Stereoselectivity in the Wittig Reaction of Aromatic Ketones: Origin of Preference for the Olefin Geometry

Kumiko Takeuchi,*,† Jonathan W. Paschal, and Richard J. Loncharich*

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

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Investigation of the stereoselectivity observed in the Wittig reaction of aromatic ketones with "nonstabilized" phosphonium ylides revealed that the nature of the substituent on the phenyl ring of phenyl 3-pyridyl ketone determined the stereoselectivity. Generally the Wittig reaction of such ketones with carboxy phosphonium ylides proceeded preferentially to yield (*Z*)-olefin, albeit with modest selectivity. However, the reaction with aryl sulfonamido-substituted aromatic ketones resulted in high (*E*)-stereoselectivity. In order to understand the origin of this high (*E*)-selectivity, a semiempirical conformational analysis of the four uncharged diastereomeric oxaphosphetane intermediates was performed with a cumulatively modified sampling procedure to generate initial conformations, followed by full energy optimization. Computational studies of the unsubstituted and 4-nitrophenyl-substituted oxaphosphetane intermediates were consistent with the low (*Z*)-stereoselectivity observed. The results in the calculations of the aryl sulfonamido-substituted intermediate likewise were consistent with the high (*E*)-stereoselectivity observed. Calculations of the potassium-coordinated acid anion of the latter species were also performed. All calculations supported interaction of the sulfonamido and carboxylate groups by either hydrogen bonding or salt bridge formation which appears to effect the final stereochemical outcome. Furthermore, we investigated the stereoselectivity of Wittig reactions in which the sulfonamido NH or the carboxylate were removed. In both cases, the (*Z*)-olefin was formed preferentially, thereby supporting the existence of intramolecular hydrogen bonding or salt bridge formation.

Introduction

Since its discovery, the Wittig carbonyl olefination reaction by means of phosphorus ylides has been a favorite tool in preparative organic chemistry.[1] This olefination method has enjoyed widespread prominence and recognition because of its simplicity, convenience, and efficiency. The conventional Wittig reaction involves the reaction of a phosphonium ylide with an aldehyde or a ketone. One of the main virtues of this synthetic method is its complete structural specificity: namely, the new carbon–carbon double bond formation in the Wittig reaction appears exclusively at the site of the former carbonyl function.[2] Despite this chemoselectivity, the usefulness of the Wittig reaction often hinges upon its effective control for the preferential formation of (*E*)- or (*Z*)-olefin geometry, depending on the desired outcome under a particular circumstance. Such stereocontrol is in fact possible by carefully selecting the type of ylide, type of carbonyl compound, or reaction conditions.[3]

Phosphorus ylides are classified as "stabilized", "semistabilized", and "nonstabilized" according to their general reactivity which is dictated by certain substituents on the ylidic carbon (e.g., ester, nitrile, and phenylsulfonyl for "stabilized"; phenyl and allyl for "semistabilized"; and none for "nonstabilized"). Stereoselectivity of Wittig reactions with these ylides generally is favored and shifts from (*E*) to (*Z*) according to the ylide's stability in the "more-stable to less-stable" order.[4] A reaction of so-called "nonstabilized" triphenylphosphonium ylide with an aldehyde preferentially forms the contrathermodynamic (*Z*)-alkene.[3] However, there are exceptions to this generalized stereoselectivity. For example, Maryanoff and Duhl-Emswiler observed[5] anomalous (*E*)-stereoselective Wittig reactions of aromatic aldehydes with (4-carboxybutylidene)triphenylphosphorane (**1**: $Ph_3P{=}CH(CH_2)_3COO^-M^+$; M = Li, Na, or K), an ylide commonly employed in the synthesis of prostaglandins and related compounds because of its high (*Z*)-stereoselectivity when reacted with aliphatic aldehydes.[6] Pronounced (*E*)-stereoselectivity in reactions of aldehydes with triphenylphosphorus ylides bearing anionic groups has received considerable attention.[4,7] However, to our knowledge, such study with ketones have not been reported.

We have observed unusual stereoselectivity in the Wittig reaction of aromatic ketones with carboxy phosphonium ylides. Our results show that the substituent on the phenyl ring of phenyl 3-pyridyl ketones dictates the (*E*) or (*Z*) predominance in the reaction. Abnormally high (*E*)-stereoselectivity was observed with ketones bearing an aromatic sulfonamido group. We have attempted to collate our observations into a plausible mechanistic explanation with both experimental verification and computational analysis. We have also probed

† Please send all correspondence to: Dr. Kumiko Takeuchi, Lilly Research Laboratories, Drop 0528, Lilly Corporate Center, Indianapolis, IN 46285.

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(1) (a) Johnson, A. W. *Ylid Chemistry*; Academic: New York, 1966. (b) Maercker, A. *Org. React.* **1965**, *14*, 270.

(2) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; John Wiley: New York, 1992; pp 956–963.

(3) (a) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (b) Gosney, I.; Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic: New York, 1979; pp 17–153.

(4) An excellent review has appeared on the stereochemistry, mechanism, and selected synthetic aspects of phosphonium ylides and phosphoryl-stabilized carbanions, see Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(5) Maryanoff, B. E.; Duhl-Emswiler, B. A. *Tetrahedron Lett.* **1981**, *22*, 4185.

(6) (a) Mitra, A. *The Synthesis of Prostaglandins*; Wiley-Interscience: New York, 1977. (b) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977. (c) Roberts, S. M.; Scheinmann, F., Eds. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic: London, 1982; Chapters 2–7.

(7) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

0022-3263/95/1960-0156$09.00/0

Table 1. (*E*/*Z*) Ratio of 3- and 4-[(Benzenesulfonyl)amino]phenyl 3-Pyridyl Alkenoic Acids Derived from eq 1

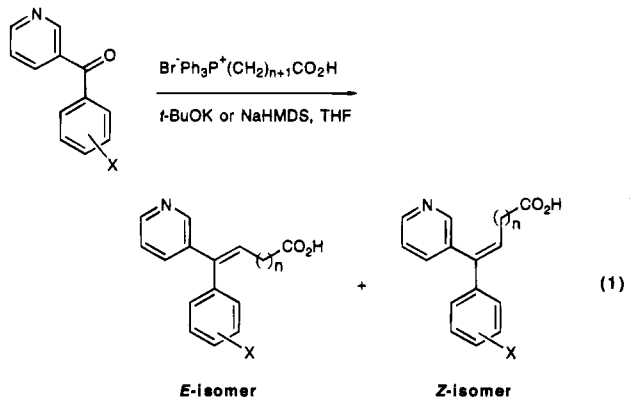
entry	*n*	X	base	*E*/*Z*[a]	yield, %[b]
2a	2	3-$NHSO_2Ph$	NaHMDS	90:10	48
2b	3	3-$NHSO_2Ph$	NaHMDS	77:23	55
2c	4	3-$NHSO_2Ph$	NaHMDS	84:16	54
2d	5	3-$NHSO_2Ph$	NaHMDS	100:0	9
2e	6	3-$NHSO_2Ph$	NaHMDS	96:4	34
2f[c]	7	3-$NHSO_2Ph$	NaHMDS	73:27	2
3a	3	4-$NHSO_2Ph$	*t*-BuOK	98:2	92
3b	4	4-$NHSO_2Ph$	*t*-BuOK	97:3	88
3c	5	4-$NHSO_2Ph$	*t*-BuOK	93:7	100
3d	6	4-$NHSO_2Ph$	*t*-BuOK	96:4	100
22[d]	3	4-$(CH_2)_2NHSO_2Ar$	*t*-BuOK	95:5[e]	78

[a] The (*E*/*Z*) ratio was determined by HPLC analysis. [b] The reactions have not been optimized. [c] Prepared from 3-[(benzenesulfonyl)amino]phenyl 3-pyridyl ketone and [9-(*tert*-butyldimethylsiloxy)nonyl]triphenylphosphonium bromide, followed by Jones oxidation. [d] Soyka, R. et al. See ref 21 (Ar = Ph-*p*-Cl). [e] Isolated ratio.

if there is any similarity or discrepancy between aromatic ketones and aromatic aldehydes for their unusual stereoselectivity in the Wittig reaction with "nonstabilized" phosphonium ylides.

Results and Discussion

(A) Experimental Results. In the course of developing a therapeutic agent which exhibits dual action to inhibit the thromboxane receptor and thromboxane synthase for cardiovascular and renal diseases,[8] we synthesized target compounds **2a**–**f** and **3a**–**d** (Table 1) from aromatic ketones, utilizing a Wittig reaction to incorporate the alkenoic acid chain (eq 1).[9]



(1)

Compounds **2a**–**f** were synthesized from 3-[(benzenesulfonyl)amino]phenyl 3-pyridyl ketone and (ω-carboxyalkyl)triphenylphosphonium bromides, which were treated with sodium hexamethyldisilazide (NaHMDS) in THF at −78 °C to room temperature. Similarly, but more efficiently, compounds **3a**–**d** were synthesized from 4-[(benzenesulfonyl)amino]phenyl 3-pyridyl ketone and (ω-carboxyalkyl)triphenylphosphonium bromides, which were treated with *t*-BuOK in THF at 0 °C to room temperature (Table 1). All the products obtained were highly enriched in the (*E*)-isomer except for **2b** and **2f** (*vide infra* for this low (*E*)-stereoselectivity); the isomers were difficult to separate by chromatography.

Table 2. (*E*/*Z*) Ratio of Substituted Phenyl 3-Pyridyl Alkenoic Acids Derived from eq 1 (base = *t*-BuOK)

entry	*n*	X	*E*/*Z*[a]	yield, %[b]
4	4	3-NO_2	1:2.9[c]	45[c]
5	4	4-NO_2	1:5	57[c]
6	4	2-$CH_2OTBDMS$	1:2.0[d]	92
7	4	2-$(CH_2)_2OTBDMS$	1:1.5	24[c]
8a	3	3-$CH_2OTBDMS$	1:2.3	70[c]
8b	4	3-$CH_2OTBDMS$	1:~2.3[c]	84[c]
8c	5	3-$CH_2OTBDMS$	1:2.5[c]	52[c]
9a	3	4-$CH_2OTBDMS$	1:5	78
9b	4	4-$CH_2OTBDMS$	1:4.1	65
9c	5	4-$CH_2OTBDMS$	1:3.9[c]	60
21	4	4-$N(CH_3)SO_2Ph$	1:2.8	80

[a] The (*E*/*Z*) ratio was determined by ^1H NMR except entry **21** which was determined by HPLC. [b] The reactions have not been optimized. [c] As the methyl ester. [d] The (*E*/*Z*) ratio varied from 1:1.3 to 1:6. The average ratio is listed in the table.

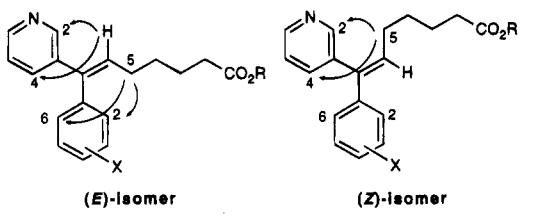


Figure 1. Nuclear Overhauser effects of trisubstituted (*E*)- and (*Z*)-alkenoic acid derivatives.

In order to confirm the structure and assess the biological activity of the individual isomers, nitro- and protected (hydroxyalkyl)phenyl 3-pyridyl ketones were prepared and subjected to the Wittig reaction. The nitro- and hydroxyalkyl groups were later converted to amines for further functionalization after isolation and separation of the (*E*/*Z*) Wittig product mixture. The (*E*)- and (*Z*)-isomers obtained from these ketones were easily separated by flash chromatography especially after esterification or in a later step. Results of these Wittig reactions are listed in Table 2.[9] The (*Z*)-isomer predominated with modest stereoselectivity in all instances (entries **4**–**9c**).

Stereochemical assignments of the trisubstituted ω-alkenoic acids rested on their ^1H NMR spectra, nuclear Overhauser effect (NOE) experiments, and their mobility on silica gel. The chemical shift of the olefinic proton of (*E*)-isomers in their ^1H NMR spectra was, in general, shielded upfield compared to that of (*Z*)-isomers. NOEs were observed between the olefinic proton of the alkenoic acid chain and the C_2 and C_4 protons of the pyridyl ring as well as between the C_5 allylic protons of the alkenoic acid chain and the C_2 and C_6 protons of the phenyl ring for the (*E*)-isomer (Figure 1). For the (*Z*)-isomer, an NOE cross peak was observed between the allylic protons of the alkenoic acid chain and the C_2 and C_4 protons of the pyridyl ring, whereas an NOE cross peak between the olefinic proton and the C_2 and C_6 protons of the phenyl ring was not observable.

Mobility of the geometrical isomers indicated that, in general, the (*E*)-isomers were less mobile (more polar) on silica gel than the (*Z*)-isomers. Observation of ^1H

(8) For reviews on thromboxane receptor antagonists and thromboxane synthase inhibitors for cardiovascular, pulmonary, and renal diseases, see: (a) Jakubowski, J. A.; Smith, G. F.; Sall, D. J. *Annu. Rep. Med. Chem.* **1992**, *27*, 99. (b) Hall, S. E. *Med. Res. Rev.* **1991**, *11*, 503. (c) Cross, P. E.; Dickinson, R. P. *Chem. Br.* **1991**, 911. (d) Remuzzi, G.; FitzGerald, G. A.; Patrono, C. *Kidney Int.* **1992**, *41*, 1483–1493. (e) Vermylen, J.; Deckmyn, H. *Cardiovasc. Drugs Ther.* **1992**, *6*, 29. (f) Gresele, P.; Deckmyn, H.; Nenci, G. G.; Vermylen, J. *Trends Pharmacol. Sci.* **1991**, *12*, 158–163.

(9) For complete details of this work, see: Takeuchi, K.; Happ, A. M.; Mais, D. E.; Layman, N.; Utterback, B. G.; Wyss, V. L.; Jakubowski, J. A. *Biomed Chem.*, in press.

NMR spectra and mobility of our compounds was consistent with literature precedent.[10]

Kato and co-workers have reported similar results in their synthesis of thromboxane synthase inhibitors.[10] Their Wittig reaction was carried out in DMSO with NaH as base, which further diminished[11] the stereoselectivity of the Wittig reactions (for example, (*E*/*Z*) ratio for 3-nitro derivatives was 1:1.5 in DMSO[10] but 1:2.9 in THF (entry **4** in Table 2)). Kato's results and ours in Table 2 show little difference between electron-withdrawing (EW) and electron-donating (ED) groups in their substituent effect on the isomeric ratio. These EW and ED substituents exerted relatively little effect on the stereochemical outcome both in degree and geometry in contrast to the sulfonamido group.

These findings indicate that the substituent on the phenyl ring has a significant effect on the stereoselectivity in the Wittig reaction of phenyl 3-pyridyl ketones. Noteworthy, in particular, was the effect of the sulfonamido group which led to high (*E*)-stereoselectivity. We speculated that the hydrogen bonding ability of the sulfonamido group might be influencing the stereoselectivity observed in these Wittig reactions, since the electronic effect of two opposite groups (EW or ED) did not affect the degree of stereoselectivity, nor did a steric effect appear to be a factor (Table 2).[12]

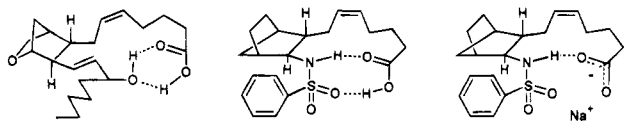
It is well documented that 1,2-oxaphosphetanes are the principal intermediates in various Wittig reactions involving "nonstabilized" phosphorus ylides with aldehydes or ketones.[4,15] Many of these types of reactions are under kinetic control, whereupon the initial ratio of *cis* and *trans* oxaphosphetanes reflects the origin of stereochemistry for carbon–carbon bond formation.[4] Diastereomeric oxaphosphetanes generally afford alkenes with retention of configuration via *syn* elimination. We speculated that intramolecular hydrogen bonding (**A**) or a salt bridge formation (**B**)/(**C**) between a sulfonamido group and a carboxylate might be taking place sometime during the intermediate oxaphosphetane formation when a sulfonamido-substituted ketone reacted with a phosphorus ylide containing carboxylate as depicted in Scheme 1. Such interactions would result in *trans*-oxaphosphetane intermediates and thus (*E*)-alkene formation. Formation of a species such as **C** would be possible in cases where a very acidic hydrogen of the sulfonamide can be deprotonated by excess base. In order to examine the existence and extent of intramolecular hydrogen bonding or salt bridge formation, we explored both experimental verification and theoretical calculations (*vide infra*). If intramolecular hydrogen bonding or salt bridge formation were facilitating the stereoselectivity of these Wittig reactions, then removal of either the sulfonamido NH or the carboxylate should result in a loss of stereoselectivity. We therefore carried out Wittig reactions using (i) a phosphonium salt which lacked carboxylic acid on one hand and (ii) an N-protected sulfonamide on the other (Scheme 2).[16] The first reaction from ketone **12** and hexyltriphenylphosphonium bromide gave the (*E*/*Z*)-mixture of product **17** in a 43:57 ratio and the second reaction from ketone **20** resulted in a 26:74 ratio of (*E*/*Z*)-isomers **21**. (The ratio of the latter, **21**, did not change when excess base and Wittig reagent were employed.) The experimental results support our proposed mechanism. In both cases, the stereoselectivity was lost and the stereochemistry was reversed, as in the examples listed in Table 2.

Maryanoff reported anomalous (*E*)-stereoselectivity in the reaction of "nonstabilized" triphenylphosphorus ylides bearing anionic groups with aromatic aldehydes and suggested that the stereoselectivity might be associated with an intramolecular interaction involving the carboxy terminus.[5] Later he and co-workers conducted a systematic study to investigate the effect of anionic, nucleophilic groups in the phosphonium ylide on the (*E*)-stereoselectivity in reactions with aldehydes.[7] Substituents investigated included oxido, carboxylate, amino, and amido groups. They performed deuterium-labeling and ^{31}P NMR studies to probe possible mechanisms. After analyzing several plausible mechanisms, they concluded that the metallooxido group facilitated interconversion of reaction adducts, oxaphosphetanes, by reaction reversal to ylide and aldehyde and thus influenced stereochemical outcome rather than affected initial carbon–carbon bond formation. Namely, they refuted preferential formation of thermodynamically stable *trans*-oxaphosphetane intermediates in the initial stage of the reaction, though not completely excluding such possibility. On the basis of the results from the deuterium-exchange experiments and ^{31}P NMR evidence which indicated oxaphosphetanes as the reaction intermediate, they have excluded a Schlosser-type[17] intramolecular "*trans*-selective Wittig" process as a major contributing factor to anomalous (*E*)-stereoselectivity for oxido and carboxy ylides. They have found that the stereochemis-

(10) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287.

(11) For the solvent effect on Wittig reaction, see: (a) Schlosser, M.; Schaub, B.; de Oliveira-Neto, J.; Jeganathan, S. *Chimia* **1986**, *40*, 244. (b) Reitz, A. B.; Nortey, S. O.; Jordan, A. D., Jr.; Mutter, M. S.; Maryanoff, B. E. *J. Org. Chem.* **1986**, *51*, 3302.

(12) The hairpin conformation hypothesis proposed by Andersen et al. states that thromboxane receptor binding requires a prostaglandin conformation with a U-shaped or approximately parallel arrangement of the α- and the ω- side chains. The hypothesis has been supported by the conformational analysis of thromboxane A_2 (TXA_2), its receptor agonist (U-46619, **10**), and its potent receptor antagonist such as S-145 (**11**), all of which low-energy conformations adopt a hairpin-like turn.[13] Moreover, Takasuka and co-workers supported the assumption that a hairpin conformation is stabilized by hydrogen bonding between the NH (sulfonamides) or OH (allylic alcohols) of the ω-side chain and carboxy terminus of the α-side chain.[14] Using FTIR spectroscopy, they have measured the degree of intramolecular hydrogen bonding of **10** and **11** in $CHCl_3$ and CCl_4 and observed twelve- to fifteen-membered macrocycles which were formed by the intramolecular hydrogen bonds between the functional groups of α- and ω-side chains as shown below.



See Andersen, N. H.; Ramwell, P. W.; Leovey, E. M.; Johnson, M. *Avd. Prostaglandin Thromboxane Res.* **1976**, *1*, 271.

(13) Ezumi, K.; Yamakawa, M.; Narisada, M. *J. Med. Chem.* **1990**, *33*, 1117. Several assumptions made in this study have been called to question, however (see ref 8(b)).

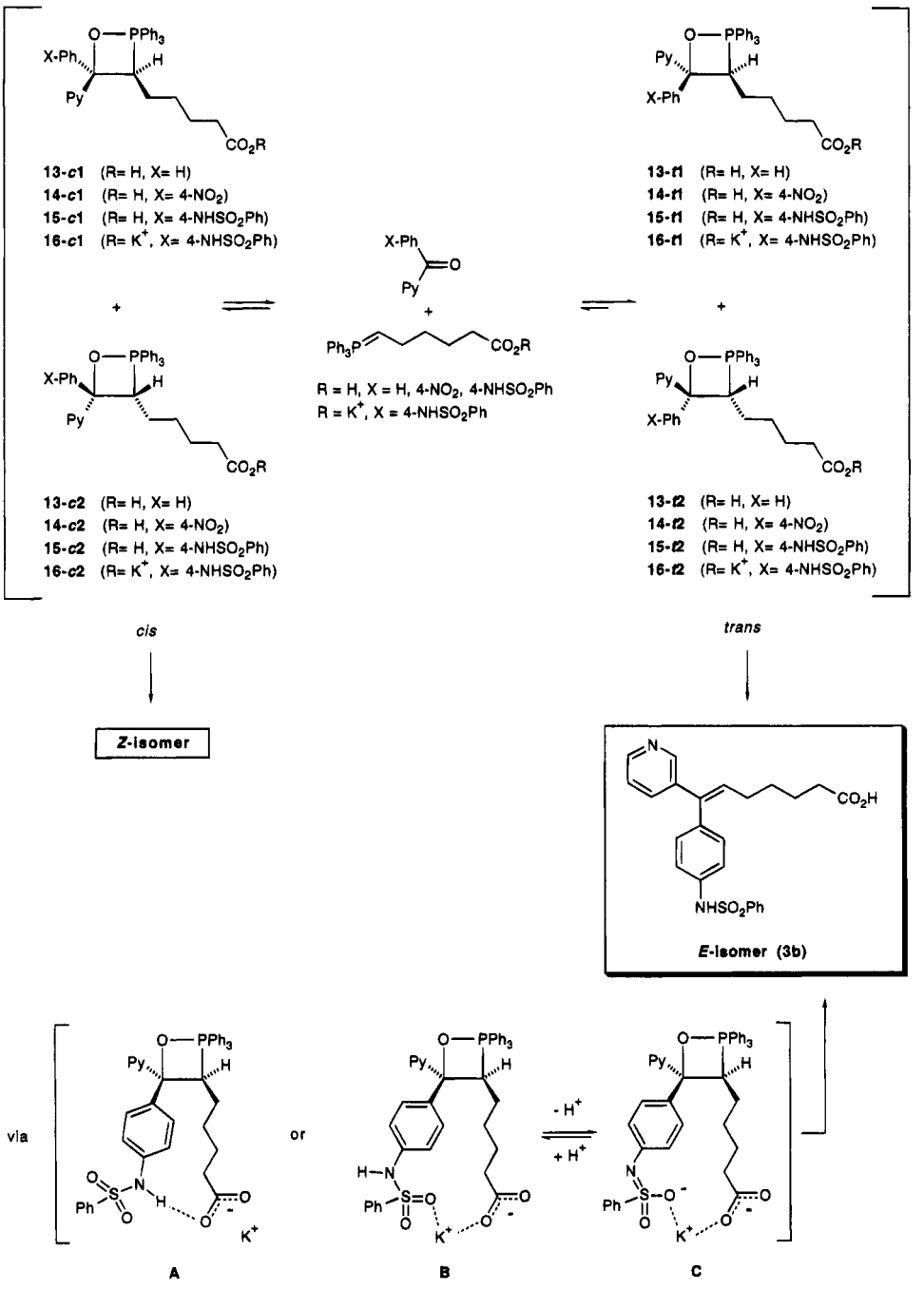
(14) (a) Takasuka, M.; Yamakawa, M.; Watanabe, F. *J. Chem. Soc. Perkin Trans. 2* **1989**, 1173. (b) Takasuka, M.; Yamakawa, M.; Ohtani, M. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1467. (c) Takasuka, M.; Yamakawa, M.; Ohtani, M. *J. Med. Chem.* **1991**, *34*, 1885. For a similar study on charge distribution and conformational analysis of inhibitory or stimulatory agents for platelet aggregation, see Ojima, M.; Tokuhiro, T. *Prostaglandins Leukotrienens Essent. Fatty Acids* **1992**, *47*, 69.

(15) Specifically, Vedejs and co-workers were the first to observe and establish that oxaphosphetanes are the sole observable intermediates in the Wittig reactions of "nonstabilized" ylides, see (a) Vedejs, E.; Snoble, K. A. J. *J. Am Chem. Soc.* **1973**, *95*, 5778. (b) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am Chem. Soc.* **1981**, *103*, 2823.

(16) We also tried a Wittig reaction of ketone **12** with (5-carbethoxypentyl)triphenylphosphonium bromide. The reaction did not proceed and ketone **12** was recovered.

(17) Schlosser, M.; Christmann, K. F. *Angew. Chem. Int. Ed. Engl.* **1966**, *5* 126.

Scheme 1



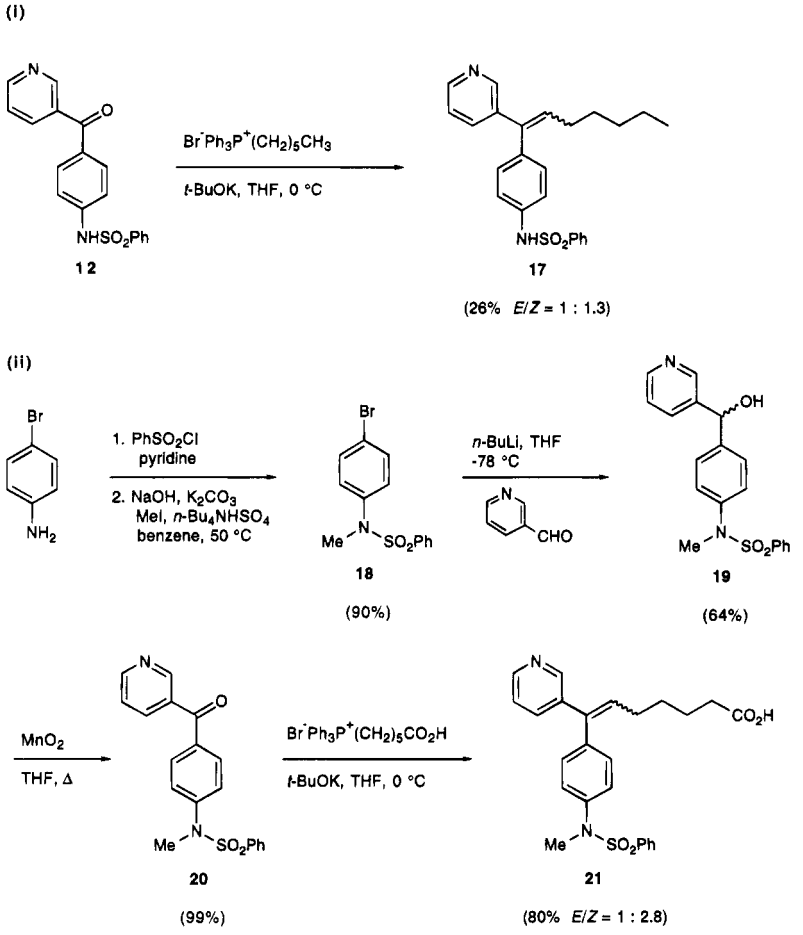
try depended on the distance between the anionic end group and the ylide center and the effect was much more pronounced with aromatic aldehydes than with aliphatic aldehydes. They also noted that the (*E*)-stereoselectivity seen for carboxy ylides was independent of the counter cation (Li, Na, or K) unlike other cases where lithium greatly biased the stereochemical outcome toward (*E*)-stereoselectivity as in the case of oxido ylides.[18]

Our results are not readily explained by Maryanoff's study described above. For example, the oxaphosphetane interconversion via reaction reversal does not explain the effect of the sulfonamido group relative to other substituents on the aromatic ketones. The effect of carbon chain length between the ylide center and the carboxy terminus is not apparent in the sulfonamide series. There are two ways to rationalize the stereochemical outcome of these reactions. The first possibility is that the reaction is thermodynamically driven and *trans*-oxaphosphetanes are formed preferentially. It is not clear, however, which isomers are thermodynamically more stable in our cases. The initial carbon–carbon bond-formation en route to oxaphosphetanes may be organized or facilitated by interaction between the sulfonamido and carboxylate groups. The second possibility is "stereochemical drift":[19] namely, the initial formation of oxaphosphetanes is *cis*-oriented but oxaphosphetane interconversion by reversible reaction takes place to cause the drift in stereochemistry. This "stereochemical drift" may be particu-

(18) Corey has postulated a "lithium-bridging" mechanism to account for the (*E*)-stereoselectivity of β-oxido ylides. See Corey, E. J.; Ulrich., P.; Venkateswarlu, A. *Tetrahedron Lett.* **1977**, 3231 and references cited therein.

(19) Coined by Maryanoff, see ref 7.

Scheme 2



larly facilitated by the sulfonamido group. Significantly, in either case, the interaction of the sulfonamido group and carboxylate may be playing a pivotal role in the oxaphosphetane formation. The ability to form hydrogen bonds or salt bridges possibly because these oxaphosphetanes are much more stable than normally observed[20] appears to be the key factor in determining the final stereochemical outcome (Table 1). We noted earlier the diminished (*E*)-stereoselectivity in **2f**, the product from the reaction of phosphorus ylide with an ether rather than the acid terminus. This loss of stereoselectivity could be explained by the diminished hydrogen bonding ability of the ether compared to that of carboxylate, even though longer chain length also may have disfavored[7] its intramolecular interaction with the sulfonamido NH. Hydrogen bonding in the intermediates can also explain the high (*E*)-stereoselectivity observed in the formation of compound **22**.[21] The stability of intermediate oxaphosphetanes may also explain scrambling of the stereoisomers and diminished stereoselectivity observed in the reactions where the ketone substrates lacked an ability to interact with the carboxylate (Table 2).

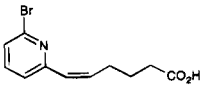
Maryanoff reported in his earlier paper[5] the effect of EW and ED groups on the benzaldehyde when reacted with **1** (M = Li). The Wittig reactions with these substituted aldehydes are (*E*)-selective and this selectivity is diminished by EW groups and enhanced by an ED group (*p*-OMe). We did not see such an effect in our study. We have reasoned that a reaction of a sulfonamido-substituted benzaldehyde with the phosphorus ylide should give preferentially the (*Z*)-alkenoic acid if our hydrogen bonding hypothesis were operating. To verify this rationale, we carried out a Wittig reaction of 4-[(benzenesulfonyl)amino]benzaldehyde (**24**) with (5-carboxypentylidene)triphenylphosphorane (**25**) potassium salt which resulted in the preferential formation of (*Z*)-heptenoic acid **26** (*E*/*Z* = 1:4.3).[22] Our colleague also observed that the (*Z*)-isomer **27** was obtained almost exclusively in an 82% yield when 3-[(4-chlorobenzenesulfonyl)amino]benzaldehyde (**28**) was treated with **1** (M = K) in THF at −40 °C to room temperature.[23]

One might also wonder if the pyridyl ring has an effect on the stereoselectivity observed in the Wittig reaction of phenyl pyridyl ketones we studied. We have therefore

(20) Stable oxaphosphetanes even above 0 °C are known and in some cases are isolated. See ref 4 and references cited therein.

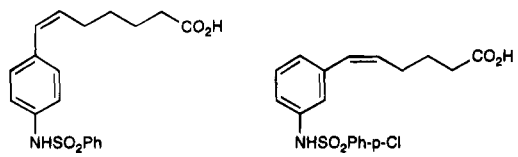
(21) Soyka, R.; Heckel, A.; Nickl, J.; Eisert, W.; Müller, T. H.; Weisenberger, H. *J. Med. Chem.* **1994**, *37*, 26−39. See also Heckel, A.; Nicki, J.; Soyka, R.; Eisert, W.; Müller, T.; Weisenberger, J.; Meade, C.; Muacevic, G. EP 397044, 1990.

(22) Morris and Wishka have reported the preferential formation of the (*Z*)-isomer **23** from 6-bromo-2-pyridinecarboxaldehyde and **1** (M = Li) (*E*/*Z* = 1:4): another example which apparently is inconsistent with Maryanoff's observation in the Wittig reaction of aldehydes with triphenylphosphorus ylides bearing anionic groups. However, the electronic effect of 2-pyridyl ring, in this case, may well be playing a role for the stereochemical outcome. See Morris, J.; Wishka, D. G. *Tetrahedron Lett.* **1988**, *29*, 143.



23

(23) Robertson, D. W.; Ladduceur, G.; Mais, D. E. Unpublished results.



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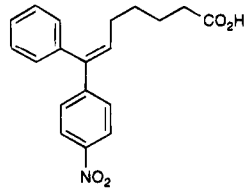

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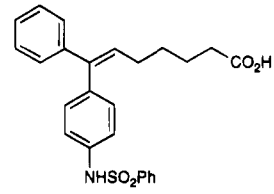

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conducted experiments with substituted benzophenones. The reaction of 4-nitrobenzophenone with **25** resulted in the preferential formation of **29** (E/Z = 3.4:1), whereas the reaction of 4-[(benzenesulfonyl)amino]benzophenone (**30**) gave exclusively **31**. These results confirm that the profound effect on the high stereoselectivity around the olefin geometry in these Wittig reactions was due to the interaction between the sulfonamido group and the carboxylate terminus of the reaction intermediates but not by an electronic effect of the pyridyl ring.[22] Thus we believe that the hydrogen bonding or salt bridge formation is a major factor for high stereoselectivity in Wittig reactions of sulfonamido-substituted aromatic aldehyde or ketones with "nonstabilized" phosphonium ylides bearing an anionic group.

(B) Theoretical Introduction and Conformational Analysis. Theoretical Introduction. The mechanism of the Wittig reaction has been studied in detail by force field,[24,25] semiempirical,[25-30] and ab initio[31-33] calculations. All levels of theory predict an absence of a betaine intermediate and a direct formation of an asynchronous cycloaddition. Calculations at the 4-31+G*//4-31G* basis set level predict the Wittig reaction of phosphonium methylide and formaldehyde to proceed through a concerted transition structure 5.2 kcal/mol above reactants, followed by formation of two isomeric oxaphosphetanes.[32] At this basis level, the oxaphosphetane with an apical oxygen, is found to be 4.2 kcal/mol lower in energy than isomer which has an equatorial oxygen. By contrast, semiempirical calculations or calculations using a smaller basis set indicate no preference for either isomeric oxaphosphetane. A second transition structure involving P–C and O–C bond breaking at a barrier of 26.3 kcal/mol from the oxaphosphetane with an equatorial oxygen is predicted prior to formation of olefin and phosphine products.[32]

Calculations in this study are not feasible at levels of theory beyond the semiempirical methods. Moreover, it has been shown recently that the AM1 method[34] is the best semiempirical procedure for calculating structural properties of aromatic amines.[35] The use of the AM1 method is supported in the study of hydrogen-bonded systems,[36] but its use may depend on the bimolecular system.[37] In addition, semiempirical calculations are useful for conformational analysis,[38] although the barriers to rotation are typically lower than experimental values. For these reasons, and others mentioned in the computational results and discussion section, we employed the AM1 level of theory[34] using the MOPAC[39] 6.02 program. Our main goals in this work were to relate oxaphosphetane conformational preferences to olefin product ratios and to investigate the feasibility of a hydrogen-bonded intermediate in a highly selective Wittig reaction that gave rise to an (*E*)-olefin. Initially we briefly present some calculations of a prototype oxaphosphetane to compare with previous theoretical investigations of the Wittig reaction.

Computational Results and Discussion. Two isomeric oxaphosphetanes from reaction of triphenylphosphonium methylide and formaldehyde have been located using the AM1 method and are shown in Figure 2. There is a large energetic difference of 2.2 kcal/mol for oxaphosphetanes **32** and **33**. Most notably oxaphosphetane **33**, with an equatorial oxygen, is predicted to be lower in energy than its isomer **32**. There is a strong preference for electronegative substituents to be in the apical position.[33] Furthermore, an X-ray crystal structure of a four-membered ring oxaphosphetane resembles structure **32** and shows the ring oxygen in the apical position. Presumably this is caused by a large bulky bis(trifluoromethyl)methoxy group.[40] To confirm a change in isomeric preference of the triphenyl-substituted oxaphosphetanes we carried out full geometry optimization of isomers **32** and **33** at the RHF/3-21G* basis level. The preference of oxaphosphetane **33** over isomer **32** was 0.2 kcal/mol.[41] Isomeric oxaphosphetane **33** was chosen as the structure for further study of substituted oxaphosphetanes because of the slight energetic preference and more importantly because it most closely resembled the final olefin and phosphine products.

It is well known from experiment that the Wittig reaction of "nonstabilized" ylides and aldehydes or ketones proceeds through an oxaphosphetane intermediate.[4,15] Under salt-free conditions the reaction gives the thermodynamically less stable (*Z*)-alkene. The possible transition states of Wittig reactions via four diastereomeric oxaphosphetane intermediates of these aromatic ketones in our study are depicted in Scheme 1. The

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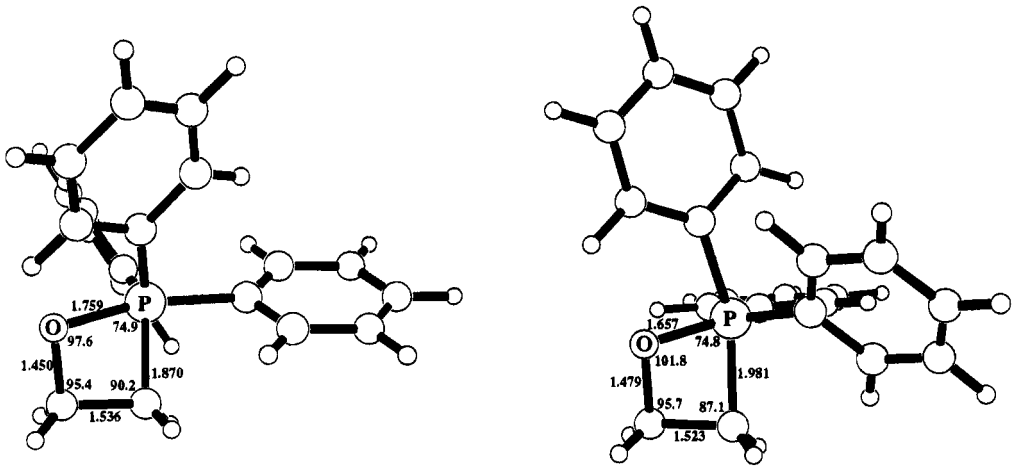

32 33

Figure 2. 3-21G* geometries of two isomeric oxaphosphetanes from Wittig reaction of triphenylphosphonium methylide and formaldehyde. The absolute energies at the 3-21G* basis level are −1177.67772 and −1177.67798 au for isomers **32** and **33**, respectively. The heats of formation at the AM1 level of **32** and **33** are 34.8 and 32.6 kcal/mol, respectively.

scheme illustrates that the preference for (*Z*)- or (*E*)-stereoselectivity depends on the stereochemistry of the oxaphosphetanes. The experimental results indicated that the (*Z*)-olefin product predominated when the phenyl ring of the aromatic ketones was unsubstituted (via **13**; X = H, R = K) or substituted with 4-NO_2 (via **14**). When X = 4-$NHSO_2Ph$, however, the (*E*)-olefin product predominated (via **15**). We undertook a computational investigation of the intermediate oxaphosphetanes **13**–**15** to elucidate why there was an unusual shift in olefin product ratio upon changing the substituent on the phenyl ring of the aromatic ketone. Our computational approach was first to study the neutral acid (R = H) of the oxaphosphetanes of **13**–**15** as a simple model of the reactions and then to elaborate the findings to the corresponding potassium counterion acid anion coordinated species **16** (R = K^+) which are more realistic intermediates in the actual reaction condition.

Calculation of the Oxaphosphetanes (R = H) of 13–15. The results of the AM1 calculations for **13** are shown in Figure 3. The AM1 calculations predicted that *cis*-isomer **13-*c*1** was thermodynamically most stable. The other *cis*-isomer, **13-*c*2**, was 1.4 kcal/mol higher in energy. The relative heats of formation of the *trans*-isomers were 2.0 and 0.1 kcal/mol for **13-*t*2** and **13-*t*1**, respectively.

The oxaphosphetane isomers **13-*c*1** and **13-*t*1** are 1.5–2.0 kcal/mol more stable than isomers **13-*c*2** and **13-*t*2** because of three prominent H–H repulsive interactions. Each of the four oxaphosphetane isomers possesses the interaction of a hydrogen of an aromatic ring d (from the former ketone) with the methylene group α to the developing double bond (Figure 3). Likewise, each isomer possesses the steric interaction of a hydrogen of phenyl ring c (attached to the phosphorus atom) with the methylene group β to the developing double bond. And, finally, each isomer possesses an H–H repulsive interaction of the two equatorial phenyl rings b and c. The former interaction is larger in isomers **13-*c*1** and **13-*t*1** than in isomers **13-*c*2** and **13-*t*2**, whereas the latter two interactions are larger in isomers **13-*c*2** and **13-*t*2** than in isomers **13-*c*1** and **13-*t*1**. The energetic preference of the four isomers is dependent upon reducing the steric interaction of the alkyl chain with the flanking aromatic groups.

A Boltzmann distribution (at 25 °C) of the AM1 heat of formation was determined on the most stable isomers of the four oxaphosphetanes of **13-*c*1, 13-*c*2, 13-*t*1,** and **13-*t*2**. The computational prediction closely resembled the experimental *E*/*Z* ratio of 1:1 from the Wittig reaction of phenyl 3-pyridyl ketone and **25**.[10]

The lowest energy oxaphosphetane intermediates were also located for the Wittig reaction of 3-nitrophenyl 3-pyridyl ketone and **25**. The relative heats of formation of the four isomers were 0.0, 1.9, 0.4, and 2.0 kcal/mol for **14-*c*1**, **14-*c*2**, **14-*t*2**, and **14-*t*1**, respectively. The energetic preference of the four isomers arises from both steric and electronic factors. Each of these four isomers possessed nearly the same steric preferences described above for the oxaphosphetane series **13**. In addition, there probably is an electronic preference that caused an increase in the (*Z*)-stereoselectivity as compared to the unsubstituted case. Unfortunately, molecular electrostatic potential calculations did not give any detailed differences in the charge character of each of these isomers. However, we speculate that the resonance effect in the nitrophenyl ring may have contributed more appreciably to the stereochemical bias for (*Z*) than the unsubstituted phenyl ring.

The results of AM1 calculations of the isomeric oxaphosphetanes **14** predicted a (*Z*/*E*) product ratio of 72:28 at the experimental temperature of −10 °C. The *cis*-isomer was preferred by a factor greater than two. The calculated value was less than the experimental (*Z*) preference of 5:1.

Figure 4 shows the four thermodynamically most stable structures for the four oxaphosphetane isomers of **15** (X = 4-$NHSO_2Ph$). The calculations predicted that isomer **15-*t*1**, with a heat of formation of −38.7 kcal/mol, was the most stable of all isomeric oxaphosphetanes. This structure was greatly stabilized because the acid hydrogen was hydrogen-bonded to a sulfonyl oxygen at a distance of 2.093 Å. This distance is consistent with typical hydrogen bonding interactions predicted for various hydrogen-bonded complexes.[36,37] Isomer **15-*c*1** is the

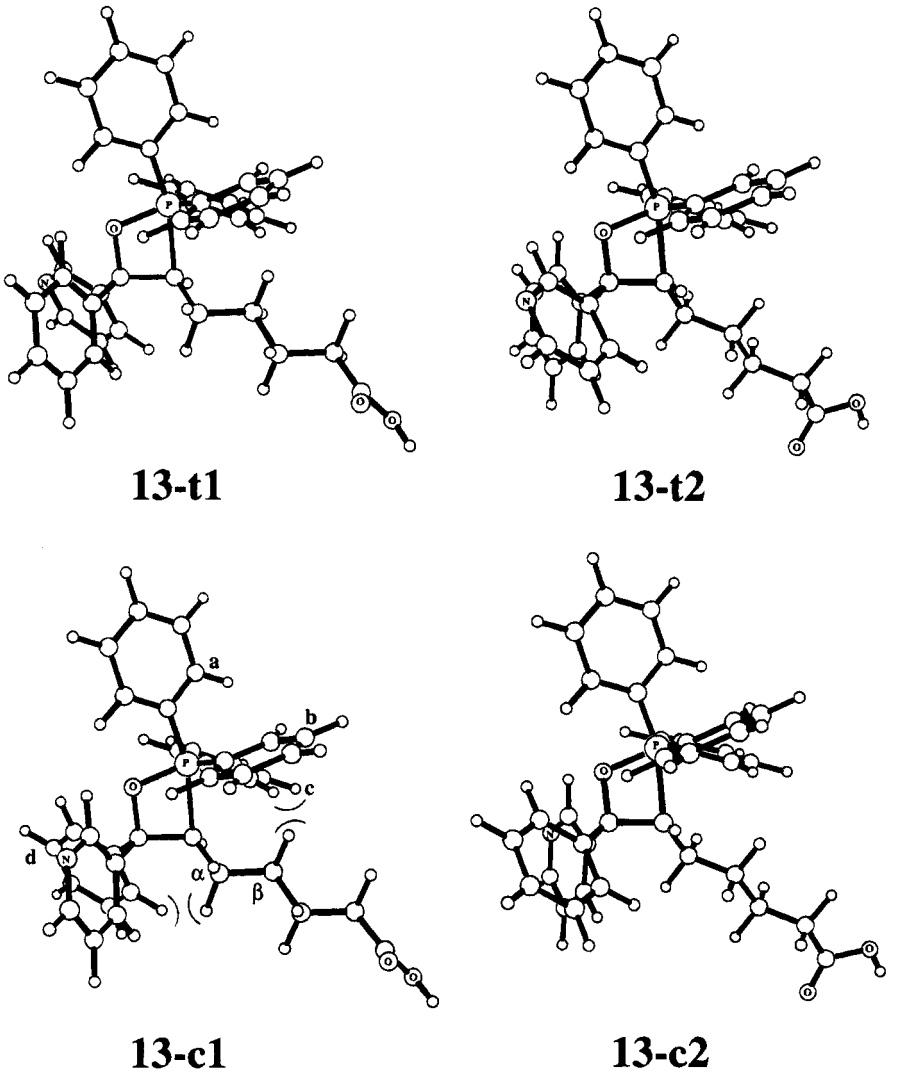

Figure 3. The four isomeric oxaphosphetanes **13-*c*1**, **13-*c*2**, **13-*t*1**, **13-*t*2** from AM1 calculations. Heats of formation and some dihedral angles are given in the supplementary material.

cis-oxaphosphetane located with lowest heat of formation. This structure was disfavored by 1.1 kcal/mol. The other *cis*-oxaphosphetane was 3.7 kcal/mol higher in energy than isomer **15-*t*1**. The highest energy isomer was the *trans*-isomer, **15-*t*2**, which was disfavored by 4.3 kcal/mol.

The calculations indicate that this Wittig reaction preferentially forms the *trans*-oxaphosphetane, regardless of its mechanism being thermodynamically driven or caused by stereochemical drift. The most significant point is that there is strong interaction between the sulfonamido and the carboxylic acid groups. Comparison of structure **15-*t*1** with an optimized structure in which the carboxylic acid chain is in the fully extended conformation (not shown) gives an energetic difference of −1.6 kcal/mol which gives an estimate of the thermodynamic stability of sulfonamido−carboxylic acid interaction. This is consistent with a 0.5−2 kcal/mol enthalpy of stabilization for a variety of hydrogen bond interactions.[42]

A Boltzmann distribution was performed on the four lowest energy isomers from the AM1 calculations of oxaphosphetane **15** (X = 4-$NHSO_2Ph$). The calculation predicted a *trans*/*cis* ratio of 89:11 at the experimental temperature of −10 °C. A seven-fold preference was predicted for the *trans*-isomer. This result is in accord with the experimental observation of the large predominance for (*E*)-isomer in the product ratio of 97:3.

The heat of formation of the most stable isomer **15-*t*1**, which involves hydrogen bonding interaction between the sulfonyl and the acid group, was compared with that of structure **34**, which involves hydrogen bonding interaction of the amine and the acid group. Oxaphosphetane **34** was disfavored by 11.6 kcal/mol. The NH···O=COH distance of 2.307 Å is slightly longer than the hydrogen bond predicted between S=O···HOC=O in **15-*t*1** (2.093 Å) and indicates a weaker interaction.

An MNDO-PM3 semiempirical study[26] has also been done on the stabilities of oxaphosphetane intermediates formed from reactions of unstabilized ylides and aldehydes. The experimental reactions yield preferentially to the (*Z*) product, whereas the calculations predict the *trans*-oxaphosphetane as the more stable intermediate. Several transition structures for the Wittig half-reaction were also located and were found to be highly asynchronous. The transition structures leading to the *trans*-oxaphosphetanes were lower in energy than half-reactions leading to *cis*-oxaphosphetanes. Neither of these results can account for the experimentally observed (*Z*)

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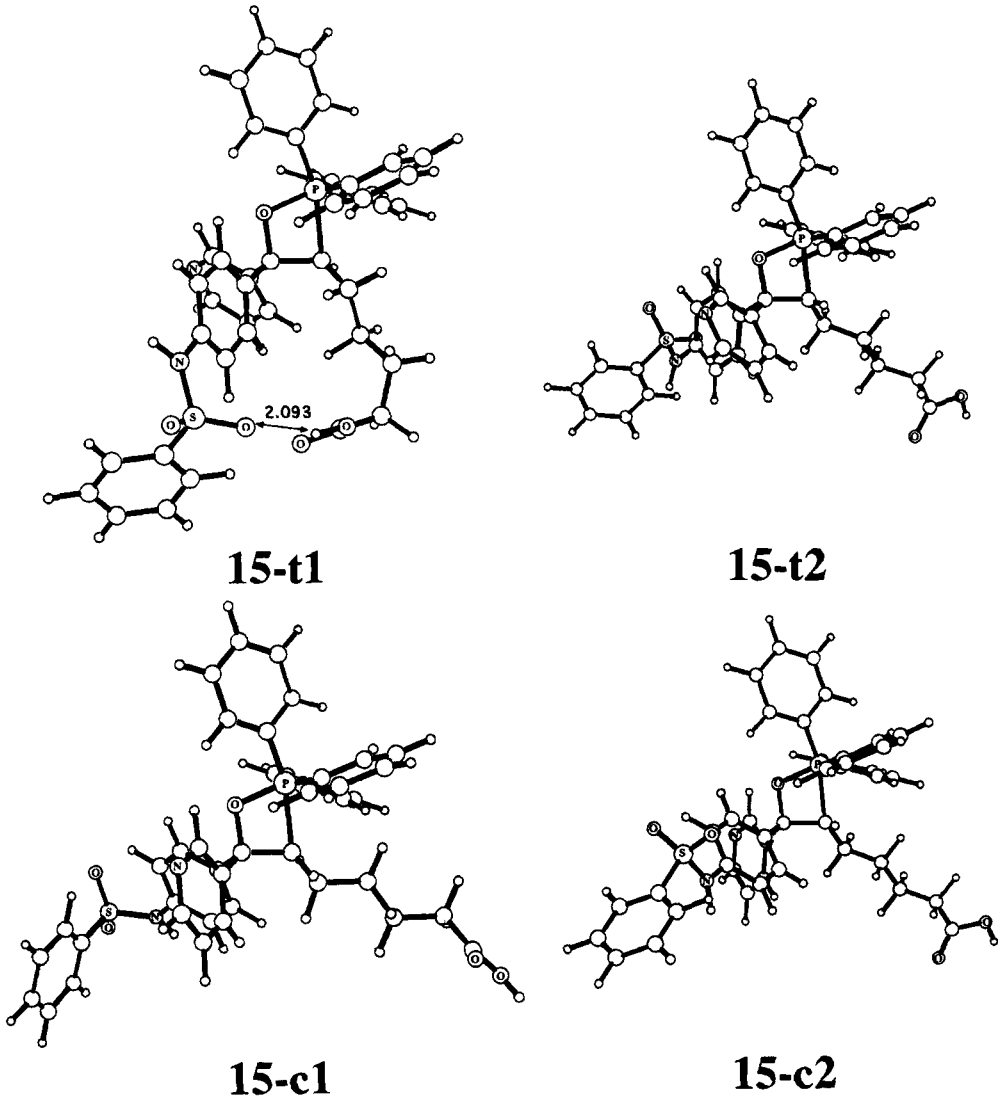
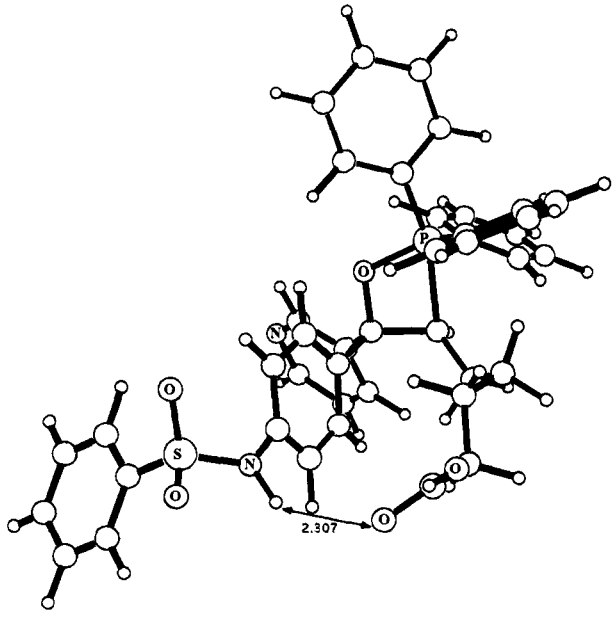


Figure 4. The four lowest energy isomeric oxaphosphetanes **15-c1**, **15-c2**, **15-*t*1**, **15-*t*2** from AM1 calculations. Heats of formation and some dihedral angles are given in the supplementary material.



34

stereoselectivity. Unfortunately, these calculations were performed with mixed parameters which the developers[43,44] and others[35] indicate are hazardous, if not invalid, to the results.

Effect of the Acid Side Chain Length. We were intrigued by the large 12 kcal/mol energy difference between the oxaphosphetane **15-*t*1** and **34** which differs by the nature of the hydrogen bonding between the sulfonamido and acid groups. We anticipated that the large energy difference between the two structures was due to larger steric interaction in **34** because the hydrogen-bonded species formed a 14-membered ring, whereas a 15-membered ring was formed in **15-*t*1**. We investigated the energetic difference in the hydrogen-bonded species among the macrocycles by lengthening the alkenoic acid connecting chain. We fully optimized twelve randomly generated hydrogen-bonded *trans*-isomers for each oxaphosphetanes with a C_5, C_6, and C_7 alkyl chain between the oxaphosphetane four-membered ring and the acid group. In each case, the species with a hydrogen bond

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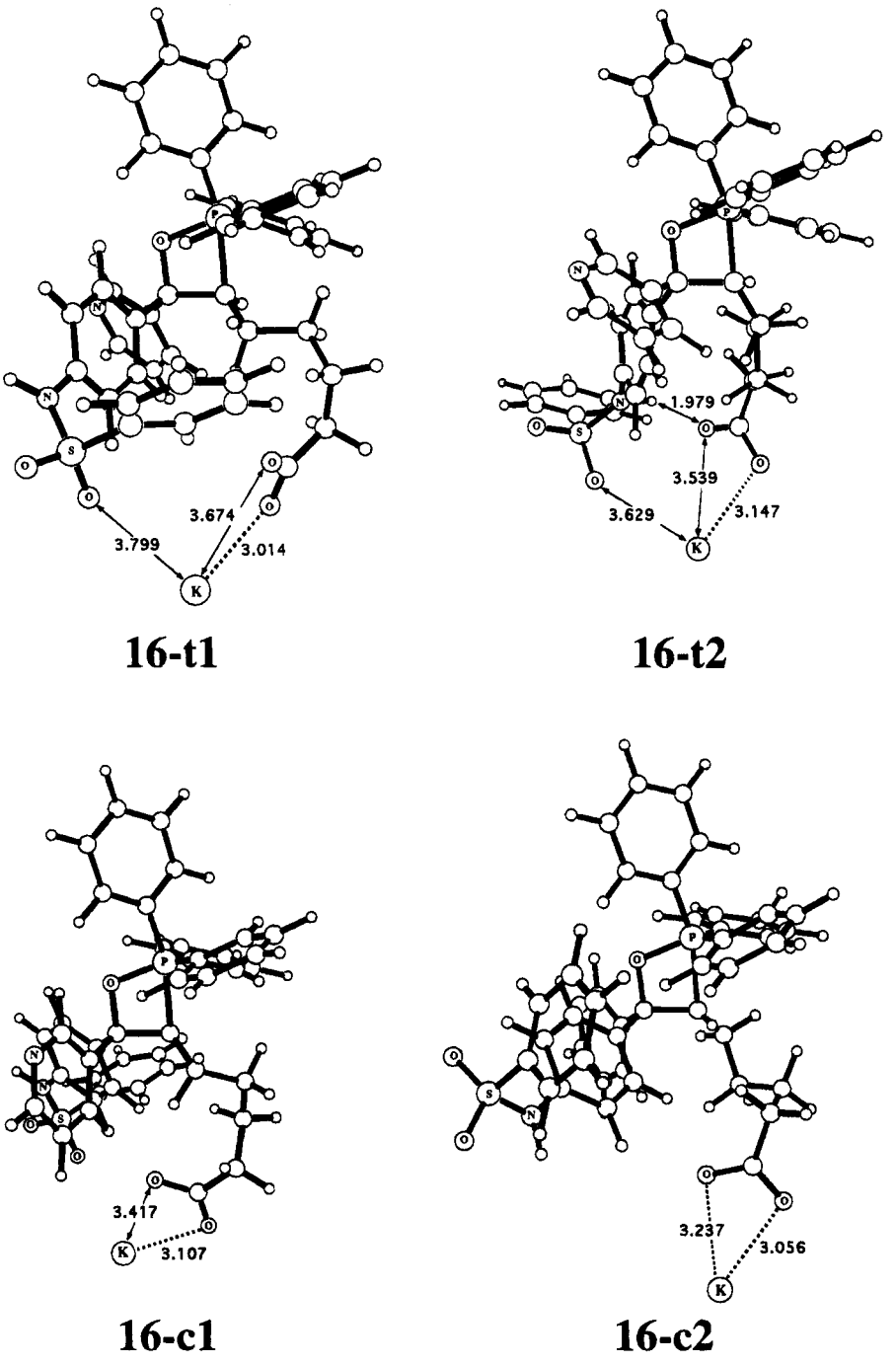


Figure 5. The four lowest energy isomeric oxaphosphetanes **16-*c*1**, **16-*c*2**, **16-*t*1**, **16-*t*2** from AM1 calculations. Heats of formation and some dihedral angles are given in the supplementary material.

between the sulfonyl oxygen and the acid group hydrogen was lower in energy than the species with a hydrogen bond between the amine hydrogen and the carbonyl oxygen. However, the energy difference between the two hydrogen bonded species decreases with longer alkyl connecting chain. The difference in the heat of formation between the two different hydrogen bonded structures was 1.8, 2.1, and 0.8 kcal/mol for the oxaphosphetanes with C_5, C_6, and C_7 connecting chains, respectively. In all cases, the species with S=O···HOC=O hydrogen bond was shorter than the species with a NH···O=COH hydrogen bond.

Potassium Complexed Acid Anions of Oxaphosphetane 16 (R = K^+, X = 4-$NHSO_2Ph$). In order to investigate the feasibility of salt bridge formation between the sulfonamido and carboxylate groups, we performed calculations on the potassium counterion complexed acid anions. Figure 5 shows the four lowest energy structures of the four isomers of the potassium complexed acid anions of oxaphosphetane **16** (X = 4-$NHSO_2Ph$, R = K^+). The overall energy trends were quite similar to the results of calculations of the neutral oxaphosphetane **15**. Again, AM1 calculations predicted the *trans*-isomer **16-*t*1** as lowest in energy with a heat of formation of −119.7 kcal/mol. The other *trans*-isomer **16-*t*2** was disfavored by 6.2 kcal/mol. Isomers **16-*c*1** and **16-*c*2** were the two lowest energy *cis*-isomers located and were disfavored over **16-*t*1** by 1.2 and 8.0 kcal/mol, respectively.

The results of AM1 calculations of the potassium

complexed acid anions of oxaphosphetane **16** predicted an (*E*/*Z*) ratio of 91:9, using a Boltzmann distribution at −10 °C over the lowest energy structures of each isomer. This is almost identical to the results for the neutral oxaphosphetane calculations.

As with the neutral acid calculations for **15-*t*1** and **34**, these calculations also revealed two different ***t*1** isomers of **16** that differed by the nature of the hydrogen bonding between the sulfonamido group and the alkenoic acid. Comparison of the structures indicates that the species involving loose coordination between the sulfonyl group and the acid group is 10.3 kcal/mol lower in energy than the NH···O=COH hydrogen-bonded species. The energetic difference here is similar to the value seen for the interaction of the two termini in neutral species, **15-*t*1** and **34**.

In structure **16-*t*1** the potassium counterion is tightly coordinated to the acid anion at a distance of 3.0 Å. There is very loose coordination of the potassium with the sulfonyl oxygen as the distance is 3.8 Å. Comparison of **16-*t*1** with an optimized structure (not shown) in which the alkyl chain is in the fully extended conformation while maintaining solely carboxylate coordination of the potassium counterion indicates a 2.1 kcal/mol stabilizing interaction of the carboxylate and sulfonamido groups via salt bridge formation. Although the distance between the sulfonyl and the potassium counterion of the carboxylate is long, there is still substantial interaction. The magnitude of interaction is consistent with computed association energies of salt bridges, but is smaller than the stabilization energies from mutation experiments.[42b]

We also questioned whether the energetic difference between the two hydrogen-bonded species of the lowest energy *trans*-isomers with C_5, C_6, and C_7 chain lengths would vary upon replacement of the acid group hydrogen with a potassium counterion. In all three cases, the lowest energy structures located were those that involved tight hydrogen bonding of the amine with a carboxylate oxygen and potassium ion coordinated tightly to a carboxylate oxygen and loosely to a sulfonyl oxygen.

The high (*E*)-stereoselectivity in cases where phosphorus ylides with the shorter carbon chains were employed may be more difficult to explain. We cursorily examined the feasibility of salt bridge formation between the sulfonyl and carboxylate groups for the C_2 and C_3 connecting chains. Even in the case of the C_2 acid side chain the two termini still have an albeit reduced interaction of about 0.7 kcal/mol. Although it is energetically more difficult for the hydrogen bond formation or salt bridge formation with the shorter side chains, the observed high (*E*)-stereoselectivity may possibly be explained by coordination of solvent to the reaction intermediates. In these cases the solvent (THF) could bridge and aid hydrogen bonding or salt bridge formation between the two termini.

The central theme of this article is not changed: the sulfonamido-substituent causes a dramatic preference for (*E*)-stereoselectivity. Whether the sulfonamido and carboxylate groups interact through hydrogen bond formation or through salt bridge formation, there is substantial interaction to effect overall observed stereoselectivity. Possible deprotonation of the sulfonamide proton by excess base (resulting such species as **C** shown in Scheme 1) would further facilitate the salt bridge formation between the sulfonyl and carboxylate groups and strengthen the interaction of the two termini because of the more negative sulfonyl oxygen. Unfortunately, such species were not optimized because the termination criteria in the program were never reached due to energy fluctuations. The AM1 method is not parameterized for such species as **C** and presumably considerable difficulty is encountered upon optimization.

Conclusion

We have presented experimental evidence as well as computational support for the dramatic increase in stereoselectivity and reversal of stereochemistry by the sulfonamido substituent effect in the Wittig reaction of aromatic ketones. It is clear that the sulfonamido group interacts with the carboxylate group via hydrogen bonding or salt bridge formation and stabilizes a *trans*-oxaphosphetane intermediate by about 2 kcal/mol which leads to the observed (*E*)-olefin product when a sulfonamido-substituted phenyl 3-pyridyl ketone was reacted with a phosphorous ylide bearing a carboxylate.

Experimental Section

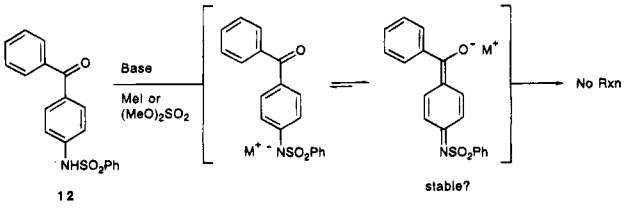
General Procedure. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Triethylamine and pyridine were distilled from CaH_2 and stored over 4 Å molecular sieves. Benzene and toluene were dried over sodium metal. All reactions were performed under a positive pressure of dry nitrogen. The "preparative HPLC" was performed on a Waters PrepLC System 500A with the solvent indicated. Analytical HPLC was carried out on a Waters Model 510 using Nova C_{18} column with CH_3CN–MeOH–H_2O solvent system which contained either 0.5% NH_4OAc or 1% HOAc, or Chiralcel OD-R column with CH_3CN–H_2O solvent system which contained 0.1% $NaClO_4$. Flash chromatography was carried out on E. Merck Kieselgel 60 (230–400 mesh). ^1H NMR spectra were recorded on a GE QE-300 (routine) and on Bruker AM-500 (NOE) spectrometer. The chemical shifts are given in δ values relative to residual proton resonances of the deuterated solvents used ($CDCl_3$ 7.26, DMSO-d_6 2.49, Acetone-d_6 2.05). Field desorption (FDMS) and fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB-3F or VG 70-SE instrument. Infrared spectroscopy was performed on Nicolet 510P, using either KBr pellet or $CHCl_3$ solution.

Preparation of Phenyl 3-Pyridyl Ketones. A typical procedure for the preparation of substituted phenyl 3-pyridyl ketones consists of metal–halogen exchange of an appropriately substituted bromobenzene followed by nucleophilic attack on 3-pyridinecarboxaldehyde in THF at −78 °C. Preparation of most of the ketones used in this study has been reported elsewhere.[9]

4-[Benzenesulfonyl(methyl)amino]phenyl 3-Pyridyl Ketone (20). The title compound **21** was prepared in four steps (56% overall yield) from 4-bromoaniline as described below.[45]

N-Methylsulfonamido-substituted bromobenzene **18** was prepared in two steps (90%) by (1) sulfonamide formation of 4-bromoaniline with $PhSO_2Cl$ in pyridine and (2) N-methylation of the resultant sulfonamide according to the

(45) Methylation of ketone **12** was not successful possibly due to the resonance form of the anion which may have been too stable to react. Ketone **12** was recovered from the reaction.



literature:[46] ^{1}H NMR ($CDCl_3$) δ 7.59–7.40 (m, 7H), 6.97 (d, J = 8.7 Hz, 2H), 3.15 (s, 3H); FDMS 325 (M − 1). Anal. Calcd for $C_{13}H_{12}BrNO_2S$: C, 47.87; H, 3.71; N, 4.29. Found: C, 48.04; H, 3.81; N, 4.39.

A solution of 1.61 g (4.9 mmol) of bromobenzene **18** in 40 mL of THF was treated with 3.7 mL (5.9 mmol) of 1.6 M *n*-BuLi in hexanes at −78 °C for 45 min. To this was added dropwise 0.56 mL (5.9 mmol) of 3-pyridinecarboxaldehyde and the mixture was stirred at −78 °C for 75 min. The cold bath was removed and the mixture was stirred for another 10 min and then quenched with ca. 30 mL of saturated aqueous NH_4Cl. The reaction mixture was taken up in 100 mL of CH_2Cl_2 and 20 mL of brine. The organic layer was separated and washed with 50 mL of brine. The aqueous layers were back-extracted with 2 × 100 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography using 2:48:50 MeOH–EtOAc–CH_2Cl_2 to yield 1.11 g (64%) of 3-pyridylcarbinol **19**: ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 8.46 (br dd, J = ~4.0, 0.8 Hz, 1H), 7.70 (dd, J = 7.9, 1.7 Hz, 1H), 7.59–7.27 (m, 8H), 7.07 (d, J = 8.5 Hz, 2H), 5.86 (s, 1H), 3.14 (s, 3H), 2.62 (br s, 1H); FDMS 354 (M+). Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90. Found: C, 64.64; H, 5.31; N, 7.95.

The carbinol **19** thus obtained (1.10 g) was oxidized with 4.42 g (4× by weight) of MnO_2 in 30 mL of THF at gentle reflux for 1 h 45 min. The removal of the oxidant through a Celite pad by filtration provided 1.09 g (99%) of the clean crude ketone **20** as a yellow viscous oil which was used without further purification: IR ($CHCl_3$) 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.98 (br s, 1H), 8.83 (br s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.6 Hz, 2H), 7.62–7.45 (m, 6H), 7.29 (d, J = 8.6 Hz, 2H), 3.24 (s, 3H); FDMS 352 (M+). Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.57; N, 7.95. Found: C, 64.99; H, 4.65; N, 7.73.

Preparation of Phosphonium Salts. Phosphonium salts used in this work (which are not commercially available) were prepared according to the literature method.[9,10]

Typical Wittig Reaction Conditions. Experimental detail for Wittig reactions have been reported elsewhere.[9] In general, 2–3 equiv of triphenylphosphonium salt and 4–6 equiv of base per ketone in THF were employed for best product yields. The best mode of reaction was *in situ* formation of ylide in the presence of ketone via dropwise addition of the base solution (1.0 M in THF) to a mixture of ketone and phosphonium salt, rather than the conventional method of forming ylide first and then adding a ketone. Reactions were run at −78 °C overnight and then warmed to room temperature for a couple of days when NaHMDS was employed as base. They were run below or at 0 °C overnight and then warmed to room temperature for a few days when *t*-BuOK was employed as base. The reactions were monitored by TLC for completion. Some reactions were complete in much shorter period at which time they were quenched and subjected to workup. Analysis of the (*E*/*Z*) ratio of alkene isomers was accomplished either by analytical HPLC or ^{1}H NMR. In the latter method, the ratio was obtained from integration of the olefinic proton of the product acids or their esters. The purity of products was determined primarily by analytical HPLC since the hygroscopic nature of these compounds made correct elemental analysis difficult.

(*E*)- and (*Z*)-1-[4-[(Benzenesulfonyl)amino]phenyl]-1-(3-pyridyl)hept-1-ene (17). To a suspension of 172.3 mg (0.51 mmol) of ketone **12**[9] and 651.6 mg (1.52 mmol) of hexyltriphenylphosphonium bromide in 4.0 mL of THF was added dropwise 1.52 mL of 1.0 M *t*-BuOK in THF over 5–7 min. The mixture was stirred at 0–15 °C for 24 h and then at room temperature for 3 days. The reaction was quenched with ca. 15 drops of 1.0 N HCl adjusting to pH ~ 6. The mixture was concentrated and purified by flash chromatography using 20% EtOAc–CH_2Cl_2 as eluent to afford 53.4 mg (26%) of the (*E*/*Z*)-mixture of product **17** as a hygroscopic sticky solid (*E*/*Z* = 43:57): ^{1}H NMR ($CDCl_3$) δ 6.09 (t, J = 7.6 Hz, CH_E); 6.12 (t, J = 7.6 Hz, CH_Z) for the olefinic protons (1H). All other proton signals were overlapped and shown as multiplets since the product was a ~1:1 mixture of (*E*/*Z*)-isomers: δ 8.57–8.40 (broad 3 singlets, 2H), 7.83–7.70 (3H), 7.57–7.41 (4H), 7.34–7.18 (1H), 7.12–6.99 (4H), 2.11–2.03 (2H), 1.44–1.38 (2H), 1.26–1.24 (4H), 0.89–0.85 (3H); FDMS 406 (M$^+$); 98.9% pure by analytical HPLC.

(*E*)- and (*Z*)-7-[4-[Benzenesulfonyl(methyl)amino]-phenyl]-7-(3-pyridyl)hept-6-enoic Acids (21). To a mixture of 173 mg (0.49 mmol) of ketone **20** and 247.3 mg (0.54 mmol) of (5-carboxypentyl)triphenylphosphonium bromide (**25s**)[10] in 2.5 mL of THF was added dropwise 1.1 mL (1.1 mmol) of 1.0 M *t*-BuOK in THF at 0 °C. After stirring for 1 h, the reaction was quenched with 10 drops of 1.0 N HCl at 0 °C and the reaction mixture was concentrated. Flash chromatography with 2:48:50 HOAc–EtOAc–CH_2Cl_2 afforded 176.5 mg (80%) of the (*E*/*Z*) mixture of product **21** (*E*/*Z* = 26:74). The (*E*/*Z*) ratio was virtually the same (29:71) when the reaction was carried out as above for **17** using 2.2 equiv of phosphonium salt and 4.4 equiv of base at 0 °C for 24 h and at room temperature for 3 days: ^{1}H NMR ($CDCl_3$, (*Z*)-isomer) δ 8.57 (br s, 1H), 8.45 (br s, 1H), 7.59–7.29 (m, 7H), 7.09 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 6.20 (t, J = 7.5 Hz, 1H; for (*E*)-isomer, 6.14 (t, J = 7.5 Hz)), 3.15 (s, 3H; for (*E*)-isomer, 3.21 (s)), 2.30 (dd, J = 7.2, 7.1 Hz, 2H), 2.11 (m, 2H), 1.63 (m, 2H), 1.52 (m, 2H); FDMS 450 (M$^+$). Anal. Calcd for $C_{25}H_{26}N_2O_4S \cdot 0.61H_2O$: C, 65.06; H, 5.94; N, 6.07. Found: C, 65.07; H, 5.71; N, 5.88.

Preparation of 4-[(Benzenesulfonyl)amino]benzaldehyde (24). The aldehyde **24** was prepared in three steps from ethyl 4-aminobenzoate (59%): (1) sulfonylation with benzenesulfonyl chloride in pyridine at 0 °C; (2) DIBAL-H reduction of the ester to the corresponding alcohol in THF at −30 to −40 °C; and (3) MnO_2 oxidation of the alcohol to **24** in THF at reflux: mp 135–137 °C; IR (KBr) 3238, 1688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.57 (m, 1H), 7.49 (m, 2H), 7.37 (s, 1H), 7.24 (d, J = 8.5 Hz, 2H); FDMS 261 (M$^+$). Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.76; H, 4.24; N, 5.36. Found: C, 60.04; H, 4.50; N, 5.48.

(*Z*)-7-[4-[(Benzenesulfonyl)amino]phenyl]hept-6-enoic Acid (26) and Its (*E*)-Isomer. A suspension of 1.004 g of **25s** in 3.0 mL of THF was treated with 4.4 mL of 1.0 M *t*-BuOK in THF at 0 °C for 30 min. To the bright orange colored ylide suspension was then cannulated 260.7 mg of the aldehyde in 2.0 mL of THF and the mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with ca. 6 mL of 1.0 N HCl at 0 °C. The solution was then taken up in ca. 70 mL of EtOAc and washed with ca. 25 mL of brine which was back-extracted with 2 × 70 mL of EtOAc. The combined extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography with 40:1:59 EtOAc–HOAc–hexanes as eluent to afford 328.9 mg (92%) of the heptenoic acids as an oil which was enriched in (*Z*)-isomer **26** (*E*/*Z* = 1 :4.3 by ^{1}H NMR): IR ($CHCl_3$) 3366, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.59–7.30 (m, 4H:), 7.12 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.31 (d, J = 11.6 Hz, 1H; for (*E*)-isomer 6.28, (d, J = 15.8 Hz)), 5.59 (dt, J = 11.6, 7.2 Hz, 1H; for (*E*)-isomer 6.10 (dt, J = 15.8, 6.8 Hz)), 2.42–2.21 (m, 4H), 1.65 (m, 2H), 1.47 (m, 2H); FDMS 360 (M + 1). Anal. Calcd for $C_{19}H_{21}NO_4S \cdot 0.61C_2H_4O_2$: C, 61.32; H, 5.96; N, 3.54. Found: C, 61.30; H, 5.95; N, 3.60.

(*E*)-7-(4-Nitrophenyl)-7-phenylhept-6-enoic Acid (29) and Its (*Z*)-Isomer. A suspension of 770 mg of **25s** in 2.0 mL of THF was treated with 3.4 mL of 1.0 M *t*-BuOK in THF at 0 °C for 30 min. To this was cannulated 254.9 mg of 4-nitrobenzophenone in 3.6 mL of THF. The mixture turned to dark green and then to dark brown color as the addition was completed. The reaction mixture was stirred at 0 °C for 8 h, overnight (15.5 h) while allowed to warm to 15 °C on its own, and then at room temperature for 24 h. The reaction was quenched with ca. 4–5 mL of 1.0 N HCl at 20 °C, taken up in ca. 70 mL of EtOAc, and washed with ca. 20 mL of brine which was back-extracted with 2 × 70 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography with 49:1:50 Et_2O–HOAc–hexanes to give 261.8 mg (72%) of the product which

(46) Gajda, T.; Zwierzak, A. *Synthesis* **1981**, 1005.

was enriched in (*E*)-isomer **29** (*E*/*Z* = 3.3:1 by ^{1}H NMR): IR (KBr) 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.9 Hz, 2H; for (*Z*) isomer 8.24 (d, J = 8.7 Hz)), 7.44–7.32 (m, 3H), 7.35 (d, J = 8.9 Hz, 2H), 7.14 (m, 2H), 6.25 (t, J = 7.4 Hz, 1H; for (*Z*)-isomer 6.16 (t, J = 7.5 Hz)), 2.33 (dd, J = 7.4, 7.0 Hz, 2H), 2.18 (ddd, J = 7.4, 7.2, 7.2 Hz, 2H), 1.64 (m, 2H), 1.54 (m, 2H); FDMS 325 (M^+). Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.04; H, 5.86; N, 4.47.

4-[(Benzenesulfonyl)amino]benzophenone (30). The ketone **30** was prepared from 4-aminobenzophenone reacted with benzenesulfonyl chloride in pyridine at 0 °C in quantitative yield: mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.90 (d, J = 7.3 Hz, 2H), 7.72 (d, J = 8.6 Hz, 4H), 7.56 (m, 2H), 7.46 (m, 4H), 7.23 (d, J = 8.6 Hz, 2H); FDMS 337 (M^+). Anal. Calcd for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15. Found: C, 67.37; H, 4.52; N, 4.14.

(*E*)-7-[4-[(Benzenesulfonyl)amino]phenyl]-7-phenylhept-6-enoic Acid (31). To a mixture of 313.9 mg of ketone **30** and 936.1 mg of **25s** in 5.0 mL of THF was added dropwise 4.1 mL of 1.0 M t-BuOK in THF at 0 °C over 10 min period. The orange colored suspension was stirred at 0 °C for 8 h and overnight (~15 h) while allowed to warm to ~15 °C on its own. The reaction was quenched with ca. 5 mL of 1.0 N HCl and the mixture was taken up in ca. 70 mL of EtOAc and washed with ca. 20 mL of 1.0 N HCl and 25 mL of brine. The aqueous layers were back-extracted with 2 × 70 mL of EtOAc. The combined extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography with 40:1:59 EtOAc–HOAc–hexanes as eluent to yield 147.8 mg (47%) of the unreacted ketone **30** and 197.2 mg (48%) of a viscous liquid which was identified solely as the (*E*)-isomer **31** by an NOE experiment: mp 42–45 °C; IR ($CHCl_3$) 3360, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.55 (m, 1H), 7.45 (m, 2H), 7.26–7.01 (m, 9H), 6.94 (s, 1H), 6.02 (t, J = 7.4 Hz, 1H), 2.30 (dd, J = 7.4, 7.2 Hz, 2H), 2.06 (ddd, J = 7.5, 7.4, 7.1 Hz, 2H), 1.61 (m, 2H), 1.47 (m, 2H); FDMS 435 (M^+). Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 68.66; H, 6.05; N, 3.16.

Calculation of the Oxaphosphetanes (R = H) of 13–15. The AM1 method[34] was used to optimize the fully extended alkyl chain conformation of the isomeric oxaphosphetanes **13–15** with X = H, 4-NO_2, and 4-$NHSO_2Ph$. With the resulting conformation as a starting point, the program QUANTA[47] 3.2 was then used to generate the random conformations by a random sampling procedure in which the torsional angles in a structure were changed at random by 15° increments and each new structure created was cumulatively modified until 1000 conformations were generated. For the isomeric oxaphosphetanes **13** (X = H), twelve conformations of each of the four isomers were chosen at random, typically every 100 structure, for further optimization. No van der Waals interactions were included in the conformer generation, thus some unreasonable conformations were created. This necessitated a manual search nearly every 100th conformation to select a reasonable and diverse set of conformations for each oxaphosphetane isomer. For the isomeric oxaphosphetanes **14** (X = 4-NO_2) and **15** (X = 4-$NHSO_2Ph$), seven conformers of each of the four isomers were chosen based on an interatomic distance criterion (less than 5.0 Å) between the nitrogen of the X-substituent, and the oxygen of the carbonyl group and seven conformers were chosen at random 100 structure intervals. All 56 structures of each substituted oxaphosphetane were minimized with the AM1 Hamiltonian[34] without constraints to a resulting gradient less than 0.01 kcal/mol·Å. Many structures were optimized in internal coordinates because optimization in Cartesian coordinates led to different molecular structures due to large steric contacts. All optimizations of the oxaphosphetanes were performed on a Silicon Graphics SG-410/VGX workstation and a CRAY-2 128/2S supercomputer. The average amount of cpu time required by a Silicon Graphics workstation to optimize a given conformation was 16 h. Any conformation that did not complete optimization within 24 h was optimized on a CRAY-2 supercomputer.

Calculation of Potassium Complexed Acid Anions of Oxaphosphetane 16 (R = K^+, X = 4-$NHSO_2Ph$). In these calculations the potassium counterion is an integer charge at the center of a repulsion sphere with unipositive charge distributed over its surface. A potassium sparkle is suitable for use as a counterion for acid anions, but is not computed as rigorously as other atoms in the wavefunction. As described above, the program QUANTA[47] 3.2 was used to generate random conformations of each isomer of the oxaphosphetanes. All structures were fully optimized with the AM1 method.[34]

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Supplementary Material Available: A figure showing computational results of oxaphosphetanes **14**, and a table indicating their geometries as well as those of other isomers discussed in the text (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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