Dimethylaluminum Chloride Catalyzed Ene Reactions of Aldehydes

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Abstract: Dimethylaluminum chloride, which is a mild Lewis acid and a proton scavenger, catalyzes the ene reactions of aliphatic and aromatic aldehydes with alkenes containing a disubstituted vinylic carbon. Proton-initiated rearrangements do not occur, since the alcohol-Lewis acid complex formed in the ene reaction reacts rapidly to give methane and a nonacidic aluminum alkoxide. Formaldehyde and excess Me₂AlCl give good yields of ene adducts with all types of alkenes. With 1 equiv of Me₂AlCl, formaldehyde and mono- and 1,2-disubstituted alkenes give γ -chloro alcohols resulting from cis addition of chlorine and hydroxymethyl groups to the double bond.

The ene reaction of carbonyl compounds with alkenes is a potentially valuable route to homoallylic alcohols.² With reactive, i.e., electron deficient, aldehydes such as chloral or methyl glyoxylate, these reactions can be carried out thermally at 100-200 °C.^{3,4} Formaldehyde reacts with alkenes at 180 °C with optimal yields often being obtained when acetic acid-acetic anhydride is the solvent.5

In the presence of acid, aldehydes and alkenes undergo the Prins reaction.⁶ Stepwise addition of the alkene to the aldehyde gives a carbenium ion intermediate which can lose a proton to give an ene-type product, react with nucleophiles present in solution, or react with another molecule of aldehyde to give a m-dioxane. 1,3-Diols and *m*-dioxanes are the major product in aqueous acid. Ene-type products have been obtained from Lewis acids, formaldehyde, and alkenes which can give a tertiary carbenium ion.⁷ Methyl glyoxylate³ and chloral⁴ react with a wide variety of alkenes to give ene adducts in the presence of Lewis acids. Unfortunately, formation of γ -chloro alcohols by incorporation of a chlorine from the Lewis acid is a serious problem with alkenes which give a secondary carbenium ion.

We have found that dimethylaluminum chloride (Me₂AlCl), in equivalent or greater amounts, is a useful catalyst for the ene reactions of aliphatic and aromatic aldehydes and leads to improved yields of ene adducts from formaldehyde.⁸ Me₂AlCl is a mild Lewis acid and a proton scavenger. A problem with Lewis acid catalyzed ene reactions of aldehydes is that the alcohol-Lewis acid complex produced in the reaction is susceptible to solvolysis and is a strong protic acid capable of protonating the double bond of the ene adduct or alkene. The alcohol-Me₂AlCl complex formed in the reaction decomposes rapidly to give methane and

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Table I. Me, AlCl Catalyzed Ene Reactions of Aldehydes Other Than Formaldehydea



^a 1.5 equiv of Me₂ AlCl was used in all cases. ^b Pivalaldehyde gives only 3,3-dimethyl-2-butanol. ^c Benzaldehyde gives only 1phenylethanol.

a nonbasic aluminum alkoxide which does not undergo these side reactions.

These reactions are Prins reactions. A zwitterionic intermediate is formed which selectively undergoes a 1,5-proton shift to give the ene adduct Me_2AlCl complex which loses methane (eq 1). Formation of a chloro alcohol as a byproduct is observed when the carbenium ion is secondary. However, in the presence of excess Me₂AlCl, the chloro alcohol is unstable, forming ene adduct in the case of acyclic alkenes and a complex mixture from cyclic alkenes.

The methyl group of Me₂AlCl can also act as a nucleophile. It is remarkable that any alkene is more nucleophilic toward the

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R = H, R' = H or alkvl; R = alkvl, $R' \neq H$

aldehyde than the methyl group. Addition of the methyl group to the aldehyde occurs in some cases, limiting the scope of the reaction.

Results and Discussion

Alkyl- and Aryl-Substituted Aldehydes. The results of the Me₂AlCl catalyzed reactions of alkyl- and aryl-substituted aldehydes with alkenes are shown in Table I. Moderate to good yields of ene adducts are obtained from alkenes which can give a tertiary carbenium ion.

1,1-Disubstituted alkenes are the most reactive class of alkenes. Good to excellent yields of ene adduct 1 are obtained from methylenecyclohexane and acetaldehyde (or paraldehyde), isovaleraldehyde, pivalaldehyde, or benzaldehyde as well as formaldehyde (as trioxane or paraformaldehyde). Since methylenecyclohexane is easily isomerized to 1-methylcyclohexene, the success of these reactions indicates the effectiveness of Me₂AlCl as a proton scavenger.

Ene reactions with tri- and tetrasubstituted double bonds also occur readily. However, due to the slower rates of these reactions, two competing reactions are also observed. Addition of a methyl group to the aldehyde leads to alcohols. This problem becomes more serious as the alkene is made more hindered (compare yields of 2, 6, and 9). Hindered and aromatic aldehydes react primarily via methyl group addition. With aliphatic aldehydes, acid-catalyzed aldol reactions also lead to byproducts. The aldol condensation has limited the use of aliphatic aldehydes in the Prins reaction.⁹ The byproducts formed in Me₂AlCl-catalyzed ene reactions are easily removed by distillation, since the methyl addition product is much more volatile, and the aldol product less volatile, than the ene adduct. Alkenes which would give a secondary carbenium ion do not react with aldehydes other than formaldehyde.

The ene reaction of isovaleraldehyde with isoprene provides a one-step synthesis of ipsenol (3), a pheromone of the bark beetle Ips confusus.¹⁰ Treatment of isovaleraldehyde with isoprene gives a 16% yield of ipsenol (3) and a 60% yield of Diels-Alder adduct 4,¹¹ which is related to nerol oxide and rose oxide.¹¹ The 3/4 ratio does not change during the course of the reaction. The related reaction of chloral with isoprene, catalyzed by AlCl₃, has been studied by Gill.4c Similar products were obtained in varying ratios, since the ene adduct was converted to the dihydropyran during the reaction by protonation to give an allylic carbenium ion which closes to give the dihydropyran.^{4c} Use of Me₂AlCl allows the isolation of acid-sensitive ipsenol, since protic acids are not present in the reaction mixture.

The formation of 4 indicates that Me₂AlCl is a useful catalyst for the synthesis of dihydropyrans by the Diels-Alder reactions of aldehydes with dienes. The use of formaldehyde or aromatic aldehydes as dienophiles is well-known.¹² The reaction of isoprene with acetaldehyde for 24 h at 150 °C has been reported to give a 4% yield of Diels-Alder adduct.13

The reaction of methylenecyclobutane with isovaleraldehyde gives 5 in 43% yield. Cyclobutene 5 has previously been synthesized by longer routes and converted to ipsenol by pyrolysis.¹⁴

The reaction of aldehydes with limonene occurs exclusively at the less substituted double bond as reported by Blomquist for the reaction with formaldehyde.^{7a} Lewis acid catalyzed reactions of methyl propiolate with limonene show only slight (×1.5) preference for the less substituted double bond, presumably due to the smaller steric bulk of the acetylene.¹⁵ Isovaleraldehyde and limonene give a 70% yield of 2b, an intermediate in Crawford's synthesis of dihydro-ar-turmerone.16

Formaldehyde. Formaldehyde is a more versatile enophile, reacting, even with mono- and 1,2-disubstituted alkenes, in the presence of Me₂AlCl to give good yields of ene adducts (see Table II). The 1,2-disubstituted double bonds formed in these reactions are ca. 90% trans. The results with terminal alkenes contrast favorably with Blomquist's report of a 17% yield of 3-octen-1-ol from the reaction of heptene and formaldehyde for 60 h in acetic acid at 190 °C.5

When 1 equiv of Me₂AlCl was used, chloro alcohols were formed as byproducts. When 1.5-2 equiv of Me₂AlCl was used, chloro alcohols were formed as transient intermediates. With acyclic alkenes they are converted to the ene adducts. With cyclopentene and cyclohexene, a mixture of products is formed. The nature of this reaction is discussed in more detail later.

The chloro alcohols formed from 1,2-disubstituted alkenes result from the stereospecifically cis addition of the hydroxymethyl group and the chloride to the double bond. Since all previous Prins reactions have been shown to proceed predominantly by trans addition,⁶ the determination of stereochemistry is discussed in detail.

cis- and trans-2-butene each give a single chloro alcohol, 12a and 11a respectively. These compounds have been obtained with the opposite, trans stereoselectivity by Stapp and Weinberg from 2-butene, paraformaldehyde, and hydrogen chloride.¹⁷ They assigned stereochemistry based on the coupling constant for the methine protons, which is 6.5 Hz for the $2R^*, 3S^*$ isomer 11a and 3.0 Hz for the $2R^*$, $3R^*$ isomer 12a. The spectral data and melting points of the dinitrobenzoates leave no doubt that the stereochemistry of addition with Me₂AlCl is opposite to that with hydrogen chloride.

The stereochemistry of **11b**-*d* and **12b**-*d* is assigned by analogy. In addition, the relative chemical shifts of the methine and methyl protons are consistent with the NMR spectra of 11a and 12a.

The stereochemistry of *cis*-2-chlorocyclohexanemethanol (14b) is assigned from the proton and ¹³C NMR spectrum. The proton α to the chlorine absorbs at δ 4.6 ($W_{1/2} = 8$ Hz). The downfield shift from chlorocyclohexane (δ 3.95) is consistent with that expected for a substituent trans to the methine hydrogen and a change in conformation making the hydrogen equatorial. The $W_{1/2}$ is consistent only with an equatorial hydrogen, which would be present in the cis but not the trans isomer. The ¹³C NMR spectrum shows the upfield γ shifts relative to cyclohexane-

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Table II. Me₂AlCl-Catalyzed Ene Reactions of Formaldehyde with Mono- and 1,2-Disubstituted Alkenes

alkene	equiv of Me₂AlCl	products, % yield
RCH2 CH2R'		$HO - CH_2R' + \frac{RCH_2}{H} + \frac{H}{H} + \frac{H}{H$
a, $R = R' = H$ b, $R = R' = CH_2CH_3$ c(d), ^b $R = n$ -Pr, $R' = H$	1 1.5 1 1.5	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
R'CH ₂		$HO - CH_2R' + R'CH_2 - HCI -$
a, $R = R' = H$ b, $R = R' = CH_2CH_3$ c(d), ^b $R = n$ -Pr, $R' = H$	1 1 1.5 1	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
(CH2)		$(CH_{2})_{0} \rightarrow OH + (CH_{2})_{0} + (CH_{2}OH + (CH_{2})_{1})_{CH_{2}OH} + (CH_{2})_{1} + (CH_{2}OH + (CH_{2})_{0})_{CH_{2}OH} + (CH_{2})_{0} + (CH_{2})_{0} + (CH_{2}OH + (CH_{2})_{0})_{CH_{2}OH} + (CH_{2})_{0} + (C$
a, n = 2	1 2	13a (7), 14a (39), 15a (1) 13a (10), 14a (4), 15a (44), 16a (10)
b, <i>n</i> = 3	1 1.5	$13b (36), 14b (17) 13b (54), 14b (3), 15b (8),c 16b (24) \checkmark 4^{C_1}$
	1	18 (46)
		(I) + (I)
C5H11	1	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
	1 2 1.4 ^d 1 ^e	73 <i>a</i> 8 80 <i>a</i> 0 30 <i>a</i> 90 <i>a</i>
$\bigcirc $		
	1	24 (72)

^a 9:1 trans cis ratio. ^b d and the yields in parentheses refer to the compounds with R and R' switched. ^c This isomer decomposes slowly during the course of the reaction. ^d Et₂AlCl. ^e EtAlCl₂.

methanol¹⁸ expected for an axial chloride.¹⁹ Reaction of cyclohexene with formaldehyde and hydrogen chloride gave a chloro alcohol, assigned the trans stereochemistry based on mechanistic arguments, whose dinitrobenzoate melted at 86 °C.²⁰ The dinitrobenzoate of 14b melts at 120 °C.

The stereochemistry of 18 is assigned from the coupling constants of <3 Hz for the methine protons as determined by decoupling and the ¹³C NMR spectrum which shows the upfield γ

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shifts relative to 3-cyclohexene-1-methanol, expected for a pseudoaxial chloride.19

The stereochemistry of 14a was determined by analysis of the NMR signals of the downfield protons. The proton α to the chlorine absorbs δ 0.18 downfield from the same proton of chlorocyclopentane. The methylene group α to the alcohol absorbs δ 0.25 downfield from the same protons of cyclopentanemethanol. For the same protons, cis-2-hydroxycyclopentanol has shifts of δ 0.04 downfield and δ 0.23 downfield, relative to cyclopentanol and cyclopentanemethanol, respectively, while the trans isomer has shifts of δ 0.30 upfield and δ 0.12 downfield, respectively.²¹ This spectroscopic argument would be strengthened by comparison with the trans isomer. Stapp and Randall reported that cyclopentene, formaldehyde, and hydrogen chloride gave primarily one isomer which was assigned trans by analogy to cyclohexene. Repetition of their procedure gave primarily the same isomer obtained with Me₂AlCl. Fortunately, small amounts of the trans isomer could be isolated by preparative GC. The shifts of δ 0.38 upfield and δ 0.15 downfield, respectively, confirm the stereochemical assignment of 14a.

The Prins reaction of formaldehyde with hydrogen chloride proceeds with primarily trans addition to acyclic alkenes and cyclohexene but with cis addition to cyclopentene. The anomalous behavior of cyclopentene has been previously noted.²²

Mechanism. The formation of chloro alcohols suggests that these reactions proceed through a zwitterionic intermediate. Due to the absence of nucleophiles in the medium these reactions are more selective than typical Prins reactions, usually giving primarily ene adduct. m-Dioxanes, a common product of the Prins reaction, are not formed because the aldehyde cannot act as a nucleophile since it is fully complexed to Me₂AlCl. The only nucleophiles present are the ligands on the aluminum. The methyl group of Me₂AlCl is not sufficiently nucleophilic to add to the carbenium ion. The chloride does add intramolecularly to the carbenium ion resulting in the stereospecific cis addition of a hydroxymethyl group and chloride to the double bond. Secondary chlorides are isolated. Tertiary chlorides are not observed, although they may be formed reversibly as we have observed in related intramolecular reactions.23

The stereospecifically cis addition requires that the intermediate have a short lifetime; i.e., chloride transfer is faster than bond rotation. The existence of the carbenium ion intermediate can be demonstrated in cases where rearrangement is possible. 1,5-Cyclooctadiene gives ene adduct and bicyclic products derived from transannular addition.²⁴ β -Pinene gives mixtures of ene adduct and products derived from rearrangement of the carbenium ion. The mixture consists of 15% ene adduct with BF₃·Et₂O, 40% with Me₂AlCl, and 60% with Me₃Al. Decreasing the Lewis acidity makes the oxygen of the intermediate more basic, thereby accelerating the 1,5-proton shift relative to rearrangement and leading to a greater percentage of ene adduct.

The ratio of ene adduct to chloride is a function of alkene structure. In general, cis-alkenes give more chloride than trans alkenes. This is probably related to the preference for transfer of a hydrogen from an alkyl group syn to the vinyl hydrogen which is observed in the ene reactions of trisubstituted alkenes (vide infra). Cyclic alkenes give even more chloride than acyclic alkenes since the cyclic structures make it difficult for the oxygen to reach a proton aligned properly relative to the vacant π orbital.

2-Butene gives a much greater percentage of chloride than 4-octene since the relative instability of the terminal double bond of 10a is reflected in the activation energy for the 1,5-proton shift. Addition to 2-heptene occurs mainly at the 2-carbon since it is more accessible and the carbenium ion at the 3-carbon is more stable due to the greater inductive effect of the larger alkyl group.

Secondary (γ -chloroalkoxy)dimethylaluminum compounds, e.g., 11b (see eq 2), are stable in the absence of excess Me_2AlCl . In



the presence of excess Me₂AlCl, 11b reacts to give ene adduct 10b. The cation 25 may be formed followed by loss of a proton to give 10b. Alternatively, a concerted Lewis acid assisted E_2 elimination is possible.

 $(\gamma$ -Chloroalkoxy)dimethylaluminum compounds derived from cyclic alkenes, e.g., 14a (see eq 3), undergo solvolysis in the



presence of excess Me₂AlCl. Chloride 11b gives 27 which loses a proton to give the allylic alkoxide 15a and undergoes two 1,2hydride shifts to give 28 which reacts further to give 16a. Clearly, the carbenium ion intermediate 27 formed from solvolysis is not the same as the zwitterionic intermediate 26, since its reactions are quite different. This difference is likely due to the incorporation of a second equivalent of Lewis acid which makes the oxygen of 27 nonbasic so that a 1,5-proton shift does not occur. Hydride shifts corresponding to those which give rise to 28 have been observed in Prins reactions of cyclohexene and cyclopentene²⁵ and related intramolecular reactions.²³ The different behavior of 11b and 14a is presumably due to the steric constraints present in the cyclic system.

The 2:1 adducts are usually not formed if a slight excess (10%) of alkene is used. This is due to the fact that the aluminum alkoxide deactivates an adjacent double bond. For instance, cis-3-hexenol after conversion to the aluminum alkoxide is not nucleophilic enough to react with CH2O·Me2AlCl. Vinylcyclohexane is an exception, giving exclusively 2:1 adduct 24. The

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Table III. Me₂AlCl-Catalyzed Ene Reactions of Formaldehyde with 1,1-Di- and Trisubstituted Alkenes



^a An 18% yield of 2,3,3-trimethyl-1-pentanol was also isolated.

initially formed ene adduct 3-(cyclohexylidene)propoxychloromethylaluminum (29) has a trisubstituted double bond, and even though it is deactivated by the aluminum alkoxide, it is still more reactive than vinylcyclohexane. The 2:1 adducts can be obtained from alkenes which give a tertiary carbenium ion if 2 equiv of formaldehyde and Me₂AlCl are used. For instance isobutylene gives 30c, 31c, and 32a (see Table III).²⁶ The allylic alcohols formed are stable since they are converted to the aluminum alkoxide. In a related reaction 3-methyl-2-buten-1-ol reacts to give 37

Regioselectivity. After correction for statistical factors, a methylene hydrogen is twice as reactive as a methyl or methine hydrogen. Trisubstituted double bonds are formed $\approx 70\% E$. We have observed a high preference for transfer of a hydrogen from the alkyl group syn to the vinylic hydrogen in the ene reactions of methyl α -chloroacrylate with a wide variety of alkenes.²⁷ Uskoković and Wovkulich have observed a similar preference in the BF₃-catalyzed ene reaction of formaldehyde with (E)- and (Z)-ethylidene-2-methylcyclopentane.²⁸ We have observed varying amounts of regioselectivity in the reactions of formaldehyde with other alkenes. (E)-3-Methyl-2-pentene gives a 4:1 mixture of 34-33. (Z)-3-Methyl-2-pentene gives a 1.25:1 mixture of 33-34. The difference in selectivity is due to the greater reactivity of the ethyl hydrogens. 1-Methylcyclopentene gives a 3:1 mixture of 36a-35a while 1-methylcyclohexene gives a 0.7:1 mixture of 36b-35b.

We believe the preferential abstractive of a hydrogen from the alkyl group syn to the vinylic hydrogen is due to steric interaction of the Lewis acid, which is exo for steric reasons, with the substituent on the less substituted end of the double bond.^{2b} This interaction is minimized if the vinylic substituent is hydrogen

rather than an alkyl group. The degree of selectivity will be determined by the geometry of the transition state leading to the zwitterion and the lifetime of the intermediate. Similar interactions are responsible for the greater percentage of chloride formed from cis-1,2-disubstituted alkenes. Proton transfer is faster for the zwitterion derived from trans-4-octene than for the zwitterion derived from cis-4-octene.

Use of weaker Lewis acids should lead to enhanced selectivity since the oxygen of the intermediate will be more basic resulting in a faster 1,5-proton shift, thereby minimizing bond rotation in the intermediate. This was observed with (Z)-3-methyl-2-pentene. BF₃ gave a 0.8:1 ratio of 33-34, Me₂AlCl gave a 1.25:1 ratio, and Me₃Al gave a 3:1 ratio, although methyl addition to the cation now occurs.29

Effect of Lewis Acid. We have briefly explored the use of BF₃ and SnCl₄ for these ene reactions. Complex mixtures of products were obtained in all cases which contained varying amounts of the desired ene adduct. Methylenecyclohexane and formaldehyde gave a 5% yield of 1d with SnCl₄ and a 20% yield of 1d with BF₃·OEt₂. Methylenecyclohexane and acetaldehyde gave a 46% yield of 1a with SnCl₄ and a 28% yield of 1a with BF₃·OEt₂. 1-Octene and formaldehyde gave a 10% yield of 22 with $SnCl_4$ and a 5% yield of 22 with BF3 OEt2. Clearly Me2AlCl which gives 80% of 1d, 91% of 1a, and 80% of 22 is superior.

Et₂AlCl is a less useful catalyst since the ethyl group is more nucleophilic than the methyl group of Me₂AlCl and can also reduce the aldehyde via β -hydride delivery. Reaction of 1-octene with formaldehyde and Et₂AlCl gives only 30% of 22. EtAlCl₂ is a stronger Lewis acid which is useful in the reactions of formaldehyde with nonnucleophilic alkenes; 1-octene gives 90% of 22. Alkenes which are not nucleophilic enough to react with CH₂O·Me₂AlCl will often react with CH₂O·EtAlCl₂ since the alkyl group of a monoalkylaluminum dichloride is much less nucleophilic than the methyl group of Me_2AlCl .

Conclusion. Me₂AlCl is a useful catalyst for ene reactions of aldehydes. It is both a mild, but effective, Lewis acid and a proton scavenger. This last feature allows acid sensitive compounds like ipsenol (3) and 8 to be isolated. Using this catalyst, we have obtained ene adducts for the first time from aliphatic and aromatic aldehydes and 3-alken-1-ols are now readily available from the reaction of formaldehyde with mono- and 1,2-disubstituted alkenes.

Experimental Section

Dimethylaluminum chloride, manufactured by Texas Alkyls Inc., was purchased as 1.14 M solution in heptane from Stauffer Chemical. Some batches contained traces of toluene which reacted to give byproducts. Ethylaluminum dichloride, trimethylaluminum and diethylaluminum chloride were obtained from the same source. CH2Cl2 was distilled from CaH₂. Paraformaldehyde, trioxane, and other aldehydes were used without purification. Commercial samples of alkenes were used in most cases, although much better yields were obtained in some cases when the alkene was dried and distilled. Gas chromatographic analysis was carried out on a 6 ft $\times 1/4$ in. XF-1150 (A), 10 ft $\times 1/4$ in. 10% Carbowax 20M (B), or 9 ft $\times 1/4$ in. 10% DEGS (C) at flow rates of 60-70 mL/min. Analyses were performed by Galbraith Laboratories.

General Procedure. The Lewis acid solution was added via syringe to a solution of the aldehyde and alkene in CH₂Cl₂ in a flame-dried flask under nitrogen which was cooled in an ice bath. The ice bath was removed and the solution stirred with monitoring by GC or TLC. Workup was accomplished by slow addition of 5 mL of NaH₂PO₄ solution and 10 mL of ether to the reaction mixture. The precipitated alumina was dissolved by dropwise addition of 10% hydrochloric acid. The organic layer was separated. The aqueous layer was washed three times with ether. The combined organic layers were dried (MgSO₄) and evaporated in vacuo. Diols were isolated by extraction with CH₂Cl₂.

Reaction of methylenecyclohexane (0.48 g, 5.0 mmol), paraformaldehyde (0.14 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.81 mmol) in 15 mL of CH₂Cl₂ for 2.5 h at 25 °C gave, after purification by evaporative distillation (60 °C (0.05 torr)), 0.46 g (80%) of 1a: IR (neat) 3340, 1668 cm⁻¹; NMR (CCl₄) δ 5.47 (m, 1), 3.62 (br s, 1, OH), 3.60 (t, 2, J = 7 Hz), 2.39–1.12 (m, 10). Anal. Calcd for C₈H₁₄O: C, 76.14; H, 11.18. Found: C, 76.02; H, 11.33.

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⁽²⁹⁾ A detailed study of the reactions of CH2O·Me3Al with alkenes will be reported shortly.

Repetition of the reaction with $SnCl_4$ (0.29 g, 1.1 mmol) under otherwise identical conditions gave 0.57 g of a complex mixture containing about 5% of 1a.

Repetition of the reaction with boron trifluoride etherate (0.13 g, 0.9 mmol) gave 0.54 g of a complex reaction mixture which contained about 30% of **1a**.

Reaction of methylenecyclohexane (0.48 g, 5.0 mmol), **paraldehyde** (0.2 g, 1.51 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.81 mmol) in 15 mL of CH₂Cl₂ for 2 h at 25 °C gave 0.58 g (91%) of **1b** which was greater than 95% pure as determined by NMR and GC analysis: IR (neat) 3360, 3045, 1665 cm⁻¹; NMR (CCl₄) δ 5.55 (m, 1), 3.88 (tq, 1, J = 7, 7 Hz), 2.68–1.33 (m, 11), 1.09 (d, 3, J = 7 Hz). The data are identical with those previously reported.³⁰

Repetition of the reaction with $SnCl_4$ (0.29 g, 1.1 mmol) gave 0.39 g of a complex mixture which contained about 40% of 1b.

Repetition of the reaction with boron trifluoride etherate (0.13 g, 0.9 mmol) gave 0.35 g of a complex mixture which contained about 30% of 1b.

Reaction of methylenecyclohexane (0.48 g, 5.0 mmol), **isovaleraldehyde** (0.39 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 1 h at 25 °C, followed by evaporative distillation (110 °C (0.05 torr)), gave 0.61 g (74%) of 1c: IR (neat) 3470, 1665 cm⁻¹; NMR (CCl₄) δ 5.50 (br s, 1), 3.68 (m, 1), 2.52–1.08 (m, 14), 0.95 (br d, 6, J = 7 Hz).

Reaction of methylenecyclohexane (0.48 g, 5.0 mmol), **pivalaldehyde** (0.39 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 12 h at 25 °C gave 0.77 g (93%) of 1d which was >90% pure by NMR and GC analysis: IR (neat) 3500, 1710, 1660, 1070 cm⁻¹; NMR (CCl₄) δ 5.52 (m, 1), 3.23 (dd, 1, J = 10, 3 Hz), 2.46–1.18 (m, 11), 0.90 (s, 9). An analytical sample was prepared by preparative GC. Anal. Calcd for C₁₂H₂₂O: C, 79.05; H, 12.17. Found: C, 79.22; H, 12.18.

Reaction of methylenecyclohexane (0.48 g, 5.0 mmol), **benzaldehyde** (0.48 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 1 h at 25 °C, followed by evaporative distillation (105 °C (0.05 torr)) gave 0.63 g (69%) of 1e: IR (neat) 3482, 1602, 1492, 792 cm⁻¹; NMR (CCl₄) δ 7.18 (s, 5), 5.40 (m, 1), 4.61 (t, 1, J = 7 Hz), 2.88 (br s, 1, OH), 2.21 (br d, 2, J = 7 Hz), 2.10–1.21 (m, 8). An analytical sample was prepared by preparative GC. Anal. Calcd for C₁₄H₁₈O: C, 83.12; H, 8.97. Found: C, 83.32; H, 9.29.

Reaction of limonene (0.68 g, 5.0 mmol), **paraldehyde** (0.2 g, 1.51 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 2 h at 25 °C gave 0.91 g of material which was purified by evaporative distillation (75 °C (0.05 torr)) to give 0.53 g (65%) of **2a**: IR (neat) 3380, 3080, 1642 cm⁻¹; NMR (CCl₄) δ 5.42 (m, 1), 4.86 (m, 1), 4.7 (m, 1), 3.88 (tq, 1, J = 7, 7 Hz), 2.85 (m, 1, OH), 2.52–1.43 (m, 12), 1.17 (d, 3, J = 7 Hz).

Reaction of limonene (0.68 g, 5.0 mmol), **isovaleraldehyde** (0.39 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 2 h at 25 °C, followed by evaporative distillation (96 °C (0.025 torr)), gave 0.69 g (69%) of **2b**: IR (neat) 3490, 1640, 888 cm⁻¹; NMR (CCl₄) δ 5.40 (m, 1), 4.88 (m, 1), 4.72 (m, 1), 3.77 (m, 1), 2.92–1.07 (m, 13), 1.77 (br s, 3), 0.93 (br d, 6, J = 7 Hz). The spectral data are identical with those previously reported.¹⁶

Reaction of isoprene (0.39 g, 5.0 mmol), **isovaleraldehyde** (0.39 g, 4.54 mmol), and Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 5 h at 25 °C gave 0.68 g of crude material which was purified by chromatography on silica gel (1:1 pentane ether) to give 0.39 g (55%) of 4 and 0.095 g (14%) of 3.

The data for 4 are as follows: IR (neat) 3030, 1682, 1140, 1112 cm⁻¹; NMR (CCl₄) δ 5.36 (br s, 1), 4.02 (m, 2), 3.43 (m, 1), 2.12–1.04 (m, 5), 1.69 (br s, 3), 0.93 (d, 3, J = 7 Hz), and 0.91 (d, 3, J = 7 Hz); mass spectrum, m/e (%) 154 (56), 139 (13), 121 (11), 111 (20), 110 (27), 109 (10), 98 (18), 97 (65), 95 (26), 93 (14), 85 (28), 84 (20), 83 (25), 82 (17), 81 (15), 79 (12), 71 (53), 70 (77), 69 (99), 68 (100), 67 (70), 57 (31), 56 (24), 55 (52), 53 (40), 44 (16), 43 (56), 42 (22), 41 (56), 40 (19). These data correspond exactly to those reported for 4 in the literature.¹¹

The data for 3 are as follows: IR (neat) 3350, 3090, 1598, 895 cm⁻¹; NMR (CCl₄) δ 6.36 (dd, 1, J = 16 and 8 Hz), 5.22 (d, 1, J = 16 Hz), 5.08 (d, 1, J = 8 Hz), 5.01 (m, 2), 3.72 (m, 1), 2.56-1.11 (m, 6), 0.95 (d, 3, J = 7 Hz), 0.92 (d, 3, J = 7 Hz). These data correspond exactly to those reported for 3 in the literature.¹⁰

Reaction of methylenecyclobutane (0.34 g, 5.0 mmol, 80% pure), isovaleraldehyde (0.39 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M) in 15 mL of CH₂Cl₂ for 6 h at 25 °C gave 0.64 g of crude material of which 0.32 g was chromatographed on silica gel (1:1 pentane–ether) to give 0.15 g (43%) of 5: IR (neat) 3370, 1630, 1050 cm⁻¹; NMR (CCl₄) δ 5.82 (m,

1), 3.84 (m, 1), 2.84–1.15 (m, 10), 0.94 (br d, 6). These data correspond exactly to those reported for $5.^{14}$

Reaction of 2-methyl-2-butene (0.35 g, 5.0 mmol), **paraldebyde** (0.2 g, 1.51 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ at 0 °C for 45 min gave 0.29 g (56%) of pure **6a**: GC (6 ft, 10% XF-1150, 100 °C) shows a 1:1 mixture of diastereomers; $t_R = 3.8$ and 4.7 min; IR (neat) 3410, 3090, 1635, 880 cm⁻¹; NMR (CCl₄) δ 5.02–4.78 (m, 2), 3.73 and 3.68 (two dq, 1, J = 7, 7 Hz), 2.65 (s, 1, OH), 2.37–1.87 (m, 1), 1.78 and 1.75 (2s, 3), 1.15 (d, 3, J = 7 Hz), 1.10, 1.03 (2d, 3, J = 7 Hz). These data correspond well with those previously reported.³¹

Reaction of 2-methyl-2-butene (0.35 g, 5.0 mmol), **isovaleraldehyde** (0.39 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 12 h at 25 °C, followed by evaporative distillation (85 °C (0.05 torr)), gave 0.27 g (38%) of 6b: GC (6 ft, 10% XF-1150, 130 °C) showed a 1:1 mixture of diastereomers; $t_{\rm R} = 8.0$ and 9.6 min; IR (neat) 3380, 3070, 1642, 882 cm⁻¹; NMR (CCl₄) δ 4.87 (m, 2), 3.58 (m, 1), 2.53 (m, 1, OH), 2.38–1.18 (m, 4), 1.76 (br s, 3), 1.07 and 1.00 (2 d, 3, J = 7 Hz), 0.95 (d, 3, J = 7 Hz), 0.92 (d, 3, J = 7 Hz). Anal. Calcd for C₁₀H₂₀O: C, 76.86; H, 12.90. Found: C, 76.99; H, 13.08.

Reaction of 2-methyl-2-butene (0.35 g, 5.0 mmol), **nonanal** (0.64 g, 4.50 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 12 h at 25 °C gave 0.83 g of crude product which was purified by evaporative distillation (120 °C (0.05 torr)) to give 0.4 g (42%) of **6c**: IR (neat) 3480, 1645, 885 cm⁻¹; NMR (CCl₄) δ 4.78 (m, 2), 3.44 (m, 1), 2.30–0.76 (m, 21), 1.99 (m, 1, OH), 1.72 (s, 3). Anal. Caled for C₁₄H₂₈O: C, 79.18; H, 13.29. Found: C, 78.56; H, 12.74.

Reaction of 1-methylcyclohexene (0.38 g, 5.0 mmol), paraldehyde (0.2 g, 1.51 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 15 min at 0 °C gave 0.41 g (65%) of a 3:1 mixture of 7 and 8 which was 95% pure by NMR. The data for 7 are as follows: IR (neat) 3390, 1640 cm⁻¹; NMR (CCl₄) δ 5.63 (m, 1), 4.15 (m, 1), 2.63 (s, 1, OH), 2.43–1.39 (m, 7), 1.72 (br s, 3), 1.17 (d, 3, J = 6 Hz). The data for 8 are as follows: IR (neat) 3480, 1645, 872 cm⁻¹; NMR (CCl₄) δ 4.85 (m, 2), 4.15 (m, 1), 2.63 (s, 1, OH), 2.43–1.39 (m, 9), 1.03 (d, 3, J = 6 Hz). Anal. Calcd for C₉H₁₆O: C, 77.09; H, 11.50. Found: C, 76.96; H, 11.46.

Reaction of 2,3-dimethyl-2-butene (0.42 g, 5.0 mmol), **paraldehyde** (0.2 g, 1.51 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 2 h at 25 °C gave 0.21 g (36%) of **9a**: IR (neat) 3410, 3090, 1035, 880 cm⁻¹; NMR (CCl₄) δ 4.86 (m, 2), 3.72 (q, 1, J = 6 Hz), 2.22 (s, 1, OH), 1.75 (br s, 3), 1.03 (d, 3, J = 6 Hz), 1.03 (s, 3), 0.97 (s, 3).

Reaction of 2,3-dimethyl-2-butene (0.42 g, 5.0 mmol), **isovaleraldehyde** (0.39 g, 4.54 mmol), and Me₂AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH₂Cl₂ for 12 h at 25 °C, followed by evaporative distillation (40 °C (0.05 torr)), gave 0.13 g (16%) of **9b**: IR (neat) 3500, 1642, 888 cm⁻¹; NMR (CCl₄) δ 4.82 (m, 2), 3.54 (dd, 1, J = 10 and 4 Hz), 1.76 (s, 3), 1.67 (s, 1, OH), 1.35–1.00 (m, 3), 1.02 (s, 3), 0.98 (s, 3), 0.96 (d, 3, J = 6 Hz), 0.88 (d, 3, J = 6 Hz). Anal. Calcd for C₁₀H₂₂O: C, 77.58; H, 13.02. Found: C, 76.92; H, 12.81.

Reaction of trans-2-butene (0.3 g, 5.4 mmol), paraformaldehyde (0.46 g, 15 mmol, 2.8 equiv), and Me₂AlCl (15.6 mL of 1.14 M, 17.8 mmol, 3.2 equiv) in 15 mL of CH₂Cl₂ was carried out for 25 min at 25 °C in a pressure bottle. The reaction was quenched with 50 mL of saturated ammonium chloride solution followed by extraction with 3×50 mL of pentane. The organic layer was dried (MgSO₄) and evaporated at atmospheric pressure. The residue (bp > 110 °C) was evaporatively distilled (80 °C (0.5 torr)) to give 0.323 g (50%) of chloroalcohol **11a**: IR (neat) 3350, 2980, 1450, 1375, 1060 cm⁻¹; NMR (CDCl₃) δ 4.15 (qd, 1, J = 7, 6 Hz), 3.66 (d, 2, J = 7 Hz), 3.00 (s, OH), 1.97 (m, 1), 1.50 (d, 3, J = 7 Hz), 1.03 (d, 3, J = 7 Hz); ¹³C NMR (CDCl₃) δ 64.4, 59.9, 42.9, 21.2, 12.9; GC (B) 150 °C, $t_R = 11.3$ min. The 3,5-dinitrobenzoate was recrystallized twice from 95% ethanol: mp 63.5–65 °C (lit.¹⁷ 61–62 °C).

GC analysis (B, 150 °C) of the pentane extract indicates that 10a (t_R = 2.3 min) was present in ~20% yield. It could not be isolated due to its volatility.

Reaction of *cis*-2-butene with paraformaldehyde, exactly as described above, gave 0.257 g (39%) of chloroalcohol **12a**: IR (neat) 3550, 2980, 1455, 1380, 1040 cm⁻¹; NMR (CDCl₃) δ 4.42 (qd, 1, J = 7, 3 Hz), 3.59 (m, 2), 3.08 (s, OH), 1.90 (m, 1), 1.55 (d, 3, J = 7 Hz), 0.96 (d, 3, J = 7 Hz); ¹³C NMR (CDCl₃) δ 64.9, 59.6, 42.1, 22.6, 10.1; GC (B) 150 °C, $t_R = 11.2$ min. The 3,5-dinitrobenzoate was recrystallized twice from 95% ethanol: mp 91–92 °C (lit.¹⁷ 93–94 °C).

GC analysis indicated that 10a was formed in 20% yield.

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Reaction of trans-4-octene (99% pure, 0.79 g, 7.0 mmol), paraformaldehyde (0.150 g, 5.0 mmol), and 1 equiv of Me₂AlCl (4.83 mL of 1.14 M, 5.5 mmol) in 10 mL of CH₂Cl₂ for 30 min at 25 °C gave 0.490 g (\sim 70%). Evaporative distillation (90 °C (0.25 torr)) of 0.147 g gave 0.139 g (\sim 65%) of a mixture which GC and NMR analysis indicated to be an 88:12 mixture of 10b and 11b which were separated by preparative GC. GC analysis indicated that the ratio of 11b:12b was >98:2.

The spectral data for **11b** follow: IR (neat) 3360, 2965, 2940, 2880, 1465, 1025 cm⁻¹; NMR (CDCl₃) δ 4.14 (m, 1), 3.75 (apparent t, 2, J = 5 Hz), 1.96–1.2 (m, 10), 1.1–0.95 (m, 6); GC (B, 180 °C) $t_{\rm R}$ = 15.7 min.

With Excess Me₂AlCl. Paraformaldehyde (0.15 g, 5.00 mmol), Me₂AlCl (6.0 mL of 1.14 M, 6.84 mmol), and *trans*-4-octene (0.5 g, 4.54 mmol) were stirred in 15 mL of CH₂Cl₂ overnight at 25 °C. Normal workup gave 0.37 g (58%) of 10b which consisted of a 9:1 trans/cis mixture as estimated by NMR: IR (neat) 3360, 2965, 2940, 2875, 1460, 1055, 1020, 965 cm⁻¹; NMR (CDCl₃) δ 5.59 (td, 1, J = 6, 15.5 Hz), 5.19 (tdd, 1, J = 1.2, 15.5, 8.8 Hz), 3.46 (m, 2), 2.05 (m, 3), 1.6 (s, 1, OH), 1.35 (m, 4), 0.97 (t, 3, J = 7.1 Hz), 0.87 (t, 3, J = 6 Hz); GC (B, 180 °C), $t_R = 4.3$ min. The analytical sample was prepared by preparative GC. Anal. Calcd for C₉H₁₈O: C, 76.00; H, 12.75. Found: C, 76.10; H, 12.54.

Reaction of cis-4-octene (95% pure) with formaldehyde and 1 equiv of Me₂AlCl was carried out as described above giving 0.921 g of crude product. Evaporative distillation (85 °C (0.25 torr)) of 0.2 g gave 0.160 g (80%) of a 7:3 mixture of 10b and 12b. GC analysis indicated that the ratio of 12b:11b was 97:3. Chloroalcohol 12b was isolated by preparative GC: IR (neat) 3345, 2965, 2940, 2880, 1465, 1380, 1040 cm⁻¹; NMR (CDCl₃) δ 4.33 (m, 1), 3.69 (apparent t, 2, J = 6.4 Hz), 1.88–1.20 (m, 10), 0.97 (br t, 6, J = 7 Hz); GC (B, 180 °C), $t_{\rm R}$ = 17.1 min.

With excess Me₂AlCl. *cis*-4-Octene (0.67 g, 6.0 mmol), paraformaldehyde (0.15 g, 5.0 mmol), and Me₂AlCl (6.58 mL of 1.14 M, 7.5 mmol) in 10 mL of CH₂Cl₂ were stirred at 25 °C. The reaction was monitored by GC which showed a 4:1 ratio of 10b-12b after 1 min and <1% 12b after 1 h. Normal workup after 3.5 h gave 0.642 g which was purified by evaporative distillation (77 °C (0.025 torr)) to give 0.524 g (73%) of 10b which contained <3% of 12b as determined by NMR and GC analysis.

Reaction of *trans*-2-heptene (0.59 g, 6.0 mmol), **paraformaldehyde** (0.15 g, 5.0 mmol), and Me₂AlCl (4.83 mL of 1.14 M, 5.5 mmol) in 10 mL of CH₂Cl₂ for 2 h at 25 °C gave 0.530 g (80%) of a 5:1 mixture of **10c(d)** and **11c(d)** which were separated by preparative GC.

The **10c(d)** mixture was 80–90% **10c** as determined by NMR: IR (CCl₄) 3650, 3600, 3510, 1030, 970 cm⁻¹; NMR (CDCl₃) δ 5.54 (td, 1, J = 6.2, 15.5 Hz), 5.21 (dd, 1, J = 15.5, 7.3 Hz), 3.42 (m, 2), 2.32 (qd, 1, J = 6.8, 6.2 Hz), 2.02 (td, 2, J = 5.6, 7.3 Hz), 1.6–1.0 (m, 3), 0.96 (d, 3, J = 6.8 Hz), 0.87 (t, 3, J = 6.6 Hz). Peaks between δ 5.0 and 5.2 indicate the presence of **10d**; GC (B, 140 °C), $t_{\rm R} = 8.6$ min.

NMR spectra indicated that a 3:7 mixture of 11c and 11d was present: IR (CCl₄) 3650, 1030 cm⁻¹; NMR (CDCl₃) δ 4.3 (m, 1), 3.73 (m, 2), 1.99 (m, 1), 1.54 (d, 0.7 × 3, J = 6.8 Hz), 1.04 (d, 0.3 × 3, J = 6.8 Hz); GC (B, 140 °C), $t_{\rm R}$ = 51.6 min.

With excess Me₂AlCl. *trans*-2-Heptene (0.5 g, 6.0 mmol), paraformaldehyde (0.15 g, 5 mmol), and Me₂AlCl (6.58 mL of 1.14 M, 7.5 mmol) in 10 mL of CH₂Cl₂ were stirred for 26 h at 25 °C. Additional Me₂AlCl (2.20 mL, 2.5 mmol) was added and the solution stirred an additional 75 h. GC showed a ratio of 10:11 of 2.6:1 after 10 min, 4.5:1 after 2 h, 5.3:1 after 25 h, and 99:1 after 100 h. Normal workup gave 0.55 g of which 0.494 g was evaporatively distilled (90 °C (0.15 torr)) to give 0.432 g (76%) of a ~7:3 mixture of 10c and 10d containing <1% of 12c(d). A similar mixture was obtained in 20% yield on reaction of 2-heptene and formaldehyde.^{5a}

Reaction of *cis***-2-heptene** with formaldehyde was carried out as described above giving 0.584 g (91%) of a 6:1 mixture of **10c(d)** and **12c(d)**. Preparative GC gave a ca. 4:1 mixture of **10c** and **10d** and a 6:4 mixture of **12c** and **12d**: IR (CCl₄) 3650, 2960, 1460, 1380, 1030 cm⁻¹; NMR (CDCl₃) δ 4.30 (m, 1), 3.65 (m, 2), 1.98 (m, 1), 1.54 (d, 0.4 × 3, J = 6.8 Hz), 0.91 (d, 0.6 × 3, J = 6.8 Hz); GC (B, 140 °C), $t_{\rm R}$ = 55.0 min.

Reaction of cyclopentene (0.68 g, 10 mmol), **paraformaldehyde** (0.15 g, 5 mmol), and 1 equiv of Me_2AICI (4.39 mL of 1.14 M, 5 mmol) in 10 mL of CH_2Cl_2 for 1 h at 25 °C gave, after evaporative distillation (bp 93 °C (0.1 torr)), 0.300 g (47%) of a 14:2:84 mixture of 13a:15a:14a, which was separated by preparative GC.

The spectral data for 13a are as follows: IR (neat) 3250, 3020, 1625, 1030 cm⁻¹; NMR (CDCl₃) δ 5.80 (m, 2), 3.58 (d, 2, J = 7 Hz), 2.6–2.0 (m, 3), 2.0–1.3 (m, 3); GC (B, 170 °C), $t_{\rm R}$ = 3.5 min. The spectral data are the same as those previously reported.^{20c}

The spectral data for **14a** are as follows: IR (neat) 3350, 1440, 1270, 1120, 1090, 1040, 1010, 910 cm⁻¹; NMR (CDCl₃) δ 4.57 (m, 1, apparent q), 3.78 (dd, 1, J = 11.2, 8.2 Hz), 3.72 (dd, 1, J = 11.2, 6.0 Hz), 2.5–1.2 (m, 8); ¹³C NMR (CDCl₃) δ 65.6, 63.7, 48.5, 36.7, 24.9, 21.6; mass

spectrum m/e (relative intensity, %) 98 (7), 97 (6), 83 (8), 81 (6), 80 (9), 79 (7), 68 (100), 67 (58); GC (B, 170 °C), $t_{\rm R} = 12.2$ min), GC (C, 160 °C), $t_{\rm R} = 17.4$ min. This sample is identical with the major chloro alcohol prepared from cyclopentene, formaldehyde, and HCl.^{20a}

With 2.0 Equiv of Me₂AlCl. An identical reaction with twice as much Me₂AlCl was carried out for 8.3 h at 0 °C. Normal workup followed by evaporative distillation (bp 70 °C (0.1 torr)) gave 0.333 g (68%) of a mixture consisting of 13a (15%), 14a (5%), 15a (65%), and 16a (15%). The ratio of products (\pm 5%) during the reaction is as follows: 0.3 h, 13a (8), 14a (87), 15a (5), 16a (<1); 1.3 h, 13a (12), 14a (65), 15a (21), 16a (2); 3.5 h, 13a (17), 14a (32), 15a (43), 16a (8).

The data for 15a are as follows: IR (neat) 3350, 3060, 2960, 2875, 1450, 1040 cm⁻¹; NMR (CDCl₃) δ 5.63 (br s, 1), 4.18 (s, 2), 2.5 (s, 1, OH), 1.4–2.4 (m, 6).

The data for 16a are as follows: NMR (CDCl₃) δ 3.58 (qd, 1, J = 7, 7 Hz), 1.18 (d, 3, J = 7 Hz).

Reaction of excess HCl, cyclopentene (6.8 g, 0.1 mol), and **paraform-aldehyde** (4.5 g, 0.15 mol) in 50 mL of CH_2Cl_2 at -70 °C, as described in the literature,^{20a} gave 4.0 g (30%) of crude formal (bp 90-110 °C (0.06 torr)). Hydrolysis of 2.12 g in 10 mL of MeOH containing 0.5 mL of concentrated hydrochloric acid gave 1.94 g which was shown by GC to consist of 31% *trans*-2-chlorocyclopentanel, 42% of *cis*-2-chlorocyclopentanemethanol (14a), 10% of *trans*-2-chlorocyclopentanemethanol, and 7% of 3-chlorocyclopentanemethanol which were separated by preparative GC.

The spectral data for *trans*-2-chlorocyclopentanemethanol are as follows: IR (CDCl₃) 3630, 1450, 1380, 1255, 1110, 1030 cm⁻¹; NMR (CDCl₃) δ 4.01 (q, 1, J = 6 Hz), 3.65 (d, 2, J = 6 Hz), 2.5–1.2 (m, 8); ¹³C NMR (CDCl₃) δ 64.2, 61.6, 51.9, 36.5, 26.7, 22.4; mass spectrum, m/e (relative intensity %) 118 (1), 116 (2), 105 (1), 103 (1), 81 (87), 80 (25), 79 (14), 68 (89), 67 (100); GC (C, 160 °C), $t_{\rm R} = 20.3$ min.

Reaction of cyclohexene (0.49 g, 6.0 mmol), **paraformaldehyde** (0.15 g, 5.0 mmol), and **1 equiv of Me₂AlCl** (4.39 mL of 1.14 M, 5.0 mmol) in 10 mL of CH₂Cl₂ for 2.5 h at 25 °C gave 0.372 g of which 0.207 g was evaporatively distilled (140 °C (0.25 torr)) to give 0.178 g (53%) of a 2.2:1 mixture of **13b** and **14b** containing a trace of **16b**. Purification was effected by preparative GC.

The spectral data for **13b** are as follows: IR (neat) 3350, 3020, 1040 cm⁻¹; NMR (CCl₄) δ 5.67 (m, 2), 3.42 (d, 2, J = 7 Hz), 3.09 (s, 1), 2.4–1.1 (m, 7); GC (B, 170 °C), $t_{\rm R} = 6.3$ min.^{5b} The data for **14b** are as follows: IR (CCl₄) 3650, 3400, 2930, 1445, 1270, 1070, 1020 cm⁻¹; NMR (CDCl₃) δ 4.56 (br s, 1, $W_{1/2} = 8$ Hz), 3.54 (m, 2), 2.06–1.23 (m, 10); ¹³C NMR (CDCl₃) 65.2 (CH₂OH), 61.6 (C₂), 44.3 (C₁), 34.1 (C₃), 25.0 (C₅), 22.8 (C₆), 20.2 (C₄);⁴⁰ GC (B, 170 °C), $t_{\rm R} = 19.3$ min. The 3,5-dinitrobenzoate was recrystallized from 95% EtOH: mp 120–121 °C.

Reaction with 1.5 equiv of Me₂AlCl was carried out in an identical manner for 94 h at 25 °C. Normal workup gave 0.475 g (85%) of material which consisted of **13b** (64%), **14b** (4%), **15b** (8%), and **16b** (24%). GC analysis of aliquots showed that **13b** and **14b** were formed initially, that **14b** was converted mainly to **15b** and **16b**, and that **15b** slowly decomposed during the reaction. The ratio of **13b**:14b:15b:16b was as follows: 18 min, 58:38:4:0; 1.2 h, 60:33:5:1; 18 h, 56:7:22:14; 94 h, 64:4:8:24.

The data for **15b** are as follows: IR (neat) 3350, 3020, 1040 cm⁻¹; NMR (CCl₄) δ 5.62 (br s, 1), 3.88 (br s, 2), 1.9–2.2 (m, 4), 1.2–1.7 (m, 5); GC (B, 170 °C), $t_{\rm R}$ = 7.0 min.

The data for **16b** are as follows: NMR (CCl₄) δ 3.44 (m, 1), 2.18–1.07 (m, 11), 1.09 (d, 3, J = 7 Hz); GC (B, 170 °C), $t_R = 4.6$ min.

Reaction of 1,4-cyclohexadiene (0.369 g, 4.5 mmol), **paraformaldehyde** (0.45 g, 15.0 mmol), and Me₂AlCl (13.16 mL of 1.14 M, 15.0 mmol) in 15 mL of CH₂Cl₂ for 1 h at 0 °C gave 0.57 g of crude material of which 0.4 g was purified by chromatography on silica gel (1:1 pentaneether) to give 0.23 g (46% overall) of **18**: IR (neat) 3350, 3038, 1660, 1032, 666 cm⁻¹; NMR δ 5.75 (ddd, 1, J = 10, 2, 2 Hz, C₃-H), 5.56 (ddd, 1, J = 10, 2, 2 Hz, C₄-H), 4.51 (m, 1, $W_{1/2} = 8$ Hz, C₆-H), 3.62 (m, 2, CH₂OH), 3.35 (br s, 1, OH), 2.52 (br s, 2, C₅-H₂), 1.97 (br s, 3, C₁-H and C₂-H₂); ¹³C NMR (CDCl₃) δ 125.63 (d), 122.65 (d), 64.03 (t), 57.69 (d), 40.85 (d), 34.56 (t), 23.78 (t). Anal. Calcd for C₇H₁₁ClO: C, 57.35; H, 7.56; Cl, 24.18. Found: C, 57.53; H, 7.71; Cl, 24.42.

Reaction of 1,5-cyclooctadiene (0.65 g, 6.0 mmol), paraformaldehyde (0.15 g, 5.0 mmol), and Me₂AlCl (4.8 mL of 1.14 M, 5.5 mmol) in 10 mL of CH₂Cl₂ for 1 h at 25 °C gave 0.697 g (\approx 100%) which was estimated by GC to consist of 19 (37%), 20 (32%), and 21 (11%) which were isolated by preparative GC.

The spectral data for 19 are identical to those previously reported.³³ GC (B, 180 °C), $t_{\rm R}$ = 19.0 min. The spectral data for 20 are as follows: IR (CCl₄) 3655, 3030, 2940, 1470, 1430, 1255, 1060, 1010, 910 cm⁻¹; NMR (CDCl₃) δ 5.62 (m, 2), 4.59 (br t, 1, J = 5 Hz), 3.57 (d, 2, J =

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5.5 Hz), 1.3–2.7 (m, 10); GC (B, 180 °C), $t_{\rm R} = 69.2$ min. The spectral data for 21 are as follows: IR (CCl₄) 3650, 2950, 2875, 1450, 1040 cm⁻¹; NMR (CDCl₃) δ 4.00 (m, 1), 3.52 (d, 2, J = 5.7 Hz), 2.15 (s, 1, OH), 2.2-1.1 (m, 11); GC (B, 180 °C), $t_{\rm R}$ = 38.5 min.

Reaction of 1-octene (0.56 g, 5.0 mmol), paraformaldehyde (0.15 g, 5 mmol), and 1 equiv of Me₂AlCl (4.8 mL of 1.14 M, 5.5 mmol) in 12 mL of CH₂Cl₂ for 12 h at 25 °C gave 0.57 g (81%) of crude product which was a 9:1 mixture of trans- and cis-22 (90%) and 23 (10%) which were separated by preparative GC

The data for 22 are as follows: IR (neat) 3440, 1040, 968 cm⁻¹; NMR $(CDCl_3) \delta 5.8-5.2 \text{ (m, 2)}, 3.60 \text{ (td, 2, } J = 6.2, 6.2 \text{ Hz}), 2.22 \text{ (td, 2, } J$ = 6, 6.2 Hz), 1.98 (m, 2), 1.40–1.2 (m, 7), 0.86 (br t, 3, J = 7 Hz); GC (B, 170 °C), $t_{\rm R} = 6.7 \text{ min (90\%)}$, 7.3 min (10%). Anal. Calcd for C₉H₁₈O: C, 76.00; H, 12.75. Found: C, 76.15; H, 12.88.

The data for 23 are as follows: IR (CCl₄) 3650, 1040 cm⁻¹; NMR (CDCl₃) δ 4.2-4.0 (m, 1), 3.8 (m, 2), 2.0-1.10 (m, 13), 0.86 (br t, 3, J 7 Hz); GC (B, 170 °C), $t_{\rm R} = 28.7$ min.

With Excess Me2AICI. An identical reaction with 6.56 mL (7.5 mmol) of Me₂AlCl was stirred for 15 h at 25 °C. Additional Me₂AlCl (2.2 mL, 2.5 mmol) was added and the reaction stirred for 5 h and worked up to give 0.566 g (80%) of a 9:1 mixture of trans- and cis-22 containing a trace of 23.

Repetition of the reaction with Et₂AlCl (3.8 mL of 1.78 M, 6.8 mmol) for 2.5 h at 25 °C gave 0.19 g (30%) of a 9:1 mixture of trans- and cis-22.

Repetition of the reaction with EtAlCl₂ (3.6 mL of 1.53 M, 5 mmol) for 5 min at 0 °C gave 0.72 g (99%) of a 90% pure 6:1 mixture of transand cis-22. Chloro alcohol 23 was not detected. Longer reaction times gave complex mixtures.

Repetition of the reaction with SnCl₄ (0.24 g, 0.92 mmol) for 12 h at room temperature gave 0.31 g of a complex mixture which contained about 10% of 22

Repetition of the reaction with boron trifluoride etherate (0.13 g, 0.9 mmol) for 12 h at room temperature gave 0.2 g of a complex mixture which contained about 5% of 22.

Reaction of vinylcyclohexane (0.66 g, 6.0 mmol), paraformaldehyde (0.15 g, 5 mmol), and Me₂AlCl (4.82 mL of 1.14 M, 5.5 mmol) in 10 mL of CH₂Cl₂ for 12 h at 25 °C gave 0.467 g which was chromatographed on silica gel (2:1 hexane-ethyl acetate followed by ethyl acetate) to give 0.305 g (72% based on formaldehyde) of 24: IR (neat) 3350, 2920, 2860, 2840, 1440, 1050 cm⁻¹; NMR (CDCl₃) δ 5.54 (br t, 1), 3.57 (m, 4), 3.09 (br s, 2, OH), 2.25 (m, 1), 2.10-1.50 (m, 10).

Reaction of 2-methyl-1-pentene (0.5 g, 6.0 mmol), paraformaldehyde (0.15 g, 5.0 mmol), and Me₂AlCl (4.82 mL of 1.14 M, 5.5 mmol) for 18 h at 25 °C, followed by evaporative distillation (70 °C (0.25 torr)). gave 0.507 g (89%) of a 40:36:24 mixture of 30a:31a:32a as estimated from analysis of the NMR spectrum: NMR (CDCl₃) δ 30a, 4.81 (br s, 2); **31a**, 5.2 (m, 1), 1.61 (s, 3); **32a**, 5.2 (m, 1), 1.70 (d, 3, J = 0.3 Hz).

Reaction of 2,3-dimethyl-1-butene (0.5 g, 6.0 mmol), paraformaldehyde (0.15 g, 5.0 mmol), and Me₂AlCl (4.82 mL of 1.14 M, 5.5 mmol) in 10 mL of CH₂Cl₂ for 12 h at 25 °C gave 0.659 g of which 0.410 g was purified by evaporative distillation (85 °C (0.15 torr)) to give 0.345 g (96%) of a 3:1 mixture of 30b and 31b which were separated by preparative GC.

The data for 30b follow: IR (neat) 3350, 3090, 1380, 1365, 1045, 890 cm⁻¹; NMR (CDCl₃) δ 4.87 (br s, 1), 4.75 (br s, 1), 3.70 (td, 2, J = 6.2, 6.2 Hz), 2.30 (t, 2, J = 6.2 Hz), 2.15 (hept, 1, J = 6.8 Hz), 1.44 (t, 1, J = 6.2 Hz, OH), 1.03 (d, 6, J = 6.8 Hz); GC (B, 120 °C), $t_{\rm R} = 13.0$ min

The data for 31b are as follows: IR (CCl₄) 3640, 1440, 1375, 1040 cm⁻¹; NMR (CDCl₃) δ 3.65 (td, 2, J = 6.2, 6.2 Hz), 2.33 (t, 2, J = 6.2 Hz), 1.66 (br s, 9) 1.26 (t, 1, J = 6.2 Hz, OH); GC (B, 120 °C), $t_{\rm R} =$ 18.6 min. These data are identical with those previously reported.³⁴

Reaction of 3-methyl-3-buten-1-ol (0.43 g, 5.0 mmol), paraformaldehyde (0.15 g, 5 mmoi), and Me₂AlCl (9.65 mL of 1.14 M, 11 mmol) in 10 mL of CH_2Cl_2 for 1 h at 25 °C gave 0.314 g (54%) of a 47:33:20 mixture of 30c:31c:32c. Evaporative distillation (100 °C (0.25 torr)) of 0.10 g gave 0.096 g of the same mixture which was separated into components by preparative GC.

The data for 30c³⁵ are as follows: IR (CCl₄) 3650, 3085, 1055, 910 cm⁻¹; NMR (CDCl₃) δ 4.97 (s, 2), 3.75 (t, 4, J = 6.2 Hz), 2.32 (t, 4, J= 6.2 Hz), 1.60 (br s, 2, OH); GC (B, 160 °C), $t_{\rm R}$ = 57.0 min.

The data for 31c^{35,36} are as follows: IR (CCl₄) 3640, 2940, 1440, 1050 cm⁻¹; NMR (CDCl₃) δ 5.50 (t, 1, J = 7.2 Hz), 4.17 (d, 2, J = 7.2 Hz), 3.72 (t, 2, J = 6.0 Hz), 2.29 (t, 2, J = 6.0 Hz), 1.70 (s, 3), 1.25 (br s,

1, OH); GC (B, 160 °C), $t_{\rm R}$ = 76.0 min.

The data for 32c^{35,37} are as follows: IR (CCl₄) 3640, 2940, 1440, 1055 cm⁻¹; NMR (CDCl₃) δ 5.79 (t, 1, J = 7.2 Hz), 4.05 (d, 2, J = 7.2 Hz), 3.70 (t, 2, J = 5.9 Hz), 2.36 (t, 2, J = 5.9 Hz), 2.10 (br s, 1, OH), 1.77 (s, 3); GC (B, 160 °C), $t_{\rm R}$ = 69.1 min.

Reaction of isobutylene (0.59 g, 10.6 mmol), paraformaldehyde (0.95 , 32 mmol), and Me₂AlCl (27.9 mL of 1.14 M, 32 mmol) in 30 mL of CH₂Cl₂ for 1 h in a pressure bottle at 25 °C gave 0.64 g (53%) of a product mixture identical with that obtained from 3-methyl-3-buten-1-ol.

Reaction of (E)-3-methyl-2-pentene (0.5 g, 6.0 mmol), paraformaldehyde (0.16 g, 5.45 mmol), and Me₂AlCl (7.18 mL of 1.14 M, 8.18 mmol) in 15 mL of CH₂Cl₂ for 2.5 h at 25 °C gave 0.63 g of crude material which was purified by evaporative distillation (100 °C (0.05 torr)) to give 0.63 g (97%) of a 1:4 mixture of 33:34 as determined by GC analysis. The data for 33 are as follows: IR (neat) 3350, 3085, 1642, 888 cm⁻¹; NMR (CCl₄) δ 4.76 (s, 2), 3.34 (d, 2, J = 7 Hz), 2.84 (s, 1, OH), 2.42–1.82 (m, 3), 1.17–0.80 (m, 3), 0.96 (d, 3, J = 7 Hz); GC (C, 110 °C), $t_{\rm R}$ = 14.8 min. The data for 34 are as follows: IR (neat) 3350, 1668, 818 cm⁻¹; NMR (CCl₄) δ 5.25 (m, 1), 3.38 (d, 2, J = 7 Hz), 2.84 (s, 1, OH), 2.42-1.82 (m, 1), 1.66 (br d, 3, J = 6 Hz), 1.58 (br s, 3), 0.96(d, 3, J = 7 Hz); GC (C, 110 °C), $t_{\rm R} = 16.4$ min.

Reaction of (Z)-3-methyl-2-pentene (0.5 g, 6.0 mmol), paraformaldehyde (0.16 g, 5.45 mmol), and Me₂AlCl (7.18 mL of 1.14 M, 8.18 mmol) in 15 mL of CH₂Cl₂ for 1.5 h at 25 °C gave 0.612 of crude material, which was purified by evaporative distillation (100 °C at 0.05 torr), to give 0.57 g (92%) of 5:4 mixture of 33:34.

An identical reaction replacing Me₂AlCl with BF₃·Et₂O (0.14 g, 1 mmol) gave 0.455 g (80%) of a 4:5 mixture of 33:34.

An identical reaction with Me₃Al (2.9 mL of 2.35 M, 6.9 mmol) for 2 h at 25 °C gave 0.34 g (66%) of a 56:18:27 mixture of 33, 34, and 2,3,3-trimethyl-1-pentanol.

Reaction of 1-methylcyclohexene (0.5 g, 5.5 mmol), paraformaldehyde (0.15 g, 5 mmol), and Me₂AlCl (6.8 mL of 1.14 M, 7.5 mmol) in 15 mL of CH₂Cl₂ for 10 min at 0 °C gave 0.78 g of material. Evaporative distillation of 0.60 g (63 °C (0.05 torr)) gave 0.48 g (99%) of a mixture consisting of 54% of 35b, 38% of 36b and 8% of several minor components as determined by GC.

Pure samples were obtained by preparative GC.

The data for 36b³⁸ are as follows: IR (CDCl₃) 3625, 3078, 1640, 1032 cm⁻¹; NMR (CDCl₃) δ 4.79 (m, 1), 4.68 (m, 1), 3.75 (m, 2), 2.5-2.0 (m, 3), 2.0–1.2 (m, 7); GC (B, 140 °C), $t_{\rm R} = 18.2$ min. The data for 35b³⁸ are as follows: IR (CDCl₃) 3625, 3035, 1640,

1375, 1037 cm⁻¹; NMR (CDCl₃) δ 5.58 (m, 1); 3.69 (br t, 2, J = 5.5 Hz), 2.24 (m, 1), 1.98 (m, 2), 1.70 (br s, 3), 1.9–1.5 (m, 4), 1.24 (t, 1, J =5 Hz, OH); GC (B, 140 °C), $t_{\rm R} = 21.8$ min.

Reaction of 1-methylcyclopentene (0.45 g, 5.5 mmol), paraformaldehyde (0.15 g, 5.0 mmol), and Me₂AlCl (6.8 mL of 1.14 M, 7.5 mmol) in 15 mL of CH₂Cl₂ for 10 min at 0 °C gave 0.54 g which was evaporatively distilled (55 °C (0.05 torr)) to yield 0.41 g (73%) which was a 3:1 mixture of 36a and 35a as estimated by NMR. The mixture could not be separated by GC on Carbowax 20 M, SE-30, DEGS, Apiezon L or UCONLB-550X. The spectral data estimated from the mixture are as follows: IR (neat) 3350, 3075, 3045, 1650, 1023, 890 cm⁻¹; NMR $(CDCl_3) \delta 36a^{39} 4.92 (m, 1), 4.84 (m, 1); 35a 5.39 (m, 1).$

Reaction of 3-methyl-2-buten-1-ol (0.43 g, 5.0 mmol), paraformaldehyde (0.150 g, 5.0 mmol), and Me₂AlCl (13.2 mL of 1.14 M, 15.0 mmol) in 10 mL of CH₂Cl₂ for 19 h at 25 °C gave 0.67 g. Chromatography of 0.50 g on silica gel (ethyl ether) gave 0.066 g (15%) of 37: IR (neat) 3360, 3090, 2940, 2895, 1645, 1440, 1380, 1270, 1035, 1010, 910 cm⁻¹; NMR (CDCl₃) δ 4.94 (br s, 1), 4.79 (br s, 1), 3.76 (d, 4, J = 7 Hz), 3.18 (br s, 2, OH), 2.47 (m, 1), 1.79 (s, 3).

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Registry No. 1a, 24826-68-4; 1b, 76627-85-5; 1c, 76627-86-6; 1d, 3197-68-0; 1e, 76627-87-7; 2a, 76627-88-8; 2b, 37794-77-7; 3, 35628-05-8; 4, 59848-69-0; 5, 57822-34-1; 6a isomer 1, 1502-87-0; 6a isomer 2, 1502-86-9; 6b isomer 1, 76653-78-6; 6b isomer 2, 76634-89-4; 6c, 79828-20-9; 7, 79828-21-0; 8, 79828-22-1; 9a, 76627-90-2; 9b, 76627-91-3; 10a, 4516-90-9; (Z)-10b, 79828-23-2; (E)-10b, 76627-92-4; (E)-

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⁽⁴⁰⁾ The ¹³C NMR spectrum was assigned by using cyclohexanemethanol

as a base¹⁸ and by using the shift values for *cis*- and *trans*-2-chlorocyclohexane relative to methylcyclohexane.¹⁹ A good fit was obtained only with the value expected for the cis isomer.

10c, 56905-05-6; 10d, 53045-66-2; 11a, 21430-05-7; 11a 3,5-dinitrobenzoate, 21430-06-8; 11b, 79828-24-3; 11c, 79828-25-4; 11d, 79828-26-5; 12a, 21430-07-9; 12a 3,5-dinitrobenzoate, 21430-08-0; 12b, 79828-27-6; 12c, 79828-28-7; 12d, 79828-29-8; 13a, 13668-59-2; 13b, 3309-97-5; 14a, 79828-30-1; 14b, 77369-76-7; 14b 3,5-dinitrobenzoate, 79828-31-2; 15a, 1120-80-5; 15b, 4845-04-9; 16a, 52829-98-8; 16b, 1193-81-3; 18, 79828-32-3; 19, 51238-57-4; 20, 79828-33-4; 21, 79828-34-5; (Z)-22, 20125-84-2; (E)-22, 20125-85-3; 23, 79828-35-6; 24, 79828-36-7; 30a, 1803-71-0; 30b, 76019-22-2; 30c, 40760-35-8; 31a, 79828-37-8; 31b, 74126-47-9; 31c, 16933-29-2; 32a, 79828-38-9; 32c, 39149-97-8; 33, 77103-98-1; 34, 3778-92-5; 35a, 79828-39-0; 35b, 78426-31-0; 36a, 63791-10-6; 36b, 78426-32-1; 37, 79828-40-3; Me₂AlCl, 1184-58-3; methylenecyclohexane, 1192-37-6; paraformaldehyde, 30525-89-4; paraldehyde, 123-63-7; isovaleraldehyde, 590-86-3; pivalaldehyde, 630-19-3; benzaldehyde, 100-52-7; limonene, 5989-27-5; isoprene, 78-79-5; methylenecyclobutane, 1120-56-5; 2-methyl-2-butene, 513-35-9; nonanal, 124-19-6; 1-methylcyclohexene, 591-49-1; 2,3-dimethyl-2-butene, 563-79-1; trans-2-butene, 624-64-6; cis-2-butene, 590-18-1; trans-4-octene, 14850-23-8; cis-4-octene, 7642-15-1; trans-2heptene, 14686-13-6; cis-2-heptene, 6443-92-1; cyclopentene, 142-29-0; trans-2-chlorocyclopentanol, 20377-80-4; trans-2-chlorocyclopentanemethanol, 25236-94-6; 3-chlorocyclopentanemethanol, 79828-41-4; cyclohexene, 110-83-8; 1,4-cyclohexadiene, 628-41-1; 1,5-cyclooctadiene, 111-78-4; 1-octene, 111-66-0; vinylcyclohexane, 695-12-5; 2-methyl-1pentene, 763-29-1; 2,3-dimethyl-1-butene, 563-78-0; 3-methyl-3-buten-1-ol, 763-32-6; isobutylene, 115-11-7; (E)-3-methyl-2-pentene, 616-12-6; (Z)-3-methyl-2-pentene, 922-62-3; 2,3,3-trimethyl-1-pentanol, 66576-25-8; 1-methylcyclopentane, 693-89-0; 3-methyl-2-buten-1-ol, 556-82-1.

Coenzyme Models. 31. Efficient Trapping of Transient Thiazolium-Aldehyde Adducts (Active Aldehydes) by Intramolecular and Quasi-Intramolecular Flavins. Flavin-Thiamin Biscoenzyme

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Abstract: The reaction sequence of acyloin condensation of aldehydes, catalyzed by thiazolium ion bound to the CTAB micelle, can be diverted by the addition of flavin to the oxidation reaction to afford the corresponding carboxylic acids. It was found, however, that when the aldehyde concentration is elevated or the aldehyde is relatively reactive, intermolecular flavin (3methyltetra-O-acetylriboflavin, MeFl) cannot trap the intermediates (active aldehydes) formed from thiazolium ion and aldehydes completely, leading to a competition between the conventional acyloin condensation and the flavin oxidation. We have applied the concept of intramolecular catalysis to this system by two methods in order to suppress the acyloin condensation relative to the flavin oxidation. The first utilizes quasi-intramolecular flavin oxidation in which hydrophobic 10-dodecylisoalloxazine (10-DodFl) and N-hexadecylthiazolium bromide (HxdT) are bound to a CTAB micelle aggregate. The second is a flavinthiazolium biscoenzyme (FI-T) oxidation in which the intermediates on the thiazolium moiety are oxidized efficiently by the intramolecular flavin. When 4-chlorobenzaldehyde (100 mM) was employed as substrate, the trapping efficiency (=flavin oxidation product/sum of acyloin condensation products) for MeFl was 1.6. The trapping efficiency for the quasi-intramolecular flavin oxidation was improved up to 15-33-fold owing to the enhanced local concentration of 10-DodFl in the micelle phase; efficiency for the biscoenzyme system was further enhanced (>115-fold). A kinetic examination has established that the reaction is zero order in MeFl for the intermolecular flavin oxidation of 4-chlorobenzaldehyde, whereas it becomes first order in MeFl for the oxidation of more reactive pyridine-4-carboxaldehyde (pyCHO). This indicates that the rate-limiting step changes depending on the reactivity of aldehyde: the deprotonation from the thiazolium-aldehyde adduct is rate limiting in the oxidation of 4-chlorobenzaldehyde, whereas the oxidation of the deprotonated active aldehyde by MeFl becomes rate limiting in the oxidation of pyCHO. On the other hand, quasi-intramolecular flavin oxidation of pyCHO was zero order in 10-DodFl at low pyCHO concentrations (<10 mM) and was approximated by a first-order equation at high pyCHO concentrations (>50 mM). In the biscoenzyme oxidation of pyCHO, the zero-order decrease was always observed for up to 60% reaction, indicating the high efficiency of intramolecular flavin as a trapping agent. The present system is a relevant model for pyruvate oxidase which requires FAD and thiamine pyrophosphate as cofactors and catalyzes the convension of pyruvic acid to acetic acid.

Recently, it has become obvious that carbanions are employed as substrates in some biological oxidation reactions. In particular, it has been established unequivocally that the mechanisms by which flavoenzymes such as amino acid oxidases and lactate oxidases oxidize their specific substrates involve the flavin oxidation of carbanions.¹⁻⁴ This concept is also supported by model studies in nonenzymatic systems.⁵⁻⁷ However, the investigation of the Scheme I



application of the newly established concept-"flavin oxidation of carbanions"-has been very limited. In previous publications of this series, we demonstrated that the application of the concept to organic chemistry is very useful in exploiting a new class of oxidation reactions.⁸⁻¹⁰ For example, the benzoin (or acyloin)

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