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Stereoelectronic Effects in the Nucleophilic Addition to the sp-Hybridized Carbon of a Ketene and Vinyl Cation: When Is a Mesityl Effectively Smaller than a Phenyl Ring?[1]

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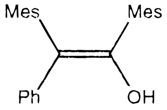
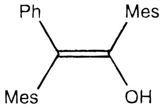
Abstract: Addition of MesMgBr to mesitylphenylketene **3** yields a ca. 3:1 mixture of the magnesium enolates **5-(*E*)** and **5-(*Z*)**, whereas reaction of enol **1-(*Z*)** with MesMgBr results in the exclusive formation of enolate **5-(*Z*)**. Acetylation of the configurationally stable **5-(*E*)** and **5-(*Z*)** yields the enol acetates **4-(*E*)** and **4-(*Z*)**, respectively. The preference for the formation of the (*E*)-enolate from **3** indicates that the attack occurs preferentially from the side of the formally bulkier mesityl ring. Ketene **3** and the two diastereomeric transition states obtained by attack of MeLi on its C=O were calculated by *ab initio* calculations. **3** adopts a conformation with a planar Ph-C=C moiety while the mesityl is nearly perpendicular to this plane. Since the attack on the C=O group occurs in the plane of the C=C double bond, the coplanar Ph is effectively bulkier to the approaching nucleophile than the twisted Mes and the preferred attack is from the mesityl side. Similar stereoelectronic effects operate in 1,2-dimesityl-2-phenylvinyl cation (**10**).

Introduction

In 1944 Fuson reported some puzzling observations involving the preparation of sterically crowded enol acetates.[2,3] When the stable enol 1,2-dimesityl-2-phenylethenol (**1-(Z)**) (of unknown configuration at that time) was acetylated with acetic anhydride in pyridine, the product obtained was an acetate of mp 160−1 °C ("low melting acetate"). The same acetate was obtained by treatment of 1,2-dimesityl-2-phenylethanone (**2**) with MeMgI/*n*-butyl ether, followed by reaction with acetyl chloride. However, when the enol acetate was prepared by addition of mesitylmagnesium bromide to mesitylphenylketene (**3**) in ether, followed by acetylation by AcCl/ether, a *different* isomeric acetate of mp 179.5−180.5 °C ("high melting acetate") was obtained.[2b] When the intermediate magnesium enolate was protonated, or on acid or basic hydrolysis of either acetate, enol **1-(Z)** was obtained. Fuson concluded, on the basis of this evidence, that the two acetates are *cis*−*trans* isomers and that a change in the configuration of the double bond had occurred in one of the hydrolysis reactions.[2b]



1-*(E)*



1-*(Z)*

Mes(Ph)CHCOMes **2**

Mes(Ph)C=C=O **3**

(Mes=mesityl=$2,4,6\text{-}Me_3C_6H_2$)

We reexamined the reaction leading to the formation of the two acetates addressing the following questions: (i) Are the "high melting" and "low melting" compounds indeed *cis*−*trans*-enol acetates? Are the reactions leading to them completely stereoselective as reported? Do different solvents or different deprotonating and acetylation reagents affect the stereochemical course of the reaction? (ii) What are the configurations of the two enol acetates? (iii) What are the stereochemistries of the magnesium enolates obtained by the reactions of **1-(Z)** and **3** with a Grignard reagent and how are they related to the stereochemistries of their precursors? Are the *cis*- and *trans*-magnesium enolates configurationally stable? Which enolate is formed preferentially and which is more stable? Finally, a more general question is raised: (iv) What is the effect of two aryl groups of different bulk on the conformation of and the stereoselectivity in nucleophilic additions to the sp carbon of diarylketenes and other sp-carbon centers, e.g., a vinyl cation?

The availability of a stable simple enol and of a relatively stable ketene facilitates the examination of these questions.

Results and Discussion

(i) Preparation of the Isomeric Acetates. Influence of the Solvent and Acetylating Reagent on the Product Ratio. Fuson's acetylation experiments of the enol and enolates were not conducted under exactly identical conditions, i.e., in the same solvent and with the same acetylating reagent. The reactions were presented as displaying complete diastereoselectivity. However, since spectroscopic methods were not available or were only at their infancy at that time, Fuson's tools were not sufficiently sensitive to determine whether the reactions proceed with complete or only partial diastereoselectivity. We therefore

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(1) Presented in part at KISPOC-VI, Kyushu International Symposium on Physical Organic Chemistry, July 25−28, 1995, Kyushu University, Japan; Abstract pp 57−60.

(2) (a) Fuson, R. C.; Armstrong, L. J.; Shenk, W. J., Jr. *J. Am. Chem. Soc.* **1944**, *66*, 964. (b) Fuson, R. C.; Armstrong, L. J.; Kneisley, J. W.; Shenk, W. J., Jr. *J. Am. Chem. Soc.* **1944**, *66*, 1464.

(3) For a review on aryl-substituted enols including Fuson's stable enols, see: Hart, H.; Rappoport, Z.; Biali, S. E. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; Chapter 8. Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1988**, *21*, 442.

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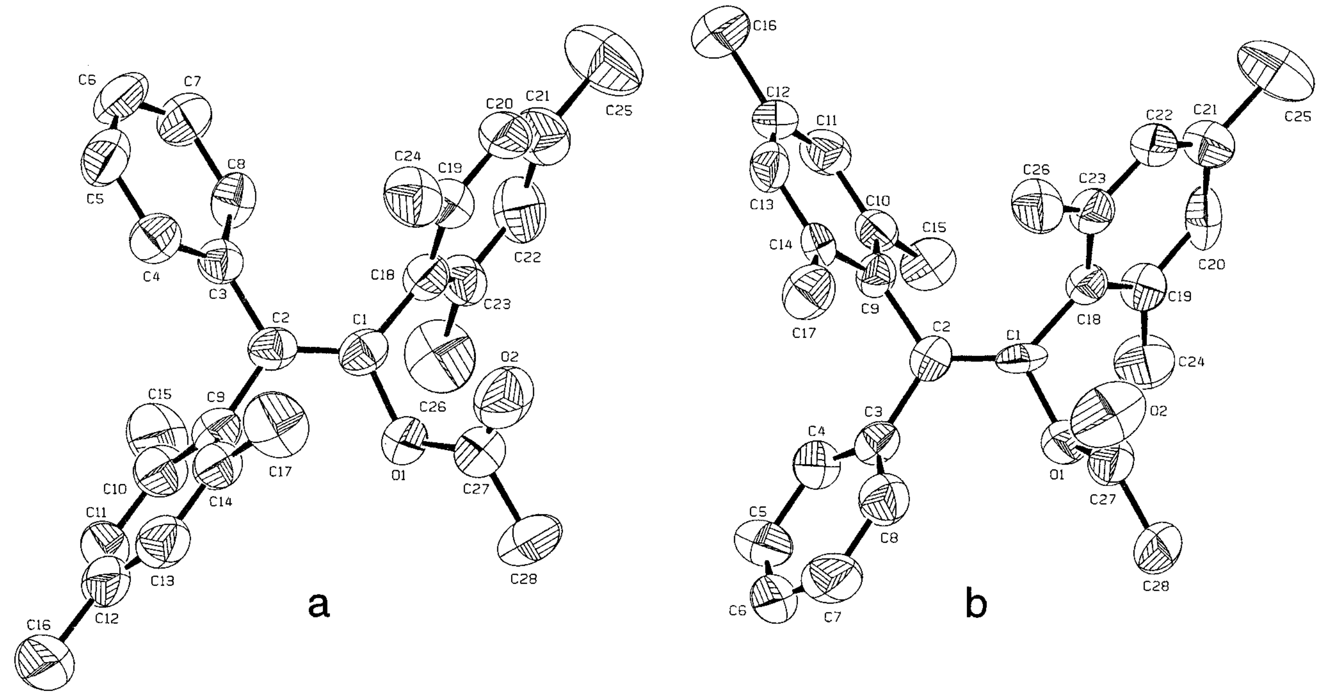

Figure 1. (a) Crystal structure and numbering scheme of (a) **4-(*Z*)** and (b) **4-(*E*)**. Selected bond lengths (Å) and angles (deg) for **4-(*Z*)** and **4-(*E*)**: O(1)C(1), 1.418(8), 1.423(8); C(1)C(2), 1.34(1), 1.331(8); C(1)C(18), 1.49(1), 1.487(9); C(2)C(3), 1.50(1), 1.487(9); C(2)C(9), 1.51(1), 1.506(9); O(1)C(1)C(2), 116.9(6), 116.3(7); O(1)C(1)C(18), 112.1(6), 115.2(7); C(1)C(2)C(3), 121.9(7), 121.2(7); C(1)C(2)C(9), 122.3(7), 122.4(7); C(2)C(1)C(18), 130.4(7), 128.0(7); C(3)C(2)C(9), 115.7(6), 116.3(7).

investigated the influence of the reaction conditions on the nature of the product and the diastereoselectivity of the reaction.[1]

Our addition of MesMgBr to ketene **3** was conducted for 2 h in THF at 60 °C, and to the mixture was added acetyl chloride. Inspection of the crude reaction mixture by ^{1}H NMR after 15 min indicated that it consisted of a mixture of two enol acetates in a ca. 3:1 ratio. The compounds were separated by fractional crystallization, and the major and minor products were identified as Fuson's high melting and low melting enol acetates,[2b] respectively, on the basis of their melting points. The two acetates are configurationally stable, and no mutual isomerization could be detected, even after refluxing solutions of either acetate in acetic acid for one week. Changing the reaction times before acetylation and the acetylating agent and/or solvent to acetic anhydride/THF (2 h, 60 °C), acetic anhydride/toluene (24 h, reflux), or acetyl chloride/ether (3 h, reflux) had only a minor influence on the ratio of the two acetates obtained (3.7:1, 3:1, and 4.4:1, respectively), as judged by the ^{1}H NMR of the crude reaction mixtures. These results indicate that the nucleophilic addition to the ketene proceeds with high but not complete diastereoselectivity. Clearly, the complete stereoselectivity reported[2b] was due to the lack of a proper spectroscopic tool to analyze the crude reaction mixture. Our experiments also suggest that the different acetylating reagents and solvents used by Fuson are not responsible for the apparent different diastereoselectivity obtained in the acetylation of the magnesium enolates.

The starting material does influence the stereochemical outcome of the reaction. When enol **1-(*Z*)** was treated with MesMgBr in THF-d_8 and the resulting magnesium enolate solution was acetylated by acetyl chloride, the product consisted *exclusively*, as judged by NMR, of the same low-melting acetate obtained from **1-(*Z*)** with acetic anhydride in pyridine.[2b]

(ii) Crystal Structures of the High and Low Melting Enol Acetates. The crystal structure of the enol has been described previously, and it has been shown that the configuration of the double bond is *(Z)*; i.e., the compound is **1-(*Z*)**.[4] Single crystals of the high melting and low melting acetates obtained in THF as described above were crystallized from ethanol and submitted to X-ray crystallography. The X-ray analysis corroborates Fuson assignment of both structures as diastereomeric enol acetates, the high and low melting forms corresponding to *(E)* (**4-(*E*)**) and *(Z)* (**4-(*Z*)**), respectively. ORTEP drawings of the crystal structures of **4-(*E*)** and **4-(*Z*)** are shown in Figure 1. Both structures exist in a chiral propeller conformation.[3,5] The twist angles between the main plane of the rings and the average plane defined by the ethene double bond and the four atoms attached to it are 62° (α-Mes), 65° (*β*-Mes), and 57° (Ph) for **4-(*E*)** and 67° (α-Mes), 77° (*β*-Mes), and 43° (Ph) for **4-(*Z*)**, indicating that in both structures the twist angles of the mesityl rings are larger than that of the phenyl ring. In both structures the $C_{ipso}(\alpha\text{-Mes})-C(\alpha)=C(\beta)$ bond angle is large (132° and 128° for **4-(*E*)** and **4-(*Z*)**, respectively), suggesting that, as observed for other triarylethenols,[6] the steric crowding is mostly relieved by opening this angle.

(iii) (a) Curtin−Hammett Principle. The enol acetates **4-(*Z*)** and **4-(*E*)** are most likely derived from the stereospecific acetylation of a diastereomeric pair of magnesium enolates **5-(*Z*)** and **5-(*E*),** respectively (Scheme 1). The stereospecific acetylation of a pair of (potentially) mutually interconverting magnesium enolates leading to a pair of noninterconverting diastereomeric enol acetates can be analyzed in terms of the Curtin−Hammett kinetic scheme.[7] Three limiting situations exist: (i) The rate of mutual interconversion between the two

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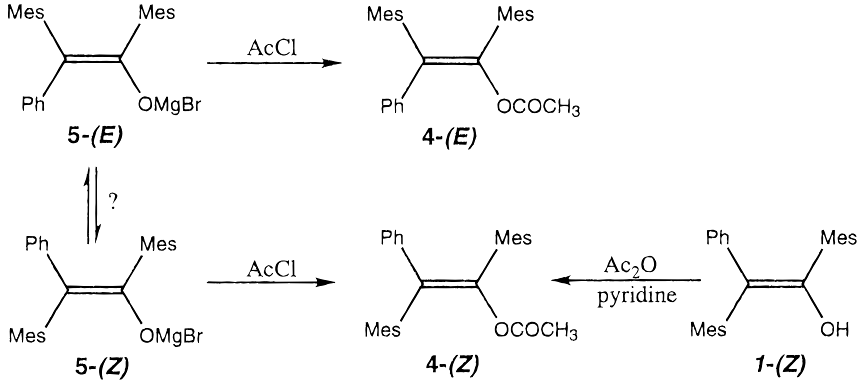
[4] Kaftori, M.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1701.

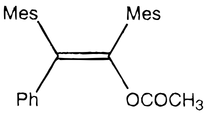
[5] (a) For a recent study on vinyl propellers, see: Rochlin, E.; Rappoport, Z. *J. Org. Chem.* **1994**, *59*, 3857. (b) Tetraarylvinyl propellers have been resolved. See: Maeda, K.; Okamoto, Y.; Morlender, N.; Haddad, N.; Eventova, I.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9686. Gur, E.; Kaida, Y.; Okamoto, Y.; Biali, S. E.; Rappoport, Z. *J. Org. Chem.* **1992**, *57*, 3689.

[6] Biali, S. E.; Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 846. Kaftory, M.; Nugiel, D. A.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 8181.

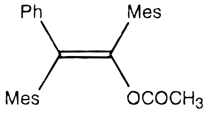
Scheme 1



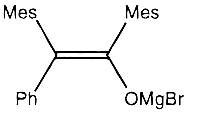
enolates is substantially faster than the rate of acetylation. The product ratio is then determined by the absolute energies of the two transition states leading to the diastereomeric acetates, the product formed preferentially being the one for which the transition state leading to it has the lower energy. (ii) The rate of mutual interconversion of the two enolates is slower than the rate of acetylation. The product ratio should reflect the ratio between the two diastereomeric enolates ("kinetic quench"). (iii) The rate of mutual interconversion is on the order of the acetylation rate. In this case the Curtin–Hammett principle in its usual form does not apply.[7]



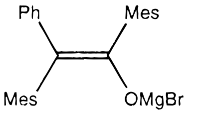
4-(*E*)



4-(*Z*)



5-(*E*)



5-(*Z*)

In order to understand the observed stereoselectivities in the acetylation reactions, it first has to be ascertained which of the three kinetic schemes is operating. This necessitates determination of whether the rate of mutual interconversion between the enolates **4-(*E*)** and **5-(*Z*)** is slower than, faster than, or similar to that of the acetylation reaction.

(b) Configurational Stability of the Magnesium Enolates. (i) ^{1}H NMR Studies. In order to find out whether the magnesium enolates derived from the reactions of MesMgBr with **3** and **1-(*Z*)** are configurationally stable on the NMR time scale, we carried out a spectroscopic ^{1}H NMR study of the system in a THF-d_8 solvent. When a 1.4 M excess of MesMgBr in THF was reacted with a solution of **1-(*Z*)** (δ 2.263, 2.275 ppm), new signals were observed at 2.11 (s, 3H), 2.16 (s, 3H), 2.28 (s, 6H), and 2.31 (s, 6H) ppm which are assigned to the *(Z)*-magnesium enolate **5-(*Z*)**. Quenching with acetyl chloride solution resulted in the exclusive formation of **4-(*Z*)** (δ 2.24 (s, 3H), 2.26 (s, 3H), 2.27 (s, 6H), 2.31 (s, 6H) ppm). Several additional signals which were observed in the range 1.94–2.15 ppm were shown by a control experiment to be due to the reaction products of MesMgBr and acetyl chloride and were not investigated further. Addition of a 1.3 M excess of MesMgBr in THF-d_8 to a solution of **3** (δ 2.21 (s, 6H), 2.30 (s, 3H) ppm) resulted after 90 min in the formation of major new signals at 1.97 (s, 6H) and 2.10 (s, 6H) ppm which are ascribed to **5-(*E*)**, together with minor signals corresponding to those of **5-(*Z*)**. Unfortunately, due to the multiplicity of nearly overlapping signals, the relative integration of **5-(*E*)** and **5-(*Z*)** could not be accurately obtained. Quenching of the reaction mixture with acetyl chloride gave a 3:1 mixture of **4-(*E*)** and **4-(*Z*)**. Since a distinct ^{1}H NMR spectrum is obtained for each enolate, we conclude that the mutual isomerization of the two enolates is slow on the ^{1}H NMR time scale.

(ii) Acid-Catalyzed Isomerization. Surprisingly, reaction of a 2.3:1 mixture of **3** and **1-(*Z*)** with a 1.5 M excess of MesMgBr in THF-d_8 did not result as judged by ^{1}H NMR in the formation of a mixture of **5-(*E*)** and **5-(*Z*)**. Instead an exclusive formation of **5-(*Z*)** was observed, and by quenching with acetyl chloride only **4-(*Z*)** was obtained. Since the independent addition of MesMgBr to **3** yields preferentially **5-(*E*)**, but this enolate could not be detected by NMR in the addition to the **1-(*Z*)**/**3** mixture, we must conclude that under the reaction conditions a fast *(E)/(Z)* isomerization took place, resulting in the thermodynamically more stable enolate (**5-(*Z*)**). The isomerization mechanism is unknown, and we tentatively suggest that it involves protonation of the enolates by the fraction of unreacted enol molecule **1-(*Z*)**. Protonation of **5-(*E*)** will give the unknown *(E)*-enol **1-(*E*)** which will undergo fast isomerization to the thermodynamically more stable isomer **1-(*Z*)** (Scheme 2). That **1-(*Z*)** is more stable is deduced from (i) Fuson's observation, which is corroborated in the present study, that protonation of the enolate(s) resulting from the addition of MesMgBr to **3** results in the isolation of only **1-(*Z*)**[2b] and (ii) the formation of only **1-(*Z*)** from hydrolysis of both **4-(*E*)** and **4-(*Z*)**.[2b] We believe that **1-(*E*)** is an intermediate in all reactions initiated with **4-(*E*)**. At present it is not clear why the magnesium enolates are configurationally stable while the corresponding enols undergo fast *(E)* → *(Z)* interconversion. However, we have found previously that closely related mesityl-substituted triarylethenols undergo (*Z*) ⇌ (*E*) isomerization in solution.[5a,8]

(iii) Thermal Isomerization. When MesMgBr was added to a toluene solution of **3**, and the mixture was refluxed for 24 h and acetylated, the products obtained were similar to those obtained in the other experiments at lower temperatures, i.e., a ca. 3:1 mixture of **4-(*E*)** and **4-(*Z*)**. The attempted isomerization of the generated magnesium enolates at a higher temperature (155 °C) in mesitylene resulted in decomposition. The lack of thermal isomerization of the thermodynamically less stable **5-(*E*)** at a high temperature (as deduced by the formation of **4-(*E*)** as the major product) indicates that the mutual isomerization of the two magnesium enolates must be slow on the laboratory

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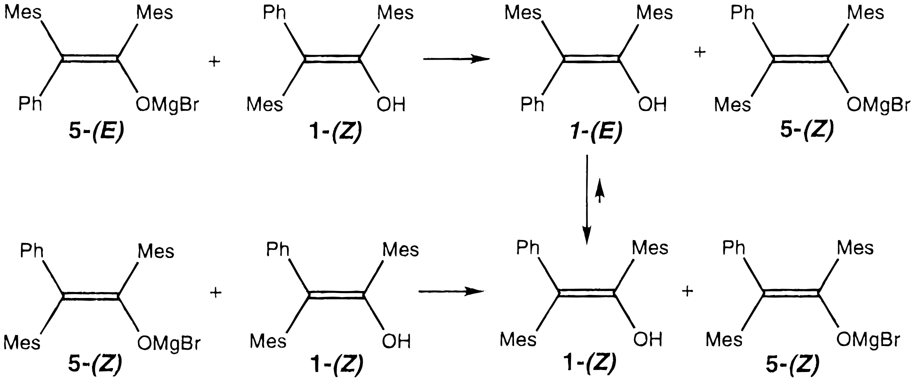
(7) For a review on the Curtin–Hammett principle, see: Seeman, J. *Chem. Rev.* **1983**, *83*, 83. See also: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 647.

(8) Rochlin, E.; Rappoport, Z. Unpublished results.

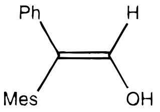
Scheme 2



time scale at the temperature used for the acetylation; i.e., the magnesium enolates **5-(*Z*)** and **5-(*E*)** can be regarded as configurationally stable. The reaction of acetyl chloride with either enolate was found to be relatively fast. By NMR monitoring, it is complete after 5−10 min at 35−55 °C. Since the acetylation rate is faster than the rate of mutual isomerization, the product ratio must reflect the ratio of the two reacting diastereomeric enolates (kinetic quenching).

(iv) (a) Stereoelectronic Effects in the Addition to 3. Neither the magnesium enolates nor the two enol acetates mutually interconvert under the reaction conditions. Hence, we conclude that the addition to ketene **3** occurs under kinetic control. Since the thermodynamically less stable *(E)*-enolate **5-(*E*)** is formed preferentially in the addition of MesMgBr to **3**, the transition state leading to it must be of a lower energy than the one leading to **5-(*Z*)**. This can be rationalized by stereoelectronic effects operating in the addition. The addition of nucleophiles to the ketene carbonyl occurs necessarily by an attack in the plane of the C═C bond of the ketene. When the ketene substituents differ in their bulk, the two faces are sterically different and the nucleophile will attack the face *cis* to the less bulky group.[9,10] This is analogous to the behavior of vinyl cations that, when substituted by two different β substituents, react with a nucleophile preferentially from the side of the less bulky substituent.[11] *In the case of **3**, the energetical preference for the (E)-enolate indicates that the attack of the Grignard reagent is preferred from the side of the apparently bulkier mesityl group*; i.e., the reaction apparently displays a "masochistic" steric effect.[12]

(b) Conjugation Effects in Ketene 3. The lowest energy conformation of **3** should be mainly dictated by an interplay of two factors: conjugation of the aryl rings with the double bond and steric effects. The conjugation is maximal when the two rings are coplanar with the double bond, but this arrangement is of high energy since it should be destabilized by repulsive steric effects between a pair of *ortho* groups in both rings. Which ring will then preferentially conjugate depends on electronic and steric effects. The conjugation energy of a mesityl vs that of a phenyl group with a double bond was estimated to be only slightly higher (4.8 vs 4.5 kcal mol^{-1}).[13] However, since both groups differ markedly in their steric requirements, it could be expected that the phenyl will have the smallest torsional angle since in this way its small *ortho*-H substituent is the one which sterically interacts with the neighboring ring. Unfortunately, ketene **3** is not solid, which precludes its structure determination by room-temperature X-ray diffraction.[14] However, in the solid state structures of the acetates **4-(*E*)/4-(*Z*)**, and enols **1-(*Z*)** [4] and **6**,[15] where the same two effects are present, the mesityl group is always more twisted (Mes vs Ph angles: 74°, 38° (**1-(*Z*)**); 65°, 57° (**4-(*E*)**); 77°, 43° (**4-(*Z*)**); 75°, 28° (**6**)).



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In order to study the preferred conformation of **3** and to model the geometries and relative energies of the two diastereomeric transition states obtained by nucleophilic attack on the sp carbon, we resorted to *ab initio* calculations.[16] Because the aim of the present study required calculations of relatively large-sized molecules (e.g., triaryl-substituted enols and vinyl cations), calculations were made at a relatively low level (HF/3-21G). However, since we compare in the present study only the relative energies of pairs of (*E*) and (*Z*) diastereomers of enols, enolates, and the transition structures for the addition to ketene **3** and the conformations of ketenes and vinyl cations, and since the calculated geometries are in good agreement with the corresponding X-ray results where such data are available (see below), the use of this level of theory seems satisfactory.

(c) Conformation of Ketene 3. *Ab initio* HF/3-21G calculations indicate that the minimum energy conformation of **3** is not a propeller conformation as determined by X-ray crystallography for the more crowded dimesitylketene,[14] but a conformation in which the phenyl ring is in the double bond plane while the mesityl ring is nearly perpendicular to it (Figure 2a). In contrast, *ab initio* HF/3-21G calculations indicate that diphenylketene exists in a propeller conformation in which both rings are twisted by 44.9° from the ethene double bond plane.[17] The arrangement found for **3** is analogous to the proposed

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(9) Gong, L.; Leung-Toung, R.; Tidwell, T. T. *J. Org. Chem.* **1990**, *55*, 3634. Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391. For a review on the mechanism of nucleophilic addition to ketenes, see: Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587. See also ref 4.

(10) For a comprehensive review on ketenes, see: Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

(11) For a review, see: Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*; Academic Press: San Francisco, 1979; Chapters III, V, and VI.

(12) Brady, W. T.; Roe, R., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 4618.

(13) Nadler, E. B.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, *109*, 2112.

(14) For an X-ray structure study of dimesitylketene, see: Gozin, M.; Biali, S. E.; Rappoport, Z. *J. Phys. Org. Chem.* **1989**, *2*, 271.

(15) Nadler, E. B.; Röck, M.; Schmittel, M.; Rappoport, Z. *J. Phys. Org. Chem.* **1993**, *6*, 233.

(16) For *ab initio* (3-21G) calculations on the reaction of ketene with lithium enolates, see: Leung-Toung, R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1990**, *112*, 1042.

(17) Diphenylketene has been previously calculated by AM1 to prefer a propeller conformation in which both rings are twisted by 30−40°: Sammynaiken, R.; Westwood, N. P. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1987.

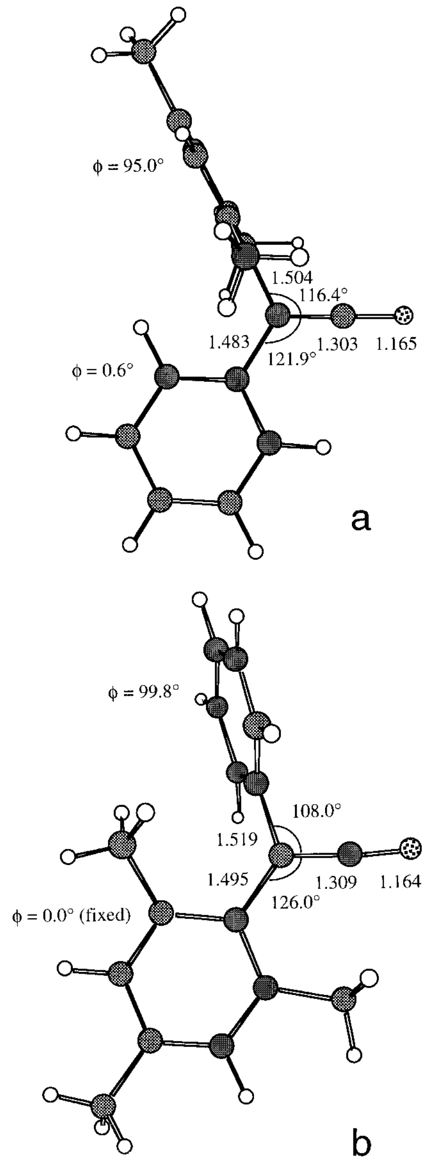


Figure 2. Calculated (HF/3-21G) conformations of ketene **3**: (a) low-energy conformation, (b) conformation with the mesityl ring constrained to be coplanar with the ketene plane.

transition state for the one-ring flip mechanism in 1,1-diarylvinyl propellers.[6,18,19] This nonpropeller arrangement seems to be the intrinsically preferred conformation for a Mes−C(sp^2)−Ph moiety as shown also by MM3 calculations of mesityl phenyl ketone which indicate that this system too adopts a conformation in which the phenyl ring is coplanar while the mesityl group is perpendicular to the carbonyl plane. When the mesityl ring of **3** was constrained to adopt a coplanar arrangement with the double bond plane, the resulting calculated conformation (in which the phenyl ring is nearly perpendicular, Figure 2b) was 12 kcal mol^{-1} above the ground state conformation. No stable conformation in which the torsional angle of the mesityl ring is in the 30−60° range could be found.

The preferred conformation of **3**, in which the less bulky phenyl group is coplanar with the double bond plane while the mesityl group is nearly perpendicular to it may rationalize the stereoselectivity of the Grignard addition, provided that in the two diastereomeric transition states the ground state conformation of the ketene moiety is partially or completely retained. Since the nucleophilic attack on the C=O group of the ketene occurs in the plane of the C=C double bond, the face carrying the coplanar phenyl group seems effectively more hindered to an approaching nucleophile than the face carrying the twisted mesityl ring and the preferred attack is from the "less bulky" mesityl side (Figure 3a).

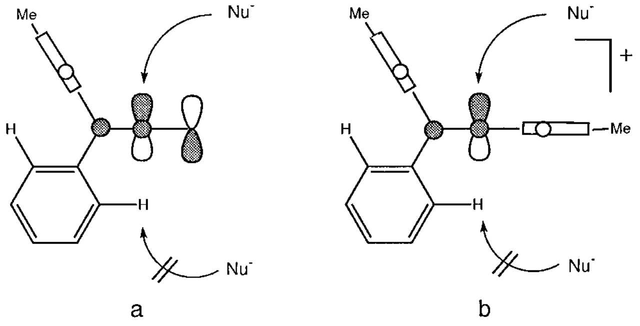
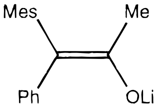
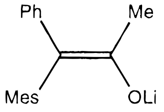


Figure 3. Diastereomeric transition states in the nucleophilic attack on the sp carbon of ketene **3** (a) and vinyl cation **10** (b). In both cases a nucleophile should prefer to attack from the side of the perpendicular mesityl ring

(d) Transition States of the Nucleophilic Attack on 3. In order to substantiate our hypothesis that the different torsional angles of the two rings are responsible for the preferred formation of **4-(*E*)** in the addition of MesMgBr to **3**, we modeled the reaction using *ab initio* calculations. We chose as a model system the nucleophilic attack of MeLi on **3** and calculated both the two diastereomeric transition states and the two (*E*)- and (*Z*)-lithium enolate products. According to the calculations, the lithium enolate **7-(*Z*)** (Figure 4b) is more stable than its isomeric enolate **7-(*E*)** (Figure 4a) by 4.9 kcal mol^{-1}, but the transition state leading to the less stable **7-(*E*)** (Figure 5a) is 1.5 kcal mol^{-1} lower in energy than the diastereomeric transition state leading to **7-(*Z*)** (Figure 5b). In both transition states the lithium atom is coordinated to the ketene oxygen. The calculations corroborate the suggestion that the preferred mode of attack of a nucleophile on a ketene is from the side of the mesityl group. They also suggest that the diastereoselectivity in the addition should not be necessarily complete as was indeed observed with MesMgBr, which is an even bulkier nucleophile than MeLi.[20]



7-(*E*)



7-(*Z*)

Inspection of the geometries of the two diastereomeric transition states (Figure 5) indicates that in the transition state leading to **7-(*E*)** the phenyl ring is coplanar with the C=C double bond while in the transition state leading to **7-(*Z*)** the phenyl is twisted in order to allow the approach of the incoming nucleophile. The increased conjugation in the first transition state is probably the main factor which determines the diastereoselectivity of the addition.

(e) (*E*)/(*Z*) Relative Energy and Preferred Conformation of Enols 1. For each enol two conformations were considered: (i) the OH group oriented *syn* to the C=C bond and (ii) the OH group oriented *anti* to the C=C bond. According to the calculations, in **1-(*E*)** and **1-(*Z*)** the *syn* arrangement of the C=C−OH moiety (**8**) is preferred over the *anti* arrangement (**9**) by 3.2 and 3.3 kcal mol^{-1}, while in their *syn* arrangement the (*Z*) form is preferred over the (*E*) form by 7.5 kcal mol^{-1}.

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(18) Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 1535.

(19) Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1984**, *106*, 477.

(20) It could be expected that, since the diastereoselectivity is the result of competing steric effects, the larger the nucleophile, the higher the diastereoselectivity of the reaction.

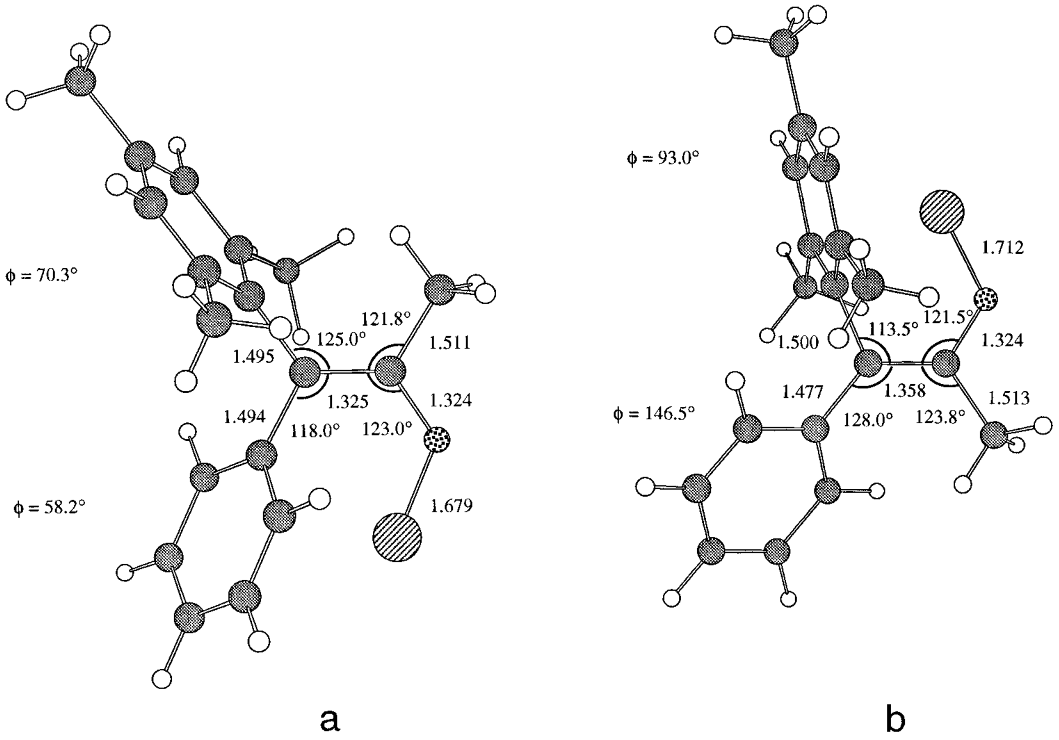


Figure 4. Calculated (HF/3-21G) structures of the lithium enolates (a) **7-(*E*)** and (b) **7-(*Z*)**.

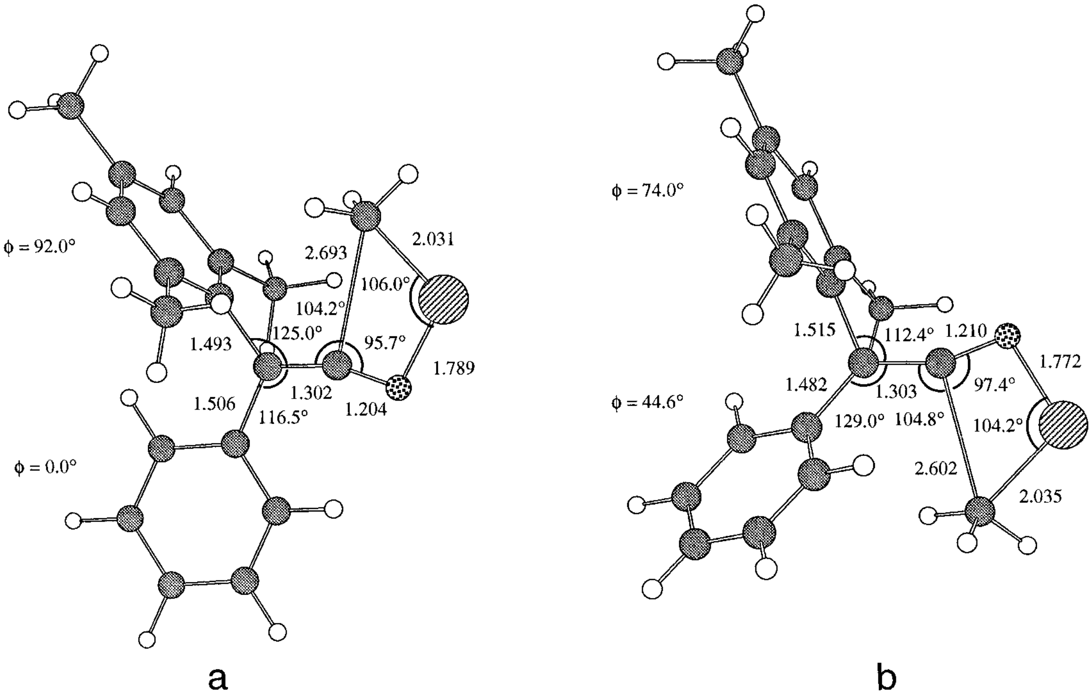
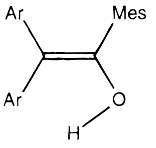


Figure 5. Calculated (HF/3-21G) transition states for the reaction of ketene **3** with MeLi: (a) (*E*) transition state, (b) (*Z*) transition state.

A preference for the *syn* form was found also in calculations for the parent and alkyl-substituted vinyl alcohols[21] and from



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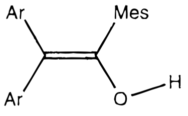

9

NMR spectra for di- and triarylvinyl alcohols in solution in non-hydrogen-bonding solvents,[22] a situation resembling the calculation for an isolated molecule in the gas phase.

The calculated preference of **1-(*Z*)** over **1-(*E*)** is consistent with the exclusive observation of **1-(*Z*)** in solution and with the **1-(*E*)** → **1-(*Z*)** isomerization suggested above.

(f) Diastereoselectivity in the Nucleophilic Attack on a Vinyl Cation. In principle, it could be expected that the same stereoelectronic effects observed in the nucleophilic addition to ketenes should be observed in other sp-hybridized systems. In order to test this assumption, we investigated another sp-hybridized system, i.e., a vinyl cation. We chose the 1,2-

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(21) Bouma, W. J.; Radom, L. *J. Mol. Struct.* **1978**, *43*, 267. Apeloig, Y.; Arad, D.; Rappoport, Z. *J. Am. Chem. Soc.* **1990**, *112*, 9131.

(22) Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1984**, *106*, 5641. Nadler, E. B.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 213.

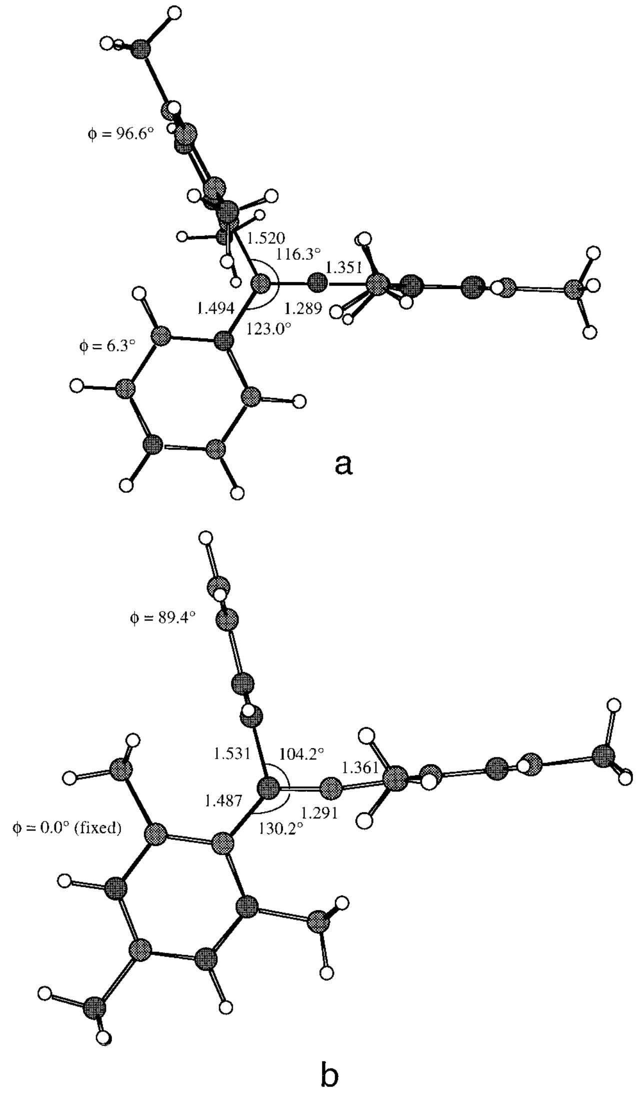

Figure 6. Calculated (HF/3-21G) conformations of the vinyl cation **10**: (a) low-energy conformation, (b) conformation with the mesityl ring constrained to be coplanar with the plane of the C=C double bond.

dimesityl-2-phenylvinyl cation (**10**) which is sterically similar to **3** and acetic acid as a solvent since its nucleophilic attack on the cationic orbital should yield one of the two vinyl acetates **4-(*E*)** and **4-(*Z*)** which were obtained by addition of MesMgBr to **3** followed by acetylation. By analogy with the analysis for **3**, **10** should be captured by the solvent from the mesityl side (Figure 3b). Vinyl cation **10** should be easily generated by solvolysis of a suitable precursor such as 1,2-dimesityl-2-phenylvinyl tosylate (**11**).

(i) Ab Initio Calculations. Two conformations of cation **10** were calculated. In both the α-mesityl group was perpendicular to the double bond plane, i.e., in the plane of the cationic p orbital, maximizing the overlap with it.[23] According to the calculations, in the lower energy conformation the phenyl ring is nearly coplanar with the double bond while the *β*-mesityl ring is nearly perpendicular to it. The conformation in which the mesityl ring is fixed to be coplanar with the double bond while the phenyl is nearly perpendicular lies ca. 7 kcal mol^{-1} above the low-energy conformation. The calculated geometries and selected structural parameters are shown in parts a and b, respectively, of Figure 6. Notably, in the high-energy conformation both the Mes—C=C and Mes—C—Ph bond angles are widened in order to reduce the repulsive steric interactions between the *o*-Me groups and the α-carbon and the geminal ring.

Table 1. Comparison of the Calculated Geometrical Parameters and Mulliken Populations of the Stable and Unstable Conformers of **3** and **10**[a]

	stable conformer		unstable conformer	
parameter	**3**	**10**	**3**	**10**
bond length				
C_1-X^b	1.165	1.351	1.164	1.361
C_1-C_2	1.303	1.289	1.309	1.291
C_2-Ph	1.483	1.494	1.519	1.531
C_2-Mes	1.504	1.520	1.495	1.487
bond angle				
$X-C_1-C_2^b$	179.3	177.7	174.7	173.4
C_1-C_2-Ph	121.9	123.0	108.0	104.2
C_1-C_2-Mes	116.4	116.3	126.0	130.2
dihedral angle				
C_1-C_2-Ph	0.6	6.3	99.8	89.4
C_1-C_2-Mes	90.5	96.6	0.0 (fixed)	0.0 (fixed)
Mulliken population				
X	−0.542	0.476	−0.557	0.446
C_1	0.585	0.316	0.629	0.308
C_2	−0.132	−0.095	−0.143	−0.079
Ph	0.016	0.145	0.036	0.137
Mes	0.073	0.159	0.035	0.187

[a] Bond lengths are in angstroms, and bond angles and dihedral angles are in degrees. [b] X is O for **3** and Mes for **10**.

Table 1 gives a comparison of bond lengths and angles for the two calculated conformations of the ketene and the vinyl cation **10**. There is a similarity between corresponding parameters, e.g., Ar—C bond lengths or Ar—C—Ar angles for each type of conformation of **3** and **10**. The bond to the planar aryl is shorter and the C(α)—C(*β*)—Ar bond angle is wider for the planar aryl in both conformations.

$Mes(Ph)C{=}C^{+}{-}Mes$
10

$Mes(Ph)C{=}C(OSO_2C_6H_4Me\text{-}p)Mes$
11

The Mulliken charges on the vinylic carbons and the aromatic substituents were calculated for the two conformations of **3** and **10** (Table 1). Some charge from the polarized C(α) on **3** is transferred to the aryl rings, more effectively so for the perpendicular aryl, suggesting a through space overlap. More extensive charge transfer occurs in cation **10**, presumably by polarization. However, here a perpendicular aryl delocalizes less of the charge than when it is planar. Tentatively, this may be ascribed to the combination of two opposing effects: the through space overlap which is favoring the perpendicular aryl group and a charge transfer by polarization to C(*β*), which is more dominant and delocalizes the charge on the coplanar aryl group.

(ii) Solvolysis of Tosylate 11. The vinyl tosylate **11** was prepared as described elsewhere by reaction of a toluene solution of the sodium enolate salt (prepared by reaction of **1-(*Z*)** and NaH) and tosyl chloride.[24] A single stereoisomer was obtained, to which the (*Z*) configuration was assigned.[24] Tosylate **11** was solvolyzed in refluxing AcOH. Examination of the crude reaction mixture indicated that the exclusive product formed was the acetate **4-(*Z*)** (eq 1). This is the acetate which is predicted to be formed if the nucleophilic attack takes place exclusively from the side of the mesityl ring. This result indicates that, similarly to what was observed for **3**, due to its

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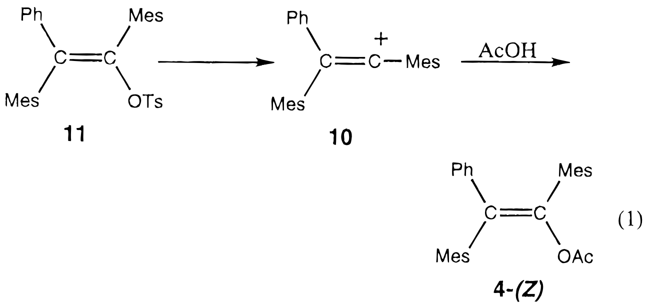
[23] Kobayashi, S.; Hori, Y.; Hasako, T.; Koga, K.-i.; Yamataka, H. *J. Org. Chem.* **1996**, *61*, 5274.

[24] Tsuji, Y.; Fujio, M.; Tsuno, Y.; Rappoport, Z. Paper in preparation.



(1)

larger twist angle the mesityl ring seems effectively smaller to the attacking solvent than the phenyl ring.

Conclusions

In the reacting conformation of ketene **3** and vinyl cation **10** the phenyl ring is coplanar with the double bond plane while the mesityl ring is perpendicular to it. Although an isolated mesityl ring is necessarily more space-filling than a phenyl ring, since the nucleophilic attack on the sp-hybridized systems occurs in the plane of the double bond, the phenyl ring is effectively bulkier and the preferred attack is from the mesityl side. The same stereoelectronic effect applies when the attacking nucleophile is bulky or moderate in size.

Experimental Section

Materials. Mesitylphenylketene was prepared according to Fuson.[2b] Mesitylmagnesium bromide (1 M in THF) and THF-d_8 were purchased from Aldrich.

General Methods. X-ray diffraction data were measured with a PW 1100 Philips four-circle computer-controlled diffractometer equipped with a five-focus Mo X-ray tube and a graphite monochromator in the incident beam.

Crystal Data for 4-(*E*): FW $C_{28}H_{30}O_2$, space group $P2_12_12_1$, a = 14.226(2) Å, b = 19.875(3) Å, c = 8.341(1) Å, V = 2358.3(5) Å^3, z = 4, ρ_{calc} = 1.122 g cm^{-3}, μ (Mo Kα) = 0.37 cm^{-1}, no. of unique reflections 1803, no. of reflections with $I \geq 1\sigma_I$ 1544, R = 0.075, R_w = 0.091.

Crystal Data for 4-(*Z*): FW $C_{28}H_{30}O_2$, space group $P2_1/c$, a = 8.903(1) Å, b = 34.220(5) Å, c = 8.980(1) Å, β = 118.8(2)°, V = 2396.5(8) Å^3, z = 4, ρ_{calc} = 1.105 g cm^{-3}, μ(Mo Kα) = 0.36 cm^{-1}, no. of unique reflections 3222, no. of reflections with $I \geq 2\sigma_I$ 1523, R = 0.078, R_w = 0.075.

Ab initio MO calculations were carried out by using the Gaussian 92[25] and 94[26] programs. All structures were fully optimized at the HF/3-21G level without any symmetry constraint except for two cases, the high-energy conformations of **3** and **10**, where the dihedral angle of the mesityl ring was fixed at 0.0°. Transition states were confirmed by vibrational frequency calculations to have only one imaginary frequency.

Attempted *cis*/*trans* Isomerization. **4-(*E*)** or **4-(*Z*)** (100 mg) was dissolved in AcOH (20 mL), to which were added acetic anhydride (0.5 mL) and NaOAc (0.11 g), and the solution was refluxed for one week. No isomerization could be detected in any of the samples by either TLC or NMR.

Spectroscopic Data for 4-(*Z*): ^{1}H NMR (300 MHz, $CDCl_3$, rt) δ 1.78 (s, 3H, Me), 2.27 (s, 3H, *p*-Me), 2.29 (s, 6H, *o*-Me), 2.31 (s, 9H, *o*-Me, *p*-Me), 6.82 (m, 4H, Mes-H + *o*-Ar-H), 6.91 (s, 2H, Mes-H), 7.04 (m, 3H, *m*-, *p*-Ar-H); ^{13}C NMR (75.460 MHz, $CDCl_3$, rt) δ 20.58, 20.70, 21.02, 21.13, 126.86, 127.81, 128.32, 128.45, 128.94, 130.27, 131.49, 135.65, 136.30, 136.41, 137.19, 137.92, 138.30, 144.67 (=C(α)), 168.28 (C=O); IR (KBr) ν_{max} 2910 (m), 1750 (s), 1640 (m) cm^{-1}; UV (MeOH) λ_{max} (ϵ) 217 (23 400), 270 sh (10 400) nm; EI MS (70 eV) *m*/*z* (rel intens) 398 (17, M), 356 (B, M − O=C=CH_2).[27]

Spectroscopic Data for 4-(*E*): ^{1}H NMR (300 MHz, $CDCl_3$, rt) δ 1.98 (s, 6H, Me), 2.04 (s, 3H, Me), 2.18 (s, 6H, *o*-Me), 2.22 (s, 6H, Me), 6.68 (s, 2H, Mes-H), 6.69 (s, 2H, Mes-H), 7.16−7.28 (m, 5H, Ar-H); ^{13}C NMR (75.460 MHz, $CDCl_3$, rt) δ 20.80, 20.92, 20.98, 21.06, 126.93, 127.84, 128.76, 128.82, 131.53, 131.62, 134.21, 136.77, 137.24, 137.72, 139.56, 144.27 (=C(α)), 170.34 (C=O); IR ν_{max} 2910 (m), 1745 (s), 1630 (m) cm^{-1}; UV (MeOH) λ_{max} (ϵ) 217 (30 900), 268 sh (18 600) nm; EI MS (70 eV) *m*/*z* (rel intens) 398 (22, M), 356 (B, M − O=C=CH_2).[27]

Enolate Solution for NMR Studies. (a) A 25 mg sample of **1-(*Z*)** (0.07 mmol) was dissolved in THF-d_8 (0.5 mL), and MesMgBr (0.1 mL of a 1 M THF solution) was added in an NMR tube. The ^{1}H NMR spectrum was measured after 2 h and displayed signals at 2.11 (3H, s), 2.16 (3H, s), 2.28 (6H, s), and 2.31 (6H, s) ppm. On addition of acetyl chloride (0.05 mL, 0.65 mmol) and recording the spectrum after 25 min only the spectrum of **4-(*Z*)** and the signals obtained independently (but not identified) from MesMgBr and acetyl chloride were observed. (b) A 73 mg sample of **3** was dissolved in 1 mL of THF-d_8, and MesMgBr (0.4 mL of a 1 M THF solution) was added in an NMR tube. The ^{1}H NMR spectrum was measured after 90 min and displayed signals at 1.97 (6H, s) and 2.10 (6H, s) ppm. A 0.5 mL sample of acetyl chloride was added, and after 30 min the solvent was evaporated. The ^{1}H NMR ($CDCl_3$) of the residue indicated that it consisted of a ca. 3:1 mixture of **4-(*E*)** and **4-(*Z*)**.

Acetylation of the Enolate Derived from 3 with Acetic Anhydride. A 1 mL sample of a 1 M solution of MesMgBr in THF was added to **3** (150 mg) dissolved in THF (1.5 mL). The mixture was stirred for 18 h at 60 °C, and then acetic anhydride (0.3 mL) was added. The solution was stirred for 20 min, and then poured into ice−water, extracted with CH_2Cl_2, and evaporated. The residue consisted of a 3.7:1 mixture of **4-(*E*)** and **4-(*Z*)**.

Acetylation of 1. To a stirred solution of **1-(*Z*)** (88 mg, 0.22 mmol) in dry THF (2 mL) was added a solution of MesMgBr (0.5 mL of a 1 M THF solution), and the mixture was stirred for 1 h at 40 °C. Acetyl chloride (0.5 mL) was then added at 40 °C, and the stirring was continued for 30 min, after which the solvent and excess acetyl chloride were evaporated. ^{1}H NMR showed that only **4-(*Z*)** was obtained in addition to side products from the reaction with acetyl chloride.

Acetolysis of Tosylate 11. A 50 mg sample of tosylate **11** was dissolved in AcOH (20 mL), to which was added NaOAc (0.05 g), and the solution was refluxed for 6 h. After evaporation of the solvent, the residue was dissolved in ether and the solution washed with water. After phase separation and drying, the organic solvent was evaporated and the residue examined by ^{1}H NMR which indicated the exclusive formation of acetate **4-(*Z*)**.

Acknowledgment. We thank Dr. Shmuel Cohen for the crystal structure determination and the USA-Israel Binational Science Foundation (BSF) for support of this work.

Supporting Information Available: A listing of positional and thermal parameters for **4-(*E*)** and **4-(*Z*)** (4 pages). See any current masthead page for ordering and Internet access instructions.

JA962573A

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[25] Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andress, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *GAUSSIAN 92*, Revision C; Gaussian Inc.: Pittsburgh, PA, 1992.

[26] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andress, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *GAUSSIAN 94*, Revision C.2; Gaussian Inc.: Pittsburgh PA, 1995.

[27] The molecular ions of **4-(*E*)** and **4-(*Z*)** undergo in the gas phase a unimolecular loss of ketene, giving a spectrum identical to that of enol **1-(*Z*)**. See: Biali, S. E.; Lifshitz, C.; Rappoport, Z.; Karni, M.; Mandelbaum, A. *J. Am. Chem. Soc.* **1981**, *103*, 2896.