# Lewis-Acid-Catalyzed Ene Reactions

BARRY B. SNIDER

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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The reaction of an alkene having an allylic hydrogen (an "ene") with a compound containing a double or triple bond (enophile) to form a new bond with migration of the ene double bond and 1,5-hydrogen shift is referred to as the ene reaction (eq 1).[1]   The ene
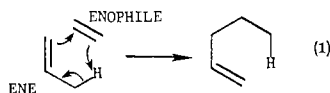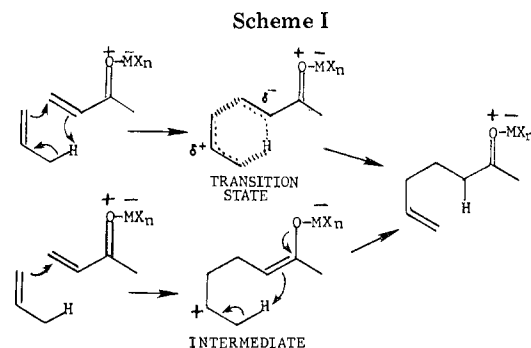

reaction is mechanistically related to the much better known Diels–Alder reaction since both reactions can be concerted, proceeding through cyclic transition states involving six electrons. Unfortunately, the activation energy for an ene reaction is higher than for an analogous Diels–Alder reaction. Therefore ene reactions typically occur at higher temperatures, which has limited the mechanistic exploration and synthetic use of this reaction.

Since the enophile, like the dienophile in a Diels–Alder reaction, should be electron deficient, complexation of Lewis acids to enophiles containing basic groups should accelerate the ene reaction. Extensive development of Lewis acid catalyzed Diels–Alder reactions indicated that this should be a promising approach. However, the greater activation energy of the ene reaction meant that longer exposure to strong Lewis acids at higher temperatures would be required than in a comparable Diels–Alder reaction.

From the standpoint of reaction mechanism, the term "ene reaction" is ambiguous. It has sometimes been defined to refer only to those reactions which are concerted, but other times to describe a reaction which forms an ene-type product, be it by a stepwise or concerted process. We will use the broader definition, in part because it is often difficult to distinguish between concerted and stepwise mechanisms. While it has been elegantly demonstrated that some ene reactions are concerted,[2] some thermal ene reactions clearly proceed through a stepwise mechanism with a diradical intermediate.[1] Lewis acid catalyzed ene reactions can proceed via a stepwise mechanism with a zwitterionic intermediate or a concerted mechanism with a polar transition state (Scheme I). The available evidence suggests that the energetics of the two mechanisms are similar and that the lower energy process varies as a function of ene, enophile, and catalyst.

In 1973, when we first became interested in the possibility of Lewis acid catalysis of ene reactions, only a few sporadic examples involving formaldehyde,[3] electron-deficient aldehydes,[4,5] and intramolecular ene reactions of aldehydes[6,7] had been reported. We found

Barry Snider received his B.S. degree at the University of Michigan in 1970 and his Ph.D. at Harvard University with E. J. Corey in 1973. Following 2 years of postdoctoral work with Ronald Breslow at Columbia University, he joined the faculty at Princeton University where he is Assistant Professor of Chemistry. He is an Alfred P. Sloan Fellow (1979–1981).

Scheme I

that ene reactions of acrylate and propiolate esters could be catalyzed by $AlCl_3$ (eq 2).[8,9]   Recently, we have
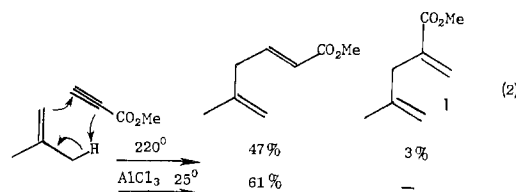
found that the use of alkylaluminum halides, which are proton scavengers, as Lewis acids vastly extends the scope of these reactions.[9b,10]   The ability to study the ene reactions of a wide variety of alkenes under mild conditions led to the discovery that ene reactions can proceed with remarkable regio- and stereoselectivity (eq 3).
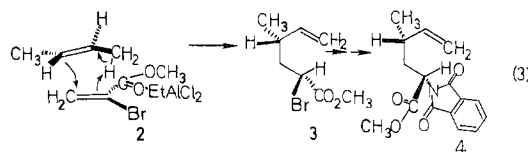
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(9) (a) B. B. Snider, *J. Org. Chem.*, **41**, 3061 (1976); (b) B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.*, **101**, 5283 (1979); (c) H. Feinemann and H. M. R. Hoffmann, *J. Org. Chem.*, **44**, 2802 (1979).

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Catalysts

The choice of Lewis acid depends upon the enophile to be used. Acrylate and propiolate esters require very acidic Lewis acids such as $AlCl_3$ or $EtAlCl_2$.[8,9,11] Acrolein and methyl vinyl ketone (MVK) are much more reactive, and limited success has been achieved with milder Lewis acids such as zinc halides or Me_2AlCl.[12] Numerous Lewis acids have been used with carbonyl compounds; these enophiles are much more susceptible to Lewis acid catalysis since the Lewis acid complexes directly to the reacting double bond. BF_3 and $SnCl_4$ have been used with formaldehyde.[3] Ene reactions of more reactive aldehydes such as chloral can be catalyzed by mild Lewis acids such as $FeCl_3$ as well as by BF_3, $AlCl_3$, $SnCl_4$, or $TiCl_4$.[4] For the reactions of glyoxylate esters, $FeCl_3$ is optimal.[5c] Zinc halides, $TiCl_4$, and $SnCl_4$ are selective catalysts for the ene reaction of citronellal to give isopulegol.[6]

A major problem in Lewis acid catalyzed ene reactions has been proton-initiated side reactions: polymerization of the ene and isomerization of double bonds in the ene or ene adduct. The protic acid may be present as an impurity in the catalyst or formed from traces of water or generated in the ene reaction (e.g., alcohol–Lewis acid complexes produced from carbonyl compounds). Methylenecyclohexane isomerizes partially to 1-methylcyclohexene in the ene reaction with methyl propiolate–$AlCl_3$.[9b] Methyl 5-methyl-5-hexenoate, produced from methyl acrylate and isobutylene with $AlCl_3$ as catalyst, isomerizes to methyl 5-methyl-4-hexenoate under the reaction conditions.[8b] The ene adduct from chloral–$AlCl_3$ and isoprene isomerizes to a dihydropyran under the reaction conditions.[4b]

We have found that the use of alkylaluminum halides prevents proton-catalyzed side reactions, since these compounds act as proton scavengers as well as Lewis acids. For instance, reaction of HX with $RAlCl_2$ gives RH and $AlCl_2X$. Alkylaluminum halides are inexpensive and easy to use as commercially available standardized solutions in heptane. The series $RAlCl_2$, R_2AlCl, and R_3Al provides a series of Lewis acids of predictably decreasing acidity. $EtAlCl_2$ works well with α,β-unsaturated esters.[9b,11] It is almost as acidic as $AlCl_3$ but gives much higher yields of ene adduct since proton-catalyzed isomerization does not occur. Me_2AlCl is a very useful catalyst for the ene reactions of α,β-unsaturated aldehydes and ketones[12] and saturated aldehydes.[10] Not only does it work well with formaldehyde, but other aliphatic and aromatic aldehydes can now be used (eq 4).

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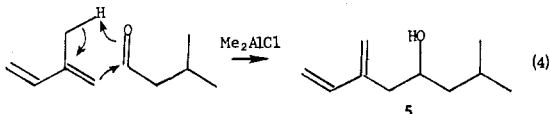
Although the alkyl group of alkylaluminum halides can act as a nucleophile as well as a base, this is not usually a problem with $RAlCl_2$. When the alkyl group of R_2AlCl acts as a nucleophile, it adds to aldehydes to give secondary alcohols. This is a significant complication when unreactive enes are used.[10] This problem is more severe with Et_2AlCl, which can also reduce al-

dehydes, and necessitates the use of more expensive, but less nucleophilic, Me_2AlCl. The use of alkylaluminum halides which are proton scavengers as Lewis acids is generally profitable when the nucleophilicity of the alkyl groups is not a problem.

The amount of Lewis acid required depends on the relative basicity of the enophile and the ene adduct. When an alkynoic ester is the enophile, the ene adduct is an alkenoic ester. Since alkynoic esters are much less basic than alkenoic esters, the product complexes preferentially with the Lewis acid. In these cases optimal yields are often obtained with slightly less than 1 equiv of Lewis acid, while more than 1 equiv of catalyst may lead to byproduct formation. The Me_2AlCl-catalyzed ene reactions of aldehydes require, of course, a full equivalent of catalyst since the ene adduct, an alcohol, reacts with the catalyst. Many ene reactions with reactive enophiles, or with enophiles and ene adducts of comparable basicity, can be successfully carried out with catalytic amounts of Lewis acids.

Two classes of solvents have been successfully used. Reactions are most rapid in halocarbons such as dichloromethane and dichloroethane. When benzene is used as solvent (toluene or chlorobenzene is also suitable), the reaction is slower since the aromatic ring is a weak base. Use of aromatic solvents is necessary in the $AlCl_3$-catalyzed ene reactions of propiolate esters since they minimize proton-catalyzed isomerization, perhaps owing to complexation of HCl to the solvent. Polar solvents such as ethers are not suitable since they complex preferentially to the Lewis acid.

The Ene

Whether the mechanism is stepwise or concerted, it is clear that considerable positive charge is developed at the central carbon of the ene in Lewis acid catalyzed ene reactions. For this reason, alkenes with at least one disubstituted vinylic carbon are much more reactive than mono- or 1,2-disubstituted ethylenes. In this respect, the Lewis acid catalyzed ene reaction differs from thermal ene reactions in which steric accessibility of the double bond and allylic hydrogen are more important. These differences have been elegantly quantified by Salomon, who showed that $\rho = -1.2$ for the thermal ene reaction of para-substituted 1-arylcyclopentenes with diethyl oxomalonate at 150–180 °C, while $\rho = -3.9$ for the reaction catalyzed by $SnCl_4$ at 25 °C.[13] The influences of steric effects in thermal reactions vs. electronic effects in Lewis acid catalyzed reactions are shown in the differing product ratios obtained with diethyl oxomalonate and 6-methyl-1,5-heptadiene (eq 5).

(5)
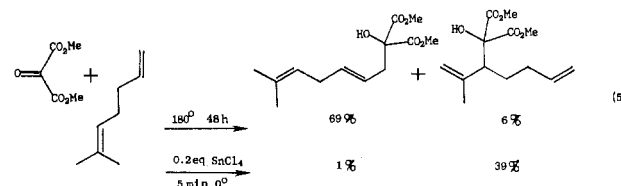
In general, the reactivity order for alkenes in Lewis acid catalyzed ene reactions is 1,1-di- > tri- > tetra-$\gg$ mono- > 1,2-disubstituted ethylenes. However, steric requirements of the enophile can perturb this order.

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Methyl propiolate, with little steric requirement, shows only a 2:1 preference for the 1,1-disubstituted double bond of limonene in Lewis acid catalyzed ene reactions. Aldehydes,[3a,10] methyl acrylate,[14] and acrolein[14] show much higher selectivity. Enophiles such as β-substituted propiolate esters or α-substituted acrylate esters have special steric requirements due to the nature of the transition state.

Side reactions are more prevalent in Lewis acid catalyzed reactions with mono- or 1,2-disubstituted ethylenes. With propiolate esters, cyclobutenes are formed.[9] With carbonyl compounds, chloro alcohols are a major side product.[4d,5c] Ene reactions of monosubstituted ethylenes are often more effectively carried out thermally.

The steric accessibility of the hydrogen abstracted is important. Methyl and methylene hydrogens are abstracted much more easily than methine hydrogens. The relative ease of abstraction of methyl and methylene hydrogens depends on the enophile, probably because of differing mechanisms. With methyl propiolate, methyl and methylene hydrogens are abstracted with equal rates. With formaldehyde, methylene hydrogens are abstracted more easily, perhaps due to product development control of the 1,5-hydrogen shift of a zwitterionic intermediate.

The Enophile

Methyl propiolate undergoes thermal ene reactions with isobutylene and 1-hexene at 220 °C.[15b] The same enophile reacts at 25 °C with a wide variety of alkenes to give good yields of 1:1 adducts in the presence of 1 equiv of $AlCl_3$ or $EtAlCl_2$.[9] 1,1-Disubstituted, trisubstituted, and tetrasubstituted ethylenes give exclusively ene adducts (eq 2), 1,2-disubstituted ethylenes give exclusively stereospecific cycloaddition (eq 6), and

(6)
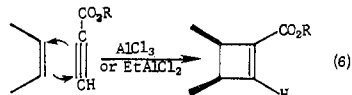
monosubstituted ethylenes give mixtures of ene adducts and cyclobutenes. Ethynyl *p*-tolyl sulfone undergoes similar reactions with $EtAlCl_2$ as catalyst.[16] Use of $ZnCl_2$ as catalyst permits the isolation of similar products from 3-butyn-2-one.[17]

β-Substituted propiolate esters were investigated in the hope that the ene reaction would provide a stereospecific trisubstituted ethylene synthesis. Not surprisingly, methyl tetrolate and methyl phenylpropiolate are unreactive, since the substituents are large and electron donating. Methyl chloro- or bromopropiolate and dimethyl acetylenedicarboxylate (DMAD), with electron-withdrawing substituents, are reactive when $AlCl_3$ or $EtAlCl_2$ is used as catalyst.[18] Depending on the alkene substitution pattern, ene adduct and/or cyclobutene are obtained. In the ene reaction a hy-

Scheme II

drogen is transferred selectively from the alkyl group anti to an alkenyl hydrogen (eq 7).

(7)

Methyl acrylate reacts with isobutylene at 230 °C to give ene adduct.[15] When $AlCl_3$ or $EtAlCl_2$ is used as catalyst, good yields of ene adducts can be obtained from reactive alkenes at 25 °C in benzene solution.[8] Acrylate esters substituted in the α position with an electron-withdrawing group such as chlorine are an order of magnitude more reactive.[11] These enophiles react selectively with the carbomethoxy group endo and transfer a hydrogen from the alkyl group syn to the alkenyl hydrogen (eq 7).

Methyl vinyl ketone (MVK) and acrolein can also be used as enophiles with reactive alkenes.[12] With MVK and Me_2AlCl, reaction occurs at -20 °C to give a moderate yield of the ene adduct 7. At room temperature

7, R = Me   8, R = Me   9, R = Me
                               10, R = H
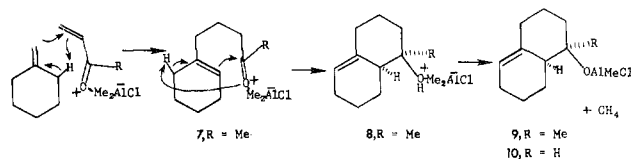
the ene adduct undergoes an intramolecular ene reaction with the complexed ketone functioning as the enophile. The alcohol–Me_2AlCl complex 8 which results reacts further to give methane and the aluminum alkoxide 9, thereby protecting the tertiary alcohol from solvolysis. Acrolein is even more reactive, giving the double ene adduct 10 at -78 °C.

Carbonyl Compounds. Aldehydes have been used extensively as enophiles in Lewis acid catalyzed ene reactions. Electron-deficient aldehydes, such as chloral and alkyl glyoxylates, and dialkyl oxomalonates react with a variety of alkenes.[4,5,13] Formaldehyde undergoes BF_3- or $SnCl_4$-catalyzed reactions with 1,1-di- or trisubstituted ethylenes, although double bond isomerization is often a problem.[3]

We have recently found that Me_2AlCl catalyzes the ene reaction of formaldehyde with all types of alkenes[10] and even terminal alkynes, which give α-allenic alcohols.[19] Use of Me_2AlCl permits aliphatic and aromatic aldehydes to be used as enophiles with alkenes possessing a disubstituted vinylic carbon (eq 4). With less reactive alkenes, aldol condensation and addition of a methyl group to the aldehyde occur exclusively. The success of Me_2AlCl as a catalyst is due to the further reaction of the ene adduct–Me_2AlCl complex to give
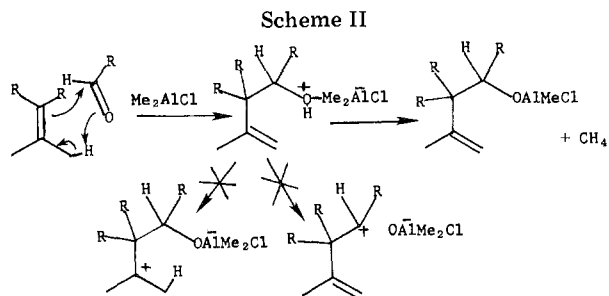
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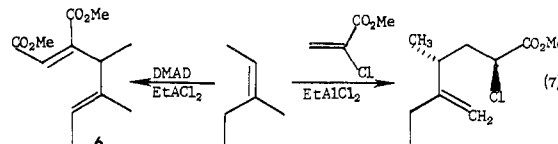
(16) B. B. Snider, T. C. Kirk, D. M. Roush, and D. Gonzalez, *J. Org. Chem.*, in press.

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(18) (a) B. B. Snider and D. M. Roush, *J. Am. Chem. Soc.*, **101**, 1906 (1979); (b) B. B. Snider, D. M. Roush, D. J. Rodini, D. Gonzalez, and D. Spindell, *J. Org. Chem.*, **45**, 2773 (1980); (c) A. W. McCulloch and A. G. McInnes, *Tetrahedron Lett.*, 1963 (1979).
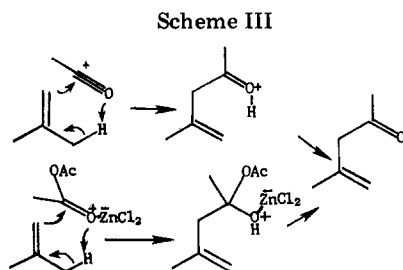
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Scheme III

Scheme IV

methane and an aluminum alkoxide. This prevents proton catalyzed rearrangements and solvolysis (see Scheme II).

Lewis acid catalyzed intramolecular ene reactions of unsaturated carbonyl compounds have been extensively studied.[1b,7,12] Two types of reaction are generally useful. Aldehyde 11 undergoes an ene reaction at 150 °C or with Lewis acid catalysis at -78 °C. Aldehyde 12 be-

11, n= 4
12, n= 3

13, n= 3
14, n= 4
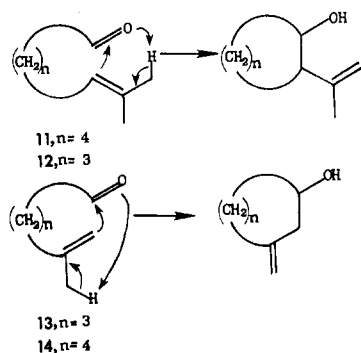
haves similarly with Lewis acid catalysis at -78 °C, although the resulting cyclopentanol undergoes a facile retro-ene reaction on warming. Cycloheptanols cannot be formed by this reaction.[7] Aldehydes 13 and 14 react thermally or with Lewis acid catalysis to give 6- and 7-membered rings. The analogous ketones undergo similar reactions, but the products cannot be isolated unless Me_2AlCl is used as the Lewis acid since the tertiary alcohol is not stable to the reaction conditions. With Me_2AlCl, ene adducts can be isolated since the alcohol is protected from solvolysis by conversion to an aluminum alkoxide (e.g., 8 to 9).

Friedel–Crafts acylation of alkenes to give β,γ-unsaturated ketones has been considered a Lewis acid catalyzed ene reaction. These reactions can be carried out by treating an alkene with $ZnCl_2$ and acetic anhydride[20] or with acetylium salts[21] in the presence of hindered amines (Scheme III). The initial ene adducts are hemiacylals or protonated ketones which lose acetic acid or H^+ to give the isolated product.

Mechanism and Stereochemistry

Lewis acid catalyzed ene reactions can proceed through a two-step mechanism with a zwitterionic intermediate or via a concerted mechanism (see Scheme I). It is likely that those reactions which are concerted proceed through a very asymmetric transition state with carbon–carbon bond formation far advanced and hydrogen shift just under way. Such a transition state is hard to distinguish from a short-lived intermediate. Mechanistic information can be obtained from isotope effects or analyses of product mixtures. However, these
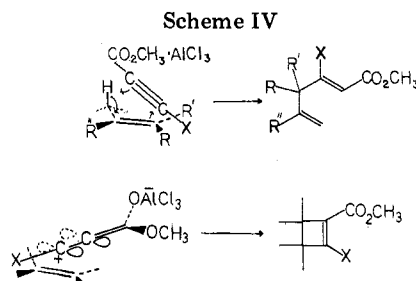
data must be interpreted cautiously since minor changes in Lewis acid, ene, or enophile can, and do, lead to changes in mechanism. A general rule is that the more reactive the ene or enophile–Lewis acid complex, the more likely the reaction is to be two step. Present evidence suggests that most reactions of acrylate or propiolate derivatives are concerted and that most reactions of carbonyl compounds are stepwise.

The reactions of propiolate derivatives proceed through two competing concerted[9,18] reactions—an ene reaction and a stereospecific $[_{\pi}2_s + _{\pi}2_a]$ cycloaddition (Scheme IV). The ratio of products varies with the β substituent on the propiolate in a manner which is not consistent with a stepwise reaction proceeding through a common intermediate. 2,3-Dimethyl-2-butene gives ene adduct with methyl propiolate in 90% yield and cyclobutene in 76% yield with methyl chloropropiolate. Examination of models for the transition state required for a concerted ene reaction indicates that for R = CH_3 and X = Cl, steric hindrance retards the ene reaction, while if X = H, steric hindrance is much less severe. While the size of the X group is not a factor in the [2 + 2] cycloaddition, the electronic character of the X group is important. β-Halogen atoms, which stabilize the vinyl cation resonance form by resonance, favor cycloaddition, while the β-carbomethoxy group retards cycloaddition.

The fact that ene reaction between methyl chloropropiolate and 2,3-dimethyl-2-butene fails to occur, due to steric hindrance between R and Cl, suggests that ene reactions of β-substituted propiolates should selectively transfer the hydrogen on the alkyl group anti to the alkenyl hydrogen. This was observed. Because the carbomethoxy group is larger than chloride, DMAD is even more selective, reacting, for instance, with (Z)-3-methyl-2-pentene to give almost exclusively 6.

The thermal ene reactions of methyl propiolate and methyl acrylate give mixtures of ene adducts containing 6–20% of adducts such as 1.[15b] This minor product corresponds to the 1,3-disubstituted cyclohexenes formed as minor products in Diels–Alder reactions. As in the Diels–Alder reactions, the use of Lewis acid catalysts increases selectivity (see eq 1).

The $[_{\pi}2_s + _{\pi}2_a]$ cycloaddition of propiolate esters has a less polar transition state than the ene reaction as indicated by the reactions of 1-alkenes which give almost 1:1 mixtures of regioisomeric cyclobutenes. Except where steric effects interfere, ene reaction predominates with alkenes containing a disubstituted vinylic carbon which can lead to a transition state with partial tertiary carbenium ion character. With monosubstituted ethylenes, ene reaction is much slower, allowing cycloaddition to compete, while with 1,2-disubstituted ethylenes steric hindrance to an ene reaction makes cycloaddition the exclusive reaction.

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(21) H. M. R. Hoffmann and T. Tsushima, *J. Am. Chem. Soc.*, 99, 6008 (1977).

We investigated the use of methyl α-haloacrylates as enophiles since they should be more reactive than acrylate esters. To our surprise, these reactions proceed regio- and stereoselectively.[11] The major product (85–100%) is formed via the transition state in which the carbomethoxy group is endo (e.g., 2). With 1,2-di- and trisubstituted ethylenes this leads to the control of stereochemistry in a 1,3 relationship. The stereochemistry was proven by conversion of the adduct 3, obtained from *trans*-2-butene, to the known phthalimide 4,[22a] whose stereochemistry had been unambiguously established. The selective formation of the product with the carbomethoxy group endo is similar to that observed in Diels–Alder reactions, probably for similar electronic reasons. Since attempted thermal ene reactions of methyl α-chloroacrylate give only polymer, the effect of the Lewis acid on their stereochemistry cannot be determined.

The ene reactions of α-haloacrylate esters with trisubstituted ethylenes are also regiospecific. Contrary to what happens with propiolate esters, transfer of a hydrogen occurs predominantly (90–100%) from the alkyl group syn to the vinylic hydrogen (see eq 7). This is due to steric interaction of the exo substituent with the substituent on the less substituted end of the ene, which is minimized if the substituent is hydrogen (15) rather than carbon (16). This regioselectivity is general
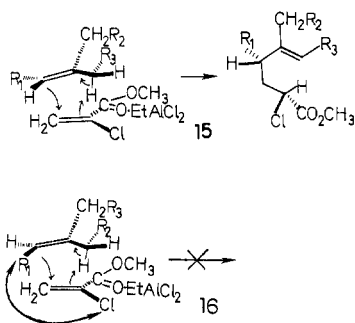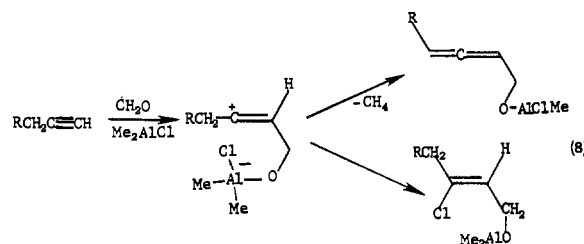

for acrylate esters, although there is also a preference for the formation of the more stable double bond. The high regio- and stereoselectivity suggests that these reactions are concerted.

Although Lewis acid catalyzed ene reactions of carbonyl compounds may be concerted in some cases, most of these reactions are probably a special case of the Prins reaction, in which a protonated aldehyde adds to an alkene to give a carbenium ion which rearranges, or reacts with water to give a 1,3-diol or with the oxygen of another aldehyde to give a *m*-dioxane.[23] The ene adduct will be formed in high yield from the carbenium ion when a 1,5-hydrogen shift is geometrically favorable, when other rearrangements are not energetically favored, and when no nucleophiles are present. One of the reasons for the success of the Me₂AlCl-catalyzed ene reactions of aldehydes is that the aldehyde is fully complexed by the equivalent of Lewis acid used so that *m*-dioxanes cannot be formed.

When metal chlorides are used as Lewis acids, formation of γ-chloro alcohols from mono- and 1,2-disubstituted ethylenes is a problem. This was observed with chloral and AlCl₃[4b] and methyl glyoxylate and FeCl₃.[5c]

This is due to attachment of chloride to the secondary carbenium site in the intermediate before the 1,5-hydrogen shift has occurred. Chlorides may also be formed from intermediates with tertiary carbenium sites. However, they are likely to be unstable to the reaction conditions, giving ene adducts by elimination of HCl. With BF₃ as catalyst, halide incorporation will not occur, but *m*-dioxanes can be formed.

With Me₂AlCl and formaldehyde, products other than ene adducts are obtained when rearrangement is facile or when a 1,5-hydrogen shift is geometrically disfavored. Cyclohexene gives a mixture of unsaturated alcohols. 1-Alkynes give 2:3 mixtures of ene adducts and (Z)-3-chloroallylic alcohols which result from intramolecular delivery of chloride to a vinyl cation (eq 8). 1,4-Cyclohexadiene gives only 6-chloro-3-cyclo-

hexen-1-ylmethanol. β-Pinene undergoes a thermal ene reaction with formaldehyde in high yield at 180 °C[24] With Lewis acid catalysis, mixtures of ene adduct and rearrangement products are formed, with milder Lewis acids giving a greater percentage of ene adduct.

The stereochemistry of ene reactions of maleic anhydride, methyl glyoxylate, and chloral, which establish stereochemistry in a 1,2 relationship, have also been studied. In thermal reactions an 80–90% preference for endo addition is observed with *cis*-2-butene and methyl glyoxylate[5c] or maleic anhydride.[25] With *trans*-2-butene, 50–60% of the endo adduct is formed. The FeCl₃-catalyzed reactions of methyl glyoxylate give a greater percentage of exo adduct, probably due to steric hindrance between the ene and the Lewis acid in the endo transition state. Gill has examined the ene reactions of chloral with β-pinene.[4c] The thermal reaction gives 82% of the exo adduct 17, presumably due
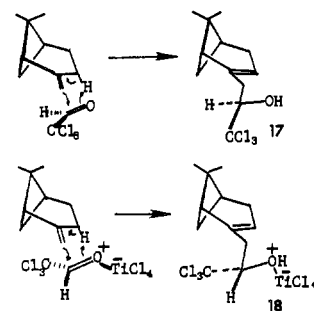
to steric hindrance in the endo transition state. With TiCl₄ as catalyst, 100% of the endo adduct 18 is formed. Presumably the TiCl₄ complexes to the carbonyl anti to the trichloromethyl group. Since TiCl₄ is large, it adds exo, forcing the trichloromethyl group to be endo.

Uskoković and Wovkulich have observed regioselectivity in the BF₃-catalyzed ene reactions of formaldehyde with 19 and 20.[26] The regioselectivity has the

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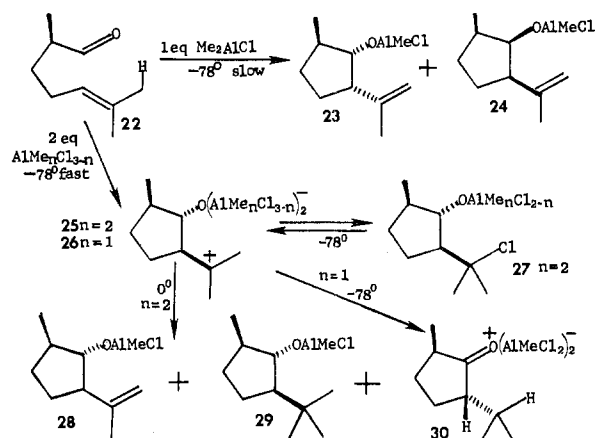
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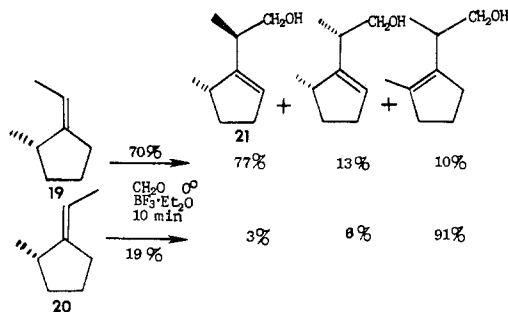
same origin as that observed with methyl α-chloroacrylate, i.e., minimization of steric interaction between the substituent on the less substituted end of the ene and the Lewis acid which is presumably exo as with chloral–TiCl$_4$ and β-pinene.

Although deuterium isotope effects are a valuable tool for exploring the mechanism of Lewis acid catalyzed ene reactions, only two cases have been reported to date. The kinetic isotope effect of 2.64 obtained in the ene reaction of methyl propiolate and $(CD_3)_2C=C(CH_3)_2$ with AlCl$_3$ suggests a concerted mechanism since secondary isotope effects in stepwise ene reactions are much smaller[9] (vide infra). Beak has shown that the ene reactions of Ac$_2$O·ZnCl$_2$ with alkenes to give β,γ-unsaturated ketones (Scheme III) are stepwise.[20] The intermolecular isotope effect with methylenecyclohexane and methylenecyclohexane-2,2,6,6,-d_4 is 1.0 ± 0.3. This indicates that the reaction is stepwise or that the reaction is concerted, with hydrogen transfer not far advanced in the transition state. The intramolecular isotope effect with methylenecyclohexane-2,2-d_2 is 3.2 ± 0.7, indicating that the reaction is proceeding by rate-determining carbenium ion formation followed by a 1,5-hydrogen shift.

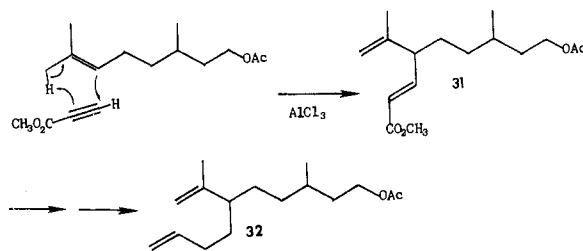The sensitivity of the mechanism to minor perturbations in conditions is illustrated by the reactions of 2,6-dimethyl-5-heptenal (22) with Lewis acids.[27] Reaction with 1 equiv of Me$_2$AlCl gives a 2:1 mixture of 23 and 24 in 50% yield. The reaction is probably concerted, since Oppolzer has shown that cis substitution results from kinetically controlled ene reactions which form 5-membered rings.[1b] When 2 equiv of Me$_2$AlCl is used, a more rapid reaction occurs to give 25 which reacts to give 27 at -78 °C and 28, 29 and 30 at 0 °C. Use of 2 equiv of MeAlCl$_2$ or BF$_3$[28] gives the

ketone 30, obtained from 26 by two 1,2-hydride shifts. A chloride may be formed as an intermediate with MeAlCl$_2$, but it is not stable to these more acidic conditions, reacting to give 22 or 26.

Synthetic Utility

Lewis acid catalyzed ene reactions appear to have general synthetic utility. They occur at moderate temperatures and, by the use of alkylaluminum halides, can be carried out on substrates which are unstable in the presence of Brønsted acids. The ene reactions of methyl propiolate will tolerate ester, ether, nitro, nitrile, alcohol and trifluoroacetamide groups in the ene.[9] When alcohols are protected as acetate esters, a second equivalent of Lewis acid may be required. This can be avoided by using a less basic ester, such as trifluoroacetate, as the protecting group. The generality of the CH$_2$O·Me$_2$AlCl ene reaction, the regiochemical control with β-substituted propiolate esters, the stereochemical control with α-substituted acrylate esters, and the regiochemical control with enophiles with a substituent exo on the atom to which hydrogen is transferred should be generally useful.

Lewis acid catalyzed ene reactions have seen considerable use in natural product synthesis. Reaction of methyl propiolate with citronellyl acetate and AlCl$_3$ gives 31, an intermediate for the synthesis of the A1 component of the female sex pheromone of the California red scale (32).[29] Reaction of isoprene, isovaleraldehyde, and Me$_2$AlCl gives ipsenol (5), a component of the pheromone of *Ips confusus*.[10] Ene reaction of formaldehyde with methyl 6-heptynoate using methylaluminum sesquichloride gives 33, an antibiotic
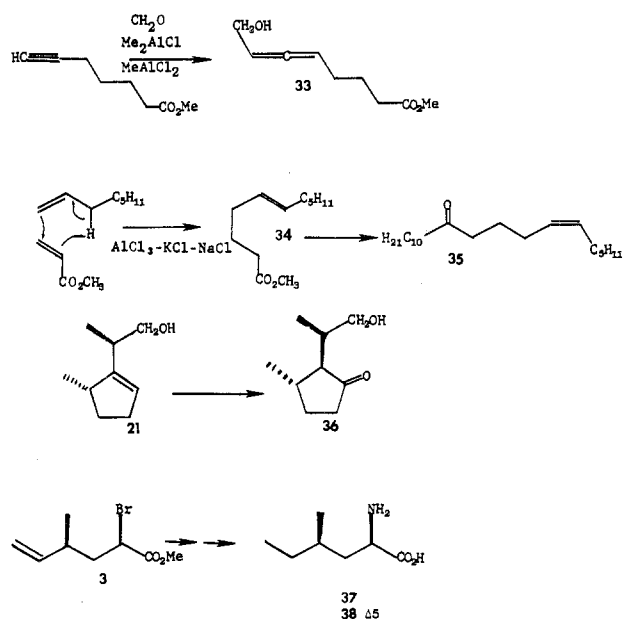
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(27) M. Karras and B. B. Snider, *J. Am. Chem. Soc.*, in press.
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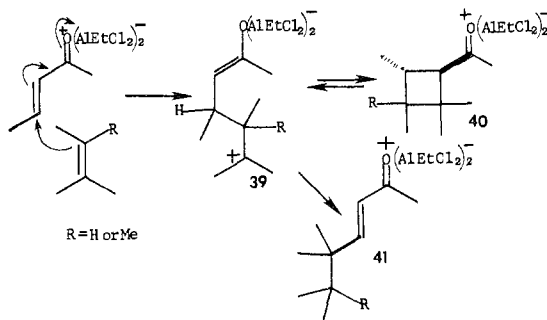(29) B. B. Snider and D. J. Rodini, *Tetrahedron Lett.*, 1399 (1978).

isolated from *Sapium japonicum*.[19] Reaction of methyl acrylate with 1-octene and the $AlCl_3/NaCl/KCl$ eutectic at 100 °C gives 34, an intermediate for the synthesis of the sex pheromone of the Douglas fur tussock moth (35).[8d] Alcohol 21 has been converted to 36,[26] an intermediate for the synthesis of the Prelog–Djerassi lactone.[30] The ene adduct 3 has been used for the stereospecific synthesis of the naturally occurring amino acids 37 and 38.[11,22] Lewis acid catalyzed intramolecular ene reactions have been used extensively, including the syntheses of junenol (eq 9), kessanol, and β-vetivone.[31]

(9)

Junenol
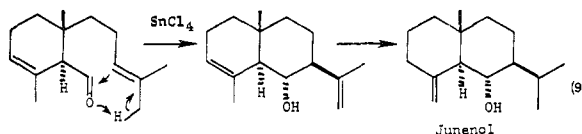
Side Reactions

Side reactions can be classified into two categories—competing concerted reactions and competing reactions from a zwitterionic intermediate. The $[_\pi 2_s + _\pi 2_a]$ cycloadditions of propiolate esters are an example of the former, as may be the reactions of aldehydes with isoprene to give Diels–Alder and ene adducts. The reactions of 22 give some idea of the possible reactions available to the zwitterionic intermediates.

Attempted extensions of the ene reactions of acrolein and MVK to β-alkyl-substituted analogues led to the development of a novel series of reactions. Although MVK undergoes ene reactions with Me_2AlCl, 3-penten-2-one does not react with alkenes, even in the presence of 1 equiv of $EtAlCl_2$. When 2 equiv of $EtAlCl_2$ is used, reversible reaction occurs to give a zwitterion 39 which collapses reversibly to the cyclo-

R = H or Me

butyl methyl ketone 40 and undergoes two 1,2-methyl or -hydride shifts to give 41.[32] This reaction is general for β-monosubstituted α,β-unsaturated carbonyl compounds. The related intramolecular reactions are more general and provide a novel variant of the cation–olefin cyclization.[33]

Related Reactions

The reagents used as enophiles will react with very nucleophilic double bonds, such as enamines, in the absence of catalyst. These reactions are stepwise and give cyclobutanes as well as ene adducts. With enol ethers, reaction does not occur in the absence of catalyst. Untch and Clark have shown that $TiCl_4$ will catalyze the [2 + 2] cycloaddition of methyl propiolate to enol silyl ethers.[34] Sakurai has explored the Lewis acid catalyzed reactions of allylsilanes with ketones and α,β-unsaturated ketones.[35,36] The products are those that would be obtained from the ene reaction with propylene.

Outlook

Lewis acid catalyzed ene reactions have been shown to have a broad scope, which complements thermal ene reactions. These studies have demonstrated that Lewis acid catalyzed ene reactions can occur with strong stereocontrol, which should be exploited and developed. Further mechanistic work, especially kinetic isotope effect studies, is needed to fully understand these reactions. Further development of reactive enophiles and selective catalysts will lead to increased synthetic use of the reaction.

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