(structures with E_1)/(structures with E_2) = $\exp[(E_1 - E_2)/kT]$, was applied to give the relative proportions shown in Table I.

The 36 starting structures for olefin 4 were generated in a similar manner. However, since the exo methylene group is conjugated to the benzo moiety, the molecules were minimized with MMP1,[10] which has provisions for structures with conjugated π electronic systems. The results for 4 in Table II were obtained as described above.

Acknowledgment. We are grateful to Joan Rogers, Roberta Acchione, and Martin Mutter for spectroscopic data. We also thank R. Rosanske (Florida State University) for 270-MHz ^{1}H NMR spectral data on 5 and 7. Thanks are also due to David McComsey for some technical assistance.

Registry No. 1, 101248-93-5; 1·HCl, 101249-00-7; 2, 101248-94-6; 3, 101248-95-7; 4, 101248-96-8; 4·$HClO_4$, 101315-91-7; 5, 101248-97-9; 5·$HClO_4$, 101399-21-7; 6, 101248-98-0; 7, 101399-20-6; 7·$^3/_2$fumarate, 101468-33-1; 8, 101248-99-1; 8 (benzamide deriv), 101249-01-8; 8 (hydrogenation product), 101249-02-9; EtOCOCl, 541-41-3.

Supplementary Material Available: List of endocyclic dihedral angles for the conformers of 4, 5, and 7 that comprise the top 99th percentile (1 page). Ordering information is given on any current masthead page.

Dramatic Concentration Dependence of Stereochemistry in the Wittig Reaction. Examination of the Lithium Salt Effect

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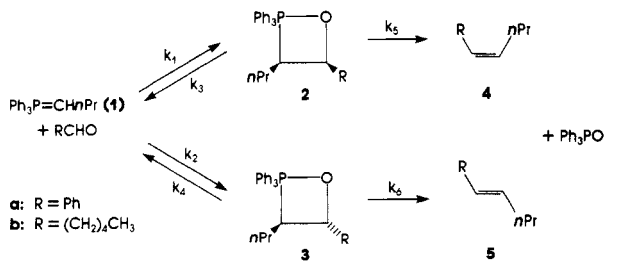
The stereochemistry for Wittig reactions of butylidenetriphenylphosphorane (1) with benzaldehyde and hexanal was examined in detail with regard to concentration effects. For the reaction of 1 and benzaldehyde in the presence of LiBr, the proportion of *trans*-oxaphosphetane (measured by low-temperature ^{31}P NMR) and (*E*)-alkene increased with respect to increasing reaction concentration in THF, approaching limiting values in a hyperbolic manner. Stereochemical drift, i.e., exaggerated production of (*E*)-alkene relative to *trans*-oxaphosphetane intermediate, was also concentration dependent, being more pronounced at higher concentrations. Experiments with varying amounts of lithium cation, and with NaBr instead of LiBr, demonstrated that this phenomenon is associated with the concentration of Li ion, which is increasingly sequestered by the THF solvent at higher dilution. In Me_2SO, the dependence of alkene stereochemistry on concentration was greatly attenuated. In toluene, the concentration effect was inverted to some extent; more (*E*)-alkene was formed at higher dilution (no betaines were observed by ^{31}P NMR at low temperature). The reaction of 1 with hexanal in THF, in the presence of LiBr, exhibited a concentration dependence similar to that observed for the reaction with benzaldehyde (at the oxaphosphetane stage). The rates of the lithium-dependent ("catalyzed") and lithium-independent ("uncatalyzed") reactions in the original carbon–carbon bond-forming step are ranked relative to each other, based on their concentration dependence in THF. For 1 and benzaldehyde in THF (with LiBr present), the catalyzed (k'') and uncatalyzed (k') rate constants have the following *relative* order: $k_1'' = 5.2$ and $k_2'' = 2.5$ mol^{-2}·dm^6·s^{-1}; $k_1' = 1.0$ and $k_2' < 0.02$ mol^{-1}·dm^3·s^{-1} (see Scheme I and Appendix). Thus, at the representative concentrations of 0.05, 0.20, and 0.50 M, the original carbon–carbon bond-forming step of this Wittig reaction is 27%, 61%, and 79% lithium catalyzed, respectively.

Control of stereochemistry in the Wittig olefination reaction has long been an area of intense research.[1,2] Over the 35 years since the reaction's utility was first demonstrated,[3] a variety of factors have been shown to influence the ratio of (*Z*/*E*)-alkenes, including temperature, solvent, choice of aldehyde, type of ylide, and the presence of lithium salts.[1,2a] Nonstabilized phosphorus ylides react with aldehydes to give mainly (*Z*)-alkenes. However, the presence of lithium salts, relative to "salt-free" conditions,

Scheme I



causes the production of (*E*)-alkene, at the expense of (*Z*)-alkene, in reactions of aromatic aldehydes (although the *E* isomer rarely predominates).[4a] Schlosser and Christmann showed that lithium salts affect the original carbon–carbon bond-forming step, by inducing more *threo*-betaine (or, as now accepted, *trans*-oxaphosphetane).[1g] More recently, Vedejs and co-workers, in dem-

(1) (a) Gosney, I.; Rowley, A. G. *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; Chapter 2, and references cited therein. (b) Bergelson, L. D.; Shemyakin, M. M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 250. (c) Bergelson, L. D.; Vauer, V. A.; Varsukov, L. I.; Shemyakin, M. M. *Tetrahedron Lett.* **1964**, 2669. (d) Bergelson, L. D.; Barsukov, L. I.; Shemyakin, M. M. *Tetrahedron* **1967**, *23*, 2709. (e) Le Bigot, Y.; Delmas, M.; Gaset, A. *Inform. Chim.* **1984**, 123. (f) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (g) Schlosser, M.; Christmann, D. F. *Liebigs Ann. Chem.* **1967**, *708*, 1. (h) McEwen, W. E.; Beaver, B. D.; Cooney, J. V. *Phosphorus Sulfur* **1985**, *20*, 255. (i) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694. (j) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

(2) (a) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823. (b) Also see: Vedejs, E.; Snoble, K. A. *Ibid.* **1973**, *95*, 5778.

(3) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.

(4) (a) Aliphatic aldehydes do not show as pronounced a shift to the (*E*)-alkene when using a Li base; e.g., see control experiments reported in ref 4b. (b) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

0022-3263/86/1951-3302$01.50/0

onstrating the importance of oxaphosphetane intermediates,[2] provided substantial evidence for the effect of lithium salts on the initial condensation.[2a] In addition, it has been suggested that lithium salts stabilize Wittig intermediates against decomposition to alkenes, allowing for enhanced reversibility of the adducts to give a measure of thermodynamic control.[1a,d,2a] The lithium salt effect occurs in nonpolar solvents[1f] and is obliterated in polar aprotic solvents, in which lithium ion is effectively solvated.[1a] Since an understanding of factors influencing the stereochemical outcome of the Wittig reaction is vital both mechanistically and synthetically, we have undertaken a systematic study of the effect of concentration on stereochemistry at the stage of oxaphosphetanes and alkenes, particularly with respect to concentration of lithium salt.

Even in the presence of 1 molar equiv of lithium salt, oxaphosphetanes such as **2** and **3** (Scheme I) are the sole observable intermediates in the Wittig reactions of nonstabilized phosphorus ylides.[2a,4b,5,6] In our investigations of the reaction of butylidenetriphenylphosphorane (**1**) and benzaldehyde, we have unambiguously observed, identified, and quantitated the individual *cis*- and *trans*-oxaphosphetanes (**2a** and **3a**, respectively) by low-temperature NMR spectroscopy.[5] Moreover, we have followed the various components of Wittig reactions during the course of decomposition to obtain a detailed kinetic analysis of this process.[5b,7a] Significantly, the original ratio of **2a** to **3a** did not correspond to the final ratio of (*Z*/*E*)-alkenes, so that a disproportionately large amount of (*E*)-alkene (**5a**) was formed. This partial thermodynamic control was termed "stereochemical drift" for convenience.[5a] Stereochemical drift is related to reversibility of the oxaphosphetanes competitive with their decomposition to alkenes.[5] During this work, we were perplexed by the considerable variation in the original ratio of **2a** to **3a** in different preparations, even at temperatures too low for significant oxaphosphetane interconversion and stereochemical drift (less than −40 °C).[5a] From some prior experience,[4b] we suspected that the exact concentration of the Wittig reaction (at least in the presence of LiBr in THF) might be an important determinant of alkene stereochemistry. In the work described here, we provide substantial experimental evidence to support this hypothesis for both the levels of *trans*-oxaphosphetanes and (*E*)-alkenes in THF. We also report experiments performed in other solvents: Me_2SO, toluene, ether, and 2,5-dimethyltetrahydrofuran. In addition, experiments with varied amounts of LiBr, and with substitution of LiBr by NaBr, were conducted.

Results and Discussion

Ylide **1** was prepared from butyltriphenylphosphonium bromide and 1 molar equiv of different bases and reacted with 0.8 molar equiv of benzaldehyde or hexanal. The results from these experiments are listed in Table I and presented graphically in Figures 1 and 2.

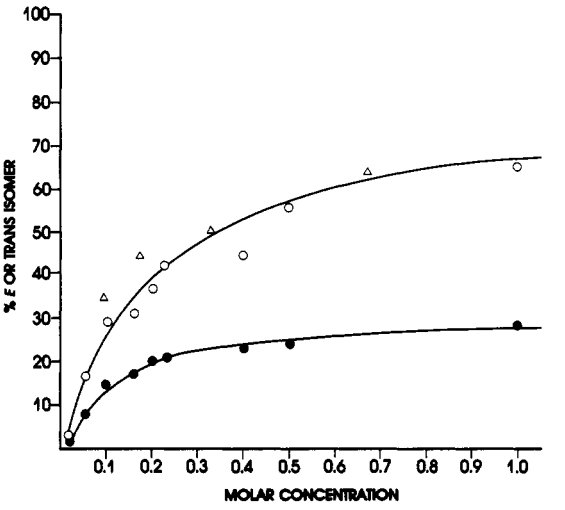


Figure 1. Plot of the relative levels of *trans*-oxaphosphetane and (*E*)-alkene vs. concentration for the reaction of ylide **1** with benzaldehyde in the presence of LiBr in THF. The lines connecting the data points are meant to serve as an aid to the reader: (●) percent **3a** determined by ^{31}P NMR at −40 °C, (○) percent **5a** from NMR experiments determined by GLC, and (△) percent **5a** from room-temperature experiments determined by GLC.

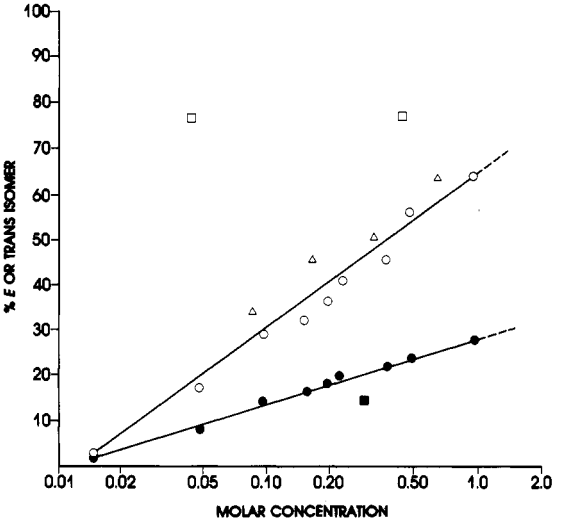


Figure 2. Semi-log plot of the relative levels of *trans*-oxaphosphetane and (*E*)-alkene vs. concentration for the reaction of ylide **1** with benzaldehyde in the presence of LiBr in THF. The two lines are derived from least-squares analysis involving (1) points defined by open triangles and open circles and (2) points defined by closed circles (r^2 = 0.94 or better): (●) percent **3a** determined by ^{31}P NMR at −40 °C, (○) percent **5a** from NMR experiments determined by GLC, (△) percent **5a** from room-temperature experiments determined by GLC, (■) percent **5a** determined by GLC, 1.6 molar equiv of cryptand-211 added, and (□) percent **5a** determined by GLC with the LiBr concentration adjusted to 1.4 M.

The reaction of **1** with benzaldehyde, involving lithium hexamethyldisilazide (LiHMDS) as base, was explored under different concentrations in THF. First, this reaction was conducted at −78 °C and the oxaphosphetanes were measured by ^{31}P NMR at −40 °C, a temperature at which decomposition to alkenes and phosphine oxide is quite slow. The relative amounts of *trans*-oxaphosphetane, **3a**, from each experiment are plotted in Figure 1 relative to the concentration of initial reactants. Analysis of the rate equations for the formation of **2a** and **3a**, separating the lithium-dependent ("catalyzed") and lithium-independent ("uncatalyzed" or "salt-free") components, is given in the Appendix. Also, the relative contributions of these two

(5) (a) Reitz, A. B.; Mutter, M. S.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1984**, *106*, 1873. (b) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr. *Ibid.* **1985**, *107*, 1068. (c) Maryanoff, B. E.; Reitz, A. B. *Phosphorus Sulfur*, in press.

(6) The question of whether acyclic, charge-separated betaines might be transient intermediates in typical reactions of nonstabilized ylides remains unanswered: (a) Piskala, A.; Rehan, A. H.; Schlosser, M. *Collect. Czech. Chem. Commun.* **1983**, *48*, 3539. (b) Schlosser, M.; Huynh, B. T. *Chimia* **1977**, *31*, 219.

(7) (a) A full paper that amplifies on the results of our preliminary communications has been prepared (Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.*, submitted for publication). The kinetic analysis is qualitatively supported by cross-over experiments reported in ref 7b using preformed mixtures of stereochemically pure β-hydroxy phosphonium salts. (b) Maryanoff, B. E.; Reitz, A. B. *Tetrahedron Lett.* **1985**, *26*, 4587.

Table I. Results for Reactions of Ylide 1

concn, (M)	base	2:3	4:5	yield (%)	δ^{31}P NMR 2a	δ^{31}P NMR 3a
		A. Reactions with PhCHO in THF				
0.015	LiHMDS	≥98:2	97:3		−61.9	--
0.05	LiHMDS	92:8	83:17		−61.7	−64.0
0.09	LiHMDS		65:35			
0.10	LiHMDS	86:14	71:29		−61.5	−63.9
0.16	LiHMDS	83:17[a]	69:31			
0.17	LiHMDS		55:45			
0.20	LiHMDS	80:20	64:36		−60.9	−63.7
0.23	LiHMDS	79:21	58:42	68	−61.0	−63.0
0.33	LiHMDS		50:50	86		
0.40	LiHMDS	77:23[a]	55:45			
0.50	LiHMDS	76:24	44:56		−60.2	−62.9
0.67	LiHMDS		36:64			
1.0	LiHMDS	72:28	36:64		−59.6	−62.5
0.33[b]	LiHMDS		84:16			
0.50[c]	LiHMDS		23:77			
0.05[c]	LiHMDS		23:77			
0.064	LDA		84:16	81		
0.20	LDA		68:32	43		
0.80	LDA		50:50	89		
0.06	NaHMDS		100:0			
0.075	NaHMDS		97:3			
0.23	NaHMDS	≥98:2	96:4		−61.8	--
0.33	NaHMDS		91:9	52		
0.90	NaHMDS		94:6			
		B. Reactions with Hexanal in THF[d]				
0.03	LiHMDS		90:10			
0.07	LiHMDS		85:15			
0.25	LiHMDS		80:20			
0.31	LiHMDS		82:18			
0.90	LiHMDS		78:22			
		C. Reactions with PhCHO in Me_2SO				
0.033	LiHMDS		72:28	45		
0.10	LiHMDS		70:30	66		
0.33	LiHMDS		69:31	53		
1.0	LiHMDS		66:34	72		
		D. Reactions with PhCHO in Toluene				
0.021	LiHMDS		15:85			
0.07	LiHMDS		17:83	60		
0.21	LiHMDS	36:64	23:77	51	−61.1	−63.1
0.70	LiHMDS		42:58	66		
		E. Reactions with PhCHO in Ether				
0.06	LiHMDS		13:87; 48:52[e]	0.8		
0.20	LiHMDS		38:62[e]	0.3		
1.0	LiHMDS		13:87	23		
		F. Reactions with PhCHO in 2,5-Di-MeTHF				
0.06	LiHMDS		73:27[e]	<1		
0.10	LiHMDS		100:0	8		
0.20	LiHMDS		100:0[e]	<1		
0.50	LiHMDS		29:71	14		
1.0	LiHMDS		20:80; 14:86	25; 32		

[a] Oxaphosphetane ratios were determined by back extrapolation to $t = 0$ (by computer analysis) of carefully monitored kinetic experiments.[5b,7a] [b] 1.6 molar equiv of cryptand-211 was added. [c] LiBr concentration was adjusted to 1.4 M. [d] Alkenes were analyzed by GLC as a mixture of epoxides (prepared with MCPBA). [e] Since very low yields were realized, the alkene ratios are unreliable. Nevertheless, we obtained reproducible results for the reactions in 2,5-dimethyltetrahydrofuran; ether posed more of a problem.

processes are discussed later on. It is sufficient to say here that the equations predict a hyperbolic increase of **3a** with increasing concentration, which is precisely the type of relationship observed. When levels of **3a** are plotted against the logarithm of concentration, a linear function ($r^2 = 0.99$), which is easier to appreciate visually, is observed (Figure 2). Increasing the concentration from 0.015 to 1.0 M also resulted in a slight downfield shift of the oxaphosphetane resonances; these data are listed in Table I. In addition, the singlets became generally broader with increasing concentration, the width at half-height ranging from 4.4 to 16.3 Hz for **2a** and 11.1 to 12.3 Hz for **3a** at concentrations ranging from 0.015 to 0.10 M. At concentrations of 0.20–1.0 M, the width at half-height ranged from 12.8 to 119.6 Hz for **2a** and 8.2 to 52.2 Hz for **3a**. The reaction mixtures were warmed to room temperature and the resultant alkene composition was determined. The relative amounts of (*E*)-alkene, **5a**, vs. the initial reactant concentration are also plotted in Figure 1. These data, as well, adhere to a linear relationship vs. the logarithm of concentration ($r^2 = 0.98$, Figure 2).

In separate experiments, alkenes were generated by reaction of 1 and benzaldehyde at room temperature (without observation of oxaphosphetanes). The alkene Z/E ratios agreed well with those from the above NMR experiments. Taken together, the values of **5a** define a linear function on the semilogarithmic graph ($r^2 = 0.94$, Figure 2). The separation between the oxaphosphetane and the alkene lines characterizes the degree of stereochemical drift, which virtually vanishes at 0.015 M.

Obviously, care must be taken with Wittig reactions in THF to obtain reproducible alkene stereochemistry. There

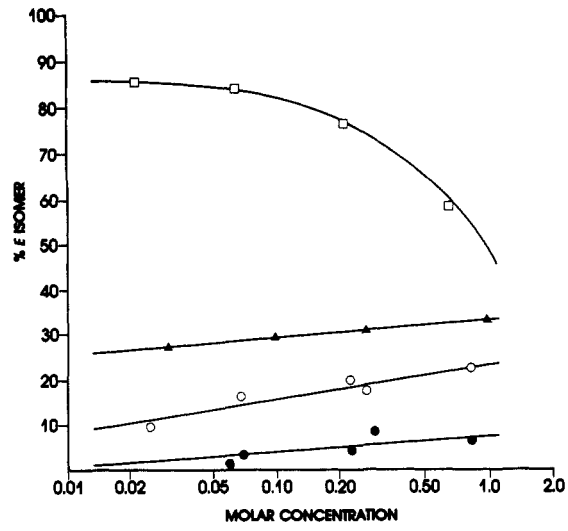


Figure 3. Semi-log plot of the relative levels of (*E*)-alkene determined by GLC vs. concentration for reactions of ylide **1** with benzaldehyde or hexanal. The straight lines defined by the open circles and closed triangles are derived from least-squares analysis (r^2 = 0.92 or better); the other two lines were drawn as an aid to the reader: (○) percent **5b** from **1** and hexanal in THF (LiHMDS), (●) percent **5a** from **1** and benzaldehyde in THF (NaHMDS), (▲) percent **5a** from **1** and benzaldehyde in Me_2SO (LiHMDS), and (□) percent **5a** from **1** and benzaldehyde in toluene (LiHMDS).

are two other important points that emerge on analysis of the results presented in Figures 1 and 2. The relative amount of **3a** increases in a clearly prescribed manner as the concentration increases. Since levels of **3a** were measured at temperatures too low for significant oxaphosphetane interconversion to occur,[2a,5] they reflect the inherent stereochemical bias in the original carbon–carbon bond-forming step. The variation in **3a**:**2a** with initial concentration arises from a concentration dependence of the relative values for the rates of formation of **2a** and **3a**. Moreover, the amount of stereochemical drift to (*E*)-alkene from *trans*-oxaphosphetane is greater at higher concentrations. Any oxaphosphetane reversal would result in recombination reflective of the ambient concentration of lithium salt. This is complemented by cooperative interaction between oxaphosphetane diastereomers.[7b]

Literature precedence surrounding the lithium salt effect in the Wittig reaction[1a-h,2a] led us to suppose that the concentration dependence is primarily due to the available lithium salt in solution. At high dilution, the lithium ions would be fully solvated and unable to influence the reaction (i.e., the Li^+ would be largely sequestered by the THF). To investigate this point further, we reacted ylide **1** and benzaldehyde at 0.33 M in the presence of 1.6 molar equiv of cryptand-211.[8] Alkenes were produced in a Z/E ratio of 84:16, which represents a considerable shift to the (*Z*)-alkene relative to the 50:50 ratio obtained without the cryptand. Reactions performed using NaHMDS, as expected,[1a] gave predominantly **4a** in THF regardless of the initial concentration (Figure 3). Adjusting the LiBr concentration to 1.4 M by adding a solution of LiBr in THF to a 0.5 M lithium salt reaction of **1** and benzaldehyde resulted in a 23:77 Z/E ratio, which corresponds to the Z/E ratio that can be extrapolated from a reaction involving **1** and benzaldehyde at 1.4 M in THF with LiBr present. A 23:77 alkene Z/E ratio was also obtained for a reaction run at 0.05 M in THF that was adjusted to be 1.4 M in LiBr by addition of the requisite amount of the salt. We also tried to examine the oxaphosphetane stereochemistry in reactions enriched in LiBr, similar to those just described. In separate experiments, reactions of **1** and benzaldehyde (at 0.03 M) were adjusted to 0.39 or 0.48 M in LiBr either before or after the addition of the aldehyde (at −78 °C), respectively. In neither instance were peaks for pentavalent phosphorus species observed; rather four peaks between 23 and 35 ppm were recorded. A major signal at 23.4 ppm in both experiments was tentatively assigned to the *erythro*-betaine–LiBr complex. In any case, the concentration dependence in THF, depicted in Figure 1, is associated with the concentration of dissolved lithium ion and its effect on the initial carbon–carbon bond-forming reactions.

The above-mentioned concentration dependence of the oxaphosphetane ^{31}P chemical shift suggests coordination of these intermediates with LiBr, a mild Lewis acid. At high dilution the THF competes favorably for LiBr, dispelling the effect. This can be appreciated by the fact that the ^{31}P NMR signal for **2a** in the 0.015 M LiHMDS experiment has nearly the same chemical shift (−61.9 ppm) as the ^{31}P signal for **2a** in the 0.23 M NaHMDS experiment (Table I).

Condensation of **1**, prepared with lithium diisopropylamide (LDA), and benzaldehyde in THF gave a concentration dependence of alkene stereochemistry similar to that for the experiments performed with LiHMDS (LDA results are listed in Table I). For the majority of experiments, we have used LiHMDS because it is nonpyrophoric and commercially available in convenient 1 M solutions in THF (Aldrich).

In a like manner, we reacted **1** with hexanal in the presence of 1 molar equiv of LiBr at various concentrations (Figure 3, Table I). Aliphatic aldehydes do not generally give oxaphosphetanes capable of reversion or stereochemical drift,[1g,2a,9] so the original ratio of **2b** to **3b** ought to correspond to the Z/E alkene ratio.[5a] The dependence of alkene stereochemistry for reaction of **1** and hexanal is similar to that of the stereochemistry at the oxaphosphetane stage for reaction of **1** and benzaldehyde in the presence of LiBr. This is important because it reflects not only the lack of stereochemical drift for the aliphatic aldehyde but also the fact that *reactions of nonstabilized ylides with aliphatic and aromatic aldehydes may not differ substantially in their intrinsic stereochemistry* (i.e., stereochemistry of original C–C bond formation). The correspondence of original stereochemistry for aliphatic and aromatic aldehydes contrasts with the alkene stereochemistry.

Reaction of **1**, prepared by using LiHMDS, with benzaldehyde in Me_2SO gave a ca. 70:30 mixture of (Z/E)-alkenes, which is exactly the ratio observed in a reaction involving dimsyl sodium in Me_2SO.[4b,10] There is only a slight concentration dependence of this alkene ratio (Figure 3), the values changing from Z/E = 66:34 at 1.0 M to 72:28 at 0.033 M. Thus, Me_2SO gives a mixture of alkenes whose ratio is insensitive to dissolved LiBr or to the initial concentration of reactants.

Similar concentration studies were performed in ether and 2,5-dimethyltetrahydrofuran (Table I). At 1.0 M concentration in either solvent at least 80% of the alkenes

(8) 4,7,13,18-Tetraoxa-1,10-diazabicyclo[8.5.5]eicosane, a lithium-selective cryptand (Parish Chemical Co.), see: Lehn, J. M. *Acc. Chem. Res.* **1978**, *11*, 49.

(9) (a) Anderson, R. J.; Henrich, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327. (b) For exceptions, see ref 4b, 9c and Reitz, A. B.; Maryanoff, B. E. *J. Chem. Soc., Chem. Commun.* **1984**, *1548*. (c) Vedejs, E.; Fang, H. W. *J. Org. Chem.* **1984**, *49*, 210.

(10) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

were the *E* isomer, reflecting the poor ability of these solvents to sequester lithium. At higher dilution, poor yields were encountered and the alkene ratios, while showing more of the *Z* isomer, were variable. Although there was not a general pattern in ether, it is certainly interesting to note the dramatic concentration dependence of stereochemistry in 2,5-di-MeTHF.

Reactions were also performed in toluene. Suspensions of butyltriphenylphosphonium bromide and LiHMDS were stirred together at four different concentrations in toluene. The red solutions of **1** were treated with benzaldehyde after 15 min, resulting in complete decolorization; data for these experiments are presented in Figure 3 and Table I. The level of **5a** did not diminish at high dilution, presumably because of the inability of toluene to solvate lithium ions and thereby abrogate their influence. Rather, the level of **5a** was less at elevated concentrations, perhaps, because of increased precipitation of lithium salt. Consistent with this idea, we noted that all of the toluene reactions contained insoluble material, which was more prevalent at the higher concentrations. The reaction at 0.21 M was examined by ^{31}P NMR at −45 °C and the ratio of **2a** to **3a** was established as 36:64; thermal decomposition gave a *Z*/*E* alkene ratio of 23:77. Although no tetravalent phosphorus species, which would arise from betaines, were observed, the undissolved solid present may have contained betaine·LiBr complex (possibly enriched in one of the diastereomers). Indeed, a reaction at 0.21 M was prepared at −78 °C and quenched with HBr resulting in a 62:38 mixture of erythro and threo β-hydroxy phosphonium salts. This quench experiment is more inclusive in that it detects all of the Wittig intermediate(s) that are formed. This discrepancy emphasizes the limitation of ^{31}P NMR in that it only detects the soluble P species. This is not normally a problem in THF, where precipitation rarely occurs, but can become important in more nonpolar solvents. In any event, the results in toluene still point to a measure of stereochemical drift between the level of *trans*-oxaphosphetane and the final level of (*E*)-alkene. Significantly, the original amount of *trans*-oxaphosphetane **3a** is greater in toluene than in THF at 0.21 M.

At this juncture, it is opportune to elaborate on the relative importance of the lithium-dependent and lithium-independent components of the Wittig reaction, alluded to earlier. The relative amounts of *cis*- and *trans*-oxaphosphetanes, measured at temperatures too low for their interconversion, reflect competition between the two forward reactions, which have rate constants k_1 and k_2 (Scheme I). In the presence of lithium salt, each pathway is comprised of two components, the catalyzed (k_1'' and k_2'') and uncatalyzed (k_1' and k_2') processes. The dependence of oxaphosphetane stereochemistry on concentration in THF affords a rare chance to assess the *relative* contributions made by each reaction component. The necessary kinetic equations to achieve this partition are presented in the Appendix.

Since k_1 and k_2 are much too fast for direct measurement, we are compelled to rely on ratios of **2a** and **3a**, from which we obtain *relative* ratios of the four rate constants k_1'', k_2'', k_1', and k_2'. The relative ranking of these rate constants for the addition of **1** to benzaldehyde in THF (with LiBr present) is 5.2 and 2.5 $mol^{-2}\cdot dm^6\cdot s^{-1}$; 1.0 and <0.02 $mol^{-1}\cdot dm^3\cdot s^{-1}$, respectively. This constitutes the first occasion where the catalyzed and uncatalyzed processes in a lithium salt Wittig reaction have been clearly dissected.

There is an important point that can be made from this ranking. In the presence of lithium ion, the rate of formation of *cis*-oxaphosphetane (in THF) is still greater than the similar rate for forming *trans*-oxaphosphetane ($k_1'' > k_2''$). This is readily appreciated from an inspection of Figure 1, in which there is clearly more *cis*-oxaphosphetane formed even on extrapolation to very high concentration. This reflects the nature of the hyperbolic function in that the competition between the lithium-dependent processes, whose rates are k_1'' and k_2'', approaches a limiting value (still cis rich) at high concentration.

Additionally, one can readily calculate the overall contribution of the catalyzed and uncatalyzed components of the original carbon–carbon bond-forming step at any specific concentration, by using the equation: % catalyzed = % **3a** + % **2a**·k_1''[LiBr]/(k_1''[LiBr] + k_1') = % **3a** + 5.3(% **2a**)[LiBr]/(5.3[LiBr] + 1). Thus, at 0.05 M the lithium-dependent process operates to the extent of 27%. However, at more typical concentrations of 0.20 and 0.50 M, there is a striking increase in the lithium-catalyzed reaction to 61% and 79%, respectively.

Conclusions

The experiments we describe here reflect a pronounced concentration effect in the reaction of a nonstabilized ylide with benzaldehyde in THF when using a lithium base to generate the ylide. Although lithium salts have long been known to affect Wittig reaction stereochemistry,[1,2] our study, entailing measurements of both oxaphosphetane and alkene composition, provides some essential information for understanding what is going on.

Our results elicit an awareness about the sensitivity of certain Wittig reactions to concentration. Considering the alkene line in Figure 1, a concentration of 0.5 M in THF would yield ca. 57% (*E*)-alkene and 0.2 M would yield 42% (*E*)-alkene. Thus, for a desired stereochemical outcome, attention should be paid to the exact conditions of Wittig reactions. At high dilution, it was possible to achieve excellent *Z* stereoselectivity for the reaction of **1** and benzaldehyde with LiBr present; however, such conditions are not especially practical. At the low concentration of 0.015 M the reaction is just borderline lithium catalyzed; it approaches a so-called salt-free reaction.

Whereas there is no lithium salt effect in Me_2SO, an inverse effect is observed in toluene, with less of the (*E*)-alkene being formed at high concentrations. Perhaps, the most important aspect of the toluene results is that there is no reduction of the *E* stereoselectivity on increasing dilution. The nonpolar solvent does not solvate the LiBr, and the salt effect is still enforced at low lithium concentration.

The levels of (*E*)-alkenes produced in THF are a combination of the original levels of *trans*-oxaphosphetanes and the stereochemical drift. Both processes are concentration dependent. It is clear that the principal effect of lithium salt in the Wittig reaction is to alter the relative rates of *cis*- and *trans*-oxaphosphetane formation from ylide and aldehyde.[2a,9c] The lithium salt does not act primarily to facilitate reversibility, which would allow more thermodynamic control.[1a,d,2a] This is apparent in the reactions of **1**, benzaldehyde, and LiBr in THF, in which the original ratio of **2a**:**3a** at −40 °C (where oxaphosphetane interconversion is slow)[2a,5] already reflects ca. 50% of the final amount of (*E*)-alkene. In other work, conditions have been identified under which oxaphosphetanes are reversible in the absence of stereochemical drift.[2a,7b] So, reversibility of Wittig intermediates is a necessary, but not a sufficient, condition for stereochemical drift to occur. The presence of either lithium salts or interacting mixtures of diastereomeric intermediates are required for stereochemical drift.[7b]

The question remains as to how soluble lithium ion can alter the initial step of the reaction to favor *trans*-oxaphosphetanes.[11] Coordination of lithium ion with the aldehyde or ylide may bring the lithium into intimate association with the incipient oxaphosphetane, which could influence the respective activation energies for the diastereomeric reaction pathways. Stronger coordination, such as with lithium tetraphenylborate,[1g] would bias the oxaphosphetane ratio toward the trans isomer.

Experimental Section

General Procedures. GLC analyses were conducted on a Perkin-Elmer 3920B instrument with a flame-ionization detector, using a Hewlett-Packard Model 3392A integrator. The ratios of olefins **4a** and **5a** were determined by GLC on a 3% SE-30 on Chromosorb Q column ($^1/_8$ in. × 6 ft). The ratios of **4b** and **5b** were determined by conversion to the corresponding epoxides with excess *m*-chloroperbenzoic acid, followed by GLC analysis on the above column. The identities of the alkenes were authenticated by comparison to samples with known stereochemical composition (established by ^{1}H and ^{13}C NMR). Solvents (except 2,5-dimethyltetrahydrofuran) were reagent grade and used without additional distillation; moreover, ether and THF were anhydrous grade; Me_2SO was dried over molecular sieves. 2,5-Dimethyltetrahydrofuran (Aldrich) was distilled from $LiAlH_4$; results with distilled and just sieve-dried 2,5-di-MeTHF were essentially the same. Butyltriphenylphosphonium bromide and LiBr were used after drying at 50 °C under high vacuum for at least 5 h. Phosphorus-31 NMR spectra were obtained at 145.8 MHz on a Bruker AM-360 instrument; chemical shifts are referenced to 85% H_3PO_4 (external). Proton NMR were obtained at 360 MHz on the Bruker AM-360 instrument; chemical shifts were referenced to Me_4Si.

Typical Wittig Reaction Conditions. To the appropriate quantity of butyltriphenylphosphonium bromide in 3 mL of solvent was added 1 molar equiv of solid LiHMDS under nitrogen or argon at 23 °C. (For experiments using LiHMDS or NaHMDS in THF, their respective 1 M solutions in THF were used as commercially obtained, adjusting the original amount of THF to arrive at a final volume of 3 mL.)[12] After 15 min, the red solutions were treated with 0.8 equiv of aldehyde at 23 °C, often completely discoloring the solution. After an additional 15 min, water was added followed by an extractive workup. The organic extract was dried ($MgSO_4$), filtered, concentrated, and analyzed by GLC. Alkenes **4b** and **5b** were converted to the epoxides before analysis by treatment with MCPBA (10 equiv) and 4,4′-thiobis(2-*tert*-butyl-6-methylphenol)[13a] (1–2 mg) in refluxing 1,2-dichloroethane for 2 h.[13b] Where yields were determined, the solutions contained a known quantity of diphenylmethane, which served as an internal GLC standard (detector response factors were determined separately).

Wittig Reactions with Added LiBr. The reaction was performed as above except that the THF used was from a 1.8 M stock solution of LiBr in THF, which was adjusted as necessary to arrive at a total dissolved LiBr concentration of 1.4 M.

Wittig Reaction with Added Cryptand-211. To a suspension of 400 mg of butyltriphenylphosphonium bromide (1 mmol) under nitrogen in 1 mL of THF was added 1.1 mL of 1 M LiHMDS/THF (1.1 molar equiv). After 5 min, cryptand-211[8] (470 mg, 1.6 molar equiv) was added to the red solution as a suspension in 0.9 mL of THF, resulting in the formation of a yellow solution with a suspended white precipitate. After an additional 15 min, benzaldehyde (0.08 mL, 0.8 molar equiv) was added; this did not completely discolor the solution. Water was added after 15 min, and the product alkenes were subjected to an extractive workup into pentane and analyzed by GLC.

Quenching Experiment in Toluene. A suspension of 250 mg of butyltriphenylphosphonium bromide (0.63 mmol) in 3 mL of toluene was treated with 114 mg of LiHMDS as a solid (1.1 molar equiv). After 20 min of vigorous stirring, the red solution still contained some undissolved material. It was cooled at −78 °C and treated with benzaldehyde dropwise (60 μL, 1 molar equiv). The discolored solution was then treated with HBr gas, warmed to room temperature, and triturated with ether and hexane, and the solvent was decanted from a yellow oil. This oil was precipitated from $CHCl_3$/hexane to obtain a yellowish powder (200 mg), which was dissolved in $CHCl_3$, treated with charcoal to remove the color, filtered, and concentrated. ^{1}H NMR ($CDCl_3$) revealed a 38:62 mixture of *erythro*- and *threo*-(1-hydroxy-1-phenyl-2-pentyl)triphenylphosphonium bromide by integration of the respective methine protons.[5a]

^{31}P{^{1}H} NMR Spectroscopic Experiments. The samples for NMR analysis were prepared as described earlier.[4b] The aldehydes (1 molar equiv) were added slowly by syringe around a drilled hole in the vortex plug of the NMR tube, to the ylide solution at −78 °C, under a stream of argon. All of the ^{31}P NMR spectra were accumulated under conditions of broad-band proton decoupling between −40 and −30 °C. Additionally, we determined that the ^{31}P nuclei in the two diastereomeric oxaphosphetanes, **2a** and **3a**, relax quickly enough relative to the rate of scan accumulation so that any differences between their relaxation rates[14] would not affect the accuracy of integration. In the toluene experiment, the oxaphosphetanes **2a** and **3a** appeared at −61.1 and −63.1 ppm, respectively.

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Appendix

Analysis[5b] of the equations describing the process shown in Scheme I can be modified when lithium salt is involved, by way of a partitioning of k_1 and k_2. Each oxaphosphetane can be formed by a lithium-dependent (catalyzed) and a lithium-independent (uncatalyzed) process,[2a] so that the rate constants k_1 and k_2 defined in Scheme I are really combinations of two rates as described in eq 1 and 2.

$$\mathrm{d[\mathbf{2a}]}/dt = k_1'[\mathrm{A}][\mathrm{Y}] + k_1''[\mathrm{A}][\mathrm{Y}][\mathrm{L}] \quad (\text{at temp} < -35\ ^\circ\mathrm{C}) \tag{1}$$

$$\mathrm{d[\mathbf{3a}]}/dt = k_2'[\mathrm{A}][\mathrm{Y}] + k_2''[\mathrm{A}][\mathrm{Y}][\mathrm{L}] \quad (\text{at temp} < -35\ ^\circ\mathrm{C}) \tag{2}$$

Since lithium is not consumed, the concentration of lithium remains constant throughout the reaction. A = aldehyde, Y = ylide, L = lithium bromide, [L] = l (initial concentration of lithium bromide). Defining the percent of **3a** as a function of lithium bromide concentration (l), we obtain

$$y = \%\ \mathbf{3a} = \frac{\mathrm{d[\mathbf{3a}]}/dt \times 100}{\mathrm{d[\mathbf{3a}]}/dt + \mathrm{d[\mathbf{2a}]}/dt} = \frac{(k_2' + lk_2'') \times 100}{k_2' + k_1' + l(k_1'' + k_2'')}$$

When $l = 0$, $y = 100k_2'/(k_2' + k_1')$. However, when $l = 0$, inspection of the data presented in Figures 1 and 2 reveals

(11) Aspects of this subject were pointedly discussed in ref 2a.

(12) Experiments with LDA in THF (1 M, Aldrich) were conducted in a similar manner. We have generally not observed any disparate stereochemical results in THF with LiHMDS, LDA, or *n*-BuLi as the base. We disfavor *n*-BuLi because of the hexane solvent that is introduced into the reaction.

(13) (a) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 65. (b) The alkenes were completely consumed. Control experiments with pure **4b** and **5b** resulted in the corresponding isomerically pure epoxides.

(14) Shortt, A. B.; Durham, L. J.; Mosher, H. S. *J. Org. Chem.* **1983**, *48*, 3125.

that $y = 0$. Thus, $k_2' \ll k_1'$ and $y = 100lk_2''/[k_1' + l(k_1'' + k_2'')]$. Reformulating this equation we find

$$k_1'y + (k_1'' + k_2'')yl = 100k_2''l$$

$$k_1'\frac{y}{l} + (k_1'' + k_2'')y = 100k_2''$$

$$y = \frac{100k_2''}{k_1'' + k_2''} - \frac{k_1'}{k_1'' + k_2''}\left(\frac{y}{l}\right) \quad (3)$$

Equation 3 defines a hyperbolic function.[15] The data for the dependence of levels of **3a** on concentration from Table I were analyzed by using eq 3, excluding the result at 0.015 M, because the level of **3a** in this case could not be accurately measured. A high degree of statistical significance to the linear relationship of y and y/l was obtained ($r^2 = 0.95$ and $F = 128.7$). Analysis of the slope and intercept of eq 3 gives the following ratios.

$$\frac{100k_2''}{k_2'' + k_1''} = 32 \qquad \frac{k_1''}{k_2''} = 2.1$$

$$\frac{-k_1'}{k_1'' + k_2''} = -0.13 \text{ mol·dm}^{-3}$$

$$\frac{k_1''}{k_1'} = 5.2 \text{ mol}^{-1}\text{·dm}^3 \text{ and } \frac{k_2''}{k_1'} = 2.5 \text{ mol}^{-1}\text{·dm}^3$$

Thus, one can rank the relative order of the four rate constants as follows: $k_1'' = 5.2$ mol^{-2}·dm^6·s^{-1}; $k_2'' = 2.5$ mol^{-2}·dm^6·s^{-1}; $k_1' = 1.0$ mol^{-1}·dm^3·s^{-1}; $k_2' < 0.02$ mol^{-1}·dm^3·s^{-1}.

Note added in proof: The interested reader should note that ylide 1 in THF solution at 0.2 or 1.0 M, in the presence of equimolar lithium bromide, is uncomplexed, as determined by ^{13}C NMR P-C and P-H one-bond coupling constants (for background, see: Albright, T. A.; et al. *J. Am. Chem. Soc.* **1976**, *98*, 6249. Albright, T. A.; Schweizer, E. E. *J. Org. Chem.* **1976**, *41*, 1168). Details will appear in ref 7a.

Registry No. 1, 3728-50-5; LiBr, 7550-35-8; benzaldehyde, 100-52-7; hexanal, 66-25-1.

(15) Eves, H. in *Standard Mathematical Tables*, 24th ed.; CRC Press: Cleveland, OH, 1976; pp 298-300.

Symmetrically Trisubstituted Triptycenes

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A simple synthesis of 1,8,13- and 1,8,16-trisubstituted triptycenes is described. Diels-Alder reaction of 1,8-disubstituted anthracenes with ortho-substituted benzynes gave 15 new triptycene compounds as mixtures of the syn (1,8,13) and anti (1,8,16) trisubstituted triptycenes, which in most cases could be separated by HPLC to afford pure isomeric products. The syn/anti ratio depends on the nature of the substituents on the anthracene and benzyne units. In addition, the improved syntheses of three 1,8-disubstituted anthracenes and a new synthetically useful ortho-substituted aryne are reported.

Rigid carbon frameworks can be used to juxtapose functional groups for a variety of purposes in organic and inorganic chemistry. Potential applications include host-guest complexes, molecular inclusion compounds, and coordination complexes with unusual geometries. Triptycene has a rigid structure with three equivalent benzene rings that provides an ideal framework for systems requiring the imposition of threefold symmetry. Consequently, we became interested in utilizing symmetrically trisubstituted triptycenes as foundations for construction of synthetic model complexes for a variety of metalloprotein active sites that have effective threefold symmetry; these include the P-clusters of nitrogenase,[2] the iron-sulfur cluster of aconitase,[3] and the blue copper proteins.[4] Low molecular weight compounds that mimic ligand types and coordination geometries present in metalloproteins have been used extensively as probes of structure and functions.[5]

Another application of these rigid molecules is the study of molecular inclusion phenomena. Triptycenes have been used as "spacers" leading to crystalline compounds containing channels capable of occluding a variety of other molecules.[6] In addition, trisubstituted triptycenes have the potential for forming clathrate compounds with varying cavity sizes.[7]

Our specific goal was to synthesize symmetrically trisubstituted triptycenes containing functional groups at the 1-, 8-, and 13-positions.[8] Although numerous substituted triptycenes have been prepared,[9] only one symmetrically trisubstituted compound was known prior to this work:

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(1) Alfred P. Sloan Fellow, 1981-1985.
(2) Averill, B. A. *Structure Bonding* **1983**, *53*, 59.
(3) Emptage, M. H.; Kent, T. A.; Kennedy, M. C.; Beinert, H.; Münck, E. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 4674.
(4) Thompson, J. S.; Marks, T. J.; Ibers, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 4180.
(5) Ibers, J. A.; Holm, R. H. *Science (Washington, D.C.)* **1980**, *209*, 223.
(6) (a) Hart, H.; Lin, L.-T. W.; Ward, D. L. *J. Am. Chem. Soc.* **1984**, *106*, 4043. (b) Toda, F.; Ward, D. L.; Hart, H. *Tetrahedron Lett.* **1981**, *22*, 3865. (c) For a review of host-guest complexes, see: Cram, D. J.; Cram, J. M. *Science (Washington, D.C.)* **1974**, *183*, 803.
(7) For a review of clathrate compounds, see: MacNicol, D. D.; McKendrick, J. J.; Wilson, D. R. *Chem. Soc. Rev.* **1978**, *7*, 65.
(8) Note that the numbering scheme of the triptycene structures in this paper is consistent with the 9,10-dihydro-9,10-o-benzenoanthracene nomenclature used by Chemical Abstracts.
(9) For a review of triptycenes, see: Skvarchenko, V. R.; Shalaev, V. K.; Klabunovskii, E. I. *Russ. Chem. Rev. (Engl. Transl.)* **1974**, *43*, 951.

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