

30.4, 36.9, 39.5, 41.5, 44.7, 46.0, 180.7.

exo-3-(Trimethylsilyl)-2-norcamphor. Into a 200-mL, three-necked, round-bottomed flask was weighed 3.37 g (15 mmol) of the silylated hydrazone. This material was covered with 120 mL of anhydrous CH_2Cl_2 , and the resulting solution was cooled to -78°C . Ozone was bubbled through the solution until the blue of excess ozone persisted. Nitrogen was bubbled through the solution as it warmed to room temperature. The organics were washed once with a dilute solution of acetic acid and twice with water and then were dried (MgSO_4). The solvent was removed on a rotary evaporator to yield a light yellow residue. The residue was purified by flash column chromatography (10/90 ether/hexane on silica gel) to yield 0.30 g (1.6 mmol, 11%) of the product: ^1H NMR (CDCl_3) δ 0.10 (s, 9 H), 1.35–1.41 (m, 2 H), 1.49 (m, 1 H), 1.55 (d, 1 H), 1.68 (m, 1 H), 1.73–1.80 (m, 2 H), 2.52 (br d, 1 H), 2.61 (br s, 1 H); ^{13}C NMR (CDCl_3) δ 1.1, 24.8, 30.2, 36.8, 38.2, 50.1, 50.4, 219.2.

exo-3-(Trimethylsilyl)-endo-2-norborneol (4-OH). Into a 50-mL, flame-dried, three-necked, round-bottomed flask was weighed 0.20 g (5.3 mmol) of lithium aluminum hydride. This material was covered with 25 mL of anhydrous ether and cooled to 0°C in an ice bath. The ketone (1.5 g, 8.2 mmol) in 15 mL of anhydrous ether was added dropwise. Once addition was complete, the ice bath was removed and the reaction was stirred for 2 h. The reaction was cooled again and quenched with water. The aqueous layer was separated and extracted once with ether. The combined organics were dried (MgSO_4), and the solvent was removed on a rotary evaporator to give 1.1 g (6.0 mmol, 73%) of the alcohol. The alcohol was purified by sublimation before use: mp $40\text{--}42^\circ\text{C}$; ^1H NMR (CDCl_3) δ 0.03 (s, 9 H), 0.10 (dd, $J_{23} = 5.8$ Hz, 1 H), 1.1–1.4 (m, 5 H), 1.58 (m, 1 H), 1.86 (m, 1 H), 2.08 (br s, 1 H), 2.20 (t, 1 H), 4.07 (m, $J_{23} = 5.8$ Hz, 1 H); ^{13}C NMR (CDCl_3) δ 2.6, 19.5, 33.9, 36.8, 38.9, 39.7, 43.1, 75.7; IR (KBr) $2700\text{--}3100\text{ cm}^{-1}$ (OH); HRMS for $\text{C}_{10}\text{H}_{20}\text{OSi}$, calcd m/z 184.1283, found m/z 184.1279. Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{OSi}$: C, 65.15; H, 10.94. Found: C, 65.20; H, 10.94.

exo-3-(Trimethylsilyl)-endo-2-norbornyl Trifluoroacetate (4-TFA). Into a 125-mL Erlenmeyer flask was placed 0.30 g (1.6 mmol) of the alcohol (4-OH). This material was covered with 15 mL of anhydrous ether, and 0.30 g (3.8 mmol) of pyridine was added. The mixture was cooled to 0°C in an ice bath, and 0.40 g (1.9 mmol) of trifluoroacetic anhydride in 10 mL of ether was added dropwise. The reaction was allowed to stand for 20 min, and the white crystals were removed by filtration. The organics were washed twice with saturated CuSO_4 and once with saturated NaHCO_3 and were dried (MgSO_4). The solvent was removed on a rotary evaporator to yield a colorless oil: ^1H NMR (CDCl_3) δ 0.03 (s, 9 H), 0.58 (dd, 1 H), 1.2–1.45 (m, 4 H), 1.6–1.75 (m, 2

H), 2.21 (br s, 1 H), 2.61 (br s, 1 H), 5.13 (m, 1 H).

endo-2-norbornyl Trifluoroacetate (5-TFA). Into a 125-mL Erlenmeyer flask were weighed 0.70 g (6.3 mmol) of *endo*-2-norborneol (Aldrich) and 0.50 g (6.3 mmol) of pyridine. Ether (15 mL) was added, and the flask was cooled to 0°C in an ice bath. A solution of 1.32 g (6.3 mmol) of trifluoroacetic anhydride in 10 mL of ether was added dropwise. Once addition was complete, the reaction was allowed to stir for an additional 10 min. The solids were removed by vacuum filtration, and the organics were washed with 2×15 mL of saturated CuSO_4 and 2×15 mL of saturated NaHCO_3 . The organics were dried (MgSO_4), and the solvent was removed on a rotary evaporator to yield a colorless oil: ^1H NMR (CDCl_3) δ 1.13 (dt, 1 H), 1.3–1.5 (m, 4 H), 1.61 (m, 1 H), 1.76 (m, 1 H), 2.09 (m, 1 H), 2.30 (br s, 1 H), 2.60 (br s, 1 H), 5.16 (m, 1 H).

Kinetics by Conductivity. The conductivity measurements were performed on solutions with substrate concentrations of approximately 10^{-3} M. The conductance cell had a 35-mL capacity and Pt electrodes. The solutions were either cooled in a Techne RB-5 refrigerated bath or warmed in a Precision H8 heating bath. The temperature was measured to 0.1°C with factory-certified (NBS standard) thermometers. The conductivity of the solutions was followed for 1–3 half-lives with a YSI Model 32 conductance meter. Linear first-order rate plots were obtained for up to 3 half-lives.

Kinetics by NMR. The probe of the Varian XLA-400 spectrometer was heated to the desired temperature and allowed to equilibrate for at least 15 min. The exact temperature was measured with an ethylene glycol standard. The sample to be studied was prepared, inserted into the probe, and allowed to equilibrate for 15 min. The time between acquisitions was set up as an array, which allowed the spectra to be acquired automatically overnight. Both the decrease of the peaks at δ 4.07 (4-OH) or δ 4.47 (3-OH) and the increase of the alkene peak at δ 6.0 could be used to calculate the rate constants.

Product Studies. A 0.3–0.5 M solution of the substrate in the solvent of choice (1–3 mL) was prepared in either an NMR tube or a Pyrex test tube. The tubes were sealed and heated in a water bath. After the reaction was complete, the products were identified by GC, GCMS, and NMR. Norbornene, *exo*-2-norborneol, and *endo*-2-norborneol were identified by comparison of the GC and NMR data with the authentic compounds. 2-(Trimethylsilyl)-2-norbornene was identified by MS peaks at 166, 138, and 73. 3-(Trimethylsilyl)-*exo*-2-norborneol was identified by MS peaks at 184, 94, 73, and 66. In order to obtain NMR spectra, the products were first extracted out of the aqueous solvents with ether and then dissolved in chloroform-*d*.

Investigation of the Mechanisms of Ene Reactions of Carbonyl Enophiles by Intermolecular and Intramolecular Hydrogen–Deuterium Isotope Effects: Partitioning of Reaction Intermediates

Zhiguo Song and Peter Beak*

Contribution from the Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801. Received April 13, 1990

Abstract: The mechanisms of ene reactions of selected carbonyl enophiles with methylenecyclohexane (**1**) and 1-methylenetetralin (**2**) have been investigated by determinations of intermolecular and intramolecular hydrogen–deuterium isotope effects. In the thermal ene reactions of **1** with dimethyl dioxosuccinate (**7**) and of **1** with diethyl oxomalonate (**8**), both of the isotope effects are primary and substantial, consistent with a concerted mechanism for each reaction. In the ene reactions of **1** with **8** catalyzed by tin tetrachloride and of **1** with acetylium hexachloroantimonate, both the intermolecular and intramolecular isotope effects are small, results that are inconsistent with either a stepwise reaction via an equilibrating intermediate or a concerted mechanism. The ene reaction of **2** with acetic anhydride catalyzed by zinc chloride has a small intermolecular and a large intramolecular isotope effect, consistent with rate-determining formation of an equilibrated intermediate. A general quantitative kinetic model is proposed to account for the observed isotope effects for these reactions in which the reactants form an intermediate that can partition between dissociation, equilibration between different isomers, and product formation.

The ene reaction, defined as the addition of an olefin bearing an allylic hydrogen, the ene component, to a double bond, the

enophile, with migration of the olefinic double bond and transfer of the allylic hydrogen from the olefin to the enophile, is illustrated

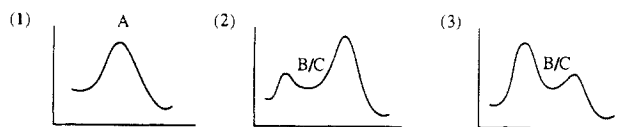
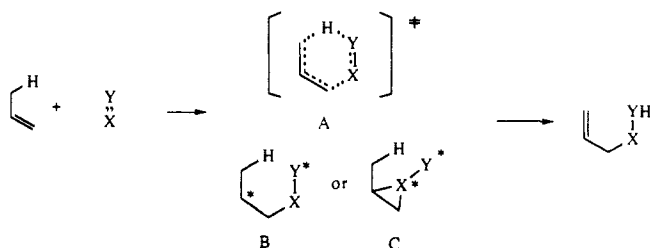


Figure 1. Reaction profiles for limiting cases of the ene reaction.

Scheme I



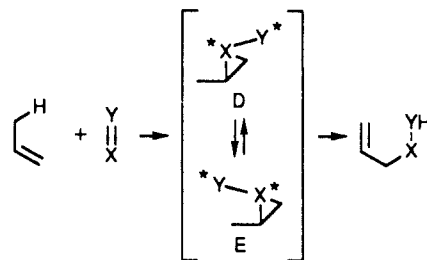
for a general enophile $X=Y$ in Scheme I.^{1,2} Carbonyl enophiles, including aldehydes, activated ketones, acid chlorides, and anhydrides, have been used in a number of important ene reactions, and the mechanisms of these ene reactions have been investigated extensively.^{3,4}

The mechanism of the ene reaction is usually discussed in terms of two limiting possibilities.¹ In one limit, an ene reaction is considered to proceed by a concerted, symmetry-allowed $2\pi_s + 2\pi_s + 2\sigma_s$ process, as shown for transition structure A in Scheme I. This limiting case can be represented as a single-barrier reaction shown as profile 1 in Figure 1.⁵ In the other limit, the mechanism can be considered to be stepwise via an intermediate, which can be either a zwitterion or a diradical with either free or restricted rotation, as illustrated by B and C in Scheme I. The formation of the intermediate can be either fast and reversible followed by slow hydrogen transfer or it can be slow and rate-determining followed by a fast hydrogen transfer. The reaction profiles of these two cases are shown as profiles 2 and 3, respectively, in Figure 1.

Comparison of intermolecular and intramolecular hydrogen-deuterium isotope effects is a powerful tool for determining if an ene reaction is stepwise or concerted.^{1h,6,7} This approach involves deuterium labeling of the hydrogens at the allylic position^{1h} and determination of isotope effects in the intermolecular and intra-

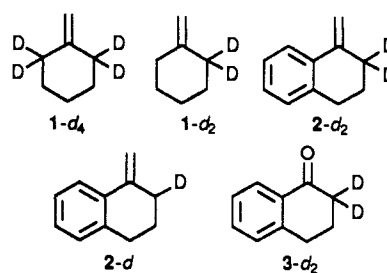
molecular competitions. A significant primary intermolecular hydrogen-deuterium isotope effect should be observed when the hydrogen transfer occurs in the rate-determining step, i.e., cases 1 and 2 in Figure 1. The intramolecular competition should also give essentially the same primary product isotope effect in these cases. In case 3, there would not be significant intermolecular primary isotope effect. A significant intramolecular isotope effect would be expected if the structure of the intermediate is such that there is unrestricted choice between transfer of the allylic hydrogen or deuterium, but such an effect would not be expected for a rigidly defined nonequilibrating intermediate. Comparison of intermolecular and intramolecular isotope effects by this approach can provide definitive information about the mechanism of the reaction.^{1,7,8} Overall, equal primary kinetic and product hydrogen-deuterium isotope effects are consistent with mechanisms that have hydrogen transfer as the rate-determining step, and different product and kinetic isotope effects are consistent with stepwise mechanisms via an equilibrating intermediate.⁹

In the present work, the mechanisms of thermal and catalyzed ene reactions of carbonyl enophiles selected to allow distinction between the concerted and stepwise pathways are presented. Determinations of intermolecular and intramolecular hydrogen-deuterium isotope effects are reported, and we provide kinetic analysis of a reaction pathway in which there is formation of geometrically defined intermediates D and E that can partition between dissociation to reactants, equilibration, and product formation. A preliminary report of this analysis has appeared.¹⁰



Results and Discussion

Preparation of Deuterium-Labeled Olefins. The olefins chosen for the determination of hydrogen-deuterium isotope effects are methylenecyclohexane (1) and 1-methylenetetralin (2). The olefins 1- d_4 and 2- d_2 are used with the corresponding unlabeled olefins for determination of the intermolecular isotope effects, and 1- d_2 and 2- d are used for the intramolecular isotope effects. With



1- d_2 , the competition between the allylic hydrogen or deuterium at two sides of the olefin can be assessed, while with 2- d , the competition between hydrogen or deuterium on different faces of the double bond is evaluated.

The preparation of 1- d_4 was accomplished by Wittig reaction of the tetradeuterated cyclohexanone, which was prepared by base-catalyzed hydrogen-deuterium exchange.^{7c,29} In the Wittig reaction, it was noted that very slow addition of the ketone to an

(1) For reviews: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Oppolzer, W.; Snieckus, Y. *Ibid.* **1978**, *17*, 476. (c) Oppolzer, W. *Ibid.* **1984**, *23*, 876. (d) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (e) Whitsell, J. K. *Ibid.* **1985**, *18*, 280. (f) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319. (g) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (h) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.

(2) For some recent examples: (a) Clennan, E. L.; Chen, X. *J. Am. Chem. Soc.* **1989**, *111*, 5786, 8212. (b) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607. (c) Jacobson, B. M.; Soteropoulos, P.; Bahadori, S. *J. Org. Chem.* **1988**, *53*, 3247. (d) Jenner, G.; Salem, R. B.; El'yanov, B.; Gonikberg, E. M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1671.

(3) (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (b) Whitesell, J. K.; Nabona, K.; Deyo, D. *J. Org. Chem.* **1989**, *54*, 2258. (c) Cartaya-Marin, C. P.; Jackson, A. C.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 2443. (d) Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988. (e) Andersen, N. H.; Hadle, S. W.; Kelly, J. D.; Racon, E. R. *J. Org. Chem.* **1985**, *50*, 4144.

(4) (a) Salomon, M. F.; Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1984**, *49*, 2446. (b) Achmattowiz, O., Jr. Szymoniak. *J. Org. Chem.* **1980**, *45*, 1228, 4774. (c) Jenner, G.; Papadopoulos, M. *J. Org. Chem.* **1982**, *47*, 4201. (d) Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200. (e) Kwart, H.; Brechbial, M. W. *J. Org. Chem.* **1982**, *47*, 3353, 5409.

(5) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: Chichester, Great Britain, 1976.

(6) (a) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980. (b) Collins, C. J.; Brown, N. S.; Eds. *Isotope Effects in Chemical Reactions*; von Nostrand Reinhold: New York, 1970. (c) Wiberg, K. B. *Chem. Rev.* **1955**, *55*, 713. (d) Bell, R. P. *Chem. Rev.* **1974**, *74*, 512. (e) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1974.

(7) (a) Dai, S. H.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3953. (b) Stephenson, L. M.; Mattern, D. L. *J. Org. Chem.* **1976**, *41*, 3614. (c) Beak, P.; Berger, K. *J. Am. Chem. Soc.* **1980**, *102*, 2848. (d) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.

(8) (a) Seymour, A. C.; Greene, D. F. *J. Am. Chem. Soc.* **1980**, *102*, 6384. (b) Cheng, C.; Seymour, C. A.; Petti, M.; Greene, F. D. *J. Org. Chem.* **1984**, *49*, 2910. (c) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5227. (d) Ohashi, S.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3472.

(9) This analysis assumes that secondary isotope effects are small relative to a significant primary isotope effect. The operation of a small primary isotope effect due to bent and unsymmetrical bonding about the hydrogen being transferred is a possibility and needs to be considered for each case.

(10) Song, Z.; Chrisope, D. R.; Beak, P. *J. Org. Chem.* **1987**, *52*, 3938.

Table I. Isotope Effects of Ene Reactions of Carbonyl Enophiles with **1** and **2**

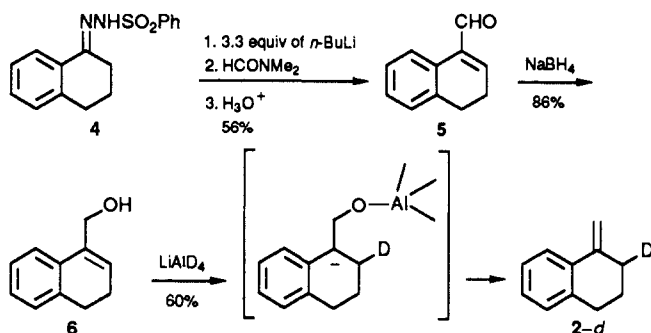
enophile reagent (conditions)	olefins	$(k_H/k_D)_{\text{inter}}$	$(k_H/k_D)_{\text{intra}}$
$(\text{MeO}_2\text{CCO})_2$ (7) (120 °C)	1 vs 1-d₄ or 1-d₂	2.7 ± 0.5^a	2.3 ± 0.2^a
$(\text{EtO}_2\text{C})_2\text{C}=\text{O}$ (8) (130 °C)	1 vs 1-d₄ or 1-d₂	2.8 ± 0.6^b	2.4 ± 0.2^b
$(\text{EtO}_2\text{C})_2\text{C}=\text{O}$ (SnCl_4 , 5 °C)	1 vs 1-d₄ or 1-d₂	1.1 ± 0.2^b	1.2 ± 0.1^b
$\text{CH}_3\text{CO}^+\text{SbCl}_6^-$ (9) (-78 °C, $\text{EtN}(i\text{-Pr})_2$)	1 vs 1-d₄ or 1-d₂	1.1 ± 0.2^a	1.1 ± 0.1^a
$(\text{CH}_3\text{CO})_2\text{O}/\text{ZnCl}_2$ (-5 to 0 °C)	2 vs 2-d₂ or 2-d	1.79 ± 0.36^c	9.7 ± 1.0^c

^a Average of three runs. ^b One run. ^c Average of two runs for the intermolecular isotope effect and average of three runs for the intramolecular effect.

ether solution of ylide at room temperature caused scrambling of deuterium to the vinyl position in the product, giving **1-d₅** and **1-d₃** products as judged by field ionization mass spectrometry (FIMS). This was attributed to enolization of the ketone by the ylide, and rapid addition of the ketone at the refluxing temperature of ether resolved the problem, providing **1-d₄** as a 95.5% d_4 /2.3% d_3 /2.0% d_5 material. Olefin **1-d₂** was prepared following a literature procedure as a 97.0% d_2 /3.0% d_1 material.¹¹

The olefin **2-d₂** was prepared by Peterson olefination of **3-d₂**. Starting from **3-d₂** as a 97.2% d_2 /2.8% d_1 material, Wittig reaction gave olefin with 5% d_3 material, whereas Peterson olefination with the same ketone gave a 98.2% d_2 /1.1% d_1 /0.7% d_0 material.¹²

The preparation of the methylenetetralin- d_1 involved **6**, prepared from **5**, which was obtained from hydrazone **4** via the Shapiro reaction followed by reaction with dimethyl formamide.¹³ Re-

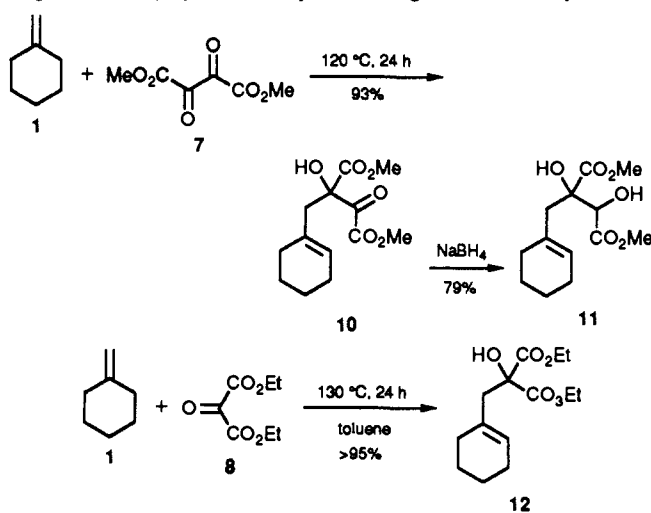


duction of **6** with lithium aluminum deuteride gave the desired olefin **2-d** in 60% yield as 97.2% d_1 /2.8% d_0 material. The reduction of **6** to **2** in THF is in contrast to the reduction of cinnamyl alcohol to the saturated alcohol by LAH in ether.¹⁴ The mechanism of the reduction is presumably hydride delivery to the double bond directed in an aluminum alkoxide complex to give an intermediate benzylic anion that undergoes elimination of the aluminum alkoxide.

Isotope Effect Determinations. Intermolecular and intramolecular hydrogen–deuterium isotope effects for the ene reaction of methylenecyclohexane (**1**) with dimethyl dioxosuccinate (**7**), diethyl oxomalonate (**8**), and acetylium hexachloroantimonate (**9**) are listed in Table I. Also listed are the isotope effects for the ene reaction of 1-methylenetetralin (**2**) with acetic anhydride catalyzed by zinc chloride. The intermolecular isotope effects were determined by competitions of equal amounts of **1** and **1-d₄** or **2** and **2-d₂** with the enophiles. Excess amounts of the olefins were always used for the intermolecular competitions so that the extent of reaction was low. The isotope ratios of both starting materials and products were determined by FIMS and the isotope effects calculated as described in the Experimental Section.^{7c} The extent of reaction and incomplete deuteration of the starting olefins have been taken into account in the calculations. The intramolecular isotope effects were calculated directly from the isotope ratio of the products from the reaction of **1-d₂** and **2-d₁**. The error limits are based on analysis of the experimental errors involved and are

$\leq 20\%$ for intermolecular cases and $\leq 10\%$ for intramolecular cases.

Concerted Ene Reactions. Ene reactions of diethyl oxomalonate (**8**) have been studied by a number of groups, and currently we are developing the ene reaction of dimethyl dioxosuccinate (**7**).^{4,15} Both enophiles react with most olefins smoothly under thermal conditions to give ene reaction products in good yield. For example, **7** reacts with methylenecyclohexane at 120 °C in toluene, to give **10** in high yield. The product **10** gives satisfactory NMR,



IR, and MS data but was reduced to the corresponding diastereomeric diols **11** for elemental analysis. The reaction of **1** with **8** gave **12** in almost quantitative yield.

As shown in Table I, the intermolecular isotope effect in the reaction of **1** and **7** is 2.7 ± 0.5 and the intramolecular isotope effect is 2.3 ± 0.2 . These effects are primary and substantial and are of the same magnitude within experimental error. They are consistent with a concerted mechanism, i.e., a cyclic transition state with carbon–carbon bond formation and hydrogen transfer occurring simultaneously, as shown for A in Scheme I. The theoretical maximum value of hydrogen–deuterium isotope effect is near 4.3 at 120 °C for a symmetrical linear transition state.^{6c} The smaller values observed are consistent with the expected reduction of the isotope effect for nonlinear and unsymmetrical hydrogen transfer based on the theoretical model by O'Ferrall.^{16a} The transition state calculated by Houk et al. for the ene reaction of formaldehyde with propene has both nonlinear and unsymmetrical hydrogen transfer.^{16b}

The isotope effects for the ene reaction of diethyl oxomalonate (**8**) with methylenecyclohexane (**1**) to give **12** under thermal conditions are 2.8 ± 0.6 for the intermolecular competition and 2.4 ± 0.2 for the intramolecular competition as shown in Table I. The isotope effects for this reaction are comparable with the isotope effects observed for the reaction of **8** with allylbenzene.^{4d} These values are similar to those observed with **7**, and a similar conclusion follows: i.e., the reaction proceeds via a concerted mechanism, consistent with earlier studies.^{2d,4}

Stepwise Ene Reactions. The competitive isotope effects for the tin tetrachloride catalyzed ene reaction of **8** with **1** were studied. An intermolecular isotope effect of 1.1 ± 0.2 was obtained

(11) Chrisope, D. R.; Beak, P.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 230.

(12) (a) Chan, T. H.; Cheng, E. *J. Am. Chem. Soc.* **1974**, *96*, 3264. (b) Buchanan, G. W.; Selwyn, J.; Dawson, B. A. *Can. J. Chem.* **1979**, *57*, 3028.

(13) Chan, T. H.; Baldassare, A.; Massuda, D. *Synthesis* **1976**, 801.

(14) Franzus, B.; Snyder, E. I. *J. Am. Chem. Soc.* **1965**, *87*, 3423 and references cited therein.

(15) Song, Z.; Resek, J. E.; Beak, P. Unpublished results.

(16) (a) O'Ferrall, R. A. *M. J. Chem. Soc. B* **1970**, 785. (b) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947.

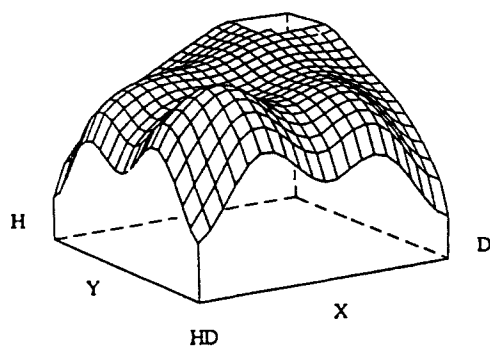
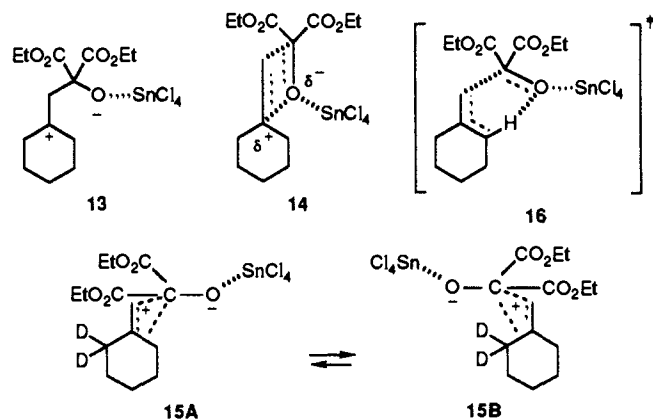


Figure 2. Potential energy surface for the intramolecular competition of Scheme II. HD is the starting material; D is the hydrogen-transferred product; H is the deuterium-transferred product.

for the competition of **1** and **1-d₄**, and an intramolecular effect of 1.2 ± 0.1 was observed with **1-d₂**. Both are quite small, different from the thermal reaction, consistent with previous work, and can be used to evaluate previous proposals of the mechanism of catalyzed ene reactions of **8**.⁴

These small values of both isotope effects suggest that this reaction does not proceed via a fully developed freely rotating zwitterion intermediate **13** because a negligible intermolecular isotope effect but large primary intramolecular effect should be observed in that case. The same criteria can be used to rule out

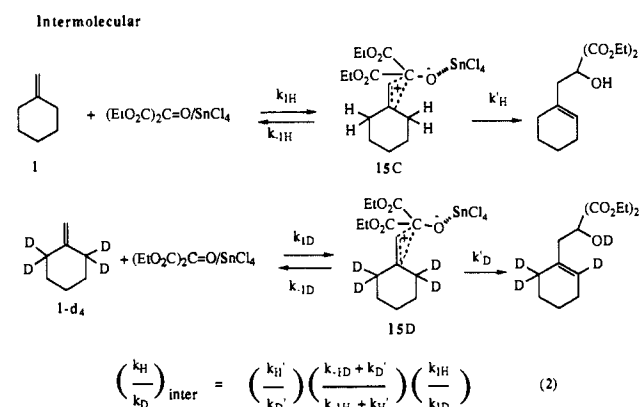
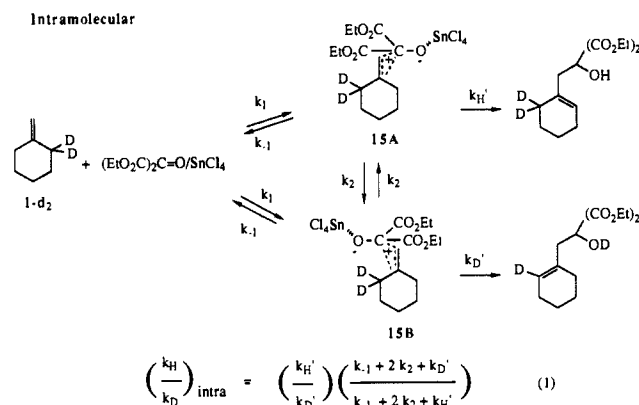


the charge transfer-complex type intermediate **14**.^{4e} Similarly, an intermediate that can freely equilibrate between different isomers, represented as **15A** and **15B**, is inconsistent with the small intramolecular isotope effect observed.^{7d} Although a concerted mechanism with very unsymmetrical hydrogen transfer in the transition state shown as **16** could be consistent with the observed isotope effects, such a mechanism seems inconsistent with the ρ of -3.9 for the catalyzed reaction of **8** with 1-arylcyclopentene and the intramolecular isotope effect of 1.5 ± 0.15 in the catalyzed reaction of **8** with *cis*-tetramethylethylene-*d*₆ (*cis*-**17-d**₆).^{4a,7d}

In order to account for the observed isotope effects, we propose a stepwise mechanism that allows analysis of the intermolecular and intramolecular isotope effects in terms of the partitioning of a geometrically defined intermediate, as shown in Scheme II. In this mechanism, a zwitterionic intermediate **15A-D** with the structure proposed by Snider^{7d} is proposed to partition between reversal, equilibration, and conversion to the product in reactions which can occur at competitive rates.¹⁷ In the proposed intermediate, the carbon-oxygen bond is perpendicular to the olefin double bond and is oriented to either side of the olefin bond, such that different isomers, **15A** and **15B**, are formed if the olefin is labeled on one side. A three-dimensional potential energy surface is illustrated in Figure 2 for the intramolecular competition in Scheme II. The starting materials from HD can proceed along

(17) The intramolecular reaction in Scheme II is written to cover the general case, and it is not kinetically necessary to have both reversal (k_{-1}) and equilibration (k_2) in a specific case. However, since either path can be operative, cases where both occur are possible.

Scheme II



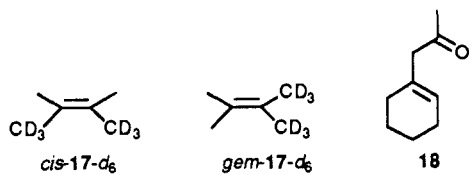
the X axis to hydrogen-transferred product D or along the Y axis to the deuterium-transferred product H. The two isomers of the intermediate, as represented by the two wells on the X and Y axes, can equilibrate with each other through the connecting valley on the surface or by reversal to reactants.

Application of the steady-state approximation to the intermediate provides the relationships between the observed intermolecular and intramolecular isotope effects and the rate constants of the various steps as expressed in eqs 1 and 2. This analysis reveals that a substantial isotope effect in the product-forming step ($k_{H'}/k_{D'}$) may not be reflected in the product ratios. From eq 1, we can see that the observed intramolecular isotope effect depends on the true isotope effect of the hydrogen-transfer step ($k_{H'}/k_{D'}$), the extent of the reversal in the first step (k_{-1}), and/or the extent of the equilibration of the different isomers (k_2).¹⁸ The previously recognized limiting cases are consistent with this analysis.^{1b,6,7} Thus, if hydrogen transfer is the rate-determining step or the intermediate is an open chain or fully equilibrated intermediate, the observed intramolecular isotope effect should be the same as the true isotope effect of the hydrogen-transfer step; if $k_{-1} \gg k_{H'}$ and $k_{D'}$, or if $k_2 \gg k_{H'}$ and $k_{D'}$, then, $(k_H/k_D)_{\text{intra}} = k_{H'}/k_{D'}$. If the formation of the intermediate is the rate-determining step, no intramolecular isotope effect will be observed even though the true isotope effect in hydrogen-transfer step could be substantial; if k_{-1} and $k_2 \ll k_{H'}$ and $k_{D'}$, then $(k_H/k_D)_{\text{intra}} = 1$. For the intermolecular case, if hydrogen transfer is the rate-determining step, the observed isotope effect should be the true isotope effect of hydrogen-transfer step and the secondary equilibrium isotope effect (>1.0) in the formation of the intermediate; if k_{-1H} , $k_{-1D} \gg k_{H'}$ and $k_{D'}$, then $(k_H/k_D)_{\text{inter}} = (k_{H'}/k_{D'}) \left[\frac{(k_{1H}/k_{-1H})}{(k_{1D}/k_{-1D})} \right]$. If the formation of the intermediate is the rate-determining step, the observed intermolecular isotope effect will be only the secondary kinetic isotope effect for the formation of the intermediate even though the true isotope effect

(18) This model does not take into account the steric isotope effect in the formation of the two isomers of the intermediate (**15A,15B**) in the intramolecular isotope effect analysis because that effect is expected to be small.^{6b}

in hydrogen-transfer step is substantial, if k_{-1H} and $k_{-1D} \ll k_H'$ and k_D' , then $(k_H/k_D)_{inter} = (k_{1H}/k_{1D})$.

The observed small intermolecular and intramolecular isotope effects in the tin tetrachloride catalyzed reaction of diethyl oxomalonate with **1** do not fit into the limiting cases discussed above. In order to illustrate how Scheme II provides an explanation of those results, we consider the tin tetrachloride catalyzed reaction of **8** with tetramethylethylene (**17**). If this reaction is considered



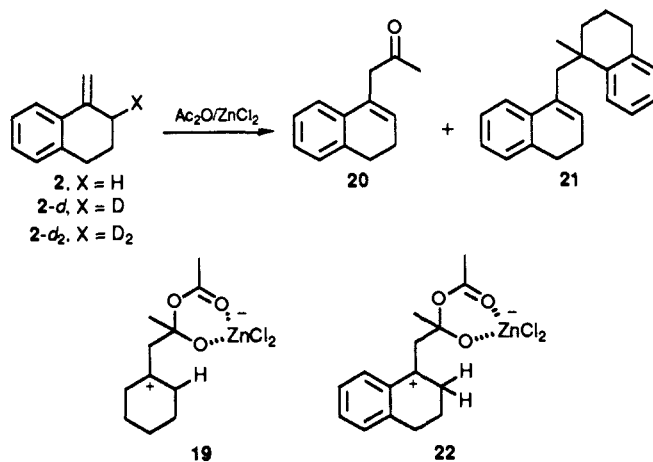
to involve a freely equilibrating intermediate, the intramolecular isotope effect of 1.5 ± 0.15 with *cis*-17-*d*₆ can be taken as the true isotope effect in that reaction.^{7d} With the same true isotope effect value, the observed intramolecular isotope effect in the reaction of **8** and **1** can be explained by proposing $k_H'/k_D' = 1.5$, $k_{-1} = 0$, and $k_2 = 0.4k_D'$ or $k_H'/k_D' = 1.5$, $k_{-1} = 0.8k_D'$, and $k_2 = 0$; then $(k_H/k_D)_{intra} = 1.1$. The observed small intramolecular isotope effect can be attributed to the partial equilibration of the intermediate or the partial reversibility in its formation.^{19a} Similarly, for the intermolecular case, if $k_H'/k_D' = 1.5$ and $k_{-1H} = k_{-1D} = 0.4k_D'$, then $(k_H/k_D)_{inter} = 1.1(k_{1H}/k_{1D})$. The observed small intermolecular isotope effect can be attributed to the partial reversibility in the formation of intermediate and the secondary isotope effect in that step.^{19b}

This analysis provides a two-step-reaction model that allows extraction of mechanistic information from the intermolecular and intramolecular isotope effects beyond the limiting cases shown in Figure 1. The equations and the example from Scheme II demonstrate how a range of isotope effects can be observed depending on the extent of reversal of the formation of the intermediate and the equilibration of the different isomers of the intermediate relative to the product formation, even if the hydrogen-transfer step has a primary substantial isotope effect. We stress that this approach does not provide exacting limits on rate constants, but it does allow a reasonable and consistent understanding of the reaction pathway.

The ene reaction of acetylum hexachloroantimonate ($\text{CH}_3\text{CO}^+\text{SbCl}_6^-$) with olefins was reported by Hoffmann and co-workers to give γ,β -unsaturated ketones.²⁰ The reaction with methylenecyclohexane at -78°C in the presence of ethyldiisopropylamine gives **18**, and the isotope effects are summarized in Table 1. The intermolecular effect for the competition between **1** and **1-d**₄ is 1.1 ± 0.2 , and the intramolecular effect for the reaction of **1-d**₂ is 1.1 ± 0.1 . An intramolecular isotope effect of 1.9 ± 0.15 has been reported for the reaction of acetylum hexachloroantimonate with *gem*-deuterated tetramethylethylene (*gem*-17-*d*₆).^{7d} These small isotope effects can readily be accommodated by the mechanism of Scheme II.

Application of the Model. The enone **18** (vide supra) is also the product of the formal ene reaction of methylenecyclohexane with acetic anhydride catalyzed by zinc chloride.^{7c} It was previously suggested, on the basis of the observation of an intramolecular isotope effect of 3.2 ± 0.7 and intermolecular isotope effect of 1.0 ± 0.3 , that an equilibrated intermediate **19**, which

has a free choice between hydrogen or deuterium at either side of the allylic position, is involved in this reaction. In addressing



the question of whether equilibration of the intermediate allows the equilibration between the two faces of the olefin, we have investigated the intermolecular and intramolecular isotope effects in the reaction of 1-methylenetetralin (**2-d**) with acetic anhydride catalyzed by zinc chloride. The ene reaction of 1-methylenetetralin (**2**) gives the expected product **20** in 65% yield, with a dimer of **2**, assigned the structure **21** in 12% yield. An intermolecular isotope effect of 1.79 ± 0.36 is observed for competition between **2** and **2-d**₂, and an intramolecular isotope effect of 9.7 ± 1.0 is observed for reaction of **2-d**. The large intramolecular effect and a much smaller intermolecular isotope effect are consistent with formation of a fully developed zwitterion intermediate **22**, in which equilibration to both faces is achieved. The intermolecular isotope effect, which is substantially larger than expected for secondary isotope effect in the formation of the carbonium ion, can be explained by the above model.²¹ If the intramolecular isotope effect is taken as the true isotope effect in the proton-transfer step, the intermolecular isotope effect observed can be attributed to the secondary isotope effect of the first step and partial reversal of the first step. For example, if $k_H'/k_D' = 9.7$, $k_{-1H} = k_{-1D} = 0.8k_D' = 0.08k_H'$, and $k_{1D}/k_{1H} = 1.1$, then $(k_H/k_D)_{inter} = 1.8$.²¹ Thus, the facial equilibration may be considered to occur partially by reversal to the reactants and recombination. If equilibration occurred exclusively by the process indicated by k_2 , i.e., if $k_{-1H} = k_{-1D} \ll k_D'$, the observed intermolecular isotope effect would be expected to be $(k_H/k_D)_{inter} = k_{1H}/k_{1D} = 1.1$, which is smaller than observed.

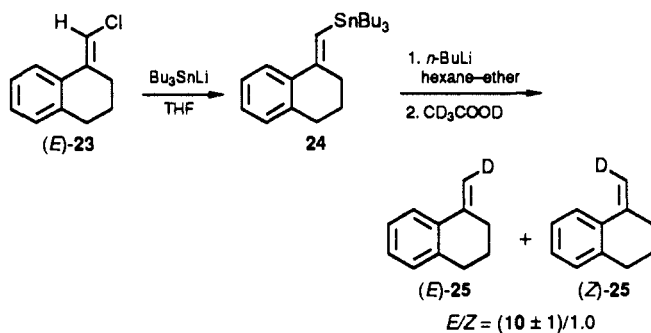
Comparison of the mechanisms of the reactions of methylenecyclohexane (**1**) and 1-methylenetetralin (**2**) with acetic anhydride as revealed by these isotope effects is interesting. Under the reverse scenario of the above analysis, there is ca. 8% reversal in the first step in the reaction of **2**, while there is no reversal in the reaction of **1**. This could be attributed to the stabilization of the carbonium center by the phenyl ring of **22**, which lowers the barrier to formation of **22** as compared to the formation of **19**. Thus, for the partitioning of **22**, both the forward reaction and the reverse reaction are faster, compared with the proton-transfer step, which can be considered essentially the same for **19** and **22**. This reduction of the activation energy in the rate-determining step is supported by the experimental observation that the reaction of 1-methylenetetralin is much faster than that of methylenecyclohexane.

The partial reversibility in the first step of the reaction of **2**, i.e., $k_{-1H} = k_{-1D} = 0.08k_H'$, can be tested by reaction of **25**, which is stereospecifically labeled with deuterium at the vinyl position. Since the intermediate is free to rotate, the deuterium would be isomerized during the process of the reaction in which there is reversibility in the first step.

(19) (a) In this case, the difference between the reactions of methylenecyclohexane and tetramethylethylene is that the intermediate of the later reaction can equilibrate between different isomers to a much larger extent than the former where only partial equilibration occurs before hydrogen transfer takes place. The difference could be attributed to the fact that a more stable trisubstituted olefin is formed in the methylenecyclohexane ene reaction, while a 1,1-disubstituted olefin is formed in the reaction of tetramethylethylene case. As a result, the rate of hydrogen transfer is faster in the former case and the intermediate does not fully equilibrate between different isomers. Again, this analysis is illustrative and should not be considered definitive. (b) In effect, the observed intermolecular isotope effect could be attributed to the secondary isotope effect in the formation of the intermediate: $k_{1H}/k_{1D} > 1.0$.

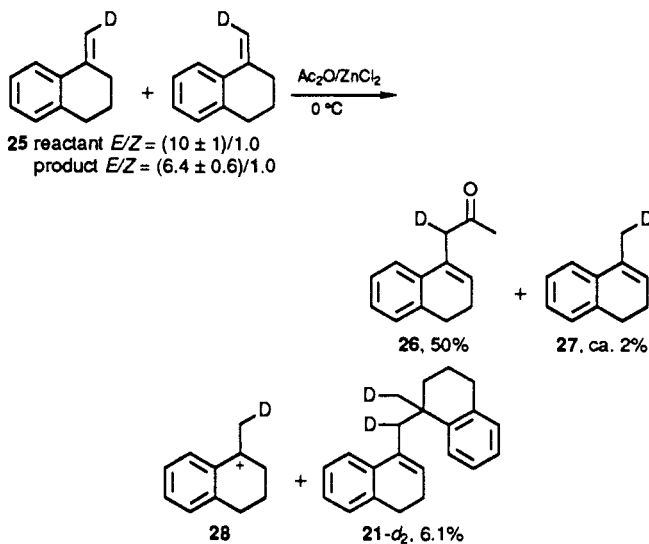
(20) Hoffmann, H. M. R.; Tsushima, T. *J. Am. Chem. Soc.* **1977**, *100*, 6008.

(21) The secondary isotope effect should be approximately 1.1–1.2 based on known analogous systems: Shiner, V. J., Jr.; Buddebaum, W. E.; Murr, B. C.; Bamaty, G. *J. Am. Chem. Soc.* **1968**, *90*, 418.

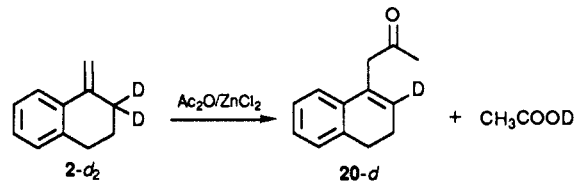


A mixture enriched in the *E*-deuterated olefin **25** was synthesized from the vinyl chloride (*E*)-**23**.²² Thus, (*E*)-**23** was converted to the vinylstannane **24** stereospecifically, and subsequent lithium–tin exchange reaction in hexane–ether mixture followed by deuterium quench gave the desired vinyl-deuterated olefin **25**.^{23,24} Although excess butyllithium was used in this reaction, the equilibrium of the reaction was such that at the end of the reaction there was still ca. 10–15% unreacted vinylstannane. This fraction of the unreacted vinyltin compound was converted to **25** by treatment with acetic acid-*d*₄ in CDCl₃ in a conversion that was shown to have low selectivity: pure (*E*)-**24** gave **25** in a ratio of *E/Z* = 1.6/1. Thus, the final product **25** was obtained in a (10 ± 1)/1.0 ratio of *E/Z* isomers as judged by ¹H NMR, with >95% deuterium incorporation.

The reaction of this 10/1 mixture of (*E*)-**25**/(*Z*)-**25** with acetic anhydride and zinc chloride was carried to a 50% yield of **26**. The recovered olefin has a ratio of *E/Z* = (6.4 ± 0.6)/1.0 compared to the (10 ± 1)/1.0 ratio of the original starting material. The observed *E/Z* ratio agrees well with the predicted value of 6.3 based on the known extent of reaction and the assumption that 8% of the intermediate returns to the reactant.²⁵

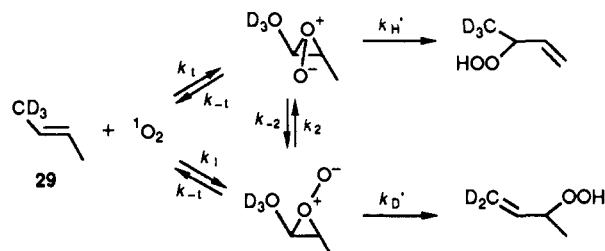


Also observed in this reaction was **21-d**₂, previously identified as a dimer of the olefin, which presumably arises from a proton-induced ene reaction of **25** via carbocation **28**. If the formation of this carbonium ion is reversible, that process could contribute to the isomerization of the deuterated olefin and, thus, compromise the reversibility test. To evaluate that possibility, a control experiment was carried out with **2-d**₂ and acetic anhydride and zinc chloride to give **20-d**. Because the accompanying product in this



ene reaction is AcOD, if the acid-catalyzed isomerization of the olefin occurs by protonation–deprotonation, the reaction with **2-d**₂ would introduce deuterium to the vinyl position. Both statistical factors and the primary isotope effect on deprotonation should favor such incorporation and give recovered *d*₃ olefin. In the actual experiment, no **2-d**₃ olefin could be detected in the recovered olefin, and the isotope ratio of the reactant olefin was unchanged. Thus, the isomerization of the olefin was not caused by protonation–deprotonation but is attributable to partial reversal of the ene reaction with acetic anhydride and zinc chloride as predicted from the mechanistic model.

The kinetic model proposed for the intermolecular and intramolecular isotope effects in stepwise ene reactions is general and can be applied to other cases. Foote and co-workers observed an isotope effect of 1.38 in the ene reaction of singlet oxygen with 1,1,1-trideuterio-*cis*-2-butene, but an isotope effect of 1.25 with *trans*-2-butene-*d*₃ (**29**). They attributed the substantial isotope



effect they observed with **29** to either equilibration of the peroxide intermediate or reversible formation of the intermediate.^{2b} Elaboration of the Foote proposal under the model of Scheme II is informative. If the true isotope effect in the hydrogen-transfer step is assumed to be equal to $k_H'/k_D' = 1.38$, the isotope effect observed in the *cis*-2-butene-*d*₃, the smaller isotope effect of 1.25 observed with *trans*-2-butene-*d*₃ (**29**) suggests that the equilibration of the intermediate is not complete before hydrogen transfer occurs. For example, if $k_{-1} = 0$ and $k_2 = 1.3k_D'$, $(k_H/k_D)_{\text{intra}} = 1.25$. The isotope effect for **29** could also be attributed to partial reversal of the intermediate, i.e., if $k_{-1} = 2.6k_D'$, then $(k_H/k_D)_{\text{intra}} = 1.25$, but the kinetic data reported by Schuster and co-workers suggest that the rate-determining step in the ene reaction of singlet oxygen is the formation of the intermediate.²⁶ Other cases to which this analysis could be applied include the ene reaction of phenyl-1,2,4-triazoline-3,5-dione and nitrosoperfluorobenzene,^{8,27} and a suggestion about such an equilibration has been made recently for the ene reaction of diethyl azodicarboxylate.^{2d}

Conclusion. The experimental observations and analyses in the present work suggest that the variations of mechanism for ene reactions can be analyzed in terms of competitive partitioning of a geometrically defined reaction intermediate. The intermediate can partition between dissociation to starting material, product formation, and equilibration between its different isomers. Variations in these steps can occur with changes in enophile, catalyst, or substrate. This analysis provides a model for understanding the observed intermolecular and intramolecular isotope effects, especially for the cases that do not fit into the limiting

(22) Miyano, S.; Izumi, Y.; Fujii, K.; Ohno, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1197.

(23) Ashe, A. J., III; Mahmoud, S. *Organometallics* **1988**, *7*, 1878.

(24) (a) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265. (b) Still, C. W. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(25) The calculation was performed on an IBM-PC with an approximation method. The extent of reaction was based on the ratio of the isolated product and recovered starting material only.

(26) (a) Hurst, J. R.; Wilson, S. L.; Schuster, G. B. *Tetrahedron* **1985**, *41*, 2191. (b) For discussion of explex in the reaction, see: Gorman, A. A.; Hamblett, I.; Lambert, C.; Spencer, B.; Standen, M. C. *J. Am. Chem. Soc.* **1988**, *110*, 8053.

(27) (a) Orfanopoulos, M.; Foote, C. S.; Smonou, I. *Tetrahedron Lett.* **1987**, *28*, 15. (b) Starfflinger, W.; Kresze, G.; Huss, K. *J. Org. Chem.* **1986**, *61*, 37.

(28) (a) Boger, D. L.; Panek, J. S.; Yasuda, M.; Sanphilippo, P. J.; Kende, A. S. *Org. Synth.* **1987**, *66*, 142. (b) Fox, H. H. *J. Org. Chem.* **1947**, *22*, 535.

mechanisms and may have appeared to be anomalous.

Experimental Section

General Procedures. ^1H and ^{13}C nuclear magnetic resonance spectra chemical shifts are reported (ppm) downfield from tetramethylsilane (TMS) standard, with reference either to TMS internal standard or to solvent residue. CDCl_3 was the solvent, except otherwise specified. The column used for GC was one of the following four: column A, 25 m \times 0.25 mm o.d. fused silica open tubular column with SE-52 as the support; column B, 30 m \times 0.25 mm i.d. Alltech Associates RSL-200 column; column C, 30 m \times 0.20 mm i.d. HP Ultra-2 column; column D, 12 m \times 0.20 mm i.d. HP-1 column. Preparative gas chromatography was carried out with a stainless steel 8 ft \times 0.25 in. i.d. column, with 10% SE-30 as the support and Chromosorb-SW as the liquid phase. Medium-pressure liquid chromatography (MPLC) was performed on Woelm silica gel (32–63- μm) columns with ethyl acetate/hexane mixture as eluent. High-performance liquid chromatography (HPLC) was performed on a Ramin Dynamics micro silica gel column with ethyl acetate/hexane mixture as eluent. Reversed-phase HPLC was carried out on a C_{18} Dynamax-60A column with water/methanol mixture as eluent. Field ionization mass spectra (FIMS) were obtained on Finnigan Mat 731 mass spectrometer. Isotope ratios were calculated by standard matrix method with reference to the FIMS spectra of the unlabeled material obtained under the same conditions, and the peak areas of the molecular ions were monitored. All mass spectra were obtained in Mass Spectrometry Center at School of Chemical Science in University of Illinois. Elemental analyses were carried out in the Microanalysis Laboratory at the University of Illinois.

Materials. Anhydrous tetrahydrofuran (THF) and ether were distilled over sodium and benzophenone under nitrogen. Anhydrous methylene chloride and toluene were distilled over calcium hydride. Anhydrous benzene was obtained by direct distillation to remove water azeotropically. All chemicals were used as received or distilled before use as specified. Yields of reactions are reported as obtained by Kugelrohr or reduced-pressure distillation, except otherwise noted. **2,2,6,6-Tetra-deuteriomethylenecyclohexane (1- d_4)** was prepared by modified method of Wittig et al.^{29,7c} from 2,2,6,6-tetradeuteriocyclohexanone. **2,2-Di-deuteriomethylenecyclohexane (1- d_2)** was prepared following the procedure of Beak and Chrisope.¹¹ **1-Methylenetetralin (2)** was prepared from 1-tetralone by Wittig reaction.^{12b} **2,2-Di-deuterio-1-tetralone (3- d_2)** was obtained by hydrogen–deuterium exchange reaction of 1-tetralone. **2,2-Di-deuterio-1-methylenetetralin (2- d_2)** was prepared from ketone **3- d_2** by the general method reported by Chan et al.^{12a}

2-Deuterio-1-methylenetetralin (2- d_1).^{13,14} To a stirred solution of 3.6 mmol (1.1 g) of the hydrazone **4** in 30 mL of THF at -78°C was added 7.5 mL of 1.6 M *n*-BuLi solution in hexane dropwise. The red-purple solution was left at -78°C for 1.5 h, allowed to warm to room temperature for 1.5 h, and cooled to -78°C , and 1.2 mL (24 mmol) of anhydrous DMF (distilled over CaH_2) was added. Then the mixture was allowed to warm to room temperature and stood for 2 h before workup with 10% HCl and ether. The product **5** was isolated by MPLC with 5% EtOAc as the eluent in 56% yield (0.32 g): ^1H NMR (200 MHz) δ 9.69 (s, 1 H), 8.20 (m, 1 H), 7.1–7.3 (m, 3 H), 7.03 (t, 1 H, $J = 5.8$ Hz), 2.7–2.9 (m, 2 H), 2.8 (t, 3 H, $J = 7.4$ Hz).

The aldehyde **5** was reduced with 1 equiv of sodium borohydride in methanol to give the alcohol **6** in 86% yield: ^1H NMR (200 MHz)³¹ δ 7.4–7.0 (m, 4 H), 6.12 (t, 1 H, $J = 4.3$ Hz), 4.53 (s, 2 H), 2.78 (t, 2 H, $J = 8.1$ Hz), 2.2–2.4 (m, 2 H), 1.5 (s, 1 H).

To a suspension of 0.96 g of LiAlD_4 (98% d_4 , 23 mmol) in 20 mL of anhydrous THF was added 0.90 g (5.6 mmol) of **6** slowly. The reaction mixture was stirred, refluxed under N_2 for 6 h, and cooled with ice, and 1 mL of 10% NaOH was added and the mixture stirred for 10 min before the precipitate was removed by filtration. The solid was washed with 50% mL of pentane. The filtrate was washed with water, and the organic layer was dried (MgSO_4). MPLC purification of the residue after solvent removal with hexane as eluent gave 0.49 g (60%) of **2- d_1** : ^1H NMR (200 MHz) δ 7.6–7.8 (m, 1 H), 7.0–7.2 (m, 3 H), 5.47 (d, 1 H, $J = 1.2$ Hz), 4.95 (d, 1 H, $J = 1.2$ Hz), 2.8 (t, 2 H, $J = 6.4$ Hz), 2.4–2.6 (m, 1 H), 1.8–2.0 (m, 2 H); FIMS showed 2.8% d_0 /97.2% d_1 material.

Dimethyl dioxosuccinate (dimethyl 2,3-dioxobutanedioate, 7) was prepared following the general procedure of Boger et al. for the preparation of the diethyl ester.²⁸ Reagent grade methanol was refluxed and distilled over magnesium turnings. Thus, a suspension of 10 g of dihydroxytartaric acid disodium salt dihydrate (Lancaster Synthesis,

Technical grade) in 100 mL of methanol was saturated with hydrogen chloride gas at 0°C (bubbling for 2 h), and the mixture was left at 0°C for 3 days. The solid was removed by filtration and washed with methanol. The solvent in the filtrate was removed on a water evaporator, and the residue was distilled under vacuum through a 10-cm Vigreux column and collected as an orange liquid, bp 95 – 100°C (ca. 1 mmHg). This material was further purified by distillation over phosphorus pentoxide (granular, ca. 0.5–1 g) to give 4.1 g (yield 54%) of **7** as an orange liquid: bp 75 – 78°C (ca. 0.5 mmHg); ^1H NMR (300 MHz, CDCl_3) δ 3.99 (s); ^{13}C NMR (75 MHz, CDCl_3) δ 182.3, 158.4, 53.9. Anal. Calcd for $\text{C}_6\text{H}_6\text{O}_6$: C, 41.39; H, 4.47. Found: C, 41.40; H, 3.49.

Ene Reaction of 7 with 1 To Give 10. In a sealed tube, 124 mg of methylenecyclohexane (1.30 mmol, Aldrich, distilled) was allowed to react with 234 mg of dimethyl dioxosuccinate (1.34 mmol) in 1.0 mL of anhydrous toluene at 120°C for 72 h. Kugelrohr distillation of the crude product gave 340 mg of **10** as colorless oil (93%): IR (neat, cm^{-1}) 3481 (s, OH), 2934 (s, CH), 1736 (s, C=O), 1437, 1307, 1269, 1219, 1103; ^1H NMR (300 MHz) δ 5.49 (s, 1 H, vinyl H), 3.87 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.86 (s, 1 H, OH), 2.74, 2.58 (AB q, $J = 4.3$ Hz, 2 H), 2.1–1.8 (m, 4 H), 1.7–1.5 (m, 4 H); ^{13}C NMR (75 MHz) δ 188.4, 170.0, 161.9, 131.4, 127.4, 81.1, 53.4, 53.0, 42.2, 29.6, 25.4, 22.8, 21.8; EIMS (70 eV) m/e (relative intensity) 252 ($\text{M}^+ - \text{H}_2\text{O}$, 2.4), 194 (34.4), 161 (29), 95 (100), 81 (56), 57 (26); FIMS m/e 270 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_6$: C, 57.77; H, 6.71. Found: C, 57.02; H, 6.56. Attempted purification of this product by column chromatography over silica gel, neutral alumina, and reversed-phase C_{18} columns resulted in decomposition.

Reduction of Dimethyl 3-(Cyclohexenylmethyl)-3-hydroxy-2-oxosuccinate (10) by Sodium Borohydride. To 35 mg of sodium borohydride (Alfa, 0.9 mmol) was added a solution of 160 mg (0.6 mmol) of **10** in 15 mL of methanol. The solution was stirred for 5 min and was worked up with ether and saturated ammonium chloride. The organic layer was dried (MgSO_4). The residue after solvent removal was purified by MPLC with 40% EtOAc/hexane as eluent to give 145 mg of **11** as a colorless oil. This material was further purified by HPLC with 50% EtOAc/hexane as eluent to give 127 mg (79%) of **11** as a colorless oil: IR (neat, cm^{-1}) 3483 (s, OH), 2924 (s, CH), 1736 (s, C=O), 1440, 1050–1300; ^1H NMR (300 MHz) δ 1.45–1.60 (m, 4 H, CH_2CH_2), 1.75–2.2 (m, 4 H, allyl CH_2 on the ring), 2.4–2.8 (m, 2 H, allyl CH_2), 3.09 (d, $J = 8.6$ Hz, 0.2 H, CHOH), 3.24 (s, 0.2 H, COH), 3.32 (d, $J = 0.8$ H, CHOH), 3.51 (s, 0.8 H, COH), 3.51 (s, $J = 0.8$ Hz, COH), 3.76, 3.79 (s, s, 0.6 H, 2 OMe), 3.81, 3.84 (s, s, 4.8 H, 2 OMe), 4.36 (d, $J = 9.4$ Hz, 0.8 H, OCH), 4.44 (d, $J = 8.6$ Hz, 0.2 H), 5.4–5.9 (s, 1 H, vinyl H); ^{13}C NMR (75 MHz) (some peaks of the two diastereomers resolved, and the weaker peaks listed in parentheses) δ 173.75, 171.62, (132.44), 132.54, (126.93), 126.62, 80.60, (79.69), (75.32), 75.08, 52.85, (52.68), 52.65, (52.61), 43.48, 42.92, 29.71, (29.66), 25.42, 22.89, 21.96; EIMS (70 eV) m/e (relative intensity) 272 (M^+ , 0.54), 254 (19), 195 (21), 163 (38), 101 (50), 95 (100), 91 (54), 81 (45), 63 (35); FIMS m/e 272. Anal. Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_6$: C, 57.34; H, 7.40. Found: C 57.05; H 7.50.

Determination of Hydrogen–Deuterium Isotope Effects: General Methods. In the intermolecular competition reactions, roughly 1/1 mixtures of deuterated and protiated olefins were used. The reactions were carried out to 5–15% completion with only 5–15% of the enophile reagents and the isotope ratio of the starting olefin, and products were analyzed by FIMS. The accuracy of the isotope ratio determination by FIMS was assured by tests with samples of known mixtures of pure deuterated and nondeuterated materials. The difference between the expected isotope ratio and measured value was taken as the error limit of the isotope ratio determination.³² The intermolecular isotope effects are calculated by the equation^{7c} $(k_{\text{H}}/k_{\text{D}})_{\text{inter}} = [\log(1 - b_{\text{H}}/a_{\text{H}})] / [\log(1 - b_{\text{D}}/a_{\text{D}})]$, where a_{H} and a_{D} are millimoles of initial protiated and deuterated olefins and b_{H} and b_{D} are millimoles of protiated and deuterated product.

The isotope ratio and chemical integrity of the unreacted olefins at the end of the reactions were checked by ^1H NMR and FIMS analyses of the recovered starting material in at least one run in each case. Specifically, in the intermolecular competition, the ratios of the deuterated olefin and undeuterated olefin in the recovered olefin mixture were found to be within 10% error of the expected ratio on the basis of the determined isotope effect and the extent of reaction. In the intramolecular competition, the recovered olefin was found to be identical with starting material. The principal error source in the isotope effect measurements is in the determination of isotope ratio of starting materials and products. Because the error limit for the isotope ratio determination for all the compounds involved was established to be $\leq 10\%$ (except for

(29) Wittig, G.; Schoellkopf, U.; Roberts, J. D.; Vogel, M. *Organic Syntheses*; Wiley: N.Y., 1973; Coll. Vol. IV, pp 751.

(30) Campbell, M. M.; Abbas, N.; Sainsbury M. *Tetrahedron* **1985**, 5644.

(31) Adamczyk, M.; Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, 49, 4226.

(32) The differences were within 10% except for deuterated methylenecyclohexane, and the systematic error is corrected in the later calculations.

Table II. Intermolecular Isotope Effect Determination for the Thermal Ene Reaction of **7** with **1** and **1-d₄** at 120 ± 5 °C^a

entry	1	2	3
olefin, mg (mmol)	194 (1.98)	190 (1.94)	194 (1.97)
7 , mg (mmol)	22 (0.13)	20 (0.11)	17 (0.10)
extent of reactn, %	5.2	4.6	4.1
NaBH ₄ , mg	5.3	2.1	4.0
overall yield, %	63	66	62
isotope ratio of 11 (<i>d</i> ₀ - <i>d</i> ₄)	70.3, 1.2, 2.2,	74.1, 1.3, 1.0,	71.3, 1.0, 1.1,
(<i>k</i> _H / <i>k</i> _D) _{inter} ^b	2.48	2.56	3.01

^a Isotope ratio of starting olefin: *d*₀, 51.3%; *d*₁, 0.5%; *d*₂, 0.6%; *d*₃, 2.6%; *d*₄, 43.3%. ^b Average 2.7 ± 0.5.

Table III. Intramolecular Isotope Effect Determination for Thermal Ene Reaction of **7** with **1-d₂** at 120 ± 5 °C^a

entry	1	2	3
olefin, mg (mmol)	102 (1.04)	94.0 (0.96)	96.1 (0.98)
7 , mg (mmol)	19.2 (0.11)	41.5 (0.24)	29.7 (0.17)
extent of reactn, %	9	18	13
NaBH ₄ , mg	5	10	10
overall yield, %	55	55	54
isotope ratio of 11 (<i>d</i> ₀ - <i>d</i> ₄)	3.2, 31.9, 64.8	5.7, 30.7, 64.1	2.7, 30.3, 67.0
(<i>k</i> _H / <i>k</i> _D) _{intra}	2.26	2.32	2.46

^a Isotope ratio of starting olefin: *d*₂, 97.0%; *d*₁, 3.0%. ^b Average 2.3 ± 0.2.

methylenecyclohexane (vide infra) from known mixtures, the error limit is 20% for the intermolecular isotope effect values and 10% for the intramolecular case. The reaction of **1** with **7** provided an example.

FIMS Control Experiment for the Isotope Ratio of **1 and **1-d₄**.** A mixture of 98 mg of **1** and 93 mg of **1-d₄** was subjected to FIMS, together with pure samples of **1** and **1-d₄**. The determined *d*₀/*d*₄ ratio was (average of three runs) 1.21 in contrast to 1.08 expected on the basis of the weights. This +12% systematic error was used to correct calculation of the *d*₀/*d*₄ ratio of **1** in the experiment.

Intermolecular Isotope Effect in the Ene Reaction of **1 and **1-d₄** with **7**.** In a sealed Carius tube, 1 mmol (120 μL, 100 mg) of **1** and **1-d₄** from a mixture made of 0.322 g of **1** and 0.335 g of **1-d₄** was allowed to react with 0.1–0.2 mmol of **7** in 1.0 mL of toluene-*d*₈ at 120 ± 5 °C for 24 h. Then ca. 7 mg of trimethylacetaldehyde was added as an internal standard, and the extent of reaction was determined by ¹H NMR. The solvent was removed, and the product was reduced with 5–10 mg of sodium borohydride in 5 mL of methanol. The crude product **11** was purified by MPLC with 40% EtOAc/hexane mixture and analyzed by FIMS for isotope ratio. The isotope effects were calculated and corrected for the incomplete deuteration of starting *d*₄ olefin. The results are listed in Table II. The average value of the isotope effect from the three experiments is 2.7 ± 0.5. In the first experiment, the product mixture before the reduction was distilled under vacuum at room temperature so that the unreacted olefin with toluene-*d*₈ was separated from the ene reaction product. The unreacted olefin was then recovered by preparative GC and analyzed by FIMS for the isotope ratio. The *d*₀/*d*₄ ratio was 1.08, compared to 1.11 expected, and was well with experimental error.

Intramolecular Isotope Effect in the Thermal Ene Reaction of **1-d₂ with **7**.** The experimental procedure was the same as for the intermolecular isotope effect but 1 mmol of **1-d₂** and 0.2 mmol of **7** were allowed to react at 120 ± 5 °C for 24 h in 1.0 mL of toluene-*d*₈. The isotope effects are the ratio of *d*₂ and *d*₁ products, corrected for incomplete deuteration of starting olefin. The results are listed in Table III. In one of the three runs, the unreacted olefin was recovered by distillation and preparative GC and was shown by ¹H NMR and FIMS to be unchanged. The average value for the intramolecular isotope effect is 2.3 ± 0.2.

Intermolecular Isotope Effect in the Thermal Ene Reaction of **8 with **1** and **1-d₄**.** To 2.00 mmol of an equal volume mixture of **1** and **1-d₄** (each 1 mmol) were added 0.20 mmol of diethyl oxomalonate, and 0.20 mmol of 2,6-di-*tert*-butylpyridine (DTBP), and the mixture was heated at 130 ± 5 °C for 24 h in a sealed tube. The yield of the reaction determined by capillary GC (column A) with methyl benzoate as the internal standard was 100%. Part of the unreacted olefin was isolated by distillation and preparative GC and analyzed by FIMS and NMR. The isotope effects were calculated as before, and a final value of (*k*_H/*k*_D) = 2.8 ± 0.6 was obtained.

Intramolecular Isotope Effect of the Thermal Ene Reaction of **8 with **1-d₂**.** To 1.00 mmol (120 μL) of **1-d₂** was added 0.20 mmol of diethyl oxomalonate, and they were allowed to react at 130 ± 5 °C for 24 h in

the presence of 0.20 mmol of 2,6-di-*tert*-butylpyridine. All other manipulations are the same as for the intermolecular isotope case above. The yield of the reaction was 90% as determined by capillary GC. An intramolecular isotope effect value of 2.4 ± 0.2 was obtained.

Intermolecular Isotope Effect of SnCl₄-Catalyzed Ene Reaction of **8 with **1** and **1-d₄**.** To 10 mL of anhydrous benzene in a flask were added 392 mg (4.0 mmol, 480 μL) of an equal volume mixture of **1** and **1-d₄**, and 0.20 mmol of **8**. The mixture was cooled until the benzene started to freeze, and then a 1.0-mL solution of 0.04 M SnCl₄ in benzene was added and the mixture shaken vigorously. After 5–6 min, the reaction mixture was quenched with 5% HCl and worked up with water and ether. The yield of the reaction was 57%. An intermolecular isotope effect value of 1.1 ± 0.2 was obtained.

Intramolecular Isotope Effect of SnCl₄-Catalyzed Ene Reaction of **8 with **1-d₂**.** The reaction conditions and workup procedures are the same as in the intermolecular case. The starting materials used were 1.00 mmol of **1-d₂**, 0.20 mmol of diethyl oxomalonate, and 0.04 mmol of SnCl₄. The yield of the reaction was 42%. The intramolecular isotope effect, after correction for *d*₁ olefin in the starting material, was 1.2 ± 0.1.

Intermolecular Isotope Effect of Ene Reaction of Acetylium Hexachloroantimonate with **1 and **1-d₄**.** Equal volumes of **1** and **1-d₄** were mixed, and 0.240 mL (194 mg, 2.00 mmol) of the mixture was dissolved in 2 mL of CH₂Cl₂, together with 0.2 mmol of EtN(i-Pr)₂. The solution was added to a mixture of 10 mL of CH₂Cl₂ and 0.20 mmol of CH₃CO⁺SbCl₆⁻, which was being vigorously stirred at -78 °C. The mixture was stirred at -78 °C for 1 h and then worked up as previously described.²⁰ The yield of **18** was determined to be 50–60% by capillary GC (column A) with chlorobenzene as the internal standard. The intermolecular isotope effects were 1.01, 1.09, and 1.19, with an average of 1.1 ± 0.2.

Determination of Intramolecular Isotope Effect in the Reaction of Acetylium Hexachloroantimonate with **1-d₂.** The reaction conditions are the same as for the intermolecular case. The starting materials were 2.00 mmol of **1-d₂**, 0.50 mmol of CH₃CO⁺SbCl₆⁻, and 0.5 mmol of EtN(i-Pr)₂. The intramolecular isotope effects of the three runs are 1.16, 1.14, and 1.09, and the average was 1.1 ± 0.1.

Ene Reaction of 1-Methylenetetralin (2**) with Acetic Anhydride Catalyzed by Zinc Chloride.** To a stirred solution of 51 mg (0.37 mmol) of ZnCl₂ in 10 mL of Ac₂O at 0 °C protected by dry N₂ was added 138 mg (0.95 mmol) of **2**. The mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. The reaction mixture was worked up with saturated sodium carbonate and pentane. The crude product was purified by MPLC with 5% EtOAc/hexane as the eluent to give four fractions. The first fraction was 21 mg of an oil that was further purified by HPLC with hexane as eluent to give 17 mg (12%) of **21** as a colorless oil: ¹H NMR (500 MHz) δ 7.0–7.5 (m, 8 H, ArH), 5.75 (t, *J* = 4.5 Hz, 1 H, vinyl H), 2.7–3.0 (m, 6 H), 2.15–2.22 (m, 2 H), 1.8–1.9 (m, 2 H), 1.4–1.5 (m, 1 H), 1.7–1.8 (m, 1 H), 1.21 (s, 3 H); ¹³C NMR (125 MHz) δ 145.2, 136.5, 136.5, 136.4, 133.9, 129.3, 129.0, 127.4, 127.2, 126.2, 125.9, 125.6, 125.3, 123.2, 43.7, 37.8, 35.7, 30.7, 30.1, 28.8, 23.3, 19.3; FIMS *m/e* 288 (M⁺). Two fractions of **7** and 4 mg of oil were not identified. The fourth fraction was 115 mg of **20** (65%): IR (neat, cm⁻¹) 2022 (m, ArH), 2831–2934 (s, CH), 1709 (s, C=O), 1225, 1557, 760, 735; ¹H NMR (300 MHz) δ 7.0–7.2 (m, 4 H, ArH), 5.99 (t, 1 H, *J* = 4.7 Hz, vinyl H), 3.47 (s, 2 H, CH₂C=O), 2.79 (t, 3 H, *J* = 3.1 Hz, ArCH₃), 2.2–2.4 (m, 2 H, CH₂), 2.14 (s, 3 H); ¹³C NMR (125 MHz) δ 208.0, 136.2, 134.0, 130.9, 129.6, 127.6, 127.2, 126.5, 122.8, 49.1, 28.5, 27.9, 23.2; EIMS (70 eV) *m/e* (relative intensity) 186 (M⁺, 32), 143 (56), 128 (94), 115 (23), 43 (100). Anal. Calcd for C₁₃H₁₄O: C, 83.83; H, 7.63. Found: C, 83.73; H, 7.63.

Intermolecular Isotope Effect in the Ene Reaction of Ac₂O/ZnCl₂ with **2 and **2-d₂**.** To a stirred mixture of 10 mL of Ac₂O and 0.4–0.5 mmol of ZnCl₂ cooled to 0 to -5 °C and protected under dry nitrogen was added about 1 mmol of a mixture of 262 mg of **2** and 268 mg of **2-d₂**. After 5 min, the reaction was quenched by addition of a mixture of saturated carbonate and pentane and worked up as before. The unreacted olefin and product were separated by MPLC with 10% EtOAc/hexane as eluent. The extent of the reaction was calculated on the basis of the weight of the isolated product. The intermolecular effects of the two runs were 1.79 and 1.79, and the average is 1.79 ± 0.36.

Intramolecular Isotope Effect in the Ene Reaction of 2-Deuterio-1-methylenetetralin (2-d**) with Ac₂O/ZnCl₂.** To a solution of 0.4 mmol of ZnCl₂ in 10 mL of Ac₂O cooled to 0 to -5 °C was added 1 mmol of **2-d**. The solution was stirred at 0 to -5 °C for 5 min and then worked up as before. The intramolecular effects of the three runs were 9.5, 9.5, and 9.9, and the average 9.7 ± 1.0 is obtained.

Preparation of 1-Chloromethylenetetralin (23**).**²² To a mixture of 7.0 g of (chloromethyl)trimethylphosphonium chloride (Aldrich, dried at 120 °C, 20 mmol) and 100 mL of anhydrous THF at 0 °C under nitrogen

was added 13 mL of 1.6 M *n*-BuLi (Aldrich, in hexanes, 20 mmol). One hour later, 2.86 g of 1-tetralone was added and the solution was then refluxed for 0.5 h. Extractive workup with pentane and water was followed by washing with brine, and the combined aqueous layers were extracted with pentane. The organic layer was dried (MgSO₄) and the solvent evaporated to give a residue that was a mixture of oil and Ph₃P=O solid. The solid was removed by filtration. The solid was washed with pentane, and the residue from the filtrate after solvent removal was Kugelrohr distilled to give a mixture of unreacted ketone and the vinyl chloride. These materials were separated by MPLC with 5% EtOAc as the eluent to give 2.5 g (69%) of **23** as colorless liquid. ¹H NMR showed this to be a mixture of two isomers in a 3.0/1.0 ratio as indicated by integrations of signals due to the vinyl hydrogens. The mixture was separated on a C₁₈ Dynamax 60A reversed-phase column with methanol as the eluent in 100-mg batches to give 1.70g (48%) of (*E*)-**23** and 0.53 g (16%) of (*Z*)-**23**: IR (neat, mixture, cm⁻¹) 745 (C-Cl), 1452, 1481, 1610, 2934 (C-H), 3017, 3065. (*E*)-**23**: ¹H NMR (300 MHz) δ 7.4–7.5 (m, 1 H), 7.0–7.2 (m, 3 H), 6.58 (t, *J* = 1.9 Hz, 1 H), 2.75 (t, *J* = 6.6 Hz, 2 H), 2.67 (dt, *J*_{ac} = 1.8 Hz, *J*_{ab} = 6.6 Hz, 2 H), 1.7–1.9 (m, 2 H); ¹³C NMR (125 MHz) δ 22.3, 27.1, 30.3, 113.5, 123.5, 126.2, 127.6, 128.9, 133.3, 137.2, 137.7; EIMS *m/e* (relative intensity) 180, 178 (M⁺, 13.5, 40.6), 143 (37.6), 141 (39.2), 115 (100), 63 (61.9), 50.4 (52.9). (*Z*)-**23**: ¹H NMR δ 8.16–8.3 (m, 1 H), 7.1–7.3 (m, 3 H), 6.10 (s, 1 H), 2.88 (t, *J* = 6.8 Hz, 2 H), 2.46 (dt, *J*_{ab} = 6.2 Hz, *J*_{ac} = 1.4 Hz, 2 H), 1.8–2.0 (m, 2 H); ¹³C NMR (125 MHz) δ 23.79, 29.60, 33.2, 110.3, 125.0, 128.0, 128.3, 128.8, 132.4, 136.3, 138.2; EIMS (70 eV) *m/e* (relative intensity) 180, 178 (M⁺, 13.4, 40.5), 143 (41.8), 141 (39.6), 115 (100), 63 (65.6), 50.6 (56.7). Anal. (mixture) Calcd for C₁₁H₁₁Cl: C, 73.95; H, 6.24; Cl, 19.84. Found: C, 73.62; H, 6.24; Cl, 19.67.

Preparation of 25.^{23,24} To a flask charged with a solution of 2.3 g of hexabutylditin (Aldrich, 4.0 mmol) in 20 mL of anhydrous THF at 0 °C under nitrogen was added 2.4 mL of 1.6 M *n*-BuLi (Aldrich, in hexane, 3.8 mmol). The mixture was stirred at 0 °C for 15 min, and then 474 mg of (*E*)-**23** (2.65 mmol) was added. The solution was stirred at room temperature for 6 h, and the solvent was removed. ¹H NMR of this crude mixture showed only the *E* isomer of vinylstannane **24**. The residue was mixed with 10 mL of anhydrous hexane and 10 mL of anhydrous ether, and 20 mL of 1.6 M *n*-BuLi (32 mmol, in hexane) was added. The mixture was stirred under nitrogen at room temperature overnight, then quenched with 2.5 g of CD₃COOD (Aldrich, 39 mmol), and stirred for 2 h. It was then worked up with pentane and water. Proton NMR of the crude product showed that there was still about 10–15% vinylstannane remaining. The crude product after removal of the solvent was dissolved in 5 mL of MeOD, and the methanol was removed again. It was then dissolved in 10 mL of CDCl₃ and allowed to react with 40 μL of CD₃COOD for 1.5 h. The mixture was worked up with saturated NaHCO₃, and the organic layer was dried (MgSO₄). The residue after solvent removal was first purified by flash column chromatography with hexane as eluent to separate most of the fast-moving tin compounds. This product was further purified by HPLC with hexane as eluent to give 0.20 g (52%) of **25**.

The longest spin–lattice relaxation time *T*₁ for the hydrogens in this molecule (the aromatic hydrogens) was 5.2 s, and 20-s relaxation time was allowed between each scan when the NMR was taken. The two vinyl

hydrogen peaks were integrated to obtain the ratio of the two isomers, which was (10 ± 1)/1.0. ¹H NMR (300 MHz) δ 1.89 (m, 2 H, CH₂), 2.55 (t, *J* = 6.0 Hz, 2 H, CH₂), 2.85 (t, *J* = 6.3 Hz, 2 H, ArCH₂), 4.94 (s, 0.091 H, *Z*-CHD), 5.45 (s, 0.909 H, *E*-CHD), 7.0–7.2 (m, 3 H, ArH), 7.6–7.7 (m, 1 H, ArH).

Reversibility Test: Ene Reaction of 25 with Acetic Anhydride Catalyzed by Zinc Chloride. To a solution of 27 mg of ZnCl₂ (0.20 mmol) in 5.0 mL of acetic anhydride (ACS Certified reagent, distilled before use) at 0 °C under nitrogen was added 69 mg of olefin **25** (0.47 mmol). The solution was stirred at 0 °C for 30 min and worked up as before. The crude product mixture was separated by MPLC, first with hexane as eluent, to give two fractions: The first fraction (14 mg) was shown by proton NMR to contain a mixture of 12 mg (17%) of unreacted **25** and 1.6 mg of **27** (2%). The second fraction was 4 mg (6%) of **21-d**₂. The eluent was changed to 5% ethyl acetate/hexane to give a third fraction: 44 mg (50%) of the ene reaction product **26**. ¹H NMR (300 MHz) data follow. For recovered **25**, the peaks that can be assigned to **25** were identical with that of the starting material except the vinyl hydrogen peaks. **25**: δ 4.94 (*Z*-CHD, 0.14 H), 5.46 (*E*-CHD, 0.86 H), (6.4 ± 0.6)/1.0 ratio of the two isomers. The peaks that are characteristic of **27** were multiplet (br t) at δ 5.85 (vinyl H, 12% relative to the total integration of the vinyl H's of **25**) and a singlet at δ 2.05 (CH₂D).³¹ **21-d**₂: δ 7.0–7.2 (m, 6 H, ArH), 7.3–7.5 (m, 2 H, ArH), 5.74 (t, *J* = 4.6 Hz, 1 H, vinyl H), 2.88 (s, 1 H, CHD), 2.6–2.8 (m, 4 H, CH₂Ar, CH₂Ar), 2.15–2.21 (m, 2 H, CH₂), 1.8–1.9 (m, 2 H, CH₂), 1.4–1.5, 1.6–1.8 (m, 2 H, CH₂H_b), 1.18 (s, 2 H, CH₂D). **26**: δ 1.93 (s, 3 H, MeC=O), 2.3–2.4 (m, 2 H, CH₂), 2.80 (t, *J* = 8.1 Hz, ArCH₂), 3.45 (s, 2 H, CH₂DC=O), 6.00 (t, *J* = 4.5 Hz, 1 H, vinyl H), 7.0–7.2 (m, 4 H, ArH).

Control Reaction: Ene Reaction of 2-d₂ with Acetic Anhydride Catalyzed by Zinc Chloride. The reaction conditions were the same as in previous reaction. Thus, 96 mg of olefin **2-d**₂ (0.64 mmol) was allowed to react with 5.0 mL of acetic anhydride and 36 mg of zinc chloride (0.27 mmol) at 0 °C for 45 min to give 7 mg (7%) of **2-d**₂, 8 mg (8%) of dimer **21-d**₄, and 75 mg (63%) of product **20-d**: ¹H NMR (300 MHz) for **21-d**₄: δ 1.20 (s, 2 H, CH₂D), 1.8–1.9 (m, 2 H, CH₂), 2.18 (t, *J* = 7.7 Hz, 2 H, CH₂), 2.68–2.77 (m, 4 H, ArCH₂, ArCH₂), 2.87, 2.92 (s, 1 H, 1 H, CH₂H_b), 7.0–7.2 (m, 6 H, ArH), 7.3–7.4 (m, 2 H, ArH). FIMS for the starting olefin **2-d**₂: *d*₁, 2.0%; *d*₂, 98.0%; *d*₃, 0.0%. FIMS for the recovered olefin **2-d**₂ (sample obtained from MPLC was further purified by HPLC with hexane as the eluent): *d*₁, 2.5%; *d*₂, 97.5%; *d*₃, 0.0%.

Acknowledgment. We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for support of this work.

Supplementary Material Available: Preparation of **1-d**₂, **1-d**₄, **2-d**₂, and **3-d**₂, data on the isotope effect determination of reaction of **1** and **1-d**₄ or **1-d**₂ with **8** and **9** and reaction of **2** and **2-d**₂ or **2-d** with acetic anhydride catalyzed by zinc chloride, examples of the calculation of the intermolecular and intramolecular isotope effects, derivation of eqs 1 and 2 in Scheme II, and prediction of the *E/Z* ratio of **25** in the reversibility test (13 pages). Ordering information is given on any current masthead page.