Dimethylaluminum Chloride Catalyzed Ene Reactions of Aldehydes

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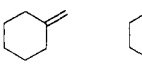
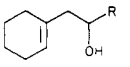
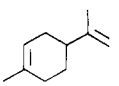
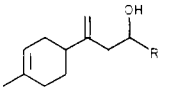
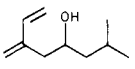
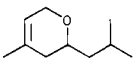
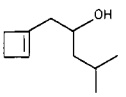
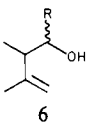
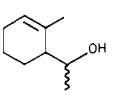
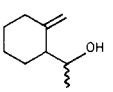
Abstract: Dimethylaluminum chloride, which is a mild Lewis acid and a proton scavenger, catalyzes the ene reactions of aliphatic and aromatic aldehydes with alkenes containing a disubstituted vinylic carbon. Proton-initiated rearrangements do not occur, since the alcohol–Lewis acid complex formed in the ene reaction reacts rapidly to give methane and a nonacidic aluminum alkoxide. Formaldehyde and excess Me_2AlCl give good yields of ene adducts with all types of alkenes. With 1 equiv of Me_2AlCl, 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 glyoxylate[3] and chloral[4] 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 (Me_2AlCl), 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] Me_2AlCl 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–Me_2AlCl complex formed in the reaction decomposes rapidly to give methane and a nonbasic aluminum alkoxide which does not undergo these side reactions.

Table I. Me_2AlCl Catalyzed Ene Reactions of Aldehydes Other Than Formaldehyde[a]

alkene	products	yield (%)
	 1	1a, R = CH_3 (91) 1b, R = $CH_2CH(CH_3)_2$ (74) 1c, R = Ph (69) 1d, R = H (80) 1e, R = $C(CH_3)_3$ (93)
	 2	2a, R = CH_3 (65) 2b, R = $CH_2CH(CH_3)_2$ (79)
	 3  4	3 (16) 4 (60)
	 5	5 (43)
	 6	6a, R = CH_3 (56) 6b, R = $CH_2CH(CH_3)_2$ (38) 6c, R = n-C_8H_{17} (42)
	 7  8	7 (49) 8 (16)
	 9	9a, R = CH_3 (35) 9b, R = $CH_2CH(CH_3)_2$ (16)

[a] 1.5 equiv of Me_2AlCl was used in all cases. [b] Pivalaldehyde gives only 3,3-dimethyl-2-butanol. [c] Benzaldehyde gives only 1-phenylethanol.

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 Me_2AlCl, 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 Me_2AlCl can also act as a nucleophile. It is remarkable that any alkene is more nucleophilic toward the

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(2) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426 and references cited therein.

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(4) (a) Gill, G. B.; Marrison, K.; Parrott, S. J.; Wallace, B. *Tetrahedron Lett.* **1979**, 4867 and references cited therein. (b) Gill, G. B.; Parrott, S. J.; Wallace, B. *J. Chem. Soc., Chem. Commun.* **1978**, 655. (c) Gill, G. B.; Wallace, B. *Ibid.* **1977**, 380.

(5) (a) Blomquist, A. T.; Passer, M.; Schollenberger, C. S.; Wolinsky, J. *J. Am. Chem. Soc.* **1957**, *79*, 4972. (b) Blomquist, A. T.; Verdol, J.; Adami, C. L.; Wolinsky, J.; Phillips, D. D. *Ibid.* **1957**, *79*, 4976. (c) Agami, C. *Ann. Chim. (Paris)* **1965**, *10*, 25. (d) Agami, C.; Prevost, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1966**, *263*, 153.

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(7) (a) Blomquist, A. T.; Himics, R. J. *J. Org. Chem.* **1968**, *33*, 1156. (b) Addy, L. E.; Baker, J. W. *J. Chem. Soc.* **1953**, 4111. (c) Yang, N. C.; Yang, D.-D. H.; Ross, C. B. *J. Am. Chem. Soc.* **1959**, *81*, 133.

(8) For a preliminary report of this work see: Snider, B. B.; Rodini, D. J. *Tetrahedron Lett.* **1980**, *21*, 1815.

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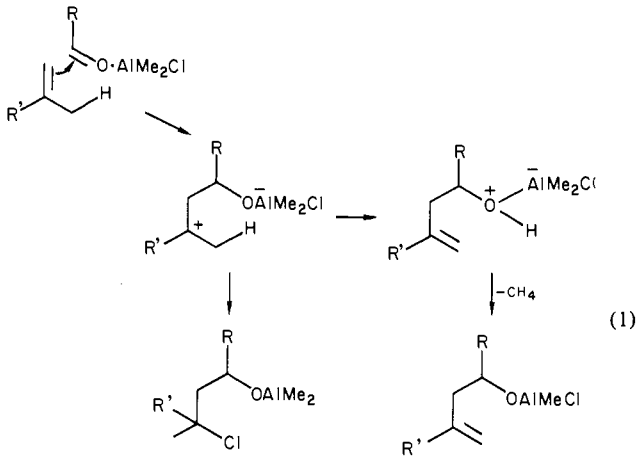


(1)

R = H, R' = H or alkyl; R = alkyl, R' ≠ 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 Me_2AlCl 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 Me_2AlCl 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 Me_2AlCl-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 $AlCl_3$, 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 Me_2AlCl allows the isolation of acid-sensitive ipsenol, since protic acids are not present in the reaction mixture.

The formation of **4** indicates that Me_2AlCl 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 Me_2AlCl 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 Me_2AlCl was used, chloro alcohols were formed as byproducts. When 1.5–2 equiv of Me_2AlCl 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.

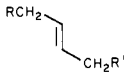
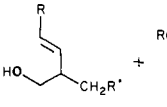
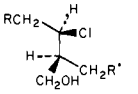
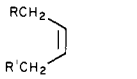
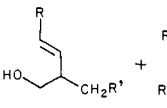
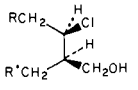
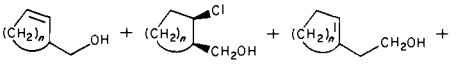
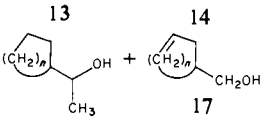
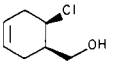
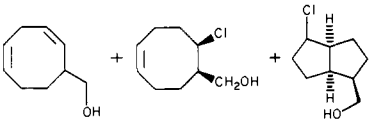
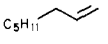
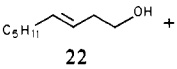
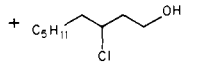
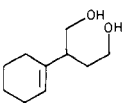
cis- and *trans*-2-butene each give a single chloro alcohol, **12a** and **11a** respectively. These compounds have been obtained with the opposite, trans stereoselectivity by Stapp and Weinberg from 2-butene, paraformaldehyde, and hydrogen chloride.[17] They assigned stereochemistry based on the coupling constant for the methine protons, which is 6.5 Hz for the 2*R**,3*S** isomer **11a** and 3.0 Hz for the 2*R**,3*R** isomer **12a**. The spectral data and melting points of the dinitrobenzoates leave no doubt that the stereochemistry of addition with Me_2AlCl 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 ^{13}C 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 ^{13}C NMR spectrum shows the upfield γ shifts relative to cyclohexane-

(9) Safarov, M. G.; Nigmatullin, N. G.; Komissarov, V. D. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1976**, 1154; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1976**, 1123.
(10) Brand, J. M.; Young, J. C.; Silverstein, R. M. *Prog. Chem. Org. Nat. Prod.* **1979**, *37*, 1.
(11) Ohloff, G.; Schulte-Elte, K.-H.; Willhalm, B. *Helv. Chim. Acta* **1964**, *47*, 602.
(12) Hamer, J.; Turner, J. A. In "*1,4-Cycloaddition Reactions*"; Hamer, J., Ed.; Academic Press: New York, 1967; p 205. Ansell, M. G.; Charalambides, A. A. *J. Chem. Soc., Chem. Commun.* **1972**, 739. Griengl, H.; Geppert, K. P. *Monatsh. Chem.* **1976**, *107*, 675. Gramenitskaya, V. N.; Vodka, V. S.; Golovkina, L. S.; Vul'fson, N. S. *Zh. Org. Khim.* **1977**, *13*, 2329; *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 2169.
(13) Dale, W. J.; Sisti, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 81.
(14) Wilson, S. R.; Phillips, L. R.; Natalie, K. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 3340.
(15) Snider, B. B.; Roush, D. M.; Rodini, D. J.; Gonzalez, D.; Spindell, D. *J. Org. Chem.* **1980**, *45*, 2773.
(16) Crawford, R. J.; Erman, W. F.; Broaddus, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 4298.
(17) Stapp, P. R.; Weinberg, D. S. *J. Org. Chem.* **1969**, *34*, 3592.

Table II. Me_2AlCl-Catalyzed Ene Reactions of Formaldehyde with Mono- and 1,2-Disubstituted Alkenes

alkene	equiv of Me_2AlCl	products, % yield	
		 **10**	 **11**
a, R = R' = H	1	20	50
b, R = R' = CH_2CH_3	**1**	57[a]	8
	1.5	58[a]	1
c(d),[b] R = *n*-Pr, R' = H	1	52 (14)	4 (10)
	1.5	53 (22)	1 (1)
		 **10**	 **12**
a, R = R' = H	1	20	39
b, R = R' = CH_2CH_3	1	57[a]	23
	1.5	73[a]	2
c(d),[b] R = *n*-Pr, R' = H	1	62 (16)	8 (5)
		 **13** **14** **15**  **16** **17**	
a, *n* = 2	1	13a (7), 14a (39), 15a (1)	
	2	13a (10), 14a (4), 15a (44), 16a (10)	
b, *n* = 3	1	13b (36), 14b (17)	
	1.5	13b (54), 14b (3), 15b (8),[c] 16b (24)	
			
	1	**18** (46)	
			
	1	**19** (37) **20** (32) **21** (11)	
		 **22**  **23**	
	1	73[a]	8
	2	80[a]	0
	1.4[d]	30[a]	
	1[e]	90[a]	
			
	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] Et_2AlCl. [e] $EtAlCl_2$.

methanol[18] 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 ^{13}C NMR spectrum which shows the upfield γ

(18) Breitmaier, E.; Haus, G.; Voelter, M. "Atlas of Carbon-13 NMR Data"; Heyden: London, 1979; No. 1596.

(19) ^{13}C NMR shifts of *cis*- and *trans*-2-chloromethylcyclohexane relative to methylcyclohexane have been reported: Schneider, H.-J.; Hopper, V. *J. Org. Chem.* **1978**, *43*, 3866.

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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 Me_2AlCl. 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]

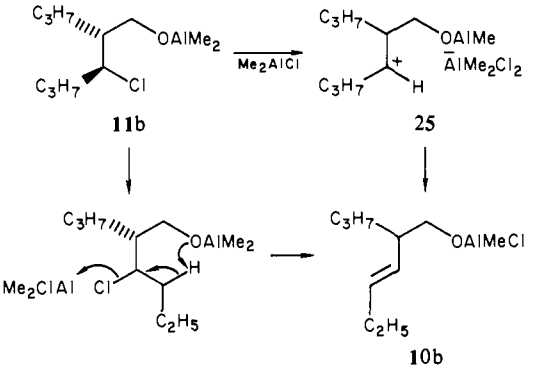
Mechanism. The formation of chloro alcohols suggests that these reactions proceed through a zwitterionic intermediate. Due to the absence of nucleophiles in the medium these reactions are more selective than typical Prins reactions, usually giving primarily ene adduct. *m*-Dioxanes, a common product of the Prins reaction, are not formed because the aldehyde cannot act as a nucleophile since it is fully complexed to Me_2AlCl. The only nucleophiles present are the ligands on the aluminum. The methyl group of Me_2AlCl 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 $BF_3{\cdot}Et_2O$, 40% with Me_2AlCl, and 60% with Me_3Al. 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.

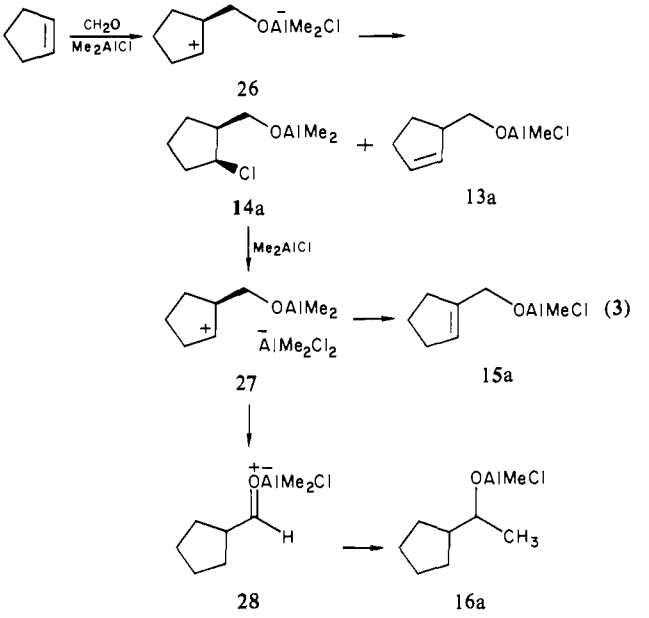
Secondary (γ-chloroalkoxy)dimethylaluminum compounds, e.g., **11b** (see eq 2), are stable in the absence of excess Me_2AlCl. In



(2)

the presence of excess Me_2AlCl, **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.

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



(3)

presence of excess Me_2AlCl. Chloride **11b** gives **27** which loses a proton to give the allylic alkoxide **15a** and undergoes two 1,2-hydride 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 cyclopentene[25] 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 $CH_2O{\cdot}Me_2AlCl$. Vinylcyclohexane is an exception, giving exclusively 2:1 adduct **24**. The

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(22) Elimination reactions giving cyclopentenes show a relatively small anti-to-syn relative rate ratio in contrast to acyclic and cyclohexyl analogues: LeBel, N. A. In "Advances in Alicyclic Chemistry"; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1971; Vol. 3, p 208.
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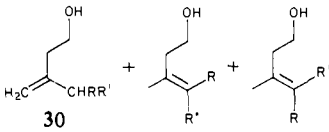
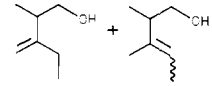
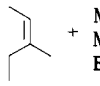
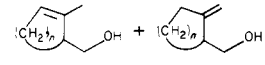
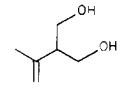
(25) Smushkevich, Y. I.; Belov, V. N.; Kleev, B. V.; Golger, A. Y. *J. Gen. Chem. USSR (Engl. Transl.)* **1964**, *34*, 3866. Smushkevich, Y. I.; Belov, V. N.; Kleev, B. V.; Akimova, A. Ya. *J. Org. Chem. USSR (Engl. Transl.)* **1965**, *1*, 278.

Table III. Me_2AlCl-Catalyzed Ene Reactions of Formaldehyde with 1,1-Di- and Trisubstituted Alkenes

alkene	products, % yield		
			
	30	**31**	**32**
a, R = H, R' = Et	36	32	21
b, R = R' = CH_3	72	24	
c, R = H, R' = CH_2OH	25	18	11
			
	33	**34**	
	19	78	
 + Me_2AlCl	33 (51)	34 (41)	
+ Me_3Al[a]	33 (36)	34 (12)	
+ $BF_3 \cdot OEt_2$	33 (36)	34 (44)	
			
	35	**36**	
a, $n = 2$	18	55	
b, $n = 3$	54	38	
			
	37 (15)		

[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 Me_2AlCl 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 ≈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 BF_3-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. BF_3 gave a 0.8:1 ratio of **33–34**, Me_2AlCl gave a 1.25:1 ratio, and Me_3Al 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 BF_3 and $SnCl_4$ 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 $SnCl_4$ and a 20% yield of **1d** with $BF_3 \cdot OEt_2$. Methylenecyclohexane and acetaldehyde gave a 46% yield of **1a** with $SnCl_4$ and a 28% yield of **1a** with $BF_3 \cdot OEt_2$. 1-Octene and formaldehyde gave a 10% yield of **22** with $SnCl_4$ and a 5% yield of **22** with $BF_3 \cdot OEt_2$. Clearly Me_2AlCl which gives 80% of **1d**, 91% of **1a**, and 80% of **22** is superior.

Et_2AlCl is a less useful catalyst since the ethyl group is more nucleophilic than the methyl group of Me_2AlCl and can also reduce the aldehyde via β-hydride delivery. Reaction of 1-octene with formaldehyde and Et_2AlCl gives only 30% of **22**. $EtAlCl_2$ 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 $CH_2O \cdot Me_2AlCl$ will often react with $CH_2O \cdot EtAlCl_2$ since the alkyl group of a monoalkylaluminum dichloride is much less nucleophilic than the methyl group of Me_2AlCl.

Conclusion. Me_2AlCl 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. CH_2Cl_2 was distilled from CaH_2. 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 × $^1/_4$ in. XF-1150 (A), 10 ft × $^1/_4$ in. 10% Carbowax 20M (B), or 9 ft × $^1/_4$ 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 CH_2Cl_2 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 NaH_2PO_4 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 ($MgSO_4$) and evaporated in vacuo. Diols were isolated by extraction with CH_2Cl_2.

Reaction of methylenecyclohexane (0.48 g, 5.0 mmol), **paraformaldehyde** (0.14 g, 4.54 mmol), and Me_2AlCl (6.0 mL of 1.13 M, 6.81 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.02; H, 11.33.

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(27) Snider, B. B.; Duncia, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 5926.
(28) Wovkulich, P. M.; Uskokovic, M. R. 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 1981, American Chemical Society: Washington, DC, 1981; ORGN 53.
(29) A detailed study of the reactions of $CH_2O \cdot Me_3Al$ 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 Me_2AlCl (6.0 mL of 1.13 M, 6.81 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 $C_{12}H_{22}O$: 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 $C_{14}H_{18}O$: 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 CH_2Cl_2 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 (CCl_4) 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 (CCl_4) 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 Me_2AlCl (6.0 mL of 1.13 M) in 15 mL of CH_2Cl_2 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 (CCl_4) 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), **paraldehyde** (0.2 g, 1.51 mmol), and Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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_R = 8.0 and 9.6 min; IR (neat) 3380, 3070, 1642, 882 cm^{-1}; NMR (CCl_4) 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 $C_{10}H_{20}O$: 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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. Calcd for $C_{14}H_{28}O$: 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 (CCl_4) 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 $C_9H_{16}O$: 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 for 2 h at 25 °C gave 0.21 g (36%) of **9a**: IR (neat) 3410, 3090, 1035, 880 cm^{-1}; NMR (CCl_4) 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 Me_2AlCl (6.0 mL of 1.13 M, 6.78 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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 $C_{10}H_{22}O$: 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 Me_2AlCl (15.6 mL of 1.14 M, 17.8 mmol, 3.2 equiv) in 15 mL of CH_2Cl_2 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 ($MgSO_4$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 Me_2AlCl** (4.83 mL of 1.14 M, 5.5 mmol) in 10 mL of CH_2Cl_2 for 30 min at 25 °C gave 0.490 g (~70%). Evaporative distillation (90 °C (0.25 torr)) of 0.147 g gave 0.139 g (~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 ($CDCl_3$) 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_R = 15.7 min.

With Excess Me_2AlCl. Paraformaldehyde (0.15 g, 5.00 mmol), Me_2AlCl (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 CH_2Cl_2 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 ($CDCl_3$) 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 $C_9H_{18}O$: 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 Me_2AlCl 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 ($CDCl_3$) 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_R = 17.1 min.

With excess Me_2AlCl. *cis*-4-Octene (0.67 g, 6.0 mmol), paraformaldehyde (0.15 g, 5.0 mmol), and Me_2AlCl (6.58 mL of 1.14 M, 7.5 mmol) in 10 mL of CH_2Cl_2 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 Me_2AlCl (4.83 mL of 1.14 M, 5.5 mmol) in 10 mL of CH_2Cl_2 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 (CCl_4) 3650, 3600, 3510, 1030, 970 cm^{-1}; NMR ($CDCl_3$) 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_R = 8.6 min.

NMR spectra indicated that a 3:7 mixture of **11c** and **11d** was present: IR (CCl_4) 3650, 1030 cm^{-1}; NMR ($CDCl_3$) 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_R = 51.6 min.

With excess Me_2AlCl. *trans*-2-Heptene (0.5 g, 6.0 mmol), paraformaldehyde (0.15 g, 5 mmol), and Me_2AlCl (6.58 mL of 1.14 M, 7.5 mmol) in 10 mL of CH_2Cl_2 were stirred for 26 h at 25 °C. Additional Me_2AlCl (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 (CCl_4) 3650, 2960, 1460, 1380, 1030 cm^{-1}; NMR ($CDCl_3$) 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_R = 55.0 min.

Reaction of cyclopentene (0.68 g, 10 mmol), **paraformaldehyde** (0.15 g, 5 mmol), and **1 equiv of Me_2AlCl** (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 ($CDCl_3$) 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_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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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_R = 12.2 min), GC (C, 160 °C), t_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 Me_2AlCl. An identical reaction with twice as much Me_2AlCl 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 (±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 ($CDCl_3$) 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 ($CDCl_3$) 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 **paraformaldehyde** (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-chlorocyclopentanol, 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 ($CDCl_3$) 3630, 1450, 1380, 1255, 1110, 1030 cm^{-1}; NMR ($CDCl_3$) δ 4.01 (q, 1, J = 6 Hz), 3.65 (d, 2, J = 6 Hz), 2.5–1.2 (m, 8); ^{13}C NMR ($CDCl_3$) 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_R = 20.3 min.

Reaction of cyclohexene (0.49 g, 6.0 mmol), **paraformaldehyde** (0.15 g, 5.0 mmol), and **1 equiv of Me_2AlCl** (4.39 mL of 1.14 M, 5.0 mmol) in 10 mL of CH_2Cl_2 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 (CCl_4) 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_R = 6.3 min.[5b] The data for **14b** are as follows: IR (CCl_4) 3650, 3400, 2930, 1445, 1270, 1070, 1020 cm^{-1}; NMR ($CDCl_3$) δ 4.56 (br s, 1, $W_{1/2}$ = 8 Hz), 3.54 (m, 2), 2.06–1.23 (m, 10); ^{13}C NMR ($CDCl_3$) 65.2 (CH_2OH), 61.6 (C_2), 44.3 (C_1), 34.1 (C_3), 25.0 (C_5), 22.8 (C_6), 20.2 (C_4);[40] GC (B, 170 °C), t_R = 19.3 min. The 3,5-dinitrobenzoate was recrystallized from 95% EtOH: mp 120–121 °C.

Reaction with 1.5 equiv of Me_2AlCl 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 (CCl_4) 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_R = 7.0 min.

The data for **16b** are as follows: NMR (CCl_4) 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 Me_2AlCl (13.16 mL of 1.14 M, 15.0 mmol) in 15 mL of CH_2Cl_2 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 pentane–ether) 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, C_3-H), 5.56 (ddd, 1, J = 10, 2, 2 Hz, C_4-H), 4.51 (m, 1, $W_{1/2}$ = 8 Hz, C_6-H), 3.62 (m, 2, CH_2OH), 3.35 (br s, 1, OH), 2.52 (br s, 2, C_5-H_2), 1.97 (br s, 3, C_1-H and C_2-H_2); ^{13}C NMR ($CDCl_3$) 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 $C_7H_{11}ClO$: 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 Me_2AlCl (4.8 mL of 1.14 M, 5.5 mmol) in 10 mL of CH_2Cl_2 for 1 h at 25 °C gave 0.697 g (≈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_R = 19.0 min. The spectral data for **20** are as follows: IR (CCl_4) 3655, 3030, 2940, 1470, 1430, 1255, 1060, 1010, 910 cm^{-1}; NMR ($CDCl_3$) δ 5.62 (m, 2), 4.59 (br t, 1, J = 5 Hz). 3.57 (d, 2, J =

(33) Stapp, P. R. *Synthesis* **1974**, 29.

5.5 Hz), 1.3–2.7 (m, 10); GC (B, 180 °C), t_R = 69.2 min. The spectral data for **21** are as follows: IR (CCl_4) 3650, 2950, 2875, 1450, 1040 cm^{-1}; NMR ($CDCl_3$) 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_R = 38.5 min.

Reaction of 1-octene (0.56 g, 5.0 mmol), **paraformaldehyde** (0.15 g, 5 mmol), and 1 equiv of Me_2AlCl (4.8 mL of 1.14 M, 5.5 mmol) in 12 mL of CH_2Cl_2 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 ($CDCl_3$) δ 5.8–5.2 (m, 2), 3.60 (td, 2, J = 6.2, 6.2 Hz), 2.22 (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_R = 6.7 min (90%), 7.3 min (10%). Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 76.15; H, 12.88.

The data for **23** are as follows: IR (CCl_4) 3650, 1040 cm^{-1}; NMR ($CDCl_3$) 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_R = 28.7 min.

With Excess Me_2AlCl. An identical reaction with 6.56 mL (7.5 mmol) of Me_2AlCl was stirred for 15 h at 25 °C. Additional Me_2AlCl (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 Et_2AlCl (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 $EtAlCl_2$ (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 *trans*- and *cis*-**22**. Chloro alcohol **23** was not detected. Longer reaction times gave complex mixtures.

Repetition of the reaction with $SnCl_4$ (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 Me_2AlCl (4.82 mL of 1.14 M, 5.5 mmol) in 10 mL of CH_2Cl_2 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 ($CDCl_3$) 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 Me_2AlCl (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 ($CDCl_3$) 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 Me_2AlCl (4.82 mL of 1.14 M, 5.5 mmol) in 10 mL of CH_2Cl_2 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 ($CDCl_3$) 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_R = 13.0 min.

The data for **31b** are as follows: IR (CCl_4) 3640, 1440, 1375, 1040 cm^{-1}; NMR ($CDCl_3$) 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_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 mmol), and Me_2AlCl (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 **30c**[35] are as follows: IR (CCl_4) 3650, 3085, 1055, 910 cm^{-1}; NMR ($CDCl_3$) 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_R = 57.0 min.

The data for **31c**[35,36] are as follows: IR (CCl_4) 3640, 2940, 1440, 1050 cm^{-1}; NMR ($CDCl_3$) 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_R = 76.0 min.

The data for **32c**[35,37] are as follows: IR (CCl_4) 3640, 2940, 1440, 1055 cm^{-1}; NMR ($CDCl_3$) 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_R = 69.1 min.

Reaction of isobutylene (0.59 g, 10.6 mmol), **paraformaldehyde** (0.95 g, 32 mmol), and Me_2AlCl (27.9 mL of 1.14 M, 32 mmol) in 30 mL of CH_2Cl_2 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 Me_2AlCl (7.18 mL of 1.14 M, 8.18 mmol) in 15 mL of CH_2Cl_2 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 (CCl_4) 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_R = 14.8 min. The data for **34** are as follows: IR (neat) 3350, 1668, 818 cm^{-1}; NMR (CCl_4) 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_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 Me_2AlCl (7.18 mL of 1.14 M, 8.18 mmol) in 15 mL of CH_2Cl_2 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 Me_2AlCl with $BF_3{\cdot}Et_2O$ (0.14 g, 1 mmol) gave 0.455 g (80%) of a 4:5 mixture of **33**:**34**.

An identical reaction with Me_3Al (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 Me_2AlCl (6.8 mL of 1.14 M, 7.5 mmol) in 15 mL of CH_2Cl_2 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 **36b**[38] are as follows: IR ($CDCl_3$) 3625, 3078, 1640, 1032 cm^{-1}; NMR ($CDCl_3$) 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_R = 18.2 min.

The data for **35b**[38] are as follows: IR ($CDCl_3$) 3625, 3035, 1640, 1375, 1037 cm^{-1}; NMR ($CDCl_3$) 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_R = 21.8 min.

Reaction of 1-methylcyclopentene (0.45 g, 5.5 mmol), **paraformaldehyde** (0.15 g, 5.0 mmol), and Me_2AlCl (6.8 mL of 1.14 M, 7.5 mmol) in 15 mL of CH_2Cl_2 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 ($CDCl_3$) δ **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 Me_2AlCl (13.2 mL of 1.14 M, 15.0 mmol) in 10 mL of CH_2Cl_2 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 ($CDCl_3$) 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 ^{13}C NMR spectrum was assigned by using cyclohexanemethanol as a base[18] 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; Me_2AlCl, 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*-2-heptene, 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-1-pentene, 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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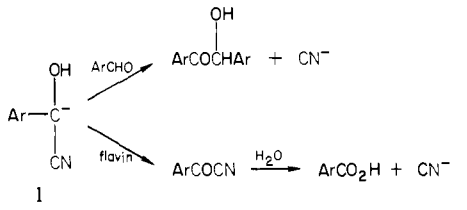
Abstract: The reaction sequence of acyloin condensation of aldehydes, catalyzed by thiazolium ion bound to the CTAB micelle, can be diverted by the addition of flavin to the oxidation reaction to afford the corresponding carboxylic acids. It was found, however, that when the aldehyde concentration is elevated or the aldehyde is relatively reactive, intermolecular flavin (3-methyltetra-*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 flavin–thiazolium biscoenzyme (Fl–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 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)

Scheme I



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