Stereoselective and Regioselective Lewis Acid Catalyzed Ene Reactions of α-Substituted Acrylate Esters

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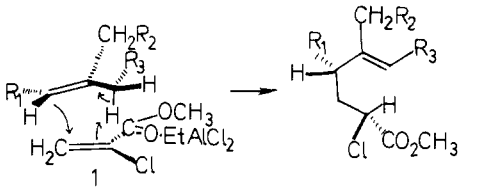
Abstract: $EtAlCl_2$ catalyzes the ene reactions of α-substituted acrylate esters with trans 1,2-di- and trisubstituted alkenes at 25 °C. The reactions are regio- and stereoselective. The ester group adds endo and a hydrogen is transferred selectively from the alkyl group syn to the vinylic hydrogen. Methyl α-chloroacrylate, α-bromoacrylate, acetamidoacrylate, and methacrylate, ethyl α-bromomethylacrylate, and dimethyl itaconate were explored. Ene reactions of phenylmenthyl α-bromoacrylate give a 3:1 mixture of diastereomers, indicating the potential for asymmetric induction in intermolecular ene reactions.

The use of carbon–carbon double bonds as activating groups for the formation of new carbon–carbon bonds under mild conditions is of considerable interest in organic synthesis. The ene reaction provides a potential solution to this problem (see Scheme I).[2] We have found that $AlCl_3$-catalyzed ene reactions of methyl acrylate[3] or methyl propiolate[4] occur at 25 °C and that $EtAlCl_2$ is a more effective catalyst for these reactions since it can also function as a proton scavenger.[4b] Lewis acid catalysis offers significant advantages over the corresponding thermal ene reactions which occur at 200–300 °C.

Methyl acrylate undergoes $AlCl_3$-catalyzed ene reactions with 1,1-disubstituted alkenes in good yield at 25 °C.[3] More recent studies have shown that tri- and tetrasubstituted alkenes give moderate yields of ene adducts[5] and that terminal alkenes react with $AlCl_3$ catalysis at 100 °C.[6] We chose to activate acrylate by placing an electron-withdrawing group in the α position which will lead to a less basic ester and therefore a more reactive Lewis acid complex. We have observed that substitution of propiolate with an electron-withdrawing group in the β position led to a more reactive Lewis acid complex.[7] Chlorine and bromine were chosen as substituents since they are inductively electron withdrawing (σ_I = 0.42 and 0.45) but resonance donating (σ_R = −0.20 and −0.19).[8]

To our surprise, methyl α-haloacrylates are not only more reactive than methyl acrylate, but also undergo stereoselective and regioselective Lewis acid catalyzed ene reactions with alkenes.[9] Reaction proceeds predominately through transition state **1**, in which the carbomethoxy group is endo and the hydrogen is transferred from the alkyl group syn to the vinylic hydrogen. Since these reactions are synthetically useful, several α-substituted acrylates have been investigated to determine the scope and limitations of these reactions.

Scheme I



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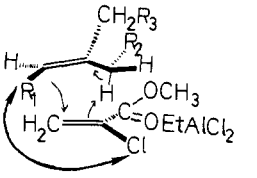

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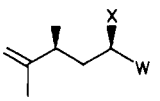
Results and Discussion

Stereochemistry. The results of $EtAlCl_2$-catalyzed ene reactions of α-substituted acrylate esters and α-chloroacrylonitrile with 2-methyl-2-butene and *trans*-2-butene are shown in Table I. In all cases predominantly one diastereomer is formed as determined by analysis of the ^{13}C NMR spectra. All attempts to determine the stereochemistry of the major isomers by spectroscopic methods were thwarted by the conformational mobility of the molecules and the presence of the methylene group between the two chiral

Table I. Ene Reactions of α-Substituted Acrylate Derivatives with 2-Methyl-2-butene and *trans*-2-Butene



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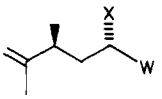

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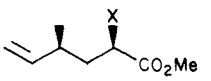

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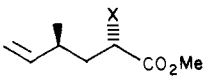

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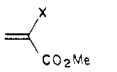
enophile 	reaction conditions,[a] days (°C)	% yield of 3	% yield of 4
a, X = Cl; W = CO_2Me	1.2 (25)	70	4
b, X = Br; W = CO_2Me	2.6 (25)	88	5
c, X = NHAc; W = CO_2Me	0.8 (0)[b]	59	5
d, X = H; W = CO_2Me	11 (25)	40	
e, X = CH_3; W = CO_2Me	6 (50)	21	2
f, X = CH_2CO_2Me; W = CO_2Me	2 (40)	55	7
g, X = CH_2Br; W = CO_2Et	4 (25)	30[c]	10[c]
h, X = Cl; W = CN	2 (25)	12	1

enophile 	reaction conditions, days (°C)	% yield of 5	% yield of 6
a, X = Cl	2 (67)	16	1
b, X = Br	3 (70)	49	3
e, X = CH_3	8 (105)	9.5	0

[a] Reactions were carried out in benzene or methylene chloride with 0.5–1 equiv of $EtAlCl_2$ as catalyst. [b] 1.5 equiv of $EtAlCl_2$ was used. [c] **20** and **21** were also isolated.

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(2) (a) For a review, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

(3) Snider, B. B. *J. Org. Chem.* **1974**, *39*, 255.

(4) (a) Snider, B. B. *J. Org. Chem.* **1976**, *41*, 3061; (b) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283.

(5) Beckwith, A. L. J.; Moad, G. *Aust. J. Chem.* **1977**, *30*, 2733. Greuter, H.; Bellus, D. *Synth. Commun.* **1976**, *6*, 409.

(6) (a) Akermark, B.; Ljungqvist, A. *J. Org. Chem.* **1978**, *43*, 4387. (b) Inukai, T. Y.; Nakamura, T. Y. Ger. Offen. 2063515 1971; *Chem. Abstr.* **1971**, *75*, 109872k.

(7) Snider, B. B.; Roush, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 1906. Snider, B. B.; Roush, D. M.; Rodini, D. J.; Gonzalez, D.; Spindell, D. *J. Org. Chem.* **1980**, *45*, 2773.

(8) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 334.

(9) For a preliminary communication see: Snider, B. B.; Duncia, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 5926.

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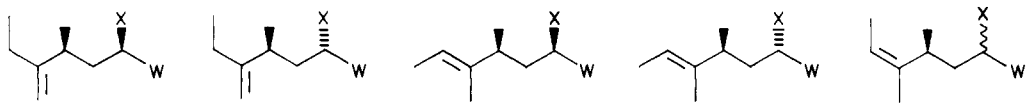
Table II. Ene Reactions of α-Substituted Acrylate Derivatives with (*E*)- and (*Z*)-3-Methyl-2-pentene



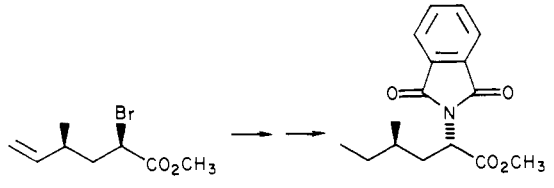
10 11 12 13 14

enophile 	reactions conditions,[a] days (°C)	% yield of[b] 10	11	12	13	14
a, X = Cl; W = CO_2Me	0.6 (25)	0 (73)	0 (4)	58 (0)	16 (9)	8 (0)
c, X = NHAc; W = CO_2Me	0.8 (0)[c]	2 (58)	2 (3)	58 (4)	4 (17)	12 (0)
d, X = H; W = CO_2Me	18 (25)	5 (30)		47 (30)		
f, X = CH_2CO_2Me; W = CO_2Me	2 (40)	1 (31)	1 (3)	45 (7)	2 (10)	4 (3)
g, X = CH_2Br; W = CO_2Et	1 (25)	3 (14)[d]		23 (6)[d]		
h, X = Cl; W = CN	1 (25)	0 (8.5)	0 (0.5)	4 (1)	1 (1)	2 (1)

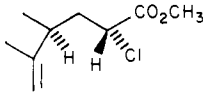
[a] Reactions were carried out in benzene or methylene chloride with 0.5–1.0 equiv of $EtAlCl_2$ as catalyst. [b] Yields from (*E*)-3-methyl-2-pentene shown first. Yields from (*Z*)-3-methyl-2-pentene are in parentheses. [c] 1.5 equiv of $EtAlCl_2$ was used. [d] Yields of products resulting from dehydrobromination of the crude reaction mixture.

centers. The lability of the halide and acidity of the α proton of **3a** and **3b** limits the reactions which can be carried out on these substrates.

Fortunately, (2*S*,4*S*)-2-amino-4-methylhexanoic acid (**7**)[10] and both diastereomers of (2*S*)-2-amino-4-methyl-5-hexenoic acid are natural products.[11,12] Unambiguous total syntheses of **7** and its diastereomer, starting with (*S*)-2-methyl-2-butanol and using an enzymatic hydrolysis of the acetamide of **7** to separate diastereomers and assign stereochemistry at the 2 carbon, provided intermediates which could be correlated with **5b**.[13,14] Displacement of the bromide of **5b** with azide, reduction of the azide and hydrogenation of the double bond over Raney Nickel and conversion to the phthalimide **8** gives material whose NMR spectrum is identical with that of the (2*R*,4*S*) isomer,[13] thereby establishing the stereochemistry of **5b**. A detailed description of this conversion and the stereospecific syntheses of both diastereomers of 2-amino-4-methyl-5-hexenoic acid has been published.[15]



5b 8



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The steroechemistry of **5e** was established by comparison of the ^{13}C NMR spectrum of the corresponding acid to that of a sample prepared by Bartlett from *meso*-2,4-dimethylglutaric anhydride.[16]

The structures of all other ene adducts were assigned by analogy. The relative stereochemistry of **3b** and **3c** was established by conversion of **3b** to **4c** by displacement with azide with a phase-transfer catalyst, reduction of the azide with chromous chloride, and acetylation.

Both **3a** and **4a** could be obtained in pure form by epimerization of **3a** by deprotonation with LDA in THF–HMPA followed by quenching and separation by HPLC. The NMR spectrum of **3a**, in which the methine hydrogens are both coupled to the methylene group as a doublet of doublets, J = 5.0 and 9.4 Hz, indicates that the molecule exists largely in conformation **9** due to attractive interactions between H-4 and the chlorine and H-2 and the double bond. As expected the dihydro derivative of **3a**, prepared by hydrogenation with diimide, has no preferred conformation (H-2 absorbs as a doublet of doublets, J = 6.9 and 8.2 Hz). The methine hydrogens of **4a**, which should have no preferred conformation, are both coupled to the methylene group as a doublet of doublets, J = 7.5 and 7.5 Hz.

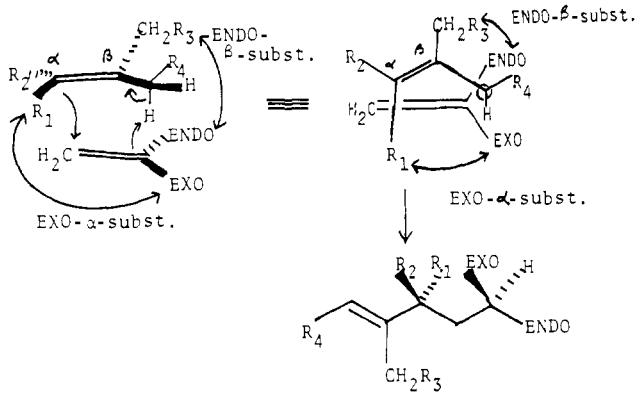
This is the first case in which the stereochemistry of an ene reaction producing 1,3-asymmetric centers has been determined. The high degree of stereospecificity is especially remarkable since Diels–Alder reactions of α-substituted acrylate esters with cyclopentadiene give mixtures of endo and exo isomers.[17] The carbomethoxy group may prefer to be endo due to secondary orbital overlap or electrostatic stabilization of a polar transition state. This preference is consistent with the results of Lewis acid catalyzed Diels–Alder reactions of acrylate esters which proceed almost exclusively through the endo transition state.[18]

Regiochemistry. The regioselectivity of these ene reactions is clearly observed in the reactions of acrylate esters with (*E*)- and (*Z*)-3-methyl-2-pentene (see Table II). The product resulting from transfer of a hydrogen from the alkyl group syn to vinylic hydrogen predominates. The ratio **10** and **11**:**12** and **13** and **14** could easily be determined from analysis of the olefin region of the proton NMR spectra. The ratio of diastereomers could be estimated from the ^{13}C NMR spectra. Although these spectra were complex, in many cases the ratio of **10**:**11** could be accurately estimated from the peaks at δ 108 and ~153 which were due to vinylic carbons. Similarly the ratio of **12**:**13** could be accurately estimated from the ratio peaks at δ ~120 and ~136 due to the vinylic carbons. The presence of the *Z* isomer **14** was indicated by a peak due to carbon-4 at δ 30.5 in a region of the spectra otherwise free of peaks. This carbon, which absorbs at δ 38 in **10**, **11**, **12**, and **13**, is shifted upfield by the γ effect of the cis vinylic methyl group. In all cases the major adducts are assumed to be **10** and **12**. The availability of two mixtures with varying component ratios aids in the assignment.

The regioselectivity appears to result from steric interaction between the exo substituent on the enophile and the substituent on the ene double bond which is cis to the allylic hydrogen being transferred. This steric hindrance, which we refer to as the

(10) Fowden, L.; Smith, A. *Phytochemistry* **1968**, *7*, 809.
(11) Kelly, R. B.; Martin, D. G.; Hanka, L. J. *Can. J. Chem.* **1969**, *47*, 2504.
(12) Rudzats, R.; Gellert, E.; Halpern, B. *Biochem. Biophys. Res. Commun.* **1972**, *47*, 290.
(13) Bernasconi, S.; Corbella, A.; Gariboldi, P.; Jommi, G. *Gazz. Chem. Ital.* **1977**, *107*, 95.
(14) Gellert, E.; Halpern, B.; Rudzats, R. *Phytochemistry* **1978**, *17*, 802.
(15) Snider, B. B.; Duncia, J. V. *J. Org. Chem.* **1981**, *46*, 3225.
(16) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625.
(17) Cantello, B. C. C.; Mellor, J. M. *Tetrahedron Lett.* **1968**, 5179. Use of $EtAlCl_2$ as catalyst for these Diels–Alder reactions does not change the endo/exo ratio significantly.
(18) Wollweber, H. "Diels–Alder Reactions"; George Thieme Verlag: Stuttgart, 1972; pp 118–138.

Scheme II



exo-α-substituent interaction, leads to a preference for the transition state shown in Scheme II in which R_1 is smaller than R_2 (see also Scheme I). Although this is the major factor, others can be identified. The most significant of these, which we refer to as the endo-β-substituent interaction (see Scheme II), leads to a preference for the transition state in which R_3 is smaller than R_4.

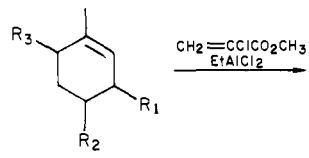
As can be seen from Table II the reactions of (*E*)-3-methyl-2-pentene are more selective than those of (*Z*)-3-methyl-2-pentene. This may be due to the greater stability of the internal double bonds of **12**, **13**, and **14** being reflected in a lower $\Delta G^{\ddagger}$ for their formation. Alternatively, loss of regioselectivity may be due to a larger endo-β-substituent interaction for (*Z*)-3-methyl-2-pentene.

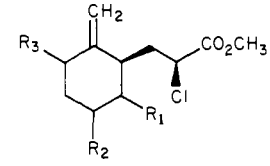
Methyl α-haloacrylates are the most regioselective enophiles. Methyl acrylate with the smallest exo substituent, hydrogen, is the least selective. Surprisingly, ene reactions of other acrylate esters with large α substituents are less regioselective than those of α-haloacrylate esters. Electronic characteristics of these substituents may change the position of the transition state on the reaction coordinate. Complexation of the Lewis acid to basic substituents may also perturb the reaction. It is of course also possible that the exo-α-substituent interaction is not entirely responsible for the regioselectivity of these reactions. The lower selectivity obtained with ethyl bromomethylacrylate may be due to a larger endo-β-substituent interaction with an ethyl ester than with a methyl ester. This is the first example of regiospecific transfer of a hydrogen from the alkyl group syn to the alkenyl hydrogen in an ene reaction. It complements the ene reactions of β-substituted propiolates which, we have discovered, regiospecifically transfer a hydrogen from the alkyl group anti to the alkenyl hydrogen.[7]

Reaction with 1-Methylcyclohexenes. The reaction of methyl α-chloroacrylate with 1-methycyclohexene gives only the methylenecyclohexane **15** as a single diastereomer (see Scheme III). The complete control of both regio- and stereochemistry results from severe exo-α-substituent interaction with the ring methylenes and the rigidity of the ring which minimizes the endo-β-substituent interaction. Since the production of 2-alkylmethylenecyclohexanes is of considerable synthetic utility, the effect of substituents on the ring was examined. All four cases are regio- and stereospecific with approach of methyl-α-chloroacrylate predominantly from the side of the ring opposite to the substituent.

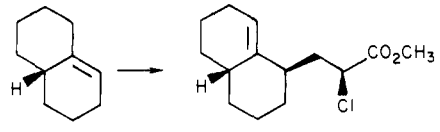
The stereochemistry of the substituents on the cyclohexane rings of **16**, **17**, **18**, and **19** was determined by analysis of the ^1H and ^{13}C NMR data. The olefin methylene group of the major, trans isomer of **16** absorbs as a broad singlet at δ 4.76. The olefin methylene group of the minor isomer is shielded by the equatorial substituent and absorbs at δ 4.43 and 4.56.[19] The methyl group of the major, trans isomer of **17** absorbs at δ 1.03 while that of the minor isomer absorbs at δ 0.93. Similar shifts are observed for the 3-methyl group of *trans*- and *cis*-2,3-dimethylcyclohexanone.[20] The stereochemistry of the major and minor isomers

Scheme III



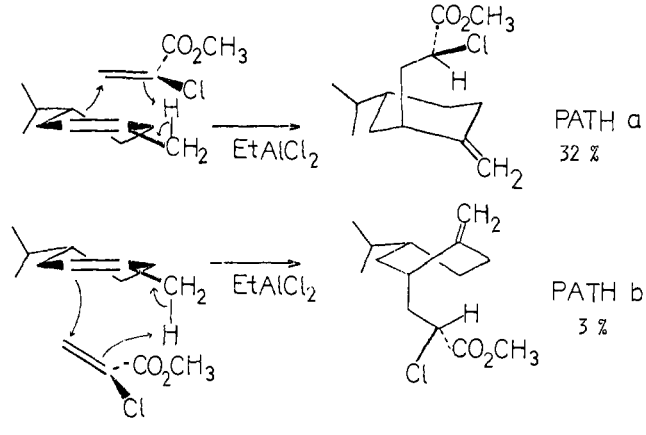


15, $R_1 = R_2 = R_3 = H$ (41%)
16, $R_1 = R_3 = H$; $R_2 = CH(CH_3)_2$ (35%, 92% trans)
17, $R_1 = R_2 = H$; $R_3 = CH_3$ (13%, 75% trans)
18, $R_1 = CH_3$; $R_2 = R_3 = H$ (18%, 67% trans)



19 (62%, 8% of diastereomer)

Scheme IV



of **18** was determined by comparison of their ^{13}C NMR spectra to those of *trans*- and *cis*-2,6-dimethylmethylenecyclohexane.[21] The C-4 (δ 21.8 major, δ 26.1 minor) and the olefinic methylene group (δ 107.6 major, δ 101.8 minor) are especially significant. Comparison of the ^{13}C NMR spectra of **19** with those calculated from the spectrum of the starting octalin[22] and shift values for equatorial and axial substituents[21] indicates that exclusively axial product, as a 92:8 mixture of diastereomers, is formed.

Menthene, in which the cyclohexene is anchored[23] and the equatorial isopropyl group does not sterically interact with the approaching enophile, indicates the preference for the formation of the chair product (Scheme IV, path a). The minor isomer of **16** must be formed initially as a twist boat (Scheme IV, path b) since formation of the minor isomer from the conformer with an axial isopropyl group is unlikely due to a 1,3-diaxial interaction when the enophile approaches from the same side as an axial isopropyl group. The results are less clear-cut when the substituent on the ring can interact sterically with the approaching enophile. The major isomer of **18** from 1,3-dimethylcyclohexene is formed as a chair cyclohexane from the conformer with a pseudoaxial methyl group and/or as a twist boat from the conformer with a pseudoequatorial methyl group to avoid the approach of methyl α-chloroacrylate from the same side of the ring as the 3-methyl

(19) Pillot, J.-P.; Dēlēris, G.; Dunoguès, J.; Calas, R. *J. Org. Chem.* **1979**, *44*, 3397.

(20) Pfeffer, P. E.; Osman, S. F. *J. Org. Chem.* **1972**, *37*, 2425.
(21) Grover, S. H.; Stothers J. B. *Can. J. Chem.* **1975**, *53*, 589.
(22) Becker, K. B. *Helv. Chim. Acta* **1977**, *60*, 68.
(23) The *A* value for an isopropyl group is ≈2.15. See: Jensen, F. R.; Bushweller, C. H. In "Advances in Alicyclic Chemistry", Hart, H.; Karabatsos, G. J., Eds.; Academic Press: New York, 1971; Vol. 3, pp 140–195.

group. Ene adduct **19** is formed exclusively by axial attack with transfer of an axial hydrogen.

Reactivity. $EtAlCl_2$, which can also act as a proton scavenger,[4b,24] gives better yields of ene adducts than $AlCl_3$. Reactions with $AlCl_3$, which is a stronger Lewis acid, are faster. Reactions were typically carried out with 0.5–0.9 equiv of $EtAlCl_2$ in benzene, which, as a π base, moderates the reaction in the presence of 1% hydroquinone at 25 °C. Reaction was faster in methylene chloride, but more complex mixtures were usually obtained. Elevated temperatures, 40–100 °C, were necessary with less reactive ene or enophile components.

The Lewis acid catalyzed ene reactions of α-substituted acrylates are probably concerted reactions with a very asymmetric transition state in which carbon–carbon bond formation is almost complete and carbon–hydrogen bond cleavage is just underway.[2b,25] Therefore substituents on the β carbon of the ene component which can stabilize the partial positive charge in the transition state will accelerate the reaction.

The reactions of methyl α-chloro-[26] and α-bromoacrylate[27] were investigated in the most detail. 1,1-Disubstituted and trisubstituted alkenes react at 25 °C. *trans*-2-Butene reacts at 70 °C. No adduct could be obtained from 2,3-dimethyl-2-butene or cyclohexene, which must react through transition states with severe exo-α-substituent interactions, or 1-hexene.

Since partial enolate character is developed in the transition states, electron-withdrawing substituents in the α position of the acrylate ester will accelerate the reaction. Unfortunately, introduction of very electron-withdrawing substituents, such as cyanide, changes the reaction mechanism. Me_2AlCl-catalyzed reactions of methyl α-cyanoacrylate with alkenes proceed through zwitterionic intermediates which go on to give complex reaction mixtures.[28]

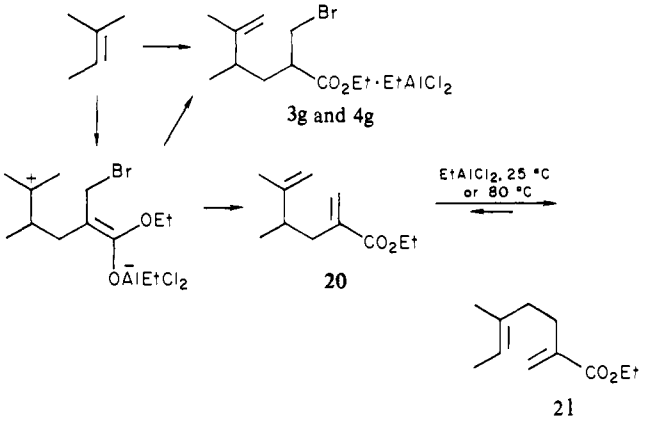
Methyl α-haloacrylates, in which the halide is inductively electron withdrawing but resonance donating, are about 10 times more reactive then methyl acrylate. For instance, methyl α-chloroacrylate gives a 41% yield of **15** from 1-methylcyclohexene after 2 days, while methyl acrylate gives only a 6% yield of ene adduct, as a 1:1 mixture of double bond isomers, after 6 days under the same conditions. Methyl α-bromoacrylate is slightly more reactive than methyl α-chloroacrylate and gives more reactive α-bromo esters.

Methyl methacrylate, with an electron-donating substitutent ($\sigma_I = -0.08$, $\sigma_R = -0.10$), is much less reactive than methyl acrylate and does not, in general, give useful yields of ene adduct. Since bromomethyl ($\sigma_I = 0.14$, $\sigma_R = -0.03$) and carbomethoxymethyl ($\sigma_I = 0.24$, $\sigma_R = -0.08$) are electron-withdrawing substituents,[29] ethyl α-bromomethylacrylate[30] and dimethyl itaconate are moderately reactive enophiles. Dimethyl itaconate gives good yields of ene adducts at 40 °C.

Methyl α-acetamidoacrylate[31] is a very reactive enophile in the presence of 1.5 equiv of $EtAlCl_2$. The first equivalent serves to complex to the more basic acetamido group, converting it to an electron-withdrawing substituent. The remaining $EtAlCl_2$ complexes to the ester, catalyzing the reaction. No reaction occurs if 1 equiv of $EtAlCl_2$ is used.

Activation of an enophile by complexation of a Lewis acid to a nitrile is less effective than complexation to an ester. α-Chloroacrylonitrile gives much lower yields of adduct than methyl α-chloroacrylate, although with similar region- and stereoselectivity.

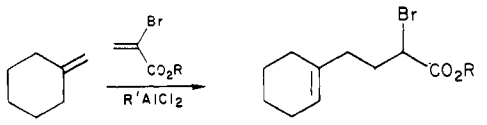
The reactions of ethyl α-bromomethylacrylate are complicated by the presence of an unstable β-bromo ester in the ene adduct which can eliminate hydrogen bromide to give an α,β-unsaturated ester. Thus, reaction with 2-methyl-2-butene gives, in addition to a 40% yield of a 3:1 mixture of **3g** and **4g**, 3% of **20** and 5% of **21**. The formation of **20** as a side product suggests that the reaction is stepwise, with elimination of bromide from the zwitterionic intermediate competing with a 1,5-proton shift since the **3g–4g** mixture is stable to the reaction conditions. Ester **21** is formed from **20** by a Lewis acid catalyzed Cope rearrangement.[32] Elimination of hydrogen bromide from **3g** and **4g** to give **20**, without concomitant Cope rearrangement, is effected by treatment with DBN in benzene for 4 days at 25 °C. Cope rearrangement of **20** in benzene at 82 °C gives a 1:1 mixture of **21** and **20** after 10 h and an equilibrium 6:1 mixture of **21** and **20** after 90 h. Reaction mixtures from (*E*)- and (*Z*)-3-methyl-2-pentene were treated with DBN to complete elimination of hydrogen bromide prior to analysis of regioselectivity.



Asymmetric Induction. The synthetic utility of the ene adducts from methyl α-haloacrylates and the well-defined transition state of the ene reaction, as indicated by its stereo- and regioselectivity, made this an attractive candidate for the exploration of asymmetric induction in Lewis acid catalyzed ene reactions. Reaction of methylenecyclohexane with methyl α-chloroacrylate with 1-menthyloxyaluminum dichloride[33] as catalyst gives 22% of **22**, $[\alpha]^{25}_D$ −0.4°. Since this was not promising, chiral esters were investigated. Reaction of menthyl α-bromoacrylate,[34] methylenecyclohexane, and $EtAlCl_2$ gives a 38% yield of ene adduct **23** as a 55:45 mixture of diastereomers as estimated by analysis of the ^{13}C NMR spectrum. Corey[35] and Oppolzer[36] have reported that phenylmenthyl esters are very effective inducers of asymmetry in Lewis acid catalyzed Diels–Alder and intermolecular ene reactions, respectively. Reaction of methylenecyclohexane, phenylmenthyl α-bromoacrylate, and $EtAlCl_2$ gives a 31% yield of **24** as a 3:1 mixture of diastereomers, which were easily separable chromatographically. Phenylmenthyl esters thus have the potential for asymmetric induction in intermolecular ene reactions. Ene reactions of phenylmenthyl α-acetamidoacrylate may provide a useful route to novel optically active amino acids.

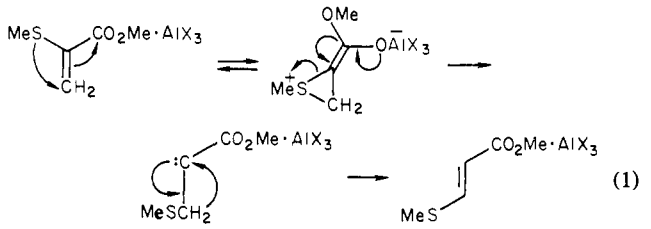
Unreactive Acrylate Esters. No adduct could be obtained from methyl crotonate or methyl *cis*- or *trans*-β-chloroacrylate, probably because of steric hindrance. Methyl α-(methylthio acrylate[41]

(24) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron.* **1981**, *37*, 3927.
(25) Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200.
(26) Pashtushak, N. O.; Dombrovskii, A. V.; Mukhova, A. N. *Zh. Org. Khim.* **1965**, *1*, 572; *J. Org. Chem. USSR (Engl. Transl.)* **1965**, *1*, 566.
(27) Marvel, C. S.; Cowan, J. C. *J. Am. Chem. Soc.* **1939**, *61*, 3158.
(28) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1981**, *46*, 2563.
(29) The values given are estimates based on the values for CH_2Cl and CH_2CN, respectively.[8]
(30) Ferris, A. R. *J. Org. Chem.* **1955**, *20*, 780.
(31) Rothstein, E. *J. Chem. Soc.* **1949**, 1968.
(32) Dauben, W. G.; Chollet, A. *Tetrahedron Lett.* **1981**, *22*, 1583.
(33) Hashimoto, S. I., Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437 and references cited therein.
(34) Undheim, K.; Wiik, T.; Borka, L.; Nordal, V. *Acta Chem. Scand.* **1969**, *23*, 2509.
(35) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(36) Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015.
(37) Factor, A.; Traylor, T. G. *J. Org. Chem.* **1968**, *33*, 2607.
(38) Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.
(39) Benhamou, M. C.; Etemad-Moghadam, G.; Speziale, V.; Lattes, A. *Synthesis* **1979**, 891.
(40) Brown, H. C.; Geohegan, P. J., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522. Brown, H. C.; Hammar, W. J. *J. Am. Chem. Soc.* **1967**, *89*, 1524. Brown, H. C.; Geohegan, P. J., Jr. *J. Org. Chem.* **1970**, *35*, 1844.
(41) Gunderman, K.-D.; Schulze, H. *Chem. Ber.* **1961**, *94*, 3258.



22, R = Me; R' = 1-menthyloxy
23, R = menthyl; R' = Et
24, R = phenylmenthyl; R' = Et

rearranges to methyl *trans*-β-(methylthio)acrylate[42] in the presence of $EtAlCl_2$ or Me_2AlCl. This unusual rearrangement may proceed via Michael addition of methylthiol followed by elimination of the 2-methylthio group to give the more stable vinylogous thiocarbonate. Alternatively, ring closure followed by opening to the carbene and hydrogen shift (eqn. 1) will give the observed product.



(1)

Reactions of 3a and 3b. The reactions of **3a** were investigated in an attempt to prepare a cyclic derivative whose stereochemistry could be determined from its NMR spectrum. Hydrolysis of the ester with sodium hydroxide in methanol leads to epimerization at the α carbon. Use of barium hydroxide leads to partial displacement of the chloride by hydroxide. Reaction with lithium iodide in DMF leads to displacement at the α carbon as well as the methyl group.

Oxymercuration of **3a** was attempted since unsaturated esters have been converted to lactones by this procedure.[37] Treatment of **3a** with mercuric acetate in aqueous acetone followed by workup with brine leads to a mixture of **25** and **26**. After 4 h a 6:1 mixture of **25** and **26** is isolated. After 42 h a 1:1 mixture is obtained. The relative stereochemistry of **25** and **26** was assigned based on the chemical shift of the methyl singlet which occurs at δ 1.41 in **25** and is shifted upfield to δ 1.21 by the cis methyl group of **26**. Ether **25** is obtained pure by fractional crystallization.

Reduction of this mixture with sodium borohydride in aqueous sodium bicarbonate solution gives **27** whose structure was proven by unambiguous synthesis from **3b** by displacement of the bromide with tetraethylammonium formate[38] and hydrolysis of the formate with potassium carbonate in methanol. Treatment of organomercury compounds analogous to **25** and **26** with sodium borohydride in aqeuous sodium hydroxide usually reductively cleaves the carbon–mercury bond. The anomolous, but not unprecedented,[39] reduction to the olefin may be due to the much lower pH of the reaction mixture which was chosen to prevent ester hydrolysis.

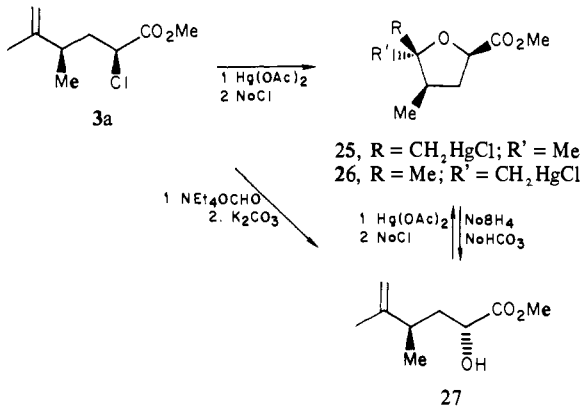
Further confirmation of the structures of **25** and **26** was obtained by oxymercuration of **27**. In this case a 1:5 mixture of **25** and **26** is obtained as the kinetic product after 5 min. The very different ratios of **25** and **26** obtained from **3a** and **27** is surprising but consistent with the mechanism of oxymercuration. Attack of the nucleophile on the olefin–mercury complex is the rate-determining step.[40] For **3a** the nucleophile is water, while for **27** it is an internal hydroxy group. Therefore very different steric contraints can apply.

Conclusion

Lewis acid catalyzed ene reactions of α-substituted acrylate esters have been shown to proceed with unprecedented stereo- and regiocontrol. These studies indicate the potential of the ene reaction as a means of controlling stereochemistry in acyclic systems and its scope as a method for the synthesis of polyfunctional molecules.

(42) Butler, P. E.; Mueller, W. H.; Reed, J. R. *Environ. Sci. Technol.* **1967**, *1*, 315.

Scheme V



Experimental Section

Materials and Methods. NMR spectra were taken on Varian A-60, Perkin-Elmer R32, and JEOL FX-90Q spectrometers. IR spectra were recorded on a Perkin-Elmer 283 spectrometer. Mass spectra were determined on an AEI-MS9 spectrometer. GC analyses were performed on a 0.25 in. × 10 ft, 10% XF-1150 column unless otherwise specified. Analyses were performed by Galbraith Laboratories.

Benzene was dried by distillation from sodium benzophenone ketyl. Methylene chloride and 1,2-dichloroethane were dried by distillation from calcium hydride. $EtAlCl_2$ was purchased as a 25.5% solution in heptane (d = 0.772, 1.57 M) from Texas Alkyls, Inc. Alkenes were purchased from Aldrich or Albany International and used without purification.

Methyl α-chloroacrylate,[26] methyl α-bromoacrylate,[27] methyl α-acetamidoacrylate,[31] ethyl α-(bromomethyl)acrylate,[30] menthyl α-bromoacrylate,[34] and methyl α-(methylthio)acrylate[41] were prepared by literature procedures. Phenylmenthyl α-bromoacrylate was prepared from phenylmenthol[35] as for menthyl α-bromoacrylate.[34] Dimethyl itaconate was a gift from Pfizer Inc. Methyl acrylate, methyl methacrylate, and α-chloroacrylonitrile were distilled before use. Hydroquinone (2%) was added to all liquid enophiles immediately after distillation, prior to storage at −15 °C.

General Reaction Procedure. All reactions were run under nitrogen in flame-dried glassware with magnetic stir-bars. Reagents were added via dry syringes through septa. $EtAlCl_2$ (≈0.45–0.9 equiv) was added to a stirred solution of enophile (≈1–2 equiv), alkene (≈1.10 equiv), and solvent (usually benzene; volume of solvent makes alkene ≈0.5 M). The progress of reaction was monitored by the disappearance of the enophile peak in the GC of worked up reaction aliquots. The reaction was quenched by slowly adding an equivalent volume of saturated aqueous sodium bicarbonate solution to the opened reaction flask. After being stirred for 30 min under N_2, the mixture was filtered by suction through Celite to remove precipitated alumina. The layers were separated, the aqueous layer was washed with three portions of ether, and the combined ether layers were washed with brine, dried (sodium sulfate), and evaporated in vacuo.

Ene Reactions with 2-Methyl-2-butene. Methyl α-chloroacrylate (1.00 g, 8.3 mmol, 1.0 equiv), 2-methyl-2-butene (0.639 g, 9.1 mmol, 1.1 equiv), $EtAlCl_2$ (4.76 mL, 1.57 M in heptane, 7.5 mmol, 0.9 equiv), and 20 mL of benzene were stirred for 31 h at 25 °C. Normal workup followed by evaporative distillation (50 °C, 0.1 torr) gave 1.176 g (74.4%) of a 19:1 mixture of pure ene adducts **3a** and **4a** as a colorless oil: IR (neat) 2960, 1745, 1437, 1378, 1315, 1270, 1195, 1165, 1117, 1022 cm^{-1}; ^1H NMR (CCl_4) δ 4.85 (br s, 2), 4.17 (d of d, 1, J = 4.7, 9.3 Hz), 3.78 (s, 3), 2.52 (d of d of q, 1, J = 4.7, 9.3, 6.7 Hz), 2.08 (d of d of d, 1, J = 4.7, 9.3, 14.3 Hz), 1.78 (d of d of d, 1, J = 4.7, 9.3, 14.3 Hz), 1.71 (br s, 3), 1.09 (d, 3, J = 7 Hz); ^{13}C NMR shows a 19:1 mixture of **3a** and **4a**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4a**) δ 170.4, 146.9, 111.9, 110.8*, 55.9, 55.0*, 52.8, 40.1*, 39.6, 38.1, 19.7, 19.0*, 18.1; GC (150 °C), t_R = 10.5 min. Anal. Calcd for $C_9H_{15}O_2Cl$: C, 56.69; H, 7.93. Found: C, 56.43; H, 8.12.

Methyl α-bromoacrylate (0.97 mL, 1.37 g, 8.3 mmol, 1.0 equiv), 2-methyl-2-butene (0.97 mL, 0.64 g, 9.1 mmol, 1.1 equiv), $EtAlCl_2$ (4.76 mL, 1.57 M in heptane, 7.5 mmol, 0.9 equiv), and 20 mL of benzene were stirred for 64 h at 25 °C. Normal workup followed by evaporative distillation (50 °C, 0.1 torr) gave 1.80 g (92.4%) of a 19:1 mixture of pure ene adducts **3b** and **4b** as a colorless oil: IR (neat) 3075, 2965, 2860, 1745, 1435, 1378, 1360, 1315, 1270, 1248, 1194, 1150, 1114, 1022, 983, 894, 785, 760 cm^{-1}; ^1H NMR (CCl_4) δ 4.88 (br s, 2), 4.19 (d of d, 1, J = 6, 9 Hz), 3.82 (s, 3), 2.70–2.20 (m, 1), 2.20–1.76 (m, 2), 1.68 (br s, 3), 1.07 (d, 3, J = 7 Hz); ^{13}C NMR shows a 19:1 mixture of **3b** and **4b**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4b**) δ 170.2,

146.8, 111.6, 110.9*, 52.6, 44.7, 39.9*, 39.2, 38.9, 19.4, 19.0*, 18.0; GC (140 °C), t_R = 28.3 min. Anal. Calcd for $C_9H_{15}O_2Br$: C, 45.98; H, 6.43, Found: C, 46.03; H, 6.55.

Methyl α-acetamidoacrylate (207.2 mg, 1.46 mmol, 1.0 equiv), 2-methyl-2-butene (304.3 mg, 4.35 mmol, 3 equiv), and 3.2 mL of 1,2-dichloroethane at 0 °C were treated with 1.16 mL of 1.88 M $EtAlCl_2$ in methylene chloride (2.18 mmol, 1.5 equiv). The solution was stirred for 20 h at 0 °C and worked up to give 292 mg (94%) of crude ene adduct (≈ 90% pure, 10% recovered enophile). Chromatography on 8 g of silica gel (ether) gave 198 mg (64%) of crystalline ene adduct as a 12:1 mixture of **3c** and **4c**. An analytical sample was prepared by recrystallization from methylene chloride–hexane: mp 87–91 °C; IR ($CHCl_3$) 3290, 2960, 1740, 1655, 1545, and 730 cm^{-1}; NMR ($CDCl_3$) δ 6.10 (br d, 1, J = 8.2 Hz), 4.78 (br s, 2), 4.57 (d of d of d, 1, J = 4.9, 8.2, 9.0 Hz), 3.77 (s, 3), 1.6–2.6 (m, 2), 2.03 (s, 3), 1.69 (s, 3) and 1.04 (d, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4c**) δ 173.3, 169.7, 148.2, 111.1, 110.1*, 52.05, 51.05, 50.8*, 37.9, 37.8*, 37.5*, 37.2, 22.9, 20.0, 19.6*, 19.2*, and 18.4. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.93; H, 9.08; N, 6.62.

Methyl methacrylate (0.835 g, 0.89 mL, 8.3 mmol, 1 equiv), 2-methyl-2-butene (1.200 g, 1.76 mL, 16.6 mmol, 2.0 equiv), $EtAlCl_2$ (4.76 mL, 1.57 M in heptane, 7.5 mmol, 0.9 equiv), and 20 mL of benzene were stirred for 6 days at 50 °C in a pressure bottle. Normal workup gave 756 mg of crude product. Column chromatography on silica gel (6:1 pentane–ethyl ether) gave 324 mg (23%) of a 10:1 mixture of pure ene adducts **3e** and **4e**: IR (neat) 1740, 1645, 1460, 1375, 1170, and 890 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.69 (br s, 2), 3.64 (s, 3), 2.60–1.80 (m, 4), 1.64 (br s, 3), 1.12 (d, 3, J = 7 Hz), 1.03 (d, 3, J = 6 Hz); ^{13}C NMR shows a 10:1 mixture of **3e** and **4e**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4e**) δ 177.1, 149.8, 110.1, 110.0*, 51.2, 51.0*, 38.9, 38.8, 37.4, 19.7, 19.5*, 18.2, 17.9*, 16.8, 16.6*; GC (140 °C), t_R = 8.0 min. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.66. Found: C, 68.36; H, 10.23.

Dimethyl itaconate (1.360 g, 8.6 mmol, 1.0 equiv), 2-methyl-2-butene (1 mL, 662 mg, 9.4 mmol, 1.1 equiv), $EtAlCl_2$ (5.05 mL, 1.53 M in heptane, 7.7 mmol, 0.9 equiv), and 19 mL of benzene were stirred for 6 h at 25 °C. The reaction was then heated to 40 °C and allowed to remain at that temperature for another 38 h when it was quenched. Normal workup yielded 1.364 g of crude product which after evaporative distillation (97 °C, 0.1 torr) gave 1.202 g (61.5%) of ene adduct. ^{13}C NMR showed trace amounts of impurity. Medium pressure liquid chromatography on silica gel (1:1 pentane–ethyl ether) gave 689 mg (35.2% overall) of an 8:1 mixture of pure ene adducts **3f** and **4f** as a colorless oil: IR (neat) 3082, 2960, 2880, 1742, 1439, 1377, 1336, 1268, 1200, 1165, 1009, 891, 841 cm^{-1}; ^{1}H NMR shows an 8:1 mixture of **3f** and **4f**, respectively; ^{1}H NMR ($CDCl_3$) δ 4.73 (br s, 2), 3.71 (s, 3), 3.68 (s, 3), 2.96–1.20 (m, 6), 1.68 (br s, 3), 1.05 (d, 0.89 × 3, J = 7.0 Hz), 1.02 (d, 0.11 × 3, J = 7.0 Hz); ^{13}C NMR shows an 8:1 mixture of **3f** and **4f**, respectively, also ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4f**) δ 172.3, 148,5, 110.7, 51.7, 51.6, 39.5, 39.2*, 39.0, 37.0, 36.6*, 35.6, 20.1*, 19.7, 18.6*, 18.5; GC (150 °C), t_R = 20.7 min. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.99; H, 8.90.

Ethyl α-(bromomethyl)acrylate (0.52 g, 2.7 mmol, 1.0 equiv), 2-methyl-2-butene (0.41 mL, 0.27 g, 3.9 mmol, 1.4 equiv), $EtAlCl_2$ (1.57 mL, 1.53 M in heptane, 2.4 mmol, 0.9 equiv), and 7.0 mL of benzene were stirred for 26 h at 25 °C. The reaction was quenched with 20 mL of a 5% NaH_2PO_4 aqueous solution. The layers were separated and the aqueous layer extracted with three 15-mL portions of ethyl ether. The organic layers were collected and dried (Na_2SO_4) and the solvent removed in vacuo to give 717 mg of crude product. Column chromatography on silica gel (95:5 hexane–ethyl acetate) gave a 46-mg (R_f 0.43) yield composed of a 1:1.4 mixture of dehydrohalogenated ene adducts **20** and **21** and a 342-mg (R_f 0.21) yield composed of a 3:1 mixture of pure ene adducts **3g** and **4g**. The data for **3g** and **4g** follow: IR (neat) 3080, 2985, 2975, 2940, 2880, 1743, 1446, 1372, 1330, 1310, 1223, 1186, 1118, 1027, 957, 893, 857, 810, 720 cm^{-1}; ^{1}H NMR shows a 3:1 ratio of **3g** and **4g**, respectively, ^{1}H NMR ($CDCl_3$) δ 4.74 (br s, 2), 4.19 (q, 2, J = 7.0 Hz), 3.54 (d, 2, J = 6.6 Hz), 2.77 (d of d of d, 1, J = 6.6, 7.0, 7.0 Hz), 2.21 (m, 1), 2.10–1.40 (m, 2), 1.68 (s, 3), 1.28 (t, 3), 1.05 (d, 0.77 × 3, J = 6.6 Hz), 1.02 (d, 0.23 × 3, J = 6.6 Hz); ^{13}C NMR shows a 3:1 ratio of **3g** and **4g**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4g**) δ 173.0*, 172.9, 148.4, 148.0*, 111.1*, 110.7, 60.8, 46.2*, 45.9, 39.2*, 38.8, 36.3*, 36.0, 33.3*, 32.6, 20.2*, 19.6, 18.6, 18.5*, 14.2. Anal. Calcd for $C_{11}H_{19}BrO_2$: C, 50.20; H, 7.28. Found: C, 50.31; H, 7.26.

The data for **20** and **21** follow: ^{1}H NMR ($CDCl_3$) (characteristic peaks only) δ 6.15 (br, s, 1), 5.52 (br s, 1), 5.24 (m, 0.58 × 1, **21**), 4.72 (br s, 0.42 × 2, **20**).

α-Chloroacrylonitrile (250 mg, 2.9 mmol, 1.0 equiv), 2-methyl-2-butene (0.33 mL, 218 mg, 3.1 mmol, 1.1 equiv), $EtAlCl_2$ (1.64 mL, 1.57 M in heptane, 2.6 mmol, 0.9 equiv), and 5.7 mL of benzene were stirred for 2 days at 25 °C. Normal workup gave 109 mg of crude product. Evaporative distillation (50 °C, 0.1 torr) gave 56 mg (12.4%) of a 16:1 mixture of pure ene adducts **3h** and **4h**: IR (neat) 3080, 2970, 2940, 2880, 2224, 1645, 1445, 1379, 1259, 1120, 1070, 1018, 940, 897 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.86 (m, 2), 4.36 (d of d, 1, J = 5.7, 8.5 Hz), 2.77–1.92 (m, 3), 1.70 (s, 3), 1.12 (d, 3, J = 7 Hz); ^{13}C NMR shows a 16:1 ratio of **3h** and **4h**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **4h**) δ 146.0, 117.4, 112.6, 112.4*, 41.1, 37.8, 26.7*, 19.1, 18.3. Anal. Calcd for $C_8H_{12}ClN$: C, 60.95; H, 7.67. Found: C, 60.22; H, 7.57.

Reactions with *trans*-2-Butene. Methyl α-Chloroacrylate. *trans*-2-Butene was slowly passed through a 2 ft × 1.5 in. column filled with activated 4-Å molecular sieves and then condensed in a pressure bottle kept at 0 °C until 10 mL (6.04 g, 108 mmol, 6.5 equiv) were collected. Methyl α-chloroacrylate (2.00 g, 16.6 mmol, 1.0 equiv), 20 mL of benzene, and $EtAlCl_2$ (2.38 mL, 1.57 M in heptane, 3.7 mmol, 0.23 equiv) were then added and the mixture stirred for 2 days at 67 °C. Normal workup was followed by precipitation of polymer by the addition of 30 mL of petroleum ether to the crude product. The supernatant was separated by suction filtration and the solvent removed in vacuo to give 0.568 g of crude product. Evaporative distillation of the crude product (50 °C, 0.1 torr) gave 0.457 g (15.6%) of a 19:1 mixture of pure ene adducts **5a** and **6a** as a colorless oil: IR (neat) 2960, 2935, 2875, 1750, 1436, 1420, 1376, 1360, 1310, 1280, 1192, 1168, 1112, 994 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.60 (d of d of d, 1, J = 7.5, 9.0, 17.5 Hz), 5.09 (d of d, 1, J = 2.5, 17.5 Hz), 5.04 (d of d, 1, J = 2.5, 9.0 Hz), 4.26 (d of d, 1, J = 6.7, 7.7 Hz), 3.78 (s, 3), 2.49 (d of d of d of q, 1, J = 7, 7, 7, 7 Hz), 1.93 (d of d, 2, J = 6.7, 7.7 Hz), 1.07 (d, 3, J = 7 Hz); ^{13}C NMR shows a 19:1 mixture of **5a** and **6a**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **6a**) δ 170.3, 141.8, 115.2, 55.9, 52.8, 41.3, 35.3, 34.7*, 21.8*, 20.7; GC (140 °C) t_R = 10.0 min. Anal. Calcd for $C_8H_{13}O_2Cl$: C, 54.40; H, 7.42. Found: C, 54.53; H, 7.48.

Reaction with methyl α-bromoacrylate was carried out as described above. Methyl α-bromoacrylate (3.56 g, 21.6 mmol, 1.0 equiv), *trans*-2-butene (10 mL, 6.04 g, 108 mmol, 5.0 equiv), $EtAlCl_2$ (6.19 mL, 1.57 M in heptane, 9.7 mmol, 0.45 equiv), and 10 mL of benzene were used. After 3 days at 70 °C, the reaction was worked up in the normal manner to yield 2.95 g of crude product. Evaporative distillation (60 °C, 0.05 torr) gave 2.46 g (51.5%) of a 19:1 mixture of pure ene adducts **5b** and **6b** as a colorless oil: IR (neat) 3090, 1748, 996, 920 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.56 (d of d of d, 1, J = 7.7, 9.5, 17.3 Hz), 5.07 (d of d, 1, J = 2.3, 17.3 Hz), 5.00 (d of d, 1, J = 2.3, 9.5 Hz), 4.13 (d of d, 1, J = 7.3, 7.3 Hz), 3.75 (s, 3), 2.44 (m, 1), 1.95 (d of d, 2, J = 7.3, 7.3 Hz), 1.09 (d, 3, J = 7.0 Hz); ^{13}C NMR shows a 19:1 mixture of **5b** and **6b**, respectively, ^{13}C NMR ($CDCl_3$) (an asterisk indicates **6b**) δ 170.4, 142.0*, 141.8, 115.1, 114.4*, 52.8, 44.8, 41.5*, 41.0, 36.4, 36.0*, 20.6, 20.0*; GC (120 °C) 6 ft column, t_R = 10.8 min. Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93; Br, 36.14. Found: C, 43.26; H, 5.98; Br, 35.97.

Methyl methacrylate (0.89 mL, 0.83 g, 8.3 mmol, 1.0 equiv), *trans*-2-butene (10 mL, 6.04 g, 108 mmol, 13.0 equiv), $EtAlCl_2$ (4.76 mL, 1.57 M in heptane, 7.5 mmol, 0.9 equiv), and 20 mL of benzene were reacted as described above. After 8 days at 105 °C, the reaction was worked up in the normal manner to yield 1.05 g of crude product. Evaporative distillation (50 °C, 0.1 torr) gave 411 mg of **5e** which by ^{1}H NMR showed large quantities of impurity. Medium pressure liquid chromatography on silica gel (95:5 hexane–ethyl acetate) gave 298 mg of product which by ^{1}H NMR was not pure either.

Impure ester **5e** (80 mg, 0.5 mmol, 1.0 equiv) was added to a stirred solution of 0.1 N NaOH (7.7 mL, 0.77 mmol, 1.5 equiv) and 7.7 mL of MeOH at 25 °C. After 72 h, 10 mL of water were added and the solution was extracted with three portions of ether to remove organic impurities. The aqueous layer was acidified to pH 6 with dropwise addition of 1 N HCl. The aqueous layer was then extracted with five 10-mL portions of ethyl ether. The organic layers were collected and dried (Na_2SO_4) and the solvent removed in vacuo to yield 37 mg of carboxylic acid. ^{1}H NMR showed it to contain trace amounts of impurity. Evaporative distillation (100 °C, 0.1 torr) gave 30 mg (9.5% overall) of pure (2*R**,4*S**)-2,4-dimethyl-5-hexenoic acid: IR (neat) 3600–2500, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.75 (s, 1), 5.5 (m, 1), 4.9 (m, 2), 1.7–2.3 (m, 4), 1.20 (d, 3, J = 7 Hz), 1.03 (d, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 183.2, 143.5, 113.6, 40.1, 37.1, 35.8, 20.6, 16.7. The ^{13}C NMR spectrum corresponds well with that reported in the literature.[16]

Reactions of 3a and 3b. Epimerization of 3a. BuLi (1.31 mL, 1.6 M, 2.1 mmol, 1.0 equiv) was added to a stirred solution of 1.33 mL of THF, 0.77 mL of HMPA, and 0.294 mL of diisopropylamine (2.1 mmol, 1.0 equiv) at 0 °C. After 15 min, the mixture was cooled to −78 °C and 400 mg of **3a** (2.1 mmol, 1.0 equiv) was added. After 3 h, the mixture was allowed to warm to room temperature and then was quenched with 20 mL of saturated NaH_2PO_4 solution. The layers were separated and the

aqueous layer was extracted with three portions of ethyl ether. The combined organic layers were washed with brine and dried over sodium sulfate and the solvent removed in vacuo to yield 251 mg of crude product which gave after evaporative distillation (50 °C, 0.1 torr) 160 mg (40.0%) of a 1:1 mixture of **3a** and **4a** which were separated by HPLC (0.5:99.5 ethyl acetate-hexane) on a Waters Radial-Pak B column at a flow rate of 1.0 mL/min. The retention times are 15.2 and 17.3 min for **4a** and **3a**, respectively. The spectral data for **4a** follow: ^{1}H NMR ($CDCl_3$) δ 4.80 (br s, 2), 4.21 (d of d, 1, J = 7.5, 7.5 Hz), 3.78 (s, 3), 2.91–1.53 (m, 3), 1.71 (br s, 3), 1.07 (d, 3, J = 7 Hz).

Methyl (2S*,4S*)-2-Azido-4,5-dimethyl-5-hexenoate from 3b. A suspension of **3b** (900 mg, 3.8 mmol, 1.0 equiv) in a solution of sodium azide (309 mg, 4.8 mmol, 1.3 equiv) and hexadecyltri-*n*-butylphosphonium bromide (192 mg, 0.4 mmol, 0.1 equiv) in 1.9 mL of water was vigorously stirred for 12 h at 25 °C. Ether (10 mL) was added and the organic phase was extracted three times with brine, dried (Na_2SO_4), and evaporated to give 740 mg of crude product. Evaporative distillation furnished 538 mg (71.3%) of pure azide: IR (neat) 3070, 2960, 2875, 2105, 1749, 1436, 1375, 1260, 1200, 1175, 1080, 1000, 890 cm^{-1}; ^{1}H NMR (CCl_4) 4.82 (m, 2), 3.94–3.62 (m, 1), 3.82 (s, 3), 2.32 (m, 1), 1.97–1.63 (m, 2), 1.7 (m, 3), 1.10 (d, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.2, 148.5, 110.6, 60.4, 52.4, 37.7, 36.6, 19.3, 19.0; GC (130 °C), t_R = 18.7 min.

Methyl (2S*,4S*)-2-Acetamido-4,5-dimethyl-5-hexenoate (4c). Distilled azido ester (50 mg, 0.25 mmol, 1.0 equiv) was reduced with $CrCl_2$ (62.5 mg, 0.50 mmol, 2.0 equiv) as previously described[15] to give 37.8 mg of crude amino ester which was acetylated immediately to give 22 mg (47%) of **4b**: ^{1}H NMR ($CDCl_3$) δ 5.95 (m, 1), 4.75 (br s, 2), 4.74 (m, 1), 3.75 (s, 3), 2.50–1.50 (m, 3), 2.03 (s, 3), 1.72 (s, 3), 1.06 (d, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.0, 169.7, 148.9, 110.3, 52.2, 50.9, 37.8, 37.5, 23.1, 19.6, 19.2.

Methyl (2S*,4S)-2-Hydroxy-4,5-dimethyl-5-hexenoate (27) from 3b. Bromo ester **3b** (200 mg, 0.85 mmol, 1.0 equiv) was added to a solution of tetraethylammonium formate (894 mg, 5.1 mmol, 6.0 equiv) in 4 mL of anhydrous acetone under nitrogen. The solution was vigorously stirred for 3.5 h and quenched by the addition of 10 mL of water. Product was isolated by extraction with three 5-mL portions of ether which were dried (Na_2SO_4) and evaporated to give 163 mg (113%) of crude formate (tetraethylammonum salts were present): IR (neat) 1760, 1730 cm^{-1}; ^{1}H NMR (CCl_4) δ 8.1 (s, 1), 5.05 (d of d, 1, J = 5.0, 8.0 Hz), 4.73 (m, 2), 3.72 (s, 3), 2.57–1.76 (m, 3), 1.73 (s, 3), 1.04 d, 3, J = 7 Hz).

Crude formate (160 mg) was added to a suspension of 111 mg of K_2CO_3 in 1 mL of anhydrous MeOH. The resulting mixture was stirred 30 min at 25 °C. NaH_2PO_4 solution (5 mL, 5%) was added and the resulting solution was extracted three times with ether. The combined organic layers were dried (Na_2SO_4) and evaporated to give 114 mg of product. Evaporative distillation (70 °C, 0.2 torr) gave 109 mg (75% from **3b**) of pure **27**.

Chloro[[(3α,5α)-5-carbomethoxy-2,3-dimethyltetrahydro-2-furanyl]methyl]mercury (25 and 26) via Oxymercuration of 3a. Chloro ester **3a** (400 mg, 2.1 mmol, 1.0 equiv) was added to a stirred yellow solution of mercuric acetate (736 mg, 2.3 mmol, 1.1 equiv) in 28 mL of a 25% aqueous acetone solution at room temperature. Within 5 min, the solution changed from milky yellow to clear and colorless. After 4 h, the solvent was removed in vacuo and the residue dissolved in 20 mL of ether. The ether was washed with one 20-mL portion of brine. The aqueous layer was then extracted with three 10-mL portions of ether. The organic layers were collected and dried (Na_2SO_4) and the solvent removed in vacuo to yield 604 mg of a 6:1 mixture of **25** and **26** by NMR spectral analysis which after prolonged storage at 0 °C produced white needles. The reaction was repeated and aliquots were worked up after 0.17, 4.30, 18.42, 30.00, and 42.00 h. ^{1}H NMR (CCl_4) shows a 6:1, 3:1, 1.75:1, and 1:1 mixture of **25** and **26** at 4.30, 18.42, 30.00, and 42.00 h, respectively. The ^{1}H NMR spectrum of the 0.17-h aliquot was too complex for interpretation. The 18.42-h aliquot (24.6 mg) was fractionally crystallized with chloroform/hexane, giving **25** (10.5 mg, 33.0% from **3a**) as clear, colorless, cubic crystals: mp 79–82 °C; IR (CCl_4) 2870, 2838, 1745, 1458, 1436, 1416, 1381, 1375, 1360, 1346, 1335, 1260, 1209, 1159, 1105, 1070, 1016, 962, 937, 867, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.46 (d of d, 1, J = 7.8, 9.0 Hz), 3.76 (s, 3), 2.24–1.58 (m, 5), 1.39 (d, 3, J = 1.1 Hz), 1.01 (d, 3, J = 6.4 Hz); mass spectrum (of 4.30-h aliquot) 404–412 consistent with isotope pattern of Hg and Cl. Anal. Calcd for $C_9H_{15}ClHgO_3$: C, 26.54; H, 3.71. Found: C, 26.53; H, 3.85.

Methyl (2S*,4S*)-2-Hydroxy-4,5-dimethyl-5-hexenoate (27) via Reduction of 25 and 26. Crude **25** and **26** obtained from oxymercuration of **3a** (604 mg, 1.4 mmol, 1.0 equiv) was dissolved in 1.4 mL of THF which was subsequently added to a stirred solution of 1.8 mL of 3 N $NaHCO_3$, 1.4 mL of water, and 1.4 mL of THF. $NaBH_4$ (32 mg, 0.8 mmol, 0.6 equiv) dissolved in 1.4 mL of 3 N $NaHCO_3$ solution was then added and immediately droplets of Hg^0 began to form. After 9 h, 10 mL of a 5% NaH_2PO_4 solution was added and the mixture extracted with five 10-mL portions of ethyl ether. The organic layers were collected and dried (Na_2SO_4) and the solvent removed in vacuo to yield 256 mg of crude product. Purification via medium-pressure liquid chromatography on silica gel (4:1 hexane–ethyl acetate) gave 149 mg of **27** (41.3% from **3a**) as a colorless oil: IR (neat) 3500 (br), 3080, 2960, 1740, 1436, 1375, 1210, 1150, 1120, 1102, 1070, 1014, 965, 885 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.72 (br s, 2), 4.21 (br d of d, 1, J = 6.2, 6.2 Hz), 3.77 (s, 3), 3.00 (m, 1), 2.49 (br d of d of q, 1, J = 7, 7, 7Hz), 1.82–1.50 (m, 2), 1.70 (br s, 3), 1.05 (d, 3, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.9, 149.6, 109.9, 69.0, 52.3, 39.8, 36.7, 19.4, 18.9. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.96; H, 9.45.

Chloro[[(3α,5α)-5-Carbomethoxy-2,3-dimethyltetrahydro-2-furanyl]methyl]mercury (25 and 26) via Oxymercuration of 27. Hydroxy ester **27** (obtained via formate anion displacement of bromo ester **3b**, see experimental (54 mg, 0.3 mmol, 1.0 equiv) was added to a stirred solution of mercuric acetate (100 mg, 0.3 mmol, 1 equiv) in 4.2 mL of 25% aqueous acetone. The reaction changed from milky yellow to clear and colorless within 5 min and the solvent was removed in vacuo and the residue dissolved in 5 mL of ether. The ether was washed with 10 mL of brine and the aqueous layer then extracted with three 10-mL portions of ether. The organic layers were collected and dried (Na_2SO_4) and the solvent removed in vacuo to give 150 mg of **25** and **26**: ^{1}H NMR shows a 5:1 mixture of **26** and **25**, respectively. The spectral data for **26** follow: IR (CCl_4) 2870, 1745, 1458, 1381, 1360, 1159, 1070, 1016 cm^{-1}; ^{1}H NMR (CCl_4) δ 4.45 (d of d, 1, J = 9, 9 Hz), 3.72 (s, 3), 2.70–1.60 (m, 6), 1.21 (br s, 3), 1.05 (d, 3, J = 7 Hz). Anal. Calcd for $C_9H_{15}ClHgO_3$: C, 26.54; H, 3.71. Found: C, 26.73; H, 3.81.

Reaction of Methyl α-(Methylthio)acrylate with Dimethylaluminum Chloride. Methyl α-(methylthio)acrylate (200 mg, 1.5 mmol, 1.0 equiv), **dimethylaluminum chloride** (1.20 mL, 1.14 M in heptane, 1.4 mmol, 0.9 equiv), and 3.0 mL of benzene were stirred for 14 days at 25 °C. Normal workup gave 125 mg of crude product which after evaporative distillation (25 °C, 0.1 torr) gave 65 mg (32.5%) of methyl *trans*-β-(methylthio)-acrylate: IR (CCl_4) 3030, 2995, 2955, 2930, 2825, 1725, 1580, 1435, 1322, 1300, 1250, 1163, 1040, 1020, 980, 941, 921, 863 cm^{-1}; ^{1}H NMR was identical with that reported in the literature,[42] ^{1}H NMR (CCl_4) δ 6.68 (d, 1, J = 14.7 Hz), 5.63 (d, 1, J = 14.7 Hz), 3.72 (s, 3), and 2.40 (s, 3).

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Registry No. 3a, 74964-44-6; **3b**, 80865-05-0; **3c**, 80865-06-1; **3d**, 61549-51-7; **3e**, 80865-07-2; **3f**, 80865-08-3; **3g**, 80865-09-4; **3h**, 80865-10-7; **4a**, 80865-11-8; **4b**, 80865-12-9; **4c**, 80865-13-0; **4e**, 80865-14-1; **4f**, 80865-15-2; **4g**, 80865-16-3; **4h**, 80865-17-4; **5a**, 74964-53-7; **5b**, 75008-88-7; **5e**, 80865-18-5; **6a**, 80865-19-6; **6b**, 80865-20-9; **10a**, 74964-45-7; **10c**, 80865-21-0; **10d**, 80865-22-1; **10f**, 80865-23-2; **10g**, 80907-71-7; **10h**, 80865-24-3; **11a**, 80865-25-4; **11c**, 80865-26-5; **11f**, 80865-27-6; **11g**, 80865-28-7; **12a**, 74964-46-8; **12c**, 80865-29-8; **12d**, 80865-30-1; **12f**, 80865-31-2; **12g**, 80865-32-3; **12h**, 80865-33-4; **13a**, 80865-34-5; **13c**, 80878-15-5; **13f**, 80865-35-6; **13g**, 80865-36-7; **14a**, 80865-37-8; **14c**, 80865-38-9; **14d**, 80865-39-0; **14f**, 80865-40-3; **14g**, 80865-41-4; **14h**, 80865-42-5; **15**, 74964-47-9; *trans*-**16**, 74985-32-3; *cis*-**16**, 74964-50-4; *trans*-**17**, 74985-30-1; *cis*-**17**, 74964-48-0; *trans*-**18**, 74985-31-2; *cis*-**18**, 74964-49-1; **19**, isomer 1, 80865-43-6; **19**, isomer 2, 80865-44-7; **20**, 80865-45-8; **21**, 80865-46-9; **25**, 80865-47-0; **26**, 80865-48-1; **27**, 80878-16-6; **3b** formate, 80878-17-7; 2-methyl-2-butene, 513-35-9; *trans*-2-butene, 624-64-6; methyl α-chloroacrylate, 80-63-7; methyl α-bromoacrylate, 4519-46-4; methyl α-acetamidoacrylate, 35356-70-8; methyl acrylate, 96-33-3; methyl methacrylate, 80-62-6; dimethyl itaconate, 617-52-7; ethyl α-(bromomethyl)acrylate, 17435-72-2; α-chloroacrylonitrile, 920-37-6; (*E*)-3-methyl-2-pentene, 616-12-6; (*Z*)-3-methyl-2-pentene, 922-62-3; methyl α-(methylthio)acrylate, 43228-10-0; methyl (2S*,4S*)-2-azido-4,5-dimethyl-5-hexenoate, 80865-49-2; methyl *trans*-β-(methylthio)acrylate, 15904-85-5; 1-methylcyclohexene, 591-49-1; (+)-*p*-menthene, 1195-31-9; 1,6-dimethylcyclohexene, 1759-64-4; 1,3-dimethylcyclohexene, 2808-76-6; bicyclo[4.4.0]-1(2)-decene, 1194-95-2.

Supplementary Material Available: Experimental Data for reactions with (*E*)- and (*Z*)-3-methyl-2-pentene and 1-methylcyclohexenes (12 pages). Ordering information is given on any current masthead page.