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DIAKLYLALUMINUM CHLORIDE CATALYZED ENE REACTIONS OF ALDEHYDES. SYNTHESIS OF IPSENOL

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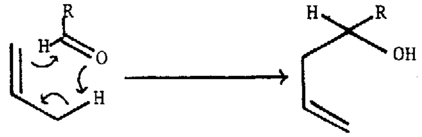
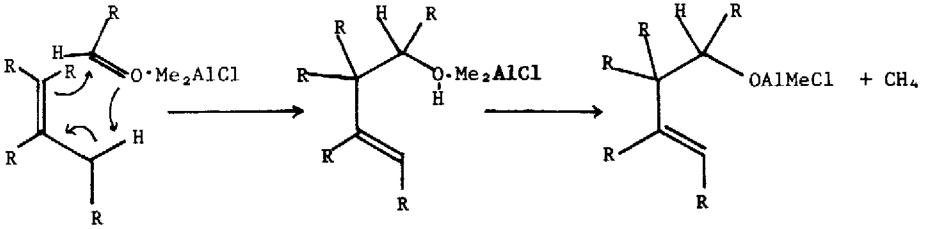
Summary: Dimethylaluminum chloride which is a mild Lewis acid and a proton scavenger, catalyzes the ene reactions of aliphatic and aromatic aldehydes. Proton initiated rearrangements do not occur, since the alcohol-Lewis acid complex formed in the ene reaction reacts rapidly to give methane and a non-acidic aluminum alkoxide.

The ene reaction[2] of aldehydes with alkenes provides a potentially valuable route to homoallylic alcohols (eq 1). Formaldehyde undergoes ene reactions with reactive alkenes at 180° in acetic anhydride-acetic acid[3] or at 25° with Lewis acid catalysis.[4] Aldehydes activated by electron withdrawing groups, such as chloral or methyl glyoxylate, are also reactive enophiles.[2,5] Aliphatic and aromatic aldehydes have not been used as enophiles. In the presence of aqueous mineral acid, aldehydes and alkenes undergo the Prins reaction.[6] Stepwise addition of a protonated aldehyde to an alkene gives a carbenium ion, which can lose a proton, react with nucleophiles present in solution, or react with another molecule of aldehyde to give m-dioxane.



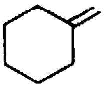
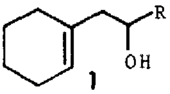
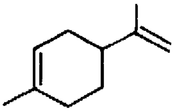
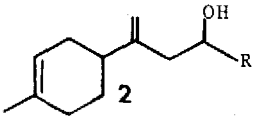
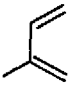
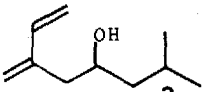
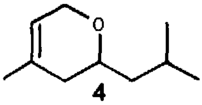
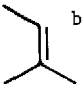
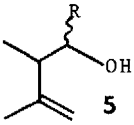
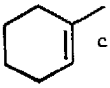
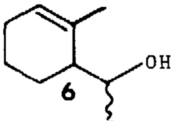
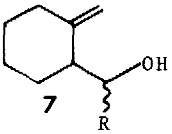
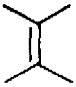
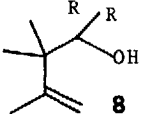
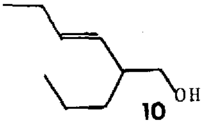
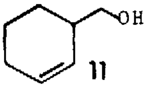
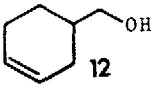
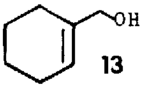
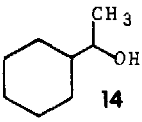
(1)

We have found that dimethylaluminum chloride (Me_2AlCl) is a useful catalyst for the ene reactions of aliphatic and aromatic aldehydes, and leads to improved yields of ene adducts from formaldehyde. Me_2AlCl is a mild Lewis acid and a proton scavenger. Use of Me_2AlCl circumvents the usual problem with Lewis acid catalyzed ene reactions of aldehydes: the alcohol-Lewis acid complex is a strong proton acid, capable of protonating the double bond of the alkene or ene adduct. The Me_2AlCl-alcohol complex formed in the ene reaction decomposes rapidly to give methane and a non-acidic aluminum alkoxide (See eq 2). $EtAlCl_2$, a catalyst we have previously used for other ene reactions,[7] is too acidic and leads to complex mixtures of products. The results of the Me_2AlCl catalyzed ene reactions of aldehydes are shown in Table 1.



(2)

TABLE 1. Me_2AlCl Catalyzed Ene Reactions of Aldehydes with Alkenes.[a]

Alkene	Products	Yield (%)
	 **1**	**1**a, R = CH_3 (91) **1**b, R = $CH_2CH(CH_3)_2$ (74) **1**c, R = Ph (69) **1**d, R = H (80) **1**e, R = $C(CH_3)_3$ (93)
	 **2**	**2**a, R = CH_3 (65) **2**b, R = $CH_2CH(CH_3)_2$ (79)
	 **3**  **4**	**3**(16) **4**(60)
 b	 **5**	**5**a, R = CH_3 (56) **5**b, R = $CH_2CH(CH_3)_2$ (38) **5**c, R = *n*-C_8H_{17} (42)
 c	 **6**  **7**	**6** (49) **7** (16)
 b, c	 **8**	**8**a, R = CH_3(35) **8**b, R = $CH_2CH(CH_3)_2$ (16)
	 **9**[d]	**9**(78)
trans-4-octene *cis*-4-octene	 **10**	**10** (58) **10**(62)
	 **11**  **12**  **13**  **14**	**11**(49) **12**(18) **13**(7) **14**(1)

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a) A 0.35 M solution of aldehyde in CH_2Cl_2 is treated with alkene (1.1 eq) and Me_2AlCl (1.5 eq, 1.1 M in heptane)[15] at 25°. The mixture is stirred overnight and quenched with pH 4 phosphate buffer. b) Pivaldehyde gives only 3,3-dimethyl-2-butanol. c) Benzaldehyde gives only 1-phenylethanol. d) 9:1 trans-cis ratio.

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), *iso*-valeraldehyde or benzaldehyde, as well as formaldehyde (as trioxane or paraformaldehye). Since methylenecyclohexane is easily isomerized to 1-methylcyclohexene, the success of these reactions indicates the effectiveness of Me_2AlCl as a proton scavenger. The reaction of aldehydes with limonene occurs exclusively at the less substituted double bond as reported by Blomquist for the reaction with formaldehyde.[4] Lewis acid catalyzed reactions of methyl propiolate with limonene show only slight (x 1.5) preference for the less substituted double bond, presumably due to the smaller steric bulk of the acetylene.[7] *Iso*-valderadldehyde and limonene give a 70% yield of 2b, an intermediate in Crawford's synthesis of dihydro-*ar*-turmerone.[8]

The ene reaction of *iso*-valeraldehyde with isoprene provides a one-step synthesis of ipsenol (3), a sex attractant of the bark beetle *Ips confusus*.[9] Treatment of *iso*-valeraldehyde with isoprene gives a 16% yield of ipsenol (3) and a 60% yield of Diels-Alder adduct 4,[10] which is related to nerol oxide and rose oxide.[10] 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. Similar products were obtained in varying ratios, since the ene adduct was converted to the diphydropyran during the reaction by protonation to give an allylic carbenium ion which closes to give the dihydropyran.[11] Use of Me_2AlCl allows the isolation of acid-sensitive ipsenol, since proton 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 hr at 150° has been reported to give a 4% yield of Diels-Alder adduct.[13]

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. 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.[14] 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. Diethylaluminum chloride can also be used as a catalyst in these reactions, but ethyl addition is faster than methyl addition and lower yields of ene adducts are obtained.

Ene reactions of 2-methyl-2-butene give good yields of ene adduct 5 as a 1:1 mixture of diastereomers. 1-Methylcyclohexene gives mixtures of regioisomers 6 and 7 as well as diastereomers. The isolation of 7 is due to the aprotic reaction conditions since 7 is easily isomerized to 6 by proton acids. Aliphatic aldehydes react with 2,3-dimethyl-2-butene to give moderate yields of 8.

Formaldehyde reacts with 1-pentene to give a 9:1 mixture of *trans*- and *cis*-3-hexen-1-ol(9) and with both *cis*-and *trans*-4-octene to give predominantly trans 2-propyl-3-hexen-1-ol. With cyclohexene and formaldehyde, a mixture of unsaturated alcohols are obtained which appear to be formed by a Prins reaction. 1,2-Disubstituted alkenes are sterically and electronically the poorest substrates for ene reactions. Cyclohexene is particularly poor because of geometric constraints.[2] No ene adducts can be obtained from mono- and 1,2-disubstituted alkenes with benzaldehyde or acetaldehyde.

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 7 to be isolated. Using this catalyst, ene adducts have been obtained 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.

References and Notes

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