Diastereoselectivity in the Mukaiyama−Michael Reaction Employing α-Acyl *β,γ*-Unsaturated Phosphonates

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The unique electronic and structural nature of the α-acylphosphonate functional group affords both dimeric and chelated complexes of diethyl crotonyl phosphonate (**1**; DECP) with stannic chloride ($SnCl_4$). The dimeric complex, $SnCl_4$·$(DECP)_2$ (**5**) results from the coordination of two DECP molecules, ligated via the phosphoryl oxygens to the tin atom. The chelated complex, $SnCl_4$·(DECP) (**6**), is best represented with both phosphoryl and carbonyl oxygens coordinated to the metal center. Both metal ligated and chelated complexes have unique ^{13}C ^{31}P, and ^{119}Sn NMR spectra. In complex **5**, the ^{13}C NMR resonances attributed to the carbonyl carbons were shifted upfield of free DECP. A monocoordinating Lewis acid, BF_3·OEt_2, produced a similar chemical shift trend in both the ^{13}C and ^{31}P NMR spectra of the BF_3·DECP complex. Essentially quantitative yields and moderate diastereomeric excesses favoring *anti* (or trans) diethyl 6-phenyl-4,5-dimethyl-6-(trimethylsilyloxy)-2-dihydropyranphosphonate (**3**) and diethyl 5-phenyl-3,4-dimethyl-1,5-dioxopentanephosphonate (**4**) were obtained from both chelated and dimeric $SnCl_4$·$(DECP)_n$ (n = 1, 2) when treated with either diastereomeric (*Z*)- or (*E*)-1-phenyl-1-(trimethylsilyloxy)-1-propene **2**. Diethyl crotonylphosphonate (**1**), **3**, and **4** were fully characterized.

The Michael reaction has become as an important synthetic methodology for promoting stereoselective carbon−carbon bond formation.[1] The Lewis acid-catalyzed analog of the Michael reaction, introduced by Mukaiyama and co-workers,[2] occurs between silyl enol ethers and α,*β*-unsaturated carbonyl substrates in the presence of a variety of catalysts.[3] More recently, studies dealing with Lewis acid diversification have been utilized to increase diastereo- and enantioselectivities[4] as well as to overcome problems associated with acid-sensitive substrates, and α-enones which are subject to acid-promoted polymerizations.[4]

Efforts to develop a more versatile and highly diastereoselective congener of this reaction led us to explore the utility of α-acyl-*β,γ*-unsaturated phosphonates as substrates in the Mukaiyama−Michael reaction. We had previously established the utility of α-acylphosphonates in the aldol reaction[5] and determined that the unique chelating nature of the proximal α-carbonyl and phosphoryl oxygens to a lithium cation insured a conformationally homogeneous enolate which gave excellent overall diastereoselectivity (>98% de)[5] when the lithio enolate was treated with benzaldehyde. In a similar way, we had anticipated preferential metal binding to the phosphoryl and possibly carbonyl oxygens to encourage structural rigidity and enhance the electrophilic nature of the enone substrate. A favorable combination of these factors would translate to unique syn *vs* anti diastereoselectivity in the Mukaiyama−Michael reaction. In this report, we describe our results from the reactions between diethyl (*E*)-but-2-enoylphosphonate (DECP; **1**)[6] and silyl enol ethers in the presence of the Lewis acid, stannic chloride ($SnCl_4$).

Results and Discussion

When a solution of DECP and (*Z*)- or (*E*)-silyl enol ether **2** was cooled to −78 °C (dry ice/*i*PrOH) in dichloromethane solvent, and subsequently treated with $SnCl_4$, diastereomeric dihydropyrans **3** and traces of diketo adducts **4**[7] were formed together in nearly quantitative yield (>99% by GLC-MS; Scheme 1). While 4,5-*trans*-5,6-*cis*-**3** and *anti*-**4** were the dominant products and their preferences were independent of the (*E*)- *vs* (*Z*)-configuration of silyl enol ethers **2**,[8] their %de's varied with the changes in reaction conditions.

DECP−Metal Complexes. Low temperature (−78 °C) ^{31}P NMR studies of the coordination of $SnCl_4$ to

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(4) See for example, Berl, V.; Helmchen, G.; Preston, S. *Tetrahedron Lett.* **1994**, *35*, 233.

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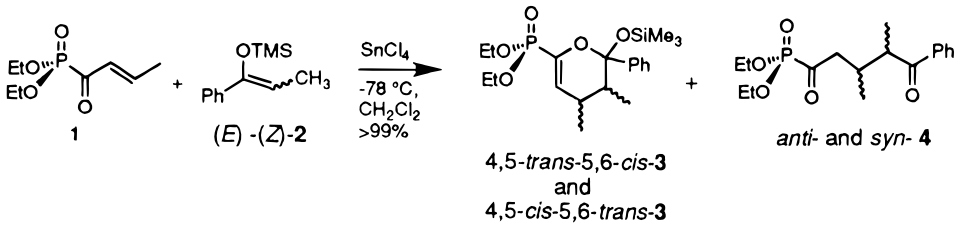
(6) Diethyl (*E*)-but-2-enoylphosphonate [diethyl crotonylphosphonate; DECP, **1**] was prepared by a Michaelis−Arbusov reaction between (*E*)-but-2-enoyl chloride and triethyl phosphite: See Szpala, A.; Tebby, J.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1363−66.

(7) Desilylated Michael adduct **4** was produced in a trace amount when catalyzed by $SnCl_4$, and in *ca.* 1:1 ratio of silyated **3**:nonsilyated **4** in the case of $TiCl_4$.

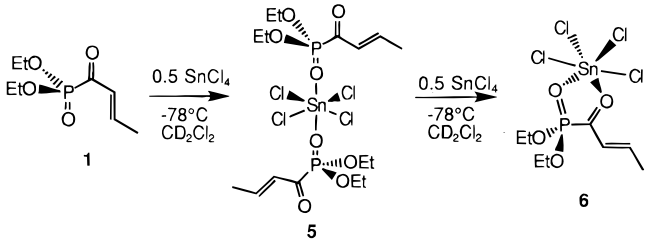
(8) Controlled experiments revealed that (*E*)-**2** rapidly isomerizes to (*Z*)-**2** under the reaction conditions.

S0022-3263(95)01085-1 CCC: $12.00

Scheme 1. Reactions of Diethyl Crotonylphosphonate with (*E*)- and (*Z*)-2 in the Presence of $SnCl_4$



Scheme 2. Tin Complexes of α-Acylphosphonate 1



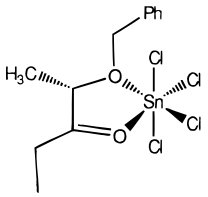
α-acylphosphonate **1** were undertaken in order to establish the structural identity of a particular or predominant metal complex contributor and perhaps provide useful information on the possible origin(s) of the *anti*-**4** (and 4,5-*trans*-5,6-*cis*-**3**) diastereoselective preferences.

(a) $SnCl_4$ Complexes. When increasing quantities of $SnCl_4$ (up to 0.5 equiv) was admixed with DECP (^{31}P NMR δ −1.0 ppm) at −78 °C, a new species exhibiting a resonance at δ −9.0 was observed; its structural constitution was consistent with a 2:1 or $(DECP)_2 \cdot SnCl_4$ stoichiometry (*e.g.*, **5**) (*vide infra*). With further addition of $SnCl_4$, the intensity of the resonance at δ −9.0 diminished and a new resonance at δ 3.4, tentatively assigned to stannacycle **6**,[9] was observed (Scheme 2).

Low temperature ^{119}Sn NMR spectroscopy (Figure 1) also confirmed that these two species were best characterized through coordination of DECP to the Sn atom in two different modes. The species (*i.e.*, complex **5**) which exhibited the singlet ^{31}P NMR resonance at δ −9.0 also gave a triplet at δ −692.1 ($^2J_{PSn}$ = 218.6 Hz) in the ^{119}Sn NMR. The singlet ^{31}P NMR resonance and the triplet ^{119}Sn NMR resonance taken together confirmed that there were two DECP molecules symmetrically disposed about the octahedral tin atom. Possible structures for the $SnCl_4 \cdot (DECP)_2$ complex possess either C_{4v} (*trans* DECP ligands) or C_{2v} (*cis* DECP ligands) symmetry, characterized by strong complexation between the phosphoryl oxygen in **1** and the tin atom. While the NMR data implied that the species with δ −9.0 ^{31}P NMR resonance (presumably, **5**) may possess an unique geometry,[10] it could exist as a strongly complexed species capable of rapid geometrical permutation.[11] However, at −78 °C, geometric permutational processes are probably slow on the reaction (*i.e.*, NMR) time scale, and NMR evidence for the existence of both cis and trans isomers should be easily discernible.[11] Ruzicka and Merbach[11] have demonstrated that the rates for isomerization of cis and trans $SnCl_4 \cdot 2L$ octahedral complexes (L = ligand with P=O oxygen binding) are significantly reduced at low temperatures, and that the equilibrium constants are highly responsive to changes in solvent polarity; the cis isomer is favored in polar solvents and the trans isomer in nonpolar solvents.

From an examination of molecular models, it appears that the DECP's P=O ligation to the Sn atom would expose a sterically bulky tetracoordinate phosphorus group which would seek the trans orientation to minimize the repulsive van der Waals interactions of another sterically imposing substituent when both are cis. While the NMR data would be consistent with either the cis or trans $SnCl_4 \cdot (DECP)_2$ complexes, we tentatively favor complex **5** in a static *trans* symmetric conformational array at −78 °C.[12]

When additional $SnCl_4$ is added to the solution containing complex **5**, the intensity of the triplet at δ −692.1 diminished and a doublet appeared at δ −588.4 ($^2J_{PSn}$ = 51 Hz) in ^{119}Sn NMR. The chemical shift and $^2J_{PSn}$ coupling pattern of the ^{119}Sn NMR resonance were consistent with a hexacoordinate tin atom bound to a single molecule of DECP, *i.e.*, stannacycle **6**. The X-ray structural data for the species formed from the reaction of $SnCl_4$ with 2-(benzyloxy)-3-pentanone indicated that complex **7** (^{119}Sn NMR δ −542.1) was monomeric with



7

Sn occupying a hexacoordinate geometry.[9] Alternatively, trigonal bipyramidal Sn complexes are certainly possibilities, but their ^{119}Sn NMR resonances are generally less shielded.[9] The *increased* inductive effect on the phosphoryl group caused by the coordination of the carbonyl oxygen to the Sn atom in **6** results in some deshielding of the ^{31}P nucleus.

The $^2J_{PSn}$ couplings, obtained from ^{117}Sn and ^{119}Sn satellites for **5** and **6** in their respective ^{31}P NMR spectra, are due to the ^{31}P coupling with ^{117}Sn and ^{119}Sn isotopes ($I = {}^1/_2$ for both, natural abundance = 7.67 and 8.68%, respectively). Finally, the ^{119}Sn NMR chemical shifts for

(9) Using the X-ray data for complex **7** as a rough structural analog, we believe that it is reasonable to propose that stannacycle **6** is monomeric in DECP and chelated to hexacoordinate tin as a cis complex. See Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881−84.

(10) (a) Branden, C. I. *Acta Chem. Scand.* **1963**, *17*, 769. (b) Colton, R.; Dakternieks, D. *Inorg. Chim. Acta* **1983**, *71*, 101−7. (c) Philips, J.; Mullins, M. A.; Curran, C. *Inorg. Chem.* **1968**, *7*, 1895. (d) See also, Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (e) Feshin, V. P.; Dolgushin, G. V.; Lazarev, I. M.; Voronkov, M. G. *Koord. Khim.* **1990**, *16*, 1038−41.

(11) Ruzicka, S. J.; Merbach, A. E. *Inorg. Chim. Acta* **1977**, *22*, 191−200.

(12) The molecular bonding consideriations which influence the stability of cis and trans isomeric $SnX_4 \cdot 2L$ complexes have been previously discussed. However, the interplay between electronic and steric influences and the role these factors play in determining stability remain vague. See, (a) Smith, J. A. S.; Wilkins, E. J. *Chem. Commun.* **1965**, 381. (b) Wilkins, C. J.; Haendler, H. M. *J. Chem. Soc.* **1965**, 3174. (c) Hill, J. C.; Drago, R. S.; Herber, R. H. *J. Am. Chem. Soc.* **1969**, *91*, 1644. (d) Zahrobsky, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 3313.

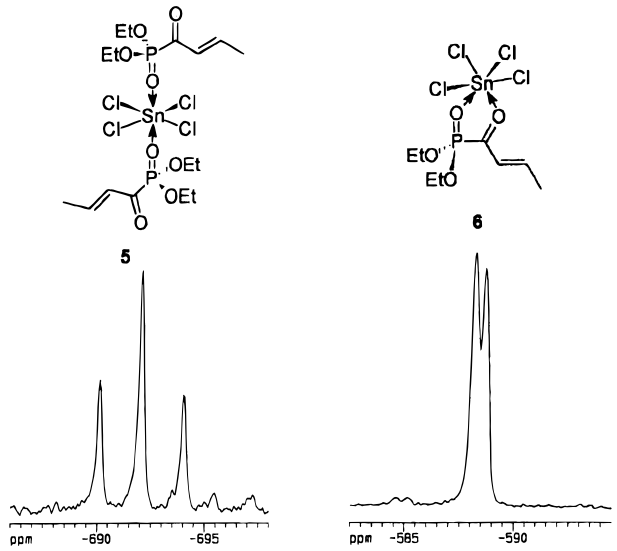


Figure 1. ^{119}Sn NMR of **5** and **6** at −78 °C.

complexes **5** and **6** occur in the region for other hexacoordinate Sn^{IV} species.[10]

The ^{31}P NMR resonances for diethyl propionylphosphonate (**8**) (δ −2.13) and tetrachlorostanne complexes **9** (δ −11.8) and **10** (δ −1.03) follow the same shift trends as those for α-acylphosphonate **1** and stanne complexes **5** and **6**, respectively.

Complexes **5** and **6** also exhibited distinct ^{13}C NMR spectra where the most perceptible feature were the ^{13}C NMR chemical shifts of the carbonyl carbons. In complex **5**, the carbonyl carbon resonance appeared at δ 194.6, which is a 3.8 ppm upfield shift accompanied by a 8.8 Hz increase in $^1J_{PC}$ compared to the NMR parameters for DECP (δ 198.4, $^1J_{PC}$ = 172.1 Hz). The increased coupling or change in Δ^1J_{PC} = 8.8 Hz from **5** → **1** is also consistent with the INDO predicted trends[13] where polarization of the phosphoryl group through Sn coordination (*i.e.*, P−O···$SnCl_4$) induces electron withdrawal of the p-electrons in the phosphorus hybridization matrix, giving rise to greater s-electron density close to the phosphorus nucleus. The net result is an increase in the Fermi contact contribution which increases the observable $^1J_{PC}$ couplings.[13] The shielding of the carbonyl carbon caused by P═O complexation with Sn (*e.g.*, O═C−P═O···$SnCl_4$) is consistent with other observations of increased shielding of carbonyl carbons when they are proximal to "electron-withdrawing substituents".[14] This ^{13}C NMR shift and $^1J_{PC}$ coupling trend is replicated in the comparisons of carbonyl shifts and $^1J_{PC}$ values between **8** and complex **9** (Scheme 3).

In complex **6**, where chelation of Sn by both P═O and C═O functional groups is implied, the carbonyl carbon resonance occurs at δ 197.7 with $^1J_{PC}$ = 152.4 Hz. By contrast, the ^{13}C NMR shifts for both saturated and α,β-unsaturated aldehydic carbons in $(RCHO)_2$·$SnCl_4$ complexes are systematically deshielded compared to the shifts in the "free aldehyde".[15] The complexation shift difference, $\Delta\delta$ (= $\delta_{complex} - \delta_{neutral}$) is systematically smaller for α,β-unsaturated aldehydes compared to saturated ones,[15] suggesting that electron transfer to the carbonyl carbon site is facilitated by the π-electrons of the enone fragment.[16] Thus, one might reasonably conclude that while a downfield shift may have been anticipated through complexation for the carbonyl carbon in complex **6**, an *offsetting* net upfield carbonyl ^{13}C NMR shift arises from (a) the inductive (*shielding*) effect of the complexed P═O group, and (b) electron delocalization between the carbonyl group and the adjacent π system, encouraged through ligation of the carbonyl oxygen.[15] Finally, Albright[13] has shown that a decrease in the O−P−C angle in organophosphorus compounds is related to a reduction in the % s-character in the phosphorus hybrid P−C orbital which translates to smaller values of $^1J_{PC}$.

The parallels in ^{13}C and ^{31}P NMR shifts, and $^1J_{PC}$ couplings between **1**, **5**, and **6** compared to **8**, **9**, and **10** strongly suggested similarities in their structures (Schemes 2 and 3).

(b) BF_3−DECP Complex. When BF_3·OEt_2, a monocoordinating Lewis acid, reacts with DECP at −78 °C, the ^{31}P NMR spectrum indicated the formation of a stoichiometric complex (*i.e.*, BF_3·DECP) exhibiting a quartet NMR resonance at δ −5.5 ($^3J_{FP}$ = 6.7 Hz). The ^{13}C NMR shift of the carbonyl carbon was shifted upfield by 7.8 ppm ($^1J_{PC}$ = 174 Hz, 4.3 Hz larger than in DECP). Only a single ^{31}P NMR resonance is observed, and from the limited data available it is not possible to speculate on whether the BF_3 group prefers the (*E*)- or (*Z*)-configuration about the P═O bond. Nevertheless, these results do indicate that the phosphoryl oxygen is exclusively coordinated to BF_3 (*e.g.*, **11**; Scheme 4), and that shielding of both ^{13}C and ^{31}P NMR nuclei in complex **11** are diagnostic indicators when compared to the shifts of analogous nuclei in **1**.

Diastereoselectivity. The corresponding diastereoselectivities are shown in Table 1. In almost all cases, the *anti* diastereomer was favored. Stereochemical assignments of silylated adducts **3** were made by NOESY 2D NMR spectroscopy, and additional structural information was obtained from COSY, homonuclear Hartman Hahn (HOHAHA),[17] heteronuclear multiple quantum correlation (HMQC),[18] and heteronuclear multiple bond connectivity (HMBC)[19] NMR techniques.

Heathcock's mechanistic proposals[20] describing the silyl enol ether approach to the Michael acceptor via an "open transition state" appropriately rationalized the stereochemical outcome of these reactions. The invariance of the *anti* diastereomer of the reactions reported here as related to the stereochemistry of the silyl enol ether was rationalized from the results of a simple control experiment. When (*E*)-**2** was treated with $SnCl_4$ at −78 °C for 3 min, it was completely equilibrated to (*Z*)-**2**, the thermodynamically more stable isomer (Scheme 5). The observation of this facile equilibration of (*E*)- → (*Z*)-silyl enol ethers **2** leads to the conclusion that, at best, a mixture of (*E*)- and (*Z*)-silyl enol ethers **2** exist under the reaction conditions, and that (*Z*)-silyl enol ether **2** may be the most abundant silyl enol ether under these conditions. A possible exception involves the reaction

(13) (a) Duangthai, Sl.; Webb, G. A. *Org. Magn. Reson.* **1983**, *21*, 125−9. (b) Albright, T. A. *Org. Magn. Reson.* **1976**, *8*, 489−499.
(14) Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley-Interscience: New York, 1972.
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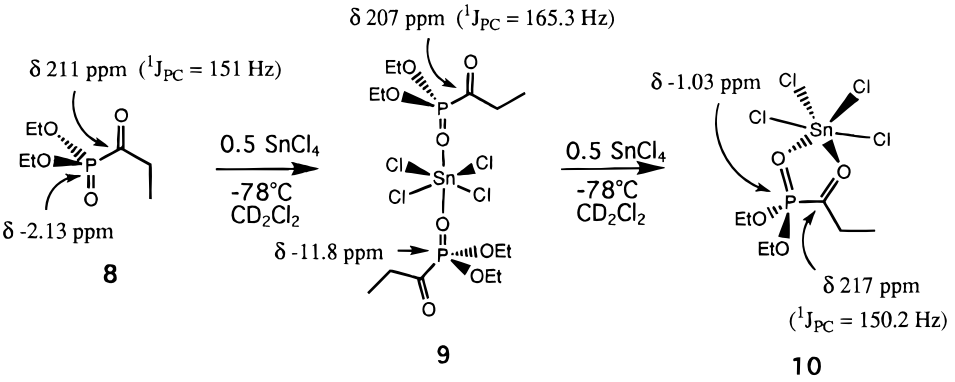
(17) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 2820−21.
(18) Norwood, T. J. *Prog. NMR Spectrosc.* **1992**, *24*, 295−375.
(19) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
(20) Oare, D. H.; Heathcock, C. H. *Top. Stereochem.* **1991**, *21*, 227.

Scheme 3. Selected NMR Parameters of Diethyl Propionylphosphonate and Tetrachlorostanne Complexes



Scheme 4. Formation of BF_3 Complex of α-Acylphosphonate 1

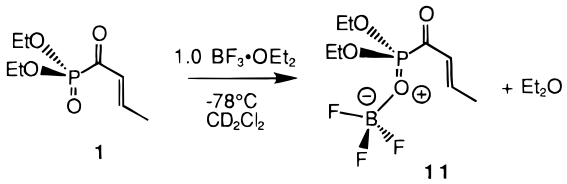
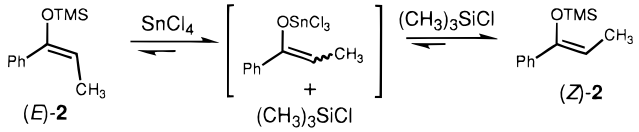


Table 1. Summary of Diastereoselectivities

entry	silyl enol ether **2**	complex	reaction time	% de	isomer
1	*Z*	6	<1 min	24	*anti*
2	*E*	6	<1 min	14	*syn*
3	*Z*	5	<5 min	52	*anti*
4	*E*	5	*ca.* 3 h	32	*anti*

Scheme 5. Equilibration of (*E*)- and (*Z*)-2 Catalyzed by $SnCl_4$



between complex **6** and (*E*)-silyl enol ether **2** (entry 2). Here, it is conveivable that the rate of the Mukaiyama−Michael reaction is comparable to the rate of the (*E*) → (*Z*) isomerization of silyl enol **2**, and the isomerization process readily compromises the stereochemical integrity of silyl enol **2** before reactions with the appropriate metal complexes. These considerations seem to adequately justify the stereoconvergence favoring the anti isomer[21] as well as the low %de favoring the syn diastereomer (entry 2).

These results also imply that the selectivity (%de) of the reaction is sensitive to the steric bulk attending the metal center. Inspection of molecular models suggest that dimeric complex **5** is spatially more demanding than its chelated counterpart, **6**. Preferences for either the *s*-cis and *s*-trans orientations of phosphoryl and carbonyl groups about the P−C bond may also have significant influence over how effectively the steric bulk of both the metal and phosphorus ligands impact the stereochemical outcome of the reaction. To minimize possible electrostatic interactions, especially in dideuterio dichloromethane solvent, we favor the *s*-trans orientation of DECP in complex **5**. Scheme 6 shows plausible transition state models for the reactions between (*Z*)-**2** and complexes, **5** and **6**.

Accordingly, both *syn* and *anti* products arise from the selective facial approach of the silyl enol ether to the DECP complexes. If the steric bulk differential between the phenyl and OTMS groups is relatively small, the facility for the facial approach of (*Z*)-silyl enol ether **2** (*vide supra*) to chelated or complexed **1** will be controlled by the severity of the methyl−methyl gauche as well as the long-range methyl−phosphonate OEt group interactions in the various transition states.

From an inspection of molecular models, it seemed evident that $TS_2^‡$ and $TS_4^‡$ possess methyl−methyl gauche interactions as well as potentially long range interactions between (a) the silyl enol methyl and the phosphoryl OEt ligand, and (b) the octahedral metal substructure which is ligated to the phosphoryl oxygen. In $TS_1^‡$ and $TS_3^‡$, these potential interactions appear to be less pronounced, implying that these particular models may actually be more reasonable representatives.

Perhaps most interesting, was the formation of dihydropyrans **3** where the 6-exo-trig chain closure[22] of a requisite intermediate to **3** was highly stereoselective (*vide infra*). Despite the possibility of creating *three* new stereocenters in **3** and the expectation of, at least, four diastereomers, GLC-MS analysis indicated the presence of only *two* isomeric substances. Their identities were established as diastereomers arising from the *syn* and *anti* acyclic stereochemistry formed in the Mukaiyama−Michael reaction, rather than from epimers arising from specific intramolecular *O*-enolate closure on the prochiral carbonyl pseudosubstituent, $C{=}O^+{-}SiMe_3$,[23] to afford diastereomeric dihydropyrans **3** (Scheme 7). The correct correlations of the GC peaks with the *anti* and *syn* diastereomers **4** (as well as 4,5-*trans*-5,6-*cis*- and 4,5-*cis*-5,6-*trans*-**3** diastereomers; *vide supra*) were established by ^1H NMR spectroscopy. The presence of two dihydropyrans differing only in their *trans*- and *cis*-4,5-dimethyl stereorelations implied that the new quaternary stereocenter *C*-6 formed during the formation of **3** was configurationally unique to both diastereomers. Scheme 7 shows a plausible mechanistic scheme for the formation of **3**.

Formation of 4,5-*trans*-5,6-*cis*-**3** was highly stereoselective. However, on standing in deuteriochloroform solution at ambient temperature, 4,5-*trans*-5,6-*cis*-**3** rapidly equilibrated to 4,5-*trans*-5,6-*trans*-**3** through epimer-

(21) Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

(22) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738. (c) Baldwin, J. E.; Thomas, R. C.; Kruse, L. L.; Silverman, L. *J. Org. Chem.* **1977**, *42*, 3846. (d) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Baca Raton, FL, 1994; esp p 203.

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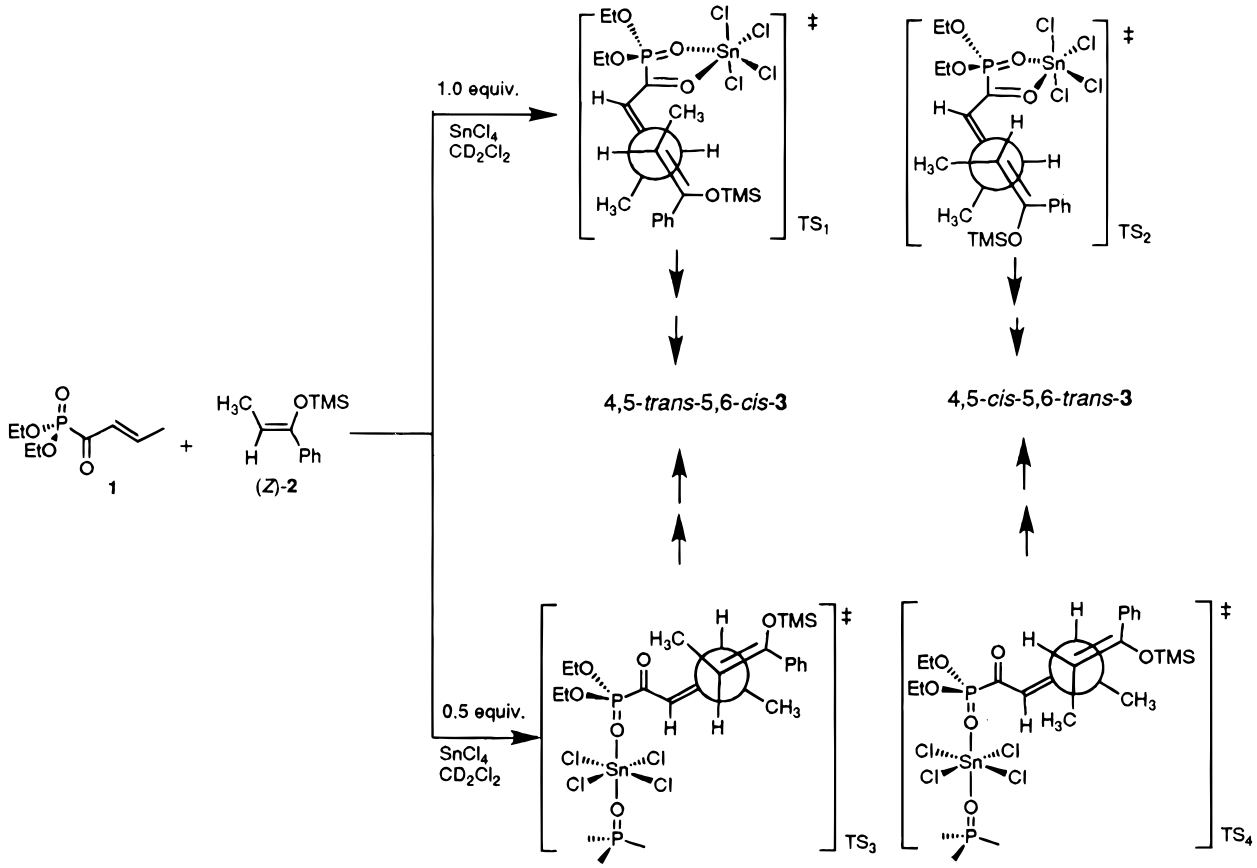
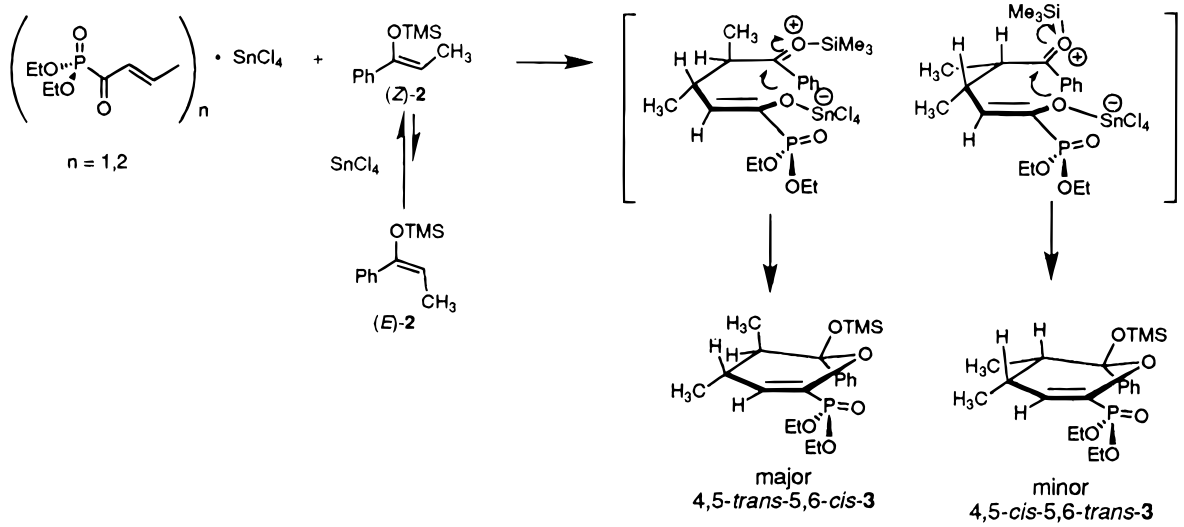
Scheme 6. Mechanistic Proposals for Diastereoselectivity Favoring of 4,5-*trans*-5,6-*cis*-3



Scheme 7. Mechanistic Rationale for Formation of the Isomeric 2-Dihydropyranylphosphonates 3



ization at the C-6 quarternary center. Desilation, followed by hydrolysis of diastereomers **3**, gave phosphonates **4** under the reaction conditions, and after 0.33 h, adducts **4** were isolated as the predominant material. The ratio (GLC) of *syn* to *anti* remained unchanged regardless of whether the isolated adduct was silylated or unsilylated. The *anti* and *syn* stereorelationships of structurally similar 3,4-dimethyl-1,5-diketones have been conclusively assigned by Enders[24] and Wulff,[25] and our assignments of *anti*- and *syn*-**4** were made by analogy. Furthermore, chemical shift and coupling constant data for the "3,4-dimethyl hydrocarbon segment" of **4** are entirely consistent with those reported for *syn* and *anti* diastereoisomers by Heathcock *et al.*[26]

The observation of the dihydropyran **3** raises the possibility of a concerted (and perhaps, nonsynchronous) hetero-Diels−Alder reaction[27] rather than formation via a Mukaiyama−Michael addition, followed by intramolecular cyclization, particularly since only *two* diastere-

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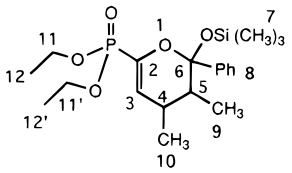
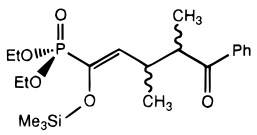


Figure 2. Skeletal numbering of 2-dihydropyran **3**.

omers were observed. In fact, one might anticipate[27c] that the electron deficient nature of the phosphoryl groups, especially when coordinated to $SnCl_4$, could cause a reduction in the oxabutadiene LUMO, and subsequently enhance the [4 + 2] cycloaddition rate with the electron-rich silyl enol ether **2**.[27c,d] If the hetero-Diels–Alder reaction is concerted[27c] the expectations are that exo approach of (*Z*)-**2** to phosphonate **1** should afford cycloadduct, 4,5-*trans*-5,6-*cis*-**3**, while endo approach of (*Z*)-**2** should give 4,5-*cis*-5,6-*cis*-**3**. The results of our studies show that the stereochemical relationship between the C-5 methyl group and the *C*-6 OTMS group (*vide infra*) is *cis* in the case of the initially formed 4,5-*trans*-5,6-*cis*-**3** cycloadduct, and *trans* in case of the 4,5-*cis*-5,6-*trans*-**3** cycloadduct starting with stereochemically homogeneous (*Z*)-**2**. The *cis* stereochemical relationship between the *C*-5 methyl and *C*-6 OTMS groups would be consistent with the expectations from either the Mukaiyama–Michael or Diels–Alder reactions involving (*Z*)-**2** with **1**. However, the trans relationship (*C*-5 methyl/*C*-6 OTMS) would only be consistent with the Mukaiyama–Michael reaction involving (*Z*)-**2** and **1** and/or cycloaddition between (*E*)-**2** and **1**. Under the reaction conditions, configurationally homogeneous (*E*)-**2** rapidly isomerizes to (*Z*)-**2**, and while it is possible that (*Z*)-**2** may be more reactive than (*E*)-**2** as a cycloaddition partner, we believe (based on the present experimental data) that the cycloaddition pathway is not the most favorable.

Structure Determination of 3. The most compelling NMR evidence for the heterocyclic structure of **3** was the presence of three phosphorus-coupled ^{13}C resonances grouped at *ca.* δ 102 (*C*-6, see Figure 2) in the ^{13}C NMR spectrum and the striking absence of any carbonyl resonances in the ^{13}C NMR spectrum.

Confirmation of the heterocyclic structure was obtained by applying HMBC NMR techniques where long range proton–carbon coupling was observed between quaternary silyloxy carbon *C*-6 and *H*-8 of the phenyl ring. This specific coupling could not exist if the structure were acyclic (*e.g.*, **12**)as had been previously reported.[25]



12

NOESY showed correlations between phenyl *H*-8 and methyl *H*-9 hydrogens of the 4,5-*trans*-5,6-*trans*-**3** and 4,5-*cis*-5,6-*trans*-**3** diastereomers. The initial cycloadduct 4,5-*trans*-5,6-*cis*-**3** exhibited an NOE between methyl *H*-9 and silyl methyl *H*-7 hydrogens. Therefore, the methyl and phenyl groups must be oriented *cis*.

Indeed, assignments of *C*-4/*C*-5-dimethyl stereorelationships were based on observations of NOEs between the *C*-9 and *C*-10 methyl hydrogens in the 4,5-*cis*-5,6-*trans*-**3** isomer. By contrast, neither 4,5-*trans*-5,6-*cis*- or 4,5-*trans*-5,6-*trans*-**3** displayed any analogous NOE's.

Previous results from our laboratory[27c] indicated that the pyranoid moiety of a structurally similar system preferred a flattened half-chair conformation (Figure 3). The presence of a long-range W-coupling between vinylic *H*-3 and tertiary *H*-5 hydrogens supported the pseudoequatorial array of the *C*-5 hydrogen on the dihydropyranoid ring. If the *C*-5 hydrogen occupied a pseudoaxial orientation in this ring system, the long range coupling would not be observable.[27c] These findings coupled with the NOE data helped to establish the *cis* and *trans* *C*-4 and *C*-5 dimethyl stereorelationships of the pyranoid ring.

^{31}P NMR resonance assignments were based on 2D HMBC experiments employing $^{1}H-^{31}P$ long range correlations.[28] The vinylic region of the ^{1}H NMR spectrum showed distinct cross peaks with ^{31}P resonances in the ^{31}P NMR spectrum.

In conclusion, the β,γ-unsaturated α-acylphosphonate is a suitable functionality for the Mukaiyama–Michael addition reaction. Our results suggest that the stereoselectivity of the Mukaiyama–Michael addition is sensitive to steric bulk at the Lewis acid metal center. In addition, isolation of synthetically valuable, silylated Michael adduct **3** provides mechanistic insight into the origin of silylated Mukaiyama–Michael adducts.

Experimental Section

General. All reactions were performed using freshly-distilled solvents under an inert atmosphere (dry N_2). Dichloromethane was distilled from P_2O_5 under an Ar atmosphere. Stannic chloride ($SnCl_4$) was distilled under a static vacuum in an all-glass apparatus and subsequently stored in an air-tight flask. Stannic chloride was considered to be homogeneous as long as it remained colorless. Boron trifluoride etherate was distilled at atmospheric pressure under an N_2 atmosphere.

(*E*)- and (*Z*)-Silyl enol ethers **2** were prepared according to literature procedures;[29] however, to minimize the potential for *E*,*Z* isomerization, it was necessary to store (*E*)-**2** in a silylated glass container. This precaution was crucial because if homogeneous (*E*)-**2** was stored in a nonsilylated glass container even for a few seconds at ambient temperature, it rapidly isomerized to (*Z*)-**2**. (*E*)-**2** was obtained from a 3:2 mixture of *Z*:*E* isomers by preparative GLC using a 1/8 e.d. inner diameter, 5-ft aluminum column packed with 20% Carbowax 20M on 45–60 mesh Chromsorb A, equipped with a thermal conductivity detector.

Diethyl propionyl phosphonate (**8**) was prepared via a Michaelis–Arbosov reaction.[5]

General Procedure for Low Temperature NMR Studies. Low temperature NMR studies were performed on a 300 MHz NMR spectrometer with a triple resonance ^{1}H, ^{13}C, and ^{31}P NMR probe. Unless otherwise noted, ^{13}C and ^{31}P NMR were obtained with broad-band decoupling. Diethyl crotonyl phosphonate (**1**) was weighed into a 5-mm, dry NMR tube, a septum was placed over the tube, and the air was removed and replaced with N_2 gas. This step was repeated at least three times, and then 0.8 mL of dry CD_2Cl_2 was added to the NMR tube via syringe. The NMR tube was then cooled to −78 °C in the NMR probe. Initial spectra were acquired, an appropriate amount of Lewis acid was added with a Hamilton GasTight syringe, and spectra of the corresponding complexes were acquired. ^{1}H and ^{13}C NMR spectra were referenced to tetramethylsilane [$(CH_3)_4Si$] while ^{31}P NMR spectra were referenced to external 85% phosphoric acid (H_3PO_4), and

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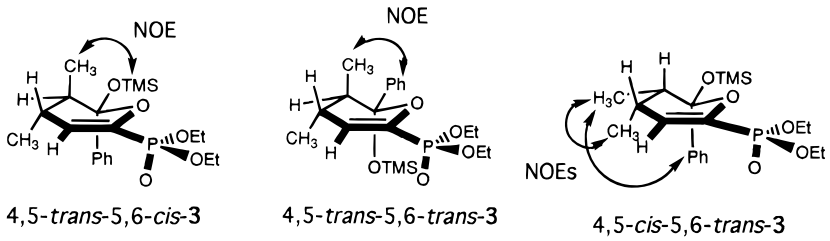

Figure 3. Configurational assignments based on observed NOEs.

^{119}Sn NMR spectra were referenced to external tetrachlorostanne ($SnCl_4$) (δ −150 in $CDCl_3$ solvent).

General Procedure for Mukaiyama−Michael Reactions. Diethyl crotonylphosphonate (**1**; 100 mg, 0.485 mmol), (*Z*)-silyl enol ether **2** (100 mg, 0.485 mmol), tetradecane (internal GLC standard; 65.5 mg, 33.1 mmol), and 10 mL of freshly-distilled CH_2Cl_2 were placed in a two-neck, 50-mL round-bottom flask equipped with a stir bar, under an N_2 atmosphere. An initial 100-μL aliquot was removed via a syringe, quenched with H_2O, extracted with diethyl ether, and dried over Na_2SO_4 for GC-MS analysis. The reaction mixture was then cooled to −78 °C (isopropyl alcohol/dry ice bath), and an appropriate amount of freshly distilled Lewis acid was added using a Hamilton GasTight syringe. Subsequent aliquots were treated similarly. The reaction was ultimately quenched at low temperature (−78 °C) with H_2O, extracted with diethyl ether, washed with a saturated NaCl solution and then water, and dried over anhydrous $MgSO_4$.

Diethyl Crotonylphosphonate (1). Freshly distilled crotonyl chloride (10.6 g, 0.100 mol) was placed in 100-mL, two-neck round bottom flask, equipped with a magnetic stir bar, under a N_2 atmosphere. The flask was cooled to −10 °C in an ice/NaCl bath with stirring, and triethyl phosphite (8.31 g, 0.050 mol) was added dropwise. The solution immediately turned yellow. After the addition was completed, the reaction mixture was allowed to warm to ambient temperature, and it was subsequently stirred for 4 h. Excess crotonyl chloride and triethyl phosphite were removed by vacuum evaporation. The crude reaction mixture was then distilled under reduced pressure to afford 3.10 g (30%)[6,30] of a yellow oil: bp 109 °C (1.0 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dq, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 15.95 Hz; 1H, C*H*), 6.35 (dt, $^3J_{HH}$ = 1.53 Hz, $^2J_{PH}$ = 3.09 Hz, 1H, C*H*), 4.14 (p, $^3J_{HH}$ = 7.05 Hz, $^3J_{PH}$ = 7.89 Hz, 4H, OCH_2), 1.94 (d, $^3J_{HH}$ = 5.31 Hz, 3H, CHCH_3), and 1.30 ($^3J_{HH}$ = 7.08 Hz, 6H, CH_2CH_3); ^{13}C NMR δ 198.4 (d, $^1J_{PC}$ = 172.1 Hz, C=O), 151.15 *C*H), 131.3 (d, $^2J_{PC}$ = 64.9 Hz, *C*H), 63.6 (d, $^2J_{PC}$ = 7.55 Hz, O*C*H_2), 19.16 (CH*C*H_3), and 16.24 (d, $^3J_{PC}$ = 5.28 Hz); ^{31}P NMR δ −1.0. Anal. Calcd for $C_8H_{15}O_4P$: C, 46.46%; H; 7.33%. Found: C, 45.99%; H, 7.36%.

Diethyl 6-Phenyl-4,5-dimethyl-6-(trimethylsilyloxy)-2-dihydropyranphosphonates: 4,5-*cis*-5,6-*trans*-3, 4,5-*trans*-5,6-*trans*-3, and 4,5-*trans*-5,6-*cis*-3. *Preparative Scale Procedure.* Diethyl crotonylphosphonate **1** (200 mg, 0.970 mmol) and (*Z*)-silyl enol ether **2** (200 mg, 0.970 mmol) were placed in 100-mL round-bottom flask under an N_2 atmosphere. The flask was cooled to −78 °C (isopropyl alcohol/dry ice bath with stirring), and $SnCl_4$ (130 mg, 48.5 mmol) was added. The reaction mixture was stirred for 5 min and then quenched with cold water (200 mL) at −78 °C. The product was extracted with diethyl ether, washed with a saturated solution of NaCl and then with water, and subsequently dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude oil was purified by flash column chromatography with anhydrous diethyl ether (R_f = 0.35) to afford 300 mg (75% yield) of homogeneous material. Crystals were obtained from a low temperature (−40 °C) recrystallization using diethyl ether solvent, but these proved to be unsuitable for an X-ray structural analysis because they were too low melting. Successful structural analyses employing NMR parameters were based on the applications of COSY, NOESY, HOHAHA, HMQC, HMBC, and DEPT NMR techniques.

4,5-*cis*-5,6-*trans*-3: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H phenyl), 7.29 (m, 3H, phenyl), 5.83 (dd, J = 11.5 Hz, 1.74 Hz, 1H, C*H* olefinic), 4.17 (p, 2H), 4.15 (p, 2H, OCH_2CH$_3$), 2.21 (m, 1H, C=CHC*H*CH$_3$CH), 1.32 (m, 1H, CHC*H*CH$_3$), 1.42 (t, 3H, OCH$_2$CH_3), 0.72 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CHCH_3CH), 1.05 (d, $^3J_{HH}$ = 7.17 Hz, 3H, CHCH_3COTMSPh), and −0.044 (s, 9H, OTMS); ^{31}P NMR δ 10.0; ^{13}C NMR δ 1.289 [Si(CH$_3$)$_3$], 13.049 [C(OTMSPh)CH*C*H$_3$], 29.66 (d, J = 13.13 Hz, C=*C*CHCH$_3$-CHCH$_3$), 44.94 (d, J = 1.81 Hz, C=CCHCH$_3$*C*HCH$_3$), 102.86 (d, J = 9.21 Hz, O*C*OTMSPh), 122.43 (d, J = 21.21 Hz, C=*C*H), and 141 [d, J = 226 Hz, P*C*(O)=C].

4,5-*trans*-5,6-*cis*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H, phenyl), 7.29 (m, 3H, phenyl), 5.74 (dt, 1H, J = 13.18 Hz, J = 1.62 Hz), 4.17 (p, 2H), 4.15 (p, 2H, OCH_2CH$_3$), 2.00 (m, 1H, C=CHC*H*CH$_3$), 1.95 (m, 1H, CHC*H*CH$_3$), 1.42 (m, 3H, OCH$_2$CH_3), 1.01 (d, 3H, C=CCHCH_3), 0.33 (d, 3H, CHCHCH_3-COTMSPh), and 0.122 [s, 9H, Si(CH_3)$_3$]; ^{31}P NMR δ 10.4; ^{13}C NMR δ 0.987 (Si(CH$_3$)$_3$), 8.63 [C(OTMSPh)CH*C*H$_3$)], 26.88 (d, J = 12.3 Hz, C=*C*CHCH$_3$CHCH$_3$), 40.4 (d, J = 1.73 Hz, C=CCHCH$_3$*C*HCH$_3$), 102.06 (d, J = 8.83 Hz, O*C*OTMSPh), 120.85 (d, J = 21.13 Hz, C=*C*H), and 140 [d, J = 264 Hz, P*C*(O)=C].

4,5-*trans*-5,6-*trans*-3: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H, phenyl), 7.29 (m, 3H, phenyl), 5.82 (d, 1H, J = 11.8 Hz, C*H* olefinic), 4.15 (p, 2H, OCH_2CH$_3$), 2.00 (m, 1H, C=CHC*H*CH$_3$), 2.10 (m, 1H, CHC*H*CH$_3$COTMSPh), 1.42 (m, OCH$_2$CH_3), 0.93 (d, $^3J_{HH}$ = 6.72 Hz, COCHCH_3), 0.97 (d, $^3J_{HH}$ = 7.20 Hz, CH$_2$CHCH_3), and 0.041 (s, 9H, Si(CH_3)$_3$); ^{31}P NMR δ 9.55; ^{13}C NMR δ 0.041 (Si(CH$_3$)$_3$), 29.67 (d, J = 13.13 Hz, C=*C*CHCH$_3$CHCH$_3$), 40.91 (d, J = 1.73 Hz, C=CCHCH$_3$-*C*HCH$_3$), 104.19 (d, J = 9.43 Hz, O*C*OTMSPh), 120.31 (d, J = 20.0 Hz, C=*C*H), and 141.85 [d, J = 218 Hz, P*C*(O)=C]. High resolution mass spectroscopy; 412.1835, consistent with the molecular formula: $C_{20}H_{33}O_5PSi$ (error = −0.6 ppm).

Diethyl 5-Phenyl-3,4-dimethyl-1,5-dioxopentanephosphonates: *syn*- and *anti*-4. Diethyl crotonylphosphonate (**1**) (200 mg, 0.970 mmol) and (*Z*)-silyl enol ether **2** (200 mg, 0.970 mmol) were placed in a 100-mL round-bottom flask under an N_2 atmosphere. The reaction mixture was cooled to −78 °C (isopropyl alcohol/dry ice bath) with stirring, and $TiCl_4$ (184 mg, 0.970 mmol) was added. The contents were stirred for 5 min and then quenched with cold water (200 mL). The product was extracted with diethyl ether, washed with a saturated NaCl solution and with water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude oil was further purified by flash column chromatography [8:2 hexanes:isopropyl alcohol solution as eluent on silica gel (R_f = 0.16)]. The isolated material was further purified by HPLC to give 200 mg (60%) of homogeneous material.

***syn*-4:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.9 (m, 2H, phenyl), 7.46 (m, 3H, Ph), 4.17 (m, 4H, POCH_2CH$_3$), 3.49 (p, 1H, J = 6.5 Hz), 2.98 (dq, 2H), 2.60 (m, 1H), 2.70 (m, 1H), 1.33 (m, 6H, POCH$_2$CH_3), 1.18 (d, J = 5.7 Hz, 3H), and 0.83 (d, J = 6.87 Hz); ^{31}P NMR δ −2.44. ***anti*-4:** δ 7.9 (2H, Ph), 7.46 (m, 3H, Ph), 4.17 (m, 4H, POCH_2CH$_3$), 3.49 (p, 1H), 2.95 (dq, 2 H), 2.60 (m, 1H), 2.70 (m, 1H), 1.13 (d, J = 6.96 Hz, 3H), and 0.98 (d, 3H, J = 6.6 Hz); ^{31}P NMR δ −2.48. High resolution mass spectroscopy: 340.1440 amu, consistent with $C_{17}H_{25}O_5P$ (error = −1.2 ppm).

(30) The low yield in this reaction results from a competing dimerization reaction. See reference 6.

Diethyl propionylphosphonate (8): ^{31}P NMR ($CDCl_3$) δ −2.13; ^{13}C NMR ($CDCl_3$) δ 15.9 ($^3J_{PC}$ = 6 Hz, OCH_2CH_3), 63.3 ($^2J_{PC}$ = 7.5 Hz, OCH_2CH_3), 5.5 ($^3J_{PC}$ = 6 Hz, CH_2CH_3), 36.8 ($^2J_{PC}$ = 53 Hz, CH_2CH_3)), and 211 ($^1J_{PC}$ = 151 Hz, C=O).

(Diethyl propionylphosphonate)$_2$·SnCl$_4$ (9): ^{31}P NMR δ −11.8; ^{13}C NMR: 207 (J = 165 Hz, C=O), 37.6 (J = 58 Hz, CH_2CH_3), 5.5 (J = 6 Hz, CH_3CH_3), 67.5 (J = 9 Hz, OCH_2CH_3), and 15.6 (J = 6.7 Hz, OCH_2CH_3); ^{119}Sn NMR δ −687 (J_{PSn} = 180 Hz).

(Diethyl propionylphosphonate)·SnCl$_4$ (10). ^{31}P NMR δ −1.0; ^{13}C NMR δ 217 (J = 150 Hz, C=O), 36 (J = 60 Hz), CH_2CH_3), 5.6 (J = 6 Hz, CH_3CH_3), 70.6 (J = 9 Hz, OCH_2CH_3), and 15.9 (J = 6 Hz, OCH_2CH_3); ^{119}Sn NMR δ −568.2 (J_{PSn} = 37.4 Hz).

Acknowledgment. We thank the National Science Foundation for generous financial support of this work, and Carol Haney of North Carolina State University for high resolution mass spectroscopy.

Note Added in Proof. The recent report by Otera et al. [Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 2951−62] illustrates the sensitivity of the Mukaiyama−Michael reaction to bulky siloxy and alkoxy groups as well as various Lewis acids such that some competition between electron transfer and nucleophilic substitution may be important. Our current report deals with strongly chelated or ligated complexes involving $SnCl_4$, and we believe that electron transfer processes are less important here.

Supporting Information Available: Experimental procedures and spectral data for all reaction products (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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