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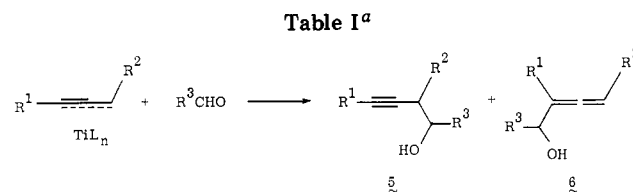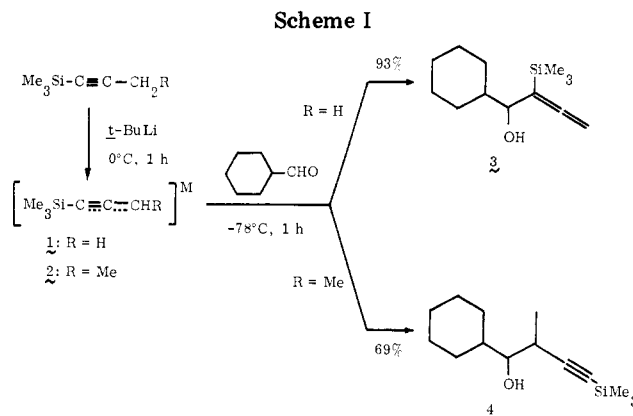*Rehovot, Israel*
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Propargylic Titanium Reagents. Regio- and Stereocontrolled Synthesis of Allenic and Acetylenic Alcohols

Summary: The highly selective condensations of propargylic titanium reagents and aldehydes are described.

Sir: The role of the propargylic anions in synthetic chemistry has become increasingly apparent.[1] An efficient and useful method for the extension of the carbon chain by means of such reactive species has recently been described.[2] In our continuing investigations we have studied the reaction of propargyltitanium reagents with aldehydes and have found unprecedented ambident behaviors of considerable synthetic interest.

The propargyllithium derivative **1**[3] (Scheme I), which was generated from 1-(trimethylsilyl)propyne and *tert*-butyllithium (THF, 0 °C, 1 h), was transformed into the corresponding titanium reagent by subsequent treatment with 1 equiv of titanium tetraisopropoxide (–78 °C, 10 min).[4] The condensation with cyclohexanecarboxaldehyde was carried out at –78 °C for 1 h to produce the α-allenic alcohol **3** in 93% yield without contamination of any β-acetylenic alcohol (99% regioselectivity).[5] A dramatic alteration in the product distribution occurred when the reaction of the homologous titanium reagent **2** was conducted with the same aldehyde. Thus, none of the corresponding α-allenic alcohol was detected, and instead the β-acetylenic alcohol **4** was obtained exclusively (69% yield, >99% regioselectivity).[5] The high regioselectivity appears to be general for a range of acetylenes and aldehydes (Table I).[6,7]

Since β-acetylenic alcohols are the main products obtained from allenic organometalics and carbonyl compounds,[1] it is currently assumed that they result from an allylic rearrangement of the organometalic by a chelate transition state of type **7** ($S_E i'$ process). Indeed, the IR spectrum of the titanium reagent **2** showed a strong absorption at 1898 cm^{-1} characteristic for allenic structure,[8] while that of the reagent **1** revealed only acetylenic absorption at 2092 cm^{-1},[8] in accord with the above speculation. Pioneering work by Chodkiewicz and co-workers
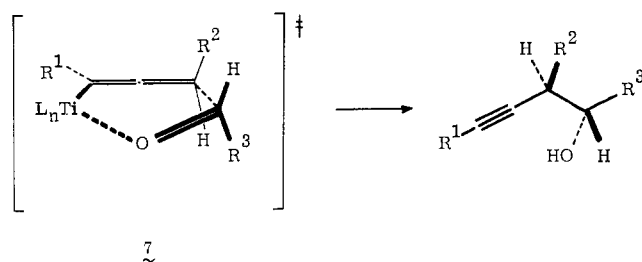
(1) For a recent review, see: Moreau, J.-L. In "The Chemistry of Ketenes, Allenes, and Related Compounds"; Patai, S., Ed.; Wiley: New York, 1980; pp 363–414.

(2) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* 1981, *103*, 5568.

(3) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* 1968, 5041.

(4) Recently, several titanium reagents were reported as useful synthetic reagents. Weidman, B.; Widler, L.; Olivero, A. G.; Maycock, D. D.; Seebach, D. *Helv. Chim. Acta* 1981, *64*, 357. Reetz, M. T.; Peter, R. *Tetrahedron Lett.* 1981, 4691 and references cited therein.

(5) Both acetylenic and allenic alcohols have been isolated and fully characterized. Satisfactory spectra and elemental analyses were obtained on all new compounds reported herein.

(6) The condensations of the titanium reagent 1 and 2 with ketones were unsuccessful, and starting ketones were recovered. Similar chemoselectivities for the titanium reagents were reported (see ref 4).

(7) Recently, Daniels and Paquette reported interesting regioselectivities at the carbonyl for additions of reagent 1 (M = Zn and Al): Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* 1981, 1579. See also: Mukaiyama, T.; Harada, T. *Chem. Lett.* 1981, 621.

(8) See pp 367–368 of ref 1.

Scheme I

Table I^a

R^1	R^2	R^3	5/6^{b-d} ratio	% isolated yield of 5 + 6
Si(CH$_3$)$_3$	H	cyclohexyl	1:99 (58:42)^e	93^f
Si(CH$_3$)$_3$	H	phenyl	<1:99 (65:35)	87^g
CH$_3$	H	cyclohexyl	1:99 (53:47)	90^h
CH$_3$	H	phenyl	1:99 (49:51)	80^i
Si(CH$_3$)$_3$	CH$_3$	cyclohexyl	>99:1	69^j
Si(CH$_3$)$_3$	CH$_3$	phenyl	>99:1	79^k
CH$_3$CH$_2$	CH$_3$	cyclohexyl	>99:1 (84:16)	42^l
phenyl	CH$_3$	cyclohexyl	94:6 (93:7)	89^m
phenyl	CH$_3$	phenyl	>99:1 (98:2)	92^n

^{a} All reactions were carried out at –78 °C for 1 h. ^{b} Both products have been isolated and fully characterized. ^{c} Determined by GC analysis. ^{d} Values in parentheses refer to ratios of 5/6 from the reactions with lithium reagents. ^{e} 56:44 using Mg ion; 75:25 using Zn ion. ^{f} IR (liquid film) 5.18 μm; NMR (CCl$_4$) δ 4.38 (d, 2 H, *J* = 2 Hz). ^{g} IR 5.18 μm; NMR δ 4.45 (d, 2 H, *J* = 3 Hz). ^{h} IR 5.08 μm; NMR δ 1.62 (d, 3 H, *J* = 3 Hz), 4.63 (m, 2 H). ^{i} IR 5.10 μm; NMR δ 1.47 (3 H), 4.68 (m, 2 H). ^{j} IR 4.63 μm; NMR δ 1.18 (d, 3 H, *J* = 7 Hz), 2.60 (dq, 1 H). ^{k} IR 4.59 μm; NMR δ 1.07 (d, 3 H, *J* = 7 Hz), 2.67 (dq, 1 H). ^{l} NMR δ 1.21 (d, 3 H, *J* = 7 Hz), 2.57 (m, 1 H). ^{m} NMR δ 1.30 (d, 3 H, *J* = 7 Hz), 2.77 (dq, 1 H). ^{n} IR 4.44 μm; NMR δ 2.80 (q, 1 H).

established the stereoregulation of condensation between allenic organometalics and carbonyl compounds, and the transition state of type **7** permits a rationalization of their

results.[9] It was of considerable interest to us to determine whether the titanium reagent would exhibit enhanced diastereoselection for the *threo*-β-acetylenic alcohol syn-

(9) (a) Saniere-Karila, M.; Capmau, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* 1973, 3371. (b) Favre, E.; Gaudemar, M. *J. Organomet. Chem.* 1975, *92*, 17. (c) See also references cited in ref 1.

Table II[a]
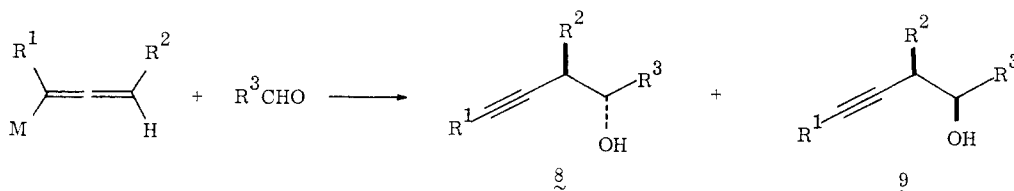
entry	R^1	R^2	R^3	metal[b]	8/9[c,d] ratio	% isolated yield of 8 + 9
1	Me$_3$Si	Me	cyclohexyl	Li	62:38	48
2	Me$_3$Si	Me	cyclohexyl	Mg	65:35	42
3	Me$_3$Si	Me	cyclohexyl	Ti	89:11 (93:7)[e]	69 (71)[e]
4	Me$_3$Si	Me	phenyl	Ti	84:16	79
5	phenyl	Me	cyclohexyl	Li	80:20	67
6	phenyl	Me	cyclohexyl	Ti	>99:1	89
7	Et	Me	cyclohexyl	Ti	91:9 (93:7)[e]	42 (35)[e]
8	Me$_3$Si	OTHP	cyclohexyl	Zn	71:29	51[f,g]
9	Me$_3$Si	OTHP	cyclohexyl	Ti	90:10	67[f,g]
10	Me$_3$Si	OTHP	n-C$_5$H$_{11}$	Ti	88:12	65[f,h]
11	Me	OTHP	cyclohexyl	Li	81:19	44[f,i]
12	Me	OTHP	cyclohexyl	Zn	88:12	48[f,i]
13	Me	OTHP	cyclohexyl	Ti	94:6	81[f,i]
14	Me	OTHP	n-C$_5$H$_{11}$	Ti	95:5	76[f,j]
15	Me	OCMe$_2$OMe	n-C$_5$H$_{11}$	Ti	93:7	57[f,j]
16	Me	OTHF	cyclohexyl	Ti	95:5	59[f,i]
17	Me	OTHF	n-C$_5$H$_{11}$	Ti	95:5	68[f,j]

[a] Unless specified, reactions were carried out at −78 °C for 1 h (entries 1-7) or at −78 ° for 0.5 h and 20 °C for 0.5 h (entries 8-17). See text for the experimental details. [b] Ti, Ti(O-i-Pr)$_n$; Mg, MgI; Zn, ZnBr. [c] Both products have been isolated and fully characterized. Authentic materials were also prepared in some cases by independent routes: (a) ring opening of (Z)- and (E)-epoxides with dialkylaluminum alkynides (entries 1-3, 5-7); (b) OsO$_4$ oxidation of the (Z)-enynes which in turn were prepared by the reported procedure (see ref 2; entries 8-10); (c) dibutylcopper-lithium reagents (excess) with erythro epoxy alcohol (from 1-hexene-3-ol + t-BuOOH-VO(acac)$_2$) gave the erythro diol[11] which was identical with the hydrogenation product from entries 14, 15, and 17. [d] Determined by GC analysis. Entries 8-17 are the ratios of diacetates. [e] The reaction was carried out at −100 °C for 1 h. [f] Yields refer to the corresponding diols produced by acid hydrolysis (p-TsOH in methanol) of the protecting groups (see text). [g] IR (liquid film) 4.54 μm; NMR (CCl$_4$) δ 4.22 (d, 1 H, J = 4 Hz). [h] IR 4.48 μm; NMR δ 4.18 (d, 1 H, J = 3 Hz). [i] IR 4.39 μm; NMR δ 4.41 (dq, 1 H, J = 3, 4 Hz), 3.32 (dd, 1 H, J = 3, 7 Hz). [j] IR 4.43 μm; NMR δ 4.28 (dq, 1 H, J = 3, 3 Hz), 3.63 (m, 1 H).

thesis. Accordingly, we have examined diastereomeric ratios of the β-acetylenic alcohols, and some of our results are illustrated in Table II.

As summarized in Table II, diastereoselection is clearly influenced by the metal center, with enhanced selectivity being observed with titanium reagents. Thus, the titanium reagent afforded predominantly *threo*-β-acetylenic alcohols (entries 3-7) and *erythro*-α,β-acetylenic diols (entries 9-17)[10] with synthetically useful levels of stereoselectivities. The comparative allenyllithium, -magnesium, and -zinc carbonyl additions (entry 1, 2, 5, 8, 11, 12) were less stereoselective in all cases. Examination of other data in Table II reveals several other trends: (1) the reaction with benzaldehyde exhibited a modest level of stereoselectivity (entry 4), and a similar anomaly of benzaldehyde has been observed elsewhere;[2,9b] (2) a trimethylsilyl group at R^1 of the reagents gave slightly lower selectivities for the reaction (entry 9, 10); (3) a lower reaction temperature leads to higher selectivities (entry 3 and 7).

The following experimental procedure is representative of the conversion (entry 14). *tert*-Butyllithium in pentane (1.8 M, 0.83 mL, 1.5 mmol) was added dropwise to a solution of 2-butyn-1-yl 2-tetrahydropyranyl ether (231 mg, 1.5 mmol) in dry THF (4 mL) with stirring under argon at −78 °C. After 40 min at −78 °C, titanium tetraisopropoxide (0.45 mL, 1.5 mmol) was added dropwise to the

resulting orange solution of the anion, and the slightly darkened solution was stirred there for 10 min. Freshly distilled hexanal (0.155 mL, 1.3 mmol) was added over a period of 5 min at −78 °C, and the mixture was stirred at −78 °C for 30 min and then at 20 °C for 30 min. The reaction mixture was poured into ice-cold 1 N hydrochloric acid, and the product was extracted with ether repeatedly. The combined ethereal layer was concentrated in vacuo to give a crude hydroxyl ether, which was directly dissolved in dry methanol (5 mL) at 0 °C. p-Toluenesulfonic acid (5 mg) was added, and the mixture was stirred at 20 °C for 30 min. After consumation all the tetrahydropyranyl ether by TLC assay, the reaction was terminated by the addition of excess sodium bicarbonate (10 mg). The suspension was concentrated in vacuo, and the slurry was directly subjected to column chromatography on silica gel (ether-hexane, 2:1) to afford 2-decyne-*erythro*-4,5-diol (168 mg, 76% yield).[12]

(10) For a similar approach to prepare erythro diols with modest regio- and stereoselectivities by using Zn and Mg ions, see: (a) Mercier, F.; Le Goff, N.; Epsztein, R. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1974**, *279*, 525. (b) *J. Organomet. Chem.* **1976**, *108*, 165.

(11) Yasuda, A.; Tanaka, S.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1701.

(12) The diol was acetylated by Ac$_2$O–pyridine, and the GC analysis of the diacetate revealed the presence of 5% of the threo isomer.

$H_3)_3$; R^2 = H; R^3 = phenyl), 78808-49-8; 6 (R^1 = CH_3; R^2 = H; R^3 = cyclohexyl), 81435-42-9; 6 (R^1 = CH_3; R^2 = H; R^3 = phenyl), 78808-42-1; 6 (R^1 = $Si(CH_3)_3$; R^2 = CH_3; R^3 = cyclohexyl), 81435-43-0; 6 (R^1 = $Si(CH_3)_3$; R^2 = CH_3; R^3 = phenyl), 81435-44-1; 6 (R^1 = CH_3CH_2; R^2 = CH_3; R^3 = cyclohexyl), 81435-45-2; 6 (R^1 = phenyl; R^2 = CH_3; R^3 = cyclohexyl), 81435-46-3; 6 (R^1 = phenyl; R^2 = CH_3; R^3 = phenyl), 81435-47-4; 8 (R^1 = Me_3Si; R^2 = Me; R^3 = cyclohexyl), 81435-48-5; 8 (R^1 = Me_3Si; R^2 = Me; R^3 = phenyl), 81435-49-6; 8 (R^1 = phenyl; R^2 = Me; R^3 = cyclohexyl), 81435-50-9; 8 (R^1 = Et; R^2 = Me; R^3 = cyclohexyl), 81435-51-0; 8 (R^1 = Me_3Si; R^2 = OTHP; R^3 = cyclohexyl), 81435-52-1; 8 (R^1 = Me_3Si; R^2 = OTHP; R^3 = C_5H_{11}), 81435-53-2; 8 (R^1 = Me; R^2 = OTHP; R^3 = cyclohexyl), 81435-54-3; 8 (R^1 = Me; R^2 = OTHP; R^3 = C_5H_{11}), 81435-55-4; 8 (R^1 = Me; R^2 = OCH_2OMe; R^3 = C_5H_{11}), 81435-56-5; 8 (R^1 = Me; R^2 = OTHF; R^3 = cyclohexyl), 81435-57-6; 8 (R^1 = Me; R^2 = OTHF; R^3 = C_5H_{11}), 81435-58-7; 9 (R^1 = Me_3Si; R^2 = Me; R^3 = cyclohexyl), 81435-59-8; 9 (R^1 = Me_3Si; R^2 = Me; R^3 = phenyl), 81435-60-1; 9 (R^1 = phenyl; R^2 = Me; R^3 = cyclohexyl), 81435-61-2; 9 (R^1 = Et; R^2 = Me; R^3 = cyclohexyl), 81435-62-3; 9 (R^1 = Me_3Si; R^2 = OTHP; R^3 = cyclohexyl), 81495-67-2; 9 (R^1 = Me_3Si; R^2 = OTHP; R^3 = C_5H_{11}), 81495-68-3; 9 (R^1 = Me; R^2 = OTHP; R^3 = cyclohexyl), 81495-69-4; 9 (R^1 = Me; R^2 = OTHP; R^3 = C_5H_{11}), 81495-70-7; 9 (R^1 = Me; R^2 = $OCMe_2$; R^3 = C_5H_{11}), 81435-63-4; R^3CHO (R^3 = cyclohexyl), 2043-61-0; R^3CHO (R^3 = phenyl), 100-52-7; R^3CHO (R^3 = C_5H_{11}), 66-25-1; $R^1C\equiv CCH_2R^2$ (R^1 = $Si(CH_3)_3$; R^2 = H), 6224-91-5; $R^1C\equiv CCH_2R^2$ (R^1 = CH_3; R^2 = H), 503-17-3; $R^1C\equiv CCH_2R^2$ (R^1 = $Si(CH_3)_3$; R^2 = CH_3), 62108-37-6; $R^1C\equiv CCH_2R^2$ (R^1 = CH_3CH_2; R^2 = CH_3), 928-49-4; $R^1C\equiv CCH_2R^2$ (R^1 = phenyl; R^2 = CH_3), 622-76-4; $R^1C\equiv CCH_2R^2$ (R^1 = Me_3Si; R^2 = OTHP), 36551-06-1; $R^1C\equiv CCH_2R^2$ (R^1 = Me; R^2 = OTHP), 39637-48-4; $R^1C\equiv CCH_2R^2$ (R^1 = Me; R^2 = $OCMe_2OMe$), 81435-64-5; $R^1C\equiv CCH_2R^2$ (R^1 = Me; R^2 = OTHF), 81435-65-6; titanium tetraisopropoxide, 546-68-9.

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Phosphonosilylations of Cyclic Enones

Summary: Diethyl trimethylsilyl phosphite reacts smoothly with a variety of cyclic enones to produce β-phosphonotrimethylsilyl enol ethers.

Sir: The synthetic utility of dipole reversal (umpolung) reactions is now well-established.[1] Recently, we have become interested in a specific type of dipole reversal process, namely, the conversion of enones into adducts which serve as enone β-anion equivalents. Examination of the literature indicates that a number of different protocols have been developed toward this end.[2] One of these involves reaction of various mixed phosphorous–silicon reagents with unsaturated aldehydes and ketones to produce 1,2- and/or 1,4-adducts of this original substrate.[3] In principle, these adducts could then be de-

protonated, alkylated, and unmasked to yield the alkylated analogue of the original substrate (vide infra). However, one of the severest limitations of this methodology involves the inability of cyclic enones to form adducts, such as 4, with these mixed phosphorous–silicon reagents. For example, Evans has previously reported that cyclohexenone (8) fails to undergo any detectable 1,4-addition with reagents of general structure 1 (e.g., 1a, R = Me, X = OMe or 1b, R = Me, X = NMe_2).[3a] In this communication we report that under the proper experimental conditions, diethyl trimethylsilyl phosphite (1c, R = Me, X = OEt)[4] reacts smoothly with a variety of cyclic enones to, in most cases, regioselectively produce 1,4-adducts of type 4. Specific results are listed in Table I.
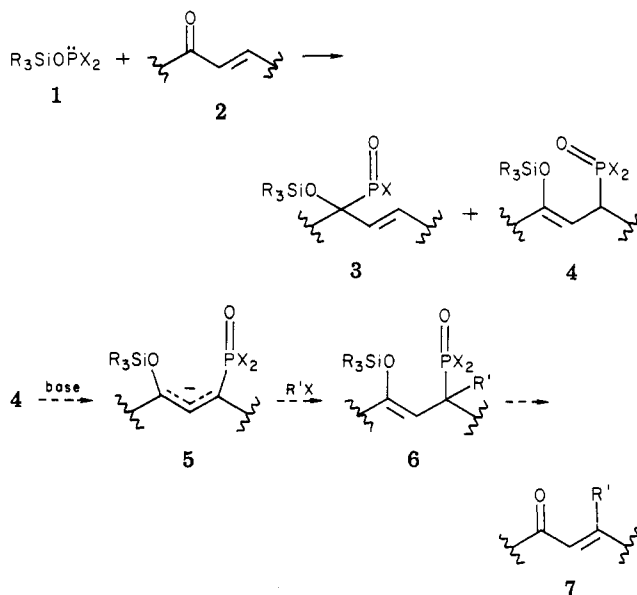
We have developed two slightly different sets of reaction conditions which are particularly effective for inducing adduct formation. These involve heating the substrate in question in acetonitrile in the presence of 1.8 equiv of diethyl trimethylsilyl phosphite (1c) for varying lengths of time at either 80 °C (simple reflux) or 180 °C (sealed tube). That the regioselectivity of these additions is in some cases significantly affected by temperature at which the reaction is performed suggests that the product ratios are the result of thermodynamic rather than kinetic control. This is easily verified by exposing a given adduct mixture, formed at 80 °C, to the 180 °C reaction conditions and then determining the changes, if any, in the adduct ratio. In all cases the newly determined isomer ratios conformed to within ±10% to those performed at 180 °C.

Simple cyclic enones such as 8 or 10 react with 1c to form 1,4-adducts with good regioselectivity. As long as the β-carbon and the carbonyl carbon atoms are at least comparably hindered, 1,4-adduct formation clearly represents the dominant reaction pathway. However, as the degree of hindrance around the β-carbon atom increases, the relative amount of 1,4-adducts formed correspondingly decreases. This is seen most graphically in the reaction

(1) (a) Seebach, D.; Kolb, M. *Chem. Ind.* 1974, 687. (b) Lever, O. W. *Tetrahedron* 1976, *32*, 1943.

(2) (a) Kondo, K.; Tsunemoto, D. *Tetrahedron Lett.* 1975, 1007. (b) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* 1971, *93*, 1724. (c) Nakai, T.; Shiono, H.; Okawara, M. *Tetrahedron Lett.* 1974, 3625. (d) Cohen, T.; Bennett, D. A.; Mura, A. J. *J. Org. Chem.* 1976, *41*, 2506. (e) Lansbury, P. T.; Britt, R. W. *J. Am. Chem. Soc.* 1976, *98*, 4578. (f) Wade, M.; Nakamura, H.; Taguchi, T.; Takei, H. *Chem. Lett.* 1977, 345. (g) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* 1972, *94*, 4395. (h) Debal, A.; Civigny, T.; Larchavigne, M. *Tetrahedron Lett.* 1977, 3187. (i) Cooper, G. K.; Dolby, L. J. *Ibid.* 1976, 4675. (j) Bakuzis, P.; Bakuzis, M. L. V.; Weingartner, T. F. *Ibid.* 1978, 2371. (k) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* 1977, *99*, 7360. (l) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* 1974, *7*, 147.

(3) (a) Evans, D. A.; Hurst, K. N.; Truesdale, L. K.; Takacs, J. M. *Tetrahedron Lett.* 1977, 2495. (b) Hata, T.; Hashizume, A.; Nakajima, M.; Sekine, M. *Tetrahedron Lett.* 1978, 363. (c) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* 1978, *100*, 3467. (d) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *Ibid.* 1979, *101*, 371.

(4) Diethyl trimethylsilyl phosphite (1c) is easily prepared by reactions of the sodium salt of diethyl phosphite with trimethylsilyl chloride in ether at room temperature (yield, >95%). This reagent, although easily hydrolyzed, exhibits a greater shelf stability than its dimethyl analogue 1a.