for 40 min, was added dropwise **1a** (0.25 g, 1.0 mmol) in THF (1.5 mL) at −78 °C, and the mixture was stirred for 50 min. An electrophile in THF (1.5 mL) was added dropwise to the mixture, and the reaction mixture was stirred for 1.0−3.0 h at this temperature. After similar workup, the residue was chromatographed on silica gel (AcOEt:hexane = 4:1) to give **2**−**8**. The reaction conditions and yields of **2**−**8** were summarized in Table 1. The compounds **2** and **4**−**7** have the following properties. The properties for compounds **3** and **8** are provided in the Supporting Information.

Diethyl 1-(trimethylsilyl)-1-(1,3-dithiolan-2-ylidene)-methylphosphonate (2): colorless oil; IR (neat) 1460, 1235 cm^{-1}; ^1H NMR δ 0.31 (9 H, s), 1.31 (6 H, t, J = 7.0 Hz), 3.37 (4 H, brs), 4.04 (4 H, dq, J = 7.0, 7.0 Hz); ^{13}C NMR δ 0.8, 16.2 (d, $^3J_{P-C}$ = 6.0 Hz), 37.6, 38.2, 61.0 (d, $^2J_{P-C}$ = 5.2 Hz), 109.3 (d, $^1J_{P-C}$ = 145.2 Hz), 172.1 (d, $^2J_{P-C}$ = 3.5 Hz); MS m/z 326 (M^+). Anal. Calcd for $C_{11}H_{23}O_3PS_2Si$: C, 40.47; H, 7.10. Found: C, 40.45; H, 7.19.

Diethyl 1-(trimethylgermyl)-1-(1,3-dithiolan-2-yliden-e)methylphosphonate (4): colorless crystal; mp 42.5−44.5 °C; IR (KBr) 1475, 1235 cm^{-1}; ^1H NMR δ 0.46 (9 H, s), 1.30 (6 H, t, J = 7.0 Hz), 3.27−3.51 (4 H, m), 4.04 (4 H, dq, $^3J_{P-H}$ = 7.0 Hz, J = 7.0 Hz); ^{13}C NMR δ 1.0, 16.2 (d, $^3J_{P-C}$ = 6.2 Hz), 37.3, 38.5, 60.9 (d, $^2J_{P-C}$ = 4.9 Hz), 110.4 (d, $^1J_{P-C}$ = 153.0 Hz), 168.9 (d, $^2J_{P-C}$ = 6.2 Hz). Anal. Calcd for $C_{11}H_{23}O_3PS_2Ge$: C, 35.61; H, 6.25. Found: C, 35.72; H, 6.21.

Diethyl 1-(triphenylstannyl)-1-(1,3-dithiolan-2-yliden-e)methylphosphonate (5): colorless crystal; mp 137.5−138.5 °C; IR (KBr) 1470, 1240 cm^{-1}; ^1H NMR δ 1.02 (6 H, t, J = 7.0 Hz), 2.88−3.48 (4 H, m), 3.52−4.08 (4 H, m), 7.04−7.76 (15 H, m); ^{13}C NMR δ 15.9 (d, $^3J_{P-C}$ = 6.9 Hz), 38.1, 39.4, 61.2 (d, $^2J_{P-C}$ = 5.2 Hz), 107.7 (d, $^1J_{P-C}$ = 156.4 Hz), 128.2, 128.7, 136.9, 139.5 (d, $^3J_{P-C}$ = 1.5 Hz); MS m/z 603 (M^+). Anal. Calcd for $C_{26}H_{29}O_3PS_2Sn$: C, 51.76; H, 4.84. Found: C, 51.42; H, 4.97.

Diethyl 1-(methylthio)-1-(1,3-dithiolan-2-ylidene)-methylphosphonate (6): colorless oil; IR (neat) 1470, 1240 cm^{-1}; ^1H NMR δ 1.35 (3 H, t, J = 7.2 Hz), 1.36 (3 H, t, J = 7.0 Hz), 3.14 (3 H, s), 3.38−3.40 (2 H, m), 3.59−3.62 (2 H, m), 4.06−4.17 (4 H, m); ^{13}C NMR δ 16.3 (d, $^3J_{P-C}$ = 6.2 Hz), 18.7, 36.3, 41.0, 62.2 (d, $^2J_{P-C}$ = 6.3 Hz), 102.1 (d, $^1J_{P-C}$ = 203.7 Hz), 175.3 (d, $^2J_{P-C}$ = 24.8 Hz). Anal. Calcd for $C_9H_{17}O_3PS_3$: C, 35.98; H, 5.70. Found: C, 36.03; H, 5.74.

Diethyl 1-iodo-1-(1,3-dithiolan-2-ylidene)methylphosphonate (7): yellow crystal; mp 82−84 °C; IR (KBr) 1480, 1220 cm^{-1}; ^1H NMR δ 1.36 (6 H, t, J = 7.0 Hz), 3.46 (2 H, dd, J = 6.5 Hz, J = 6.0 Hz), 3.86 (2 H, dd, J = 6.5 Hz, J = 6.0 Hz), 4.03−4.18 (4 H, m); ^{13}C NMR δ 16.2 (d, $^3J_{P-C}$ = 7.2 Hz), 37.2, 42.5, 59.3 (d, $^1J_{P-C}$ = 200.5 Hz), 62.7 (d, $^2J_{P-C}$ = 5.2 Hz), 167.4 (d, $^2J_{P-C}$ = 16.5 Hz). Anal. Calcd for $C_8H_{14}O_3PS_2I$: C, 25.27; H, 3.71. Found: C, 25.28; H, 3.72.

General Procedure for the Synthesis of α-Functionalized Phosphonoketene Dithioacetals 9 and 10. A solution of LTMP (1.2 mmol) in THF (3 mL) was added dropwise to a solution of **1b** (0.28 g, 1.0 mmol) and an electrophile (1.5 mmol) in THF (3 mL) *via cannula* at −78 °C, and the reaction mixture was stirred for 1.5 h at this temperature. After similar workup, the residue was chromatographed on silica gel (AcOEt:hexane = 1:1) to give **9** or **10**. The reaction conditions and yields of **9** and **10** are summarized in Table 1. The compounds **9** and **10** have the following properties.

Diethyl 1-[bis(ethylthio)methylene]-1-(trimethylsilyl)-methylphosphonate (9): colorless oil; IR (neat) 1460, 1240 cm^{-1}; ^1H NMR δ 0.25 (9 H, d, J = 4.3 Hz), 1.19−1.30 (12 H, m), 2.75−2.93 (4 H, m), 3.98−4.10 (4 H, m); ^{13}C NMR δ 2.3, 14.1, 14.2, 16.2 (d, $^3J_{P-C}$ = 7.2 Hz), 30.1, 30.4, 61.1 (d, $^2J_{P-C}$ = 6.2 Hz), 134.3 (d, $^1J_{P-C}$ = 136.6 Hz), 164.7. Compound **9** was used without further purification in the next step due to its instability.

Diethyl 1-(tributylstannyl)-1-[bis(ethylthio)methylene]methylphosphonate (10): colorless oil; IR (neat) 2950, 1460, 1230 cm^{-1}; ^1H NMR δ 0.90 (9 H, t, J = 7.4 Hz), 1.01−1.17 (6 H, m), 1.26−1.37 (12 H, m), 1.32 (6 H, t, J = 7.0 Hz), 1.44−1.59 (6 H, m), 2.88−2.95 (4 H, m), 4.02−4.13 (4 H, m); ^{13}C NMR δ 13.8, 14.3, 14.5, 14.8, 16.5 (d, $^3J_{P-C}$ = 6.2 Hz), 27.4, 29.0, 30.2, 30.4, 61.3 (d, $^2J_{P-C}$ = 6.2 Hz), 140.9 (d, $^1J_{P-C}$ = 133.5 Hz), 159.5. Anal. Calcd for $C_{22}H_{47}O_3PS_2Sn$: C, 46.08; H, 8.26. Found: C, 45.72; H, 8.05.

General Procedure for the Synthesis of α-Functionalized Vinylphosphonates 11−14. To a solution of LDA (6.0 mmol) in THF (8.0 mL) was added dropwise at −78 °C a solution of **1c** (1.0 g, 5.0 mmol) in THF (4.0 mL), and the mixture was stirred for 1.0 h. An electrophile was added dropwise to the mixture, and the reaction mixture was stirred for 1.5−13.0 h at −78 °C to room temperature. After similar workup, the residue was chromatographed on silica gel (AcOEt:hexane = 1:1) to give **11**−**14**. The reaction conditions and yields of **11**−**14** are summarized in Table 1. The compounds **11**, **13**, and **14** have the following properties. The properties for compound **12** are provided in the Supporting Information.

Diethyl (*E*)-2-ethoxy-1-(trimethylsilyl)vinylphosphonate (11): colorless oil; IR (neat) 1600, 1420, 1225 cm^{-1}; ^1H NMR δ 0.18 (9 H, s), 1.30 (9 H, t, J = 7.1 Hz), 3.71−4.26 (4 H, m), 4.03 (2 H, q, J = 7.1 Hz), 7.47 (1 H, d, $^3J_{P-H}$ = 16.4 Hz); ^{13}C NMR δ 0.5, 15.1, 16.2 (d, $^3J_{P-C}$ = 6.0 Hz), 60.6 (d, $^2J_{P-C}$ = 5.1 Hz), 69.6, 98.8 (d, $^1J_{P-C}$ = 155.1 Hz), 170.1 (d, $^2J_{P-C}$ = 15.5 Hz); MS m/z 280 (M^+). Anal. Calcd for $C_{11}H_{25}O_4PSi$: C, 8.99; H, 47.12. Found: C, 8.75; H, 46.92.

Diethyl (*Z*)-1-(tributylstannyl)-2-(ethoxy)vinylphosphonate (13): colorless oil; IR (neat) 2925, 1590, 1200 cm^{-1}; ^1H NMR δ 0.89 (9 H, t, J = 7.4 Hz), 0.92−1.07 (5 H, m), 1.26−1.35 (16 H, m) 1.41−1.57 (6 H, m), 3.94−4.06 (6 H, m), 7.51 (1 H, d, $^3J_{P-H}$ = 15.0 Hz); ^{13}C NMR δ 10.7 (d, $^3J_{P-C}$ = 2.1 Hz), 13.7, 15.3, 16.4 (d, $^3J_{P-C}$ = 7.2 Hz), 27.3, 28.9, 60.7 (d, $^2J_{P-C}$ = 5.2 Hz), 68.9, 98.0 (d, $^1J_{P-C}$ = 157.2 Hz), 167.8 (d, $^2J_{P-C}$ = 18.6 Hz). Anal. Calcd for $C_{20}H_{43}O_4PSn$: C, 48.31; H, 8.72. Found: C, 48.38; H, 8.72.

Diethyl (*Z*)-2-ethoxy-1-(iodo)vinylphosphonate (14): yellow oil; IR (neat) 1610, 1395, 1215 cm^{-1}; ^1H NMR δ 1.35−1.41 (9 H, m), 4.01−4.15 (4 H, m), 4.21 (2 H, q, J = 7.0 Hz), 7.38 (1 H, d, $^3J_{P-H}$ = 7.6 Hz); ^{13}C NMR δ 15.3, 16.2 (d, $^3J_{P-C}$ = 7.3 Hz), 55.4 (d, $^1J_{P-C}$ = 205.86 Hz), 62.4 (d, $^2J_{P-C}$ = 5.2 Hz), 70.8, 164.2 (d, $^2J_{P-C}$ = 29.0 Hz); MS m/z 334 (M^+). Anal. Calcd for $C_8H_{16}O_4PI$: C, 28.76; H, 4.83. Found: C, 28.81; H, 4.86.

General Procedure for the Friedel−Crafts Acylation of Vinylphosphonates 1a, 2, 4, and 9. To a suspension of $AlCl_3$ (0.27 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise an acid chloride (2.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 0.5 h. A solution of a vinylphosphonate **1a**, **2**, **4** or **9** in CH_2Cl_2 (5 mL) was added to the mixture, and the reaction mixture was stirred for 1−3 h. After similar workup as above, the residue was chromatographed on silica gel (AcOEt:hexane = 4:1 or 1:1) to give **15**−**19**. The reaction conditions and yields of **15**−**19** are summarized in Table 2. The compound **19** has the following properties. The properties for compounds **15**−**18** are provided in the Supporting Information.

Diethyl 1-benzoyl-1-[bis(ethylthio)methylene]methylphosphonate (19): colorless crystal; mp 66.5−68.0 °C; IR (KBr) 1670, 1520, 1250 cm^{-1}; ^1H NMR δ 1.04 (3 H, t, J = 7.4 Hz), 1.20 (6 H, t, J = 7.0 Hz), 1.38 (3 H, t, J = 7.4 Hz), 2.74 (2 H, q, J = 7.4 Hz), 2.94 (2 H, q, J = 7.4 Hz), 4.01−4.16 (4 H, m), 7.45−7.48 (2 H, m), 7.55−7.59 (1 H, m), 7.99−8.00 (2 H, m); ^{13}C NMR δ 14.7, 14.9, 16.0 (d, $^3J_{P-C}$ = 6.2 Hz), 28.9, 62.7 (d, $^2J_{P-C}$ = 6.2 Hz), 128.5, 129.4, 133.4, 136.5, 138.1 (d, $^1J_{P-C}$ = 175.9 Hz), 153.2 (d, $^2J_{P-C}$ = 7.3 Hz), 192.2 (d, $^2J_{P-C}$ = 10.3 Hz); MS m/z 388 (M^+). Anal. Calcd for $C_{17}H_{25}O_4PS_2$: C, 52.56; H, 6.49. Found: C, 52.70; H, 6.51.

General Procedure for the Palladium-Catalyzed Cross-Coupling Reaction of Vinylphosphonate 13 with Organic Halides. To a solution of **13** (0.40 g, 0.80 mmol) and an organic halide in toluene (12 mL) were added $Pd(PPh_3)_4$ (38 mg, 4 mol %) and CuCN (6.8 mg, 9 mol %) at room temperature, and the reaction mixture was refluxed for 1.5−24 h. The reaction was quenched by the addition of phosphate buffer (pH = 7), filtrated through a Celite pad. The organic layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chro-

matographed on silica gel (AcOEt:hexane = 4:1) to give **21**−**26**. The reaction conditions and yields of **21**−**26** are summarized in Table 3. The compounds **21**, **22**, and **25** have the following properties. The properties for compounds **23**, **24**, and **26** are provided in the Supporting Information.

Diethyl (*E*)-1-benzoyl-2-(ethoxy)vinylphosphonate (21): colorless oil; IR (neat) 1600, 1250 cm^{-1}; ^1H NMR δ 1.15 (3 H, t, J = 7.3 Hz), 1.29 (6 H, t, J = 7.0 Hz), 4.01 (2 H, q, J = 7.0 Hz), 4.13 (4 H, dq, J = 7.0 Hz, $^2J_{P-H}$ = 7.0 Hz), 7.42−7.45 (2 H, m), 7.47 (1 H, d, $^3J_{P-H}$ = 11.5 Hz), 7.53−7.56 (1 H, m), 7.89 (2 H, m); ^{13}C NMR δ 15.0, 16.1 (d, $^3J_{P-C}$ = 7.3 Hz), 62.2 (d, $^2J_{P-C}$ = 5.2 Hz), 71.4, 106.3 (d, $^1J_{P-C}$ = 188.1 Hz), 128.1, 129.2, 132.9, 137.5 (d, $^3J_{P-C}$ = 4.1 Hz), 163.3 (d, $^2J_{P-C}$ = 20.6 Hz), 192.2 (d, $^2J_{P-C}$ = 4.1 Hz); MS m/z 312 (M^+). Compound **21** was used in the reaction with hydrazine or hydroxylamine without further purification.

Ethyl (2*E*)-3-ethoxy-2-(diethylphosphono)propenoate (22): colorless oil; IR (neat) 1720, 1605, 1190 cm^{-1}; ^1H NMR δ 1.30 (3 H, t, J = 7.0 Hz), 1.33 (6 H, t, J = 7.0 Hz), 1.41 (3 H, t, J = 7.0 Hz), 4.04−4.17 (4 H, m), 4.23 (2 H, q, J = 7.0 Hz), 4.25 (2 H, q, J = 7.0 Hz), 7.58 (1 H, d, $^3J_{P-H}$ = 11.0 Hz); ^{13}C NMR δ 14.1, 15.2, 16.2 (d, $^3J_{P-C}$ = 6.2 Hz), 60.3, 62.1 (d, $^2J_{P-C}$ = 5.3 Hz), 73.0, 98.1 (d, $^2J_{P-C}$ = 194.4 Hz), 129.5 (d, $^1J_{P-C}$ = 261.5 Hz), 170.3 (d, $^2J_{P-C}$ = 22.6 Hz). Anal. Calcd for $C_{11}H_{21}O_6P$: C, 47.14; H, 7.55. Found: C, 47.25; H, 7.47.

Diethyl (*E*)-2-ethoxy-1-(2′-formylphenyl)vinylphosphonate (25): yellow oil; IR (neat) 1695, 1620, 1220 cm^{-1}; ^1H NMR δ 1.23 (3 H, t, J = 7.5 Hz), 1.26 (6 H, t, J = 7.0 Hz), 4.04 (2 H, q, J = 7.5 Hz), 4.05−4.11 (4 H, m), 7.35−7.44 (3 H, m), 7.53−7.60 (1 H, m), 7.95 (1 H, d, $^3J_{P-H}$ = 8.0 Hz), 10.08 (1 H, s); ^{13}C NMR δ 15.2, 16.2 (d, $^3J_{P-C}$ = 7.3 Hz), 61.9 (d, $^2J_{P-C}$ = 6.3 Hz), 70.7, 101.7 (d, $^1J_{P-C}$ = 198.4 Hz), 127.3, 127.9 (d, $^4J_{P-C}$ = 2.1 Hz), 130.9 (d, $^3J_{P-C}$ = 3.1 Hz), 133.7, 134.0 (d, $^2J_{P-C}$ = 6.2 Hz), 136.1 (d, $^3J_{P-C}$ = 5.2 Hz), 160.0 (d, $^2J_{P-C}$ = 26.8 Hz), 192.2; MS m/z 312 (M^+). Compound **25** was used in the reaction with hydroxylamine without further purification.

Reaction of 11 with Lithium Ethanethiolate. A solution of lithium ethanethiolate, generated in situ from ethanethiol (40 mg, 0.64 mmol) in THF (3.0 mL) and *n*-BuLi (1.60 M in hexane, 0.40 mL, 0.64 mmol) at −78 °C for 1.0 h, was added dropwise to a solution of **11** (0.15 g, 0.53 mmol) in THF (2.0 mL) *via cannula*. After being stirred for 10 min at this temperature, the mixture was then allowed to warm to room temperature and stirred for 3.0 h. After similar workup, the residue was purified by preparative TLC (AcOEt:hexane = 2:1) to give diethyl (*E*)- and (*Z*)-2-(ethylthio)-1-(trimethylsilyl)-vinylphosphonates [(*E*)-**20** (0.12 g, 76%) and (*Z*)-**20** (33 mg, 20%)].

(*E*)-20: colorless oil; R_f 0.43 (AcOEt:hexane = 5:1); IR (neat) 1243, 1025 cm^{-1}; ^1H NMR δ 0.27 (9 H, s), 1.30 (6 H, t, J = 7.0 Hz), 1.35 (3 H, t, J = 7.4 Hz), 2.87 (2 H, q, J = 7.4 Hz), 3.97−4.07 (4 H, m), 8.11 (1 H, d, $^3J_{P-H}$ = 31.8 Hz); ^{13}C NMR δ −0.7 (d, $^3J_{P-C}$ = 3.1 Hz), 15.6, 16.4 (d, $^3J_{P-C}$ = 6.2 Hz), 29.6, 61.2 (d, $^2J_{P-C}$ = 5.2 Hz), 122.1 (d, $^1J_{P-C}$ = 138.6 Hz), 162.1 (d, $^2J_{P-C}$ = 4.1 Hz).

(*Z*)-20: colorless oil; R_f 0.64 (AcOEt:hexane = 5:1); IR (neat) 1245, 1027 cm^{-1};^1H NMR δ 0.19 (9 H, s), 1.32−1.35 (9 H, m), 2.81 (2 H, q, J = 7.7 Hz), 4.08 (4 H, q, J = 7.0 Hz), 7.35 (1 H, d, $^3J_{P-H}$ = 55.6 Hz); ^{13}C NMR δ 0.6 (d, $^3J_{P-C}$ = 2.0 Hz), 15.3, 16.4 (d, $^3J_{P-C}$ = 7.3 Hz), 29.8, 61.2 (d, $^2J_{P-C}$ = 6.2 Hz), 123.8 (d, $^1J_{P-C}$ = 143.6 Hz), 157.9 (d, $^2J_{P-C}$ = 5.2 Hz); MS m/z 296 (M^+). Compounds (*E*)- and (*Z*)-**20** gave no satisfactory elemental analysis data due to their high viscosity.

Synthesis of Diethyl 1-(Trimethylsilyl)vinylphosphonate (28) via 11. Hydrogenation of **11** (1.0 g, 3.6 mmol) was accomplished under a hydrogen atmosphere (balloon) at room temperature for 48 h in MeOH (8.0 mL) containing palladium on activated carbon (10%, 0.50 g). After removal of the catalyst by filtration and concentration of the filtrate in vacuo, the residue was distilled under reduced pressure to give **27** (1.0 g, 99%) as a colorless oil; bp 95−98 °C/0.6 mmHg; IR (neat) 1245, 1030 cm^{-1}; ^1H NMR δ 0.16 (9 H, s), 1.18 (3 H, t, J = 7.0 Hz), 1.31 (6 H, t, J = 7.0 Hz), 1.59 (1 H, dt, $^2J_{P-H}$ = 23.8 Hz, J = 6.7 Hz), 3.45 (2 H, q, J = 7.0 Hz), 3.62−3.79 (2 H, m), 4.02−4.12 (4 H, m); ^{13}C NMR δ −0.8 (d, $^3J_{P-C}$ = 3.1 Hz), 15.1, 16.4 (d, $^3J_{P-C}$ = 7.0 Hz), 28.1 (d, $^1J_{P-C}$ = 125.0 Hz), 61.0 (d, $^2J_{P-C}$ = 4.1 Hz), 66.1, 67.1 (d, $^2J_{P-C}$ = 4.1 Hz).

To a solution of **27** (0.83 g, 3.0 mmol) in THF (5 mL) was added NaOEt (40 mg, 0.59 mmol) in THF (10 mL) at room temperature. After the reaction mixture was stirred for 10 min at this temperature, the reaction was quenched by the addition of phosphate buffer (pH = 7). After usual workup, the residue was chromatographed on silica gel (AcOEt:hexane = 2:1) to give a colorless oil (0.56 g, 80%), whose structure was identified as **28** by comparison of spectral data with those of an authentic sample:[19] IR (neat) 1250, 1030 cm^{-1}; ^1H NMR δ 0.20 (9 H, s), 1.32 (3 H, t, J = 7.0 Hz), 4.07 (2 H, q, J = 7.0 Hz), 6.34 (1 H, dd, $^3J_{P-H}$ = 58.9 Hz, J = 3.4 Hz), 6.79 (1 H, dd, $^3J_{P-H}$ = 34.5 Hz, J = 3.4 Hz); ^{13}C NMR δ −1.3 (d, $^3J_{P-C}$ = 8.5 Hz), 16.3 (d, $^3J_{P-C}$ = 7.3 Hz), 61.3 (d, $^2J_{P-C}$ = 5.2 Hz), 142.1 (d, $^1J_{P-C}$ = 135.5 Hz), 143.9 (d, $^2J_{P-C}$ = 4.2 Hz): MS m/z 236 (M^+).

General Procedure for the Synthesis of *β*-Functionalized Vinylphosphonates 31−34. To a solution of **29** or **30** (0.51 mmol) in THF (10 mL) was added dropwise *n*-BuLi (1.68 M in hexane, 0.30 mL, 0.51 mmol) at −78 °C, and then the mixture was stirred at this temperature for 0.5 h. After an electrophile (0.77 mmol) in THF (1.0 mL) was added to the mixture, the reaction mixture was stirred for 0.17−4.0 h at this temperature. After similar workup, the residue was purified by preparative TLC (AcOEt:hexane = 2:1) to give **31**−**34**. The reaction conditions and yields of **31**−**34** are summarized in Table 4. The compound **32** and **34** have the following properties. The properties for compounds **31** and **33** are provided in the Supporting Information.

Diethyl 3-benzoyl-6,7-dihydro-5*H*-1,4-dithiepin-2-ylphosphonate (32): yellow oil; IR (neat) 1670, 1250 cm^{-1}; ^1H NMR δ 1.19 (6 H, t, J = 7.2 Hz), 2.28 (2 H, tt, J = 5.8, 5.8 Hz), 3.42 (2 H, t, J = 5.8 Hz), 3.47 (2 H, t, J = 5.8 Hz), 3.93−4.07 (4 H, m), 7.46 (2 H, t, J = 8.0 Hz), 7.54−7.57 (1 H, m), 7.92−7.93 (2 H, m); ^{13}C NMR δ 16.1 (d, $^3J_{P-C}$ = 6.2 Hz), 30.5, 32.1, 32.7 (d, $^3J_{P-C}$ = 5.2 Hz), 63.0 (d, $^2J_{P-C}$ = 5.2 Hz), 126.4 (d, $^1J_{P-C}$ = 184.1 Hz), 128.5, 129.6, 133.3, 135.0, 150.2 (d, $^2J_{P-C}$ = 17.6 Hz), 191.4 (d, $^3J_{P-C}$ = 6.3 Hz); MS m/z 372 (M^+). Anal. Calcd for $C_{16}H_{21}O_4PS_2$: C, 51.60; H, 5.68. Found: C, 51.40; H, 5.84.

Diethyl 3-(tributylstannyl)-6,7-dihydro-5*H*-1,4-dithiepin-2-ylphosphonate (34): yellow oil; IR (neat) 2950, 1230 cm^{-1}; ^1H NMR δ 0.90 (9 H, t, J = 7.3 Hz), 1.01−1.15 (6 H, m), 1.32 (6 H, tt, J = 7.3, 7.3 Hz), 1.35 (6 H, t, J = 7.0 Hz), 1.45−1.65 (6 H, m), 2.18 (2 H, tt, J = 6.1, 6.1 Hz), 3.50 (2 H, t, J = 6.1 Hz), 3.61 (2 H, t, J = 6.1 Hz), 4.01−4.11 (4 H, m); ^{13}C NMR δ 13.7, 14.9, 16.3 (d, $^3J_{P-C}$ = 6.2 Hz), 27.4, 28.9, 29.1, 32.3, 34.4 (d, $^3J_{P-C}$ = 4.1 Hz), 62.1 (d, $^2J_{P-C}$ = 5.2 Hz), 119.5 (d, $^1J_{P-C}$ = 203.6 Hz), 163.8 (d, $^2J_{P-C}$ = 36.2 Hz); MS m/z 557 (M^+). Anal. Calcd for $C_{21}H_{43}O_3PS_2Sn$: C, 45.25; H, 7.78. Found: C, 45.01; H, 7.60.

General Procedure for the Palladium-Catalyzed Cross-Coupling Reaction of Vinylphosphonate 34 with Organic Halides. The reaction of **34** (0.57 g, 1.0 mmol) with an organic halide (1.5 mmol) was performed in the presence of $Cl_2Pd(PPh_3)_2$ (29 mg, 4 mol %) and CuCN (13 mg, 14 mol %) in toluene (17 mL) with stirring at 50 °C for 1.0−1.5 h, After workup similar to that described in the reaction of **13** with organic halides, the residue was purified by preparative TLC (AcOEt:hexane = 2:1) to give **32**, **35**, and **36**. The reaction conditions and yields of **32**, **35**, and **36** are summarized in Table 5. Compound **32** has physical data identical with those of **32** obtained in the above experiment, and the properties for compound **35** and **36** are provided in the Supporting Information.

Reaction of 25 with Hydroxylamine. The reaction was carried out at room temperature for 60 h with **25** (82 mg, 0.26 mmol), hydroxylamine hydrochloride (36 mg, 0.52 mmol), and Et_3N (52 mg, 0.52 mmol) in EtOH (5.0 mL). After similar workup, the residue was purified by preparative TLC (AcOEt:MeOH = 15:1) to give 4-(diethylphosphono)isoquinoline *N*-oxide (**40**) (62 mg, 85%) as a yellow oil: IR (neat) 1330, 1230 cm^{-1}; ^1H NMR δ 1.37 (6 H, t, J = 7.1 Hz), 4.18−4.30 (4 H, m), 7.68−7.73 (2 H, m), 7.78−7.80 (1 H, m), 8.44−8.46 (1 H, m),

8.64 (1 H, dd, $J = 2.0$ Hz, $^3J_{P-H} = 12.0$ Hz), 8.87 (1 H, s,); ^{13}C NMR δ 16.2 (d, $^3J_{P-C} = 6.2$ Hz), 63.3 (d, $^2J_{P-C} = 6.2$ Hz), 124.7 (d, $^1J_{P-C} = 184.0$ Hz), 125.6, 125.6, 127.8 (d, $^2J_{P-C} = 7.3$ Hz), 129.9, 123.0, 130.1, 139.1, 142.1 (d, $^2J_{P-C} = 15.6$ Hz); MS *m*/*z* 281 (M^+). The compound **40** gave no satisfactory elemental analysis data due to its high viscosity.

General Procedure for the Palladium-Mediated Cross-Coupling Reaction of Vinylphosphonate 7 with Terminal Acetylenes. After a solution of $PdCl_2$ (10 mg, 18 mol %) and PPh_3 (38 mg, 46 mol %) in THF (3 mL) was stirred at room temperature for 10 min, CuI (74 mg, 0.39 mmol), Et_3N (0.37 g, 3.7 mmol), **7** (0.12 g, 0.31 mmol) in THF (1 mL), and a solution of an acetylene (0.69 mmol) in THF (2 mL) was added to the solution in turn. The reaction mixture was stirred at this temperature for 24−60 h. The reaction was quenched by the addition of phosphate buffer (pH = 7), filtrated through a Celite pad. The organic layer was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (AcOEt: hexane = 2:1) to give **41**−**43**. The reaction conditions and yields of **41**−**43** are summarized in Table 6. Compound **42** has the following properties. The properties for compounds **41** and **43** are provided in the Supporting Information.

Diethyl 3-(trimethylsilyl)-1-(1,3-dithiolan-2-ylidene)-2-propynylphosphonate (42): colorless crystal; mp 47.5−48.5 °C; IR (KBr) 2130, 1480, 1240 cm^{-1}; ^{1}H NMR δ 0.21 (9 H, s), 1.35 (6 H, t, $J = 7.0$ Hz), 3.41−3.57 (4 H, m), 4.13 (4 H, dq, $^3J_{P-H} = 7.3$ Hz, $J = 7.0$ Hz); ^{13}C NMR δ 0.2, 16.1 (d, $^3J_{P-C} = 6.8$ Hz), 36.8, 40.5, 62.5 (d, $^2J_{P-C} = 6.1$ Hz), 95.0 (d, $^1J_{P-C} = 193.4$ Hz), 101.7 (d, $^3J_{P-C} = 8.6$ Hz), 102.6 (d, $^2J_{P-C} = 6.9$ Hz), 173.4 (d, $^2J_{P-C} = 13.8$ Hz); MS *m*/*z* 350 (M^+); HRMS calcd for $C_{13}H_{23}O_3SiPS_2$ 350.0595, found 350.0602.

Tetraethyl 1,6-Bis(1,3-dithiolan-2-ylidene)-2,4-hexadiyn-1,6-diyldiphosphonate (46). To a solution of $Cu(OAc)_2$ (67 mg, 0.37 mmol) in 3.0 mL of dry pyridine/EtOH (1:1) was added a solution of **45** (24 mg, 0.086 mmol) in THF (1.5 mL) at room temperature, and the reaction mixture was stirred at 70 °C for 30 min. After usual workup, the residue was purified by preparative TLC (AcOEt:MeOH = 15:1) to give **46** (22 mg, 93%) as a yellow crystal: mp 151.5−152.5 °C; IR (KBr) 1470, 1230 cm^{-1}; ^{1}H NMR δ 1.36 (12 H, t, $J = 7.0$ Hz), 3.45−3.49 (4 H, m), 3.55−3.58 (4 H, m), 4.08−4.20 (8 H, m); ^{13}C NMR δ 16.3 (d, $^3J_{P-C} = 7.5$ Hz), 37.2, 40.6 62.9 (d, $^2J_{P-C} = 6.3$ Hz), 82.1 (d, $^3J_{P-C} = 5.2$ Hz), 82.2 (d, $^2J_{P-C} = 8.3$ Hz), 94.1 (d, $^1J_{P-C} = 201.7$ Hz), 175.9 (d, $^2J_{P-C} = 14.5$ Hz); MS *m*/*z* 554 (M^+). Anal. Calcd for $C_{20}H_{28}O_6P_2S_4$: C, 43.31; H, 5.09. Found: C, 43.19; H, 5.09.

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Supporting Information Available: Spectral and analytical data for compounds **3**, **8**, **12**, **15**−**18**, **23**, **24**, **26**, **31**, **33**, **35**−**39**, **41**, and **43**−**45** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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