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THE ATE COMPLEXES OF ALUMINIUM

REACTIVITY AND STEREOSELECTIVITY WITH RESPECT TO EPOXIDES AND CARBONYL COMPOUNDS. CATALYTIC ACTIVATION BY SALTS OF TRANSITION METALS[a]

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Abstract—When used in non-coordinating solvents (hydrocarbons) $NaAlEt_4$ and $LiAlnBu_4$ are good alkylation agents for epoxides. The presence of catalytic quantities of transition-metal salts, particularly $NiCl_2$ or $NiBr_2$, greatly accelerate the reactions, making them possible within a reasonable time in the case of disubstituted epoxides such as cyclohexene oxide, 2-3 epoxybutane, 1 phenyl-2,3-epoxybutane. In the case of aliphatic epoxides, dialkylmagnesium, $NaAlEt_4$ and $LiAlnBu_4$ lead mainly to alkylation of the least substituted carbon of the epoxide ring; while in the case of epoxides with a C-O bond in the benzyl position, it is this carbon that is alkylated. The reaction always proceeds by total inversion of the configuration of the carbon in the epoxide ring, namely the site of the alkylation.

$NaAlEt_4$ is also a good agent for alkylating carbonyl compounds when used in solvents of low basicity such as diethylether, or in totally non-coordinating solvents such as the hydrocarbons. The yields of the alcohol are greatly improved by using catalytic quantities of $NiCl_2$. The behaviour of $NaAlEt_4$ with 2-phenylpropanol is quite remarkable: in diethylether $NaAlEt_4$ gives predominantly the pair of enantiomers predicted by Cram's rule, and with greater stereoselectivity than if EtMgBr was used, while in pentane the reaction is no longer stereoselective. Finally, with a cyclic ketone, 4-t-butylcyclohexanone, $NaAlEt_4$ in diethylether and in hexane in the presence of $NiCl_2$ gives predominantly the equatorial alcohol resulting from an axial attack, which is generally not favoured at all

The interest in the ate complexes of aluminium in organic synthesis has increased considerably since the recent discovery that a wide variety of these ate complexes can be prepared by the hydroalumination of multiple C–C bonds with LAH in the presence of transition-metal salts[1-6] or by the addition of an organoaluminium compound to a multiple C-C bond in the presence of an organolithium compound.[7-9] This has motivated us to publish the results obtained in the reaction of sodium tetraethylaluminate and lithium tetrabutylaluminate with epoxides and carbonyl compounds.

I. *The reactivity of* $NaAlEt_4$ *and* $LiAlnBu_4$ *with Mono- or disubstituted epoxides and a bifunctional compound, ethyl 3-phenylglycidate*

Our first aim was to verify that the agent responsible for alkylating the epoxides was indeed the ate complex itself and not the products of any dissociation it might have undergone. For this purpose we brought these various organometallic compounds together with a terminal epoxide, namely 1-phenyl-2,3 epoxypropane under identical experimental conditions. The results are shown in Table 1.

Examination of this Table shows that the alkylating agent is indeed the ate complexes $NaAlEt_4$ or $LiAlnBu_4$ and not the trialkylaluminium $AlEt_3$ or $AlnBu_3$, nor the nBuLi, all of which react with 1-phenyl-2,3-epoxypropane to give different products. Thus, like the dialkylmagnesiums[10,11] or the cuprates,[12,13] the tetraalkylaluminates of sodium and lithium react with a terminal epoxide such as 1-phenyl-2,3-epoxypropane to give a secondary alcohol resulting from the opening of the epoxide ring when the least substituted carbon is alkylated. A gc investigation revealed no products produced by previous isomerisation of the epoxide into carbonyl compounds. The reaction of these ate complexes is slow, requiring 24 hr at 35° for an alcohol yield higher than 90%.

Influence of the solvent and the reactant ratio. The structure of the complex aluminates has been studied in detail, both in the solid state and in a variety of solvents. In the solid state these compounds are essentially ionic, the Al atom being tetracoordinated into an AlR_4^- anion, which has a symmetry similar to that of a regular tetrahedron.[14-18] In solution,[19-22] equilibria exist between the various species (Scheme 1).

$$\underset{\text{unsolvated solid}}{M^{+}AlR_4^{-}} \rightleftharpoons \underset{\text{contact ion pairs}}{M^{(+)}AlR_4^{(-)}} \rightleftharpoons \underset{\text{solvent separated ion pairs}}{M^{(+)}\|AlR_4^{(-)}}$$

Scheme 1.

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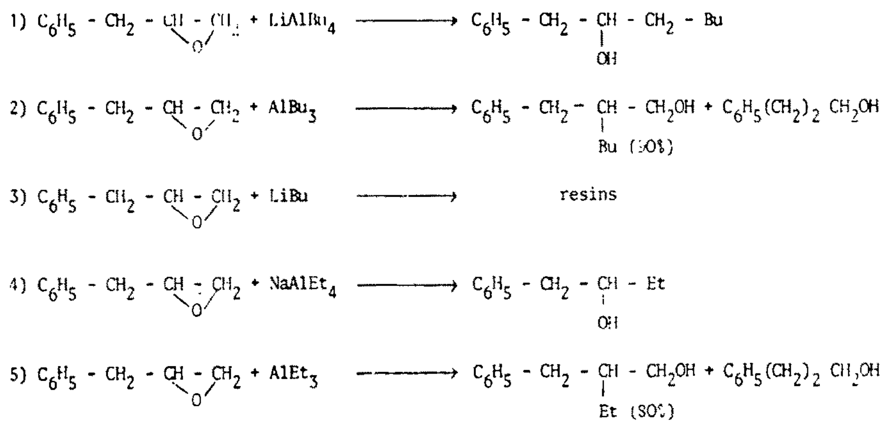
[a] Preliminary results: *Tetrahedron Letters* 2521 (1975); *Ibid.* 993 (1976).

Table 1. Reaction of − 1 phenyl-2,3 epoxy propane with sodium and lithium tetraalkylaluminates, trialkylaluminiums, and butyllithium



1) $C_6H_5-CH_2-\underset{\diagdown O \diagup}{CH-CH_2} + LiAlnBu_4 \longrightarrow C_6H_5-CH_2-\underset{OH}{CH}-CH_2-Bu$

2) $C_6H_5-CH_2-\underset{\diagdown O \diagup}{CH-CH_2} + AlBu_3 \longrightarrow C_6H_5-CH_2-\underset{Bu\ (50\%)}{CH}-CH_2OH + C_6H_5(CH_2)_2\,CH_2OH$

3) $C_6H_5-CH_2-\underset{\diagdown O \diagup}{CH-CH_2} + LiBu \longrightarrow$ resins

4) $C_6H_5-CH_2-\underset{\diagdown O \diagup}{CH-CH_2} + NaAlEt_4 \longrightarrow C_6H_5-CH_2-\underset{OH}{CH}-Et$

5) $C_6H_5-CH_2-\underset{\diagdown O \diagup}{CH-CH_2} + AlEt_3 \longrightarrow C_6H_5-CH_2-\underset{Et\ (50\%)}{CH}-CH_2OH + C_6H_5(CH_2)_2\,CH_2OH$

Solvent: pentane; Reaction time at 35° : 24 hr; Ratio: organometallic compound/epoxide = 2; Hydrolysis with aqueous NH_4Cl 20%.

The sodium salts such as $NaAlEt_4$ or $NaAlnBu_4$, if they are soluble in noncoordinating solvents such as the hydrocarbons, exist essentially in the form of contact ion pairs, whereas in sufficiently basic coordinating solvents such as THF, DMSO, or DME, in which they are always soluble, they exist essentially in the form of ion pairs separated by the solvent. The various results reported in the literature indicate that Li salts are less easy to dissociate in the form of ion pairs separated by the solvent than are Na salts. The results observed in our investigation of the reactivity as a function of the solvent are shown in Table 2.

Solvent: THF. In this basic solvent the reaction did not take place and after hydrolysis the epoxide was recovered quantitatively (Experiments 7 and 8). $LiAlnBu_4$ and $NaAlEt_4$ are probably largely present, as ion pairs separated by the solvent. It then seems plausible that the Li^+ or Na^+ cations in their strongly solvated state are no longer able to complex at the oxygen of the epoxide bridge, and that such complex formation is in all likelihood essential to the opening of the epoxide ring.

Solvent: Et_2O. The reaction did not take place with $NaAlEt_4$, but with $LiAlnBu_4$ the yield of the alcohol was 80% under similar conditions (Experiments 5 and 6). The difference in reactivity observed between $LiAlnBu_4$ and $NaAlEt_4$ may be connected with the difference in the acid assistance between Li^+ and Na^+.

Table 2. Solvent effect in the reaction of 1-phenyl-2,3-epoxypropane with $NaAlEt_4$ and $LiAlnBu_4$

Exp	M Al R_4	Solvent	Ratio $MAlR_4/epox.$	$C_6H_5-CH_2-\underset{OH}{CH}-CH_2-R$ yield %
1	$LiAlnBu_4$	pentane	1/1	90
2	$LiAlnBu_4$	pentane	2/1	96
3	$NaAlEt_4$	pentane	1/1	92
4	$NaAlEt_4$	pentane	2/1	97
5	$LiAlnBu_4$	Et_2O	1/1	80
6	$NaAlEt_4$	Et_2O	1/1	traces
7	$LiAlnBu_4$	T H F	1/1	0
8	$NaAlEt_4$	T H F	1/1	0

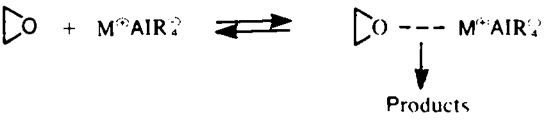
Reaction time at 35° : 24 hr.

but in our opinion it is due to the difference between the structures of these two ate complexes: $LiAlnBu_4$, the more reactive ate complex, exists mainly in Et_2O in the form of contact ion pairs, while in the same solvent $NaAlEt_4$ is largely in the form of ion pairs separated by the solvent.

The above interpretation is supported by the following facts: (a) There is no such difference in reactivity between $NaAlEt_4$ and $LiAlnBu_4$ in a noncoordinating solvent such as pentane. (b) The ate complexes are most reactive in solvents, in which they are insoluble and exist in the form of ions in contact.

Solvent: pentane. Generally in any noncoordinating solvent (hexane, cyclohexane) the reaction was almost quantitative, irrespective of whether the $MAlR_4$/epoxide ratio was 1/1 or 2/1 (Experiments 1 to 4).

As the ratio of reactants has no affect and the reactivity decreases considerably in coordinating solvents, the first stage of reaction is probably the formation of a complex between the organometallic and the epoxide. This complex then changes spontaneously without the need for any excess of organometallic as is the case with R_2Mg or R_3Al.[23-25] Consequently, we propose the following reaction Scheme:



Scheme 2

In a noncoordinating solvent the equilibrium is shifted completely towards the formation of the complex.

Catalysis by salts of the transition metals. The reaction of the ate complexes with 1-phenyl-2,3-epoxypropane is slow, requiring 24 hr at 35° for alcohols yields higher than 90%.

A number of results reported highlight the activation of the reactions of organometallics by catalytic quantities of transition-metal salts.

Thus, in the case of organoaluminiums brought together with electrophilic substrates, Ashby, showed that 1,4-addition of $AlMe_3$ and $LiAlMe_4$ to an α,β-ethylenic ketone is catalysed by nickel acetylacetonate.[26] Similary Mole *et al.* used catalytic quantities of transition-metal salts to activate the reactions of $AlMe_3$ with ketones, nitriles, and α,β-ethylenic ketones.[27-29] The reactions of $NaAlEt_4$ with 1-phenyl-2,3-epoxypropane are reported in Table 3.

Table 3. Reaction of 1-phenyl-2,3-epoxypropane with $NaAlEt_4$ in the presence of catalytic amounts of transition metal

Exp.	Catalyst	Solvent	$C_6H_5-CH_2-\underset{OH}{CH}-CH_2Et$ yield %
1	without	hexane	5
2	$NiCl_2$	hexane	95
3	$NiBr_2$	hexane	96
4	$FeCl_3$	hexane	11
5	$CoCl_2$	hexane	81
6	CuCl	hexane	20
7	PtO_2	hexane	30
8	$TiCl_4$	hexane	76
9	Ni (Raney) [a]	hexane	5
10	Ni on activated carbon	hexane	5
11	$NiCl_2$	T H F	0

Reaction time at 35°. 15 min; Ratio: $NaAlEt_4$/epoxyde/catalyst: 1,2/1/0,02; Hydrolysis with aqueous NH_4Cl 20%; a: Nickel of Raney, washed several times with methanol then toluene.

When the solvent is a hydrocarbon, the reaction rate is increased considerably in the presence of catalytic quantities (about 2%) of $NiCl_2$, $NiBr_2$, $CoCl_2$, or $TiCl_4$ (Experiments 2, 3, 5, 8). Table 3.

The most efficient catalysts were found to be $NiCl_2$ and $NiBr_2$; thus, in the presence of these salts the alcohol yield was greater than 90% after 15 min at 35°, whereas without catalyst a comparable yield was achieved only after 24 hr.

Among the other salts used, $FeCl_3$ and CuCl were less efficient. It should be noted that PtO_2 is an effective catalyst for the reaction.

In the presence or absence of these various catalysts the product was the same 1-phenyl-2-pentanol, sometimes together with small amounts of 1-phenyl-2-propanol which may have resulted from reduction of the epoxide.

Finally in THF the reaction did not take place in the presence or absence of $NiCl_2$ (Experiment 11, Table 3).

The addition of these metal salts to the ate complex produced a very finely divided black powder, or in the case of $TiCl_4$ a brown colour. Probably the salt was reduced to the metal, except perhaps in the case of $TiCl_4$.

Although Ni^0 as a catalyst proved unsuccessful (Experiments 9 and 10, Table 3), the surface condition of the metal obtained when $NiCl_2$ was reduced by the ate complexe was without doubt very different from that of Raney Ni.

In addition, the reaction of $LiAlnBu_4$ with 1-phenyl-2,3-epoxypropane was also catalysed by salts such as $NiCl_2$, $NiBr_2$ or $TiCl_4$. Whereas CuI had no catalytic action. No reaction took place in THF, even in the presence of $NiCl_2$.

The behaviour of $NaAlEt_4$ *in the presence of a stoichiometric quantity of* $NiCl_2$ *are shown in Table* 4. With an $NaAlEt_4/NiCl_2$/epoxide ratio of 2:1:1 the reactivity was similar to that of triethylaluminium with this epoxide or, more precisely, the reactivity of Et_3Al in the presence of $NiCl_2$.

This result can be explained in terms of the following Scheme:

$$2NaAlEt_4 + NiCl_2 \longrightarrow (NiEt_2) + 2NaCl + 2AlEt_3$$

$$(NiEt_2) \longrightarrow Ni^0 + \text{hydrocarbons}$$

Scheme 3.

The process is comparable to the one proposed for the reduction of $Ni(acac)_2$ by trialkylaluminium.[30]

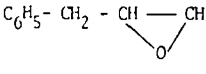
Thus, it may be supposed that when catalytic quantities of $NiCl_2$ are added to the ate complexe the nickel salt is reduced to the state of Ni^0 in accordance with a scheme analogous to the one just proposed.

On the basis of existing knowledge it does not seem reasonable to propose a reaction mechanism that would take this catalytic action into account. However, our results seem very comparable to those obtained by Mole *et al.* for the reaction of $AlMe_3$ with nitrile, ketones or α,β-ethylenically unsaturated ketones in the presence of nickel.[27-29]

Regioselectivity and stereochemistry. In addition to 1-phenyl-2,3-epoxypropane, the reactions of $LiAlnBu_4$ and $NaAlEt_4$ were investigated with various mono- or disubstituted epoxides. The results are shown in Table 5.

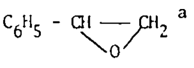
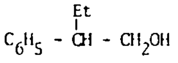
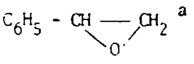
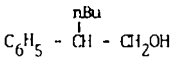
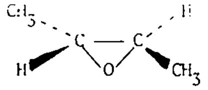
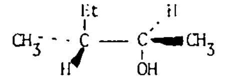
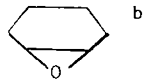
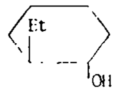
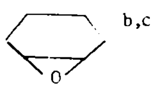
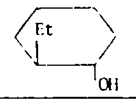
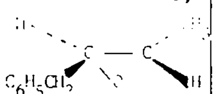
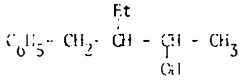
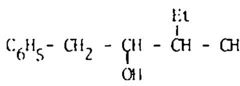
$NaAlEt_4$ and $LiAlnBu_4$ both reacted easily with styrene oxide; as in the case of the dialkylmagnesiums, the reaction product was the primary alcohol obtained when the ring was opened by alkylation of the benzyl carbon. This result emphasises the importance of acid assistance when epoxide rings are to be opened by tetraalkylaluminates. Thus, it is plausible that, as with the dialkylmagnesiums,[31,32] a partial positive charge appears in the transition state on the carbon about to by alkylated. In the case of styrene oxide this charge is

Table 4. Reactions of 1-phenyl-2,3-epoxypropane with $NaAlEt_4$ and Et_3Al in presence and absence of $NiCl_2$

	$NaAlEt_4$ [a] $NiCl_2$ catal.	2 $NaAlEt_4$ [b] 1 $NiCl_2$	Et_3Al [b,c]	Et_3Al [b,c] $NiCl_2$ catal.	Et_3Al [b,d,e]
$C_6H_5-CH_2-CH(OH)-CH_2Et$	95	5			
$C_6H_5-CH_2-CH(Et)-CH_2OH$		56	80	75	traces
$C_6H_5-CH_2-CH_2-CH_2-OH$		18	20	22	traces
$C_6H_5-CH_2-CH(OH)-CH_3$	traces	7		3	28
$C_6H_5-CH_2-CH(OH)-CH_2Cl$		10			
		4			70

Solvent: hexane; Reaction time at 35°: a: 24 hr; b: 2 hr; Ratio: $NaAlEt_4$/epoxide = 2/1; c: Et_3Al/epoxide = 2/1; d: Et_3Al/epoxide = 1/1; e: reversal introduction.

Table 5. Reaction of various epoxides with $NaAlEt_4$ and $LiAlnBu_4$

Epoxyde	M Al R_4 Catalyst	addition alcohols yield %	
 a	$NaAlEt_4$	 $C_6H_5-CH(Et)-CH_2OH$	95
 a	$LiAlnBu_4$	 $C_6H_5-CH(nBu)-CH_2OH$	92
	$NaAlEt_4$ $NiCl_2$	 $CH_3-CH(Et)-CH(OH)-CH_3$	90
 b	$NaAlEt_4$ $NiCl_2$		94
 b,c	$LiAlnBu_4$ $NiCl_2$		60
 b,d	$NaAlEt_4$ $NiCl_2$	 $C_6H_5-CH_2-CH(Et)-CH(OH)-CH_3$  $C_6H_5-CH_2-CH(OH)-CH(Et)-CH_3$	21 79

Solvent: pentane; Reaction time at 35° a: 4 hr; b: 24 hr; c: in this case the solvent is toluene. The reaction gives also 12% of cyclohexanol; d: yields of alcohols normalized to 100%. The yield of the reaction in more than 90%.

strongly stabilised on the benzyl carbon by the presence of the phenyl group.

The reaction of $NaAlEt_4$ and $LiAlnBu_4$ with styrene oxide was more rapid than that with 1-phenyl-2,3-epoxypropane, so that there was no need for a transition-metal catalyst.

The reactions with *trans*-2,3-epoxybutane, cyclohexene oxide, and *trans*-1-phenyl-2,3-epoxybutane were very slow in the absence of $NiCl_2$ or $NiBr_2$ (alcohol yields lower than 10% after 48 hr at 35°). In the presence of *ca* 2% $NiCl_2$ or $NiBr_2$ they were almost quantitative after 24 hr at 35°.

Investigation of the reactions of $NaAlEt_4$ *and* $LiAlnBu_4$ *with* trans *ethyl 3-phenylglycidate.* As $LiAlMe_4$ has no action upon esters.[33] We investigated the behaviour of tetraalkylaluminates with *trans*-ethyl 3-phenylglycidate.

The only product of the two reactions was the hydroxy ester produced by an attack of organometallic on the benzyl carbon of the epoxide bridge; the ester group being unaffected.

The action of $NaAlEt_4$ on *trans*-ethyl 3-phenylglycidate gave exclusively a pair of enantiomers: ethyl 3-phenyl-2-hydroxypentanoate (2*R*, 3*S*) (2*S*, 3*R*), and the action of $LiAlnBu_4$ gave exclusively ethyl-3-phenyl-2-hydroxy-heptanoate (2*R*, 3*S*) (2*S*, 3*R*).

Therefore the reactions of these ate complexes proceed by total inversion of the configuration of the benzyl carbon of the glycidic ester.

$AlMe_3$ and $AlnBu_4$ reacted with this glycidic ester to give the same type of hydroxy esters as $NaAlEt_4$ and $LiAlnBu_4$, but the configuration of the benzyl C atom was now largely retained.[34,35]

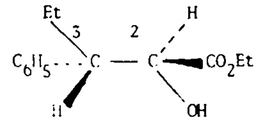
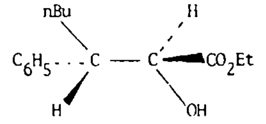
The results obtained with the ate complexes of aluminium are all the more interesting in that this glycidic ester with dialkylmagnesiums and alkyllithiums mainly gives resins.

II. *Reactivity and stereoselectivity of the alkylation of carbonyl compounds by sodium tetraethylaluminate*

Ashby *et al.*, investigating the alkylation of cyclic and bicyclic ketones by various ate complexes of Mg, Zn, B and Al,[36,37] have shown that with Al complexes the stereochemistry is different from that of the other organometallics with 4-t-butylcyclohexanone, a high percentage of the equatorial alcohol being produced.

Our own work with epoxides has revealed: (a) The considerable influence of the solvent on the reactivity of the tetraalkylaluminates and (b) the catalytic activation of these reactions by transition-metal salts, particularly Ni salts. Consequently we studied the reaction of a Na salt, namely sodium tetraethylaluminate, on carbonyl compounds in variety of

Table 6. Reactions of *trans*-3-phenyl-2,3-epoxypropanoic acid ethyl ester with $NaAlEt_4$ and $LiAlnBu_4$

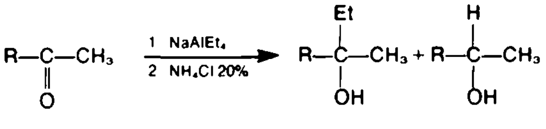
$MAlR_4$	addition alcohol yield %
$NaAlEt_4$	 (2R, 3S)(2S, 3R) 100.
$LiAlnBu_4$	 (2R, 3S)(2S, 3R) 100.

Solvent: hexane; Reaction time at 35°: 4 hr; Ratio $MAlR_4$/epoxyester = 1; Hydrolysis with aqueous NH_4Cl 20%, no catalyst used.

solvents: (THF, Et_2O, hydrocarbons) in the presence and absence of catalytic quantities of $NiCl_2$.

We investigated the reactivity with acetophenone and 1-phenyl-2-propanone, and then studied the stereoselectivity in relation to a Cram-type aldehyde, 2-phenylpropanal, and to a cyclic ketone: 4-t-butylcyclohexanone.

The reactions of $NaAlEt_4$ *with acetophenone and 1-phenyl-2-propanone.* Thus, $NaAlEt_4$ reacted with these ketones in accordance with Scheme 4 below:



R = C_6H_5, C_6H_5-CH_2

Scheme 4.

The addition alcohol was sometimes accompanied by small amounts of R–CHOH–CH_3. In THF, after hydrolysis, acetophenone was unaffected whether or not catalytic quantities of $NiCl_2$ were present (Table 7, Experiments 1–3).

This lack of reactivity could be due to enolisation but this was rejected as $NaAlEt_4$ will not react with benzophenone under similar conditions (2 hr at 35°).

In diethylether, toluene, or pentane, and in the absence of $NiCl_2$, the reaction was incomplete (Table 7, Experiments 4, 5, 7, 8, 9; Table 8, Experiments 1 and 3).

The yield of alcohol did not change if the reactant ratio $NaAlEt_4$/ketone was changed (Table 7, Experiments, 4, 5, 7, 8, 9).

Except in THF, the presence of $NiCl_2$ greatly improved the yield of alcohol (Table 7, Experiments 6, 10, 12; Table 8, Experiments 2 and 4). In these cases, besides the addition alcohol, very small amounts of the

Table 7. Solvent and ratio effects in the reaction of acetophenone with $NaAlEt_4$

Exp.	Solvent (catalyst)	Ratio $NaAlEt_4$/cétone	addition alcohol yield %	reduction alcohol yield %
1	THF	1/1	traces	0
2	THF	2/1	2	0
3	THF ($NiCl_2$)	1/1	traces	0
4	Et_2O	1/1	43	0
5	Et_2O	2/1	44	0
6	Et_2O ($NiCl_2$)	1/1	70	traces
7	Toluene	1/1	43	0
8	Toluene	2/1	44	0
9	Toluene	3/1	44	0
10	Toluène ($NiCl_2$)	1/1	79	4
11	Pentane	1/1	49	0
12	Pentane ($NiCl_2$)	1/1	84	8

Reaction time at 35°: 2 hr.

Table 8. Solvent and catalyst effect in the reaction of 1-phenyl-2-propanone with $NaAlEt_4$

Exp.	solvent (catalyst)	addition alcohol yield %	reduction alcohol yield %
1	Et_2O	12	0
2	Et_2O ($NiCl_2$)	60	traces
3	Pentane	35	0
4	Pentane ($NiCl_2$)	82	3

Reaction time at. 35 : 2 hr. Ratio $NaAlEt_4$/ketone: 1.

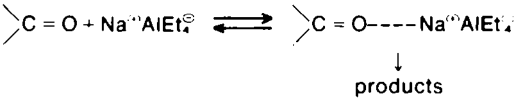
reduction alcohol were produced. As alkylation was predominant in the presence of $NiCl_2$, the use of an organometallic offering the possibility of a β-reduction was surprising. Thus, Grignard reagents, with an H atom in the β position gave the reduction product of the substrate in the presence of nickel salts.[38,39] These results show that there is a strong analogy between the reactivity of $NaAlEt_4$ with epoxides and ketones:

(a) The basicity of the solvent influences the reactivity to a considerable extent.

(b) The ratio of reactants appears unimportant

(c) Catalytic activation by $NiCl_2$.

Results (a) and (b) indicate that, as with the epoxides, the addition reaction entails the formation of a complex that subsequently changes spontaneously in accordance with Scheme 5.



Scheme 5.

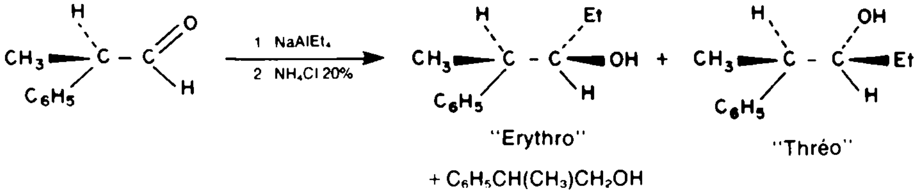
In a basic solvent such as THF formation of this complex would be strongly inhibited.

Several reports emphasise the importance of the complexing of the alkali metal cation at the CO oxygen in the reduction of ketones by double hydrides ($LiAlH_4$, $LiBH_4$, $NaBH_4$). By masking the cation by macrobicyclic coordination, it was shown that this is an indispensable feature of reduction by a tetrahydroaluminate.[40–43]

The problem is complicated since the solvent influences both the position of the equilibrium that leads to the complex and the structure of the organometallic by modifying the equilibria mentioned in Scheme 1.

Investigation of the reaction of $NaAlEt_4$ *with a Cram-type aldehyde, 2-phenylpropanal.* Table 9 shows that $NaAlEt_4$ reacted with 2-phenylpropanal to give a mixture of *threo* and *erythro* addition alcohols, according to Scheme 6.

The addition alcohols were accompanied by a very small amount of the reduction alcohol



Scheme 6.

Table 9. Reaction of 2-phenylpropanal with $NaAlEt_4$

Exp.	Solvent (catalyst)	Erythro %	Threo %	Reduction alcohol yield %	ratio $\frac{\text{Erythro}}{\text{Threo}}$
1	T H F	0	0	0	
2	Et_2O	55	17	traces	3,24
3	Et_2O ($NiCl_2$)	68	19	2	3,58
4	Pentane	37	37	traces	1,00
5	Petnane ($NiCl_2$)	45	39	1	1,15

Reaction time at: 35 : 1 hr; Ratio $NaAlEt_4$/aldehyde = 1.

$C_6H_5CH(CH_3)CH_2OH$. No reaction took place in THF.

In diethylether we obtained a mixture of the *erythro* and *threo* addition alcohols in which the *erythro* pair of enantiomers predominated.

The use of $NiCl_2$ increased the yield of addition alcohols without appreciably changing the *erythro*/*threo* ratio. It should be noted that in this solvent $NaAlEt_4$ showed a better stereoselectivity than EtMgBr, which gave an *erythro*/*threo* ratio equal to 3.[44]

In pentane the use of $NiCl_2$ improved the yield of addition alcohols without appreciably altering the stereoselectivity.

Finally, in both diethylether and pentane, the stereoselectivity remained almost the same whether the $NaAlEt_4$/aldehyde ratio was equal to 1 or 2 and the reaction time to 1 hr or 2 hr.

Investigation of the stereochemistry of the reaction of $NaAlEt_4$ *with a cyclic ketone*, 4-*t-butylcyclohexanone*. Table 10 shows that $NaAlEt_4$ reacted with this cylic ketone to give a mixture of the equatorial *E* and axial *A* addition alcohols, according to Scheme 7.

A very small amount $(<5\%)$ of a mixture of reduction alcohols was also formed. No reaction took place in THF.

In diethylether or hexane the reaction gave a high percentage of the equatorial alcohol *E*. The *E*/*A* ratio was greatest in hexane in the presence of catalytic quantities of $NiCl_2$. Ashby had already found a high percentage of the equatorial alcohol in the reaction of $LiAlMe_4$ with this cyclic ketone.[36]

Finally, the reactant ratio ($NaAlEt_4$/ketone = 1 or 2) and the reaction time (2 hr or 1 hr) had only a very small effect on the stereoselectivity of this reaction.

The fact that the equatorial alcohol *E* was obtained predominantly is rather unusual. In fact, except for trialkylaluminiums in hydrocarbon solvents with AlR_3/ketone = 2,[45–47] and for $ZnMe_2$ or $CdMe_2$ in the presence of MgX_2,[48] the other organometallics produce a preponderance of the axial alcohol.

In general three factors, steric approach control, torsional effect and compression effect are taken into account in the stereochemistry of the alkylation of 4-t-butylcyclohexanone.[37,48,50]

The compression effect acts to oppose equatorial attack, thus favouring the production of the equatorial alcohol.[39] This effect is invoked mainly to explain the high percentage of the equatorial alcohol obtained in the reaction of $AlMe_3$ with this cyclic ketone when the $AlMe_3$/ketone ratio ≥ 2. An equatorial attack of a second $AlMe_3$ molecule compresses the complexed carbonyl against the H atoms 2 and 6 in the transition state. In contrast, an axial attack decreases the steric hindrance between the complexed carbonyl and the equatorial hydrogens in positions 2 and 6. Thus, in the case of the cyclic ketones the compression effect may favour axial attack (the attack that is sterically unfavourable).

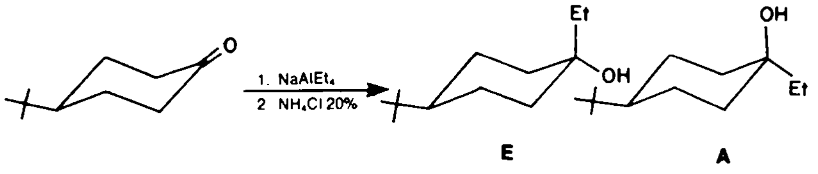
The transition states proposed for the reaction of $AlMe_3$ with ketones when the $AlMe_3$/ketone ≥ 2 are similar to those postulated for the reaction of $NaAlEt_4$ with a ketone.

In the reaction of $NaAlEt_4$ with 4t-butylcyclohexanone, as suggested by Ashby for the reaction of $LiAlMe_4$ with this ketone, the compression effect accounts for the presence of substantial quantities of the equatorial alcohol.

CONCLUSIONS

$NaAlEt_4$ and $LiAlnBu_4$ when using noncoordinating solvents (hydrocarbons), are good alkylating agents for epoxides.

The presence of catalytic $NiCl_2$ or $NiBr_2$, greatly accelerates the reactions. In the case of disubstituted

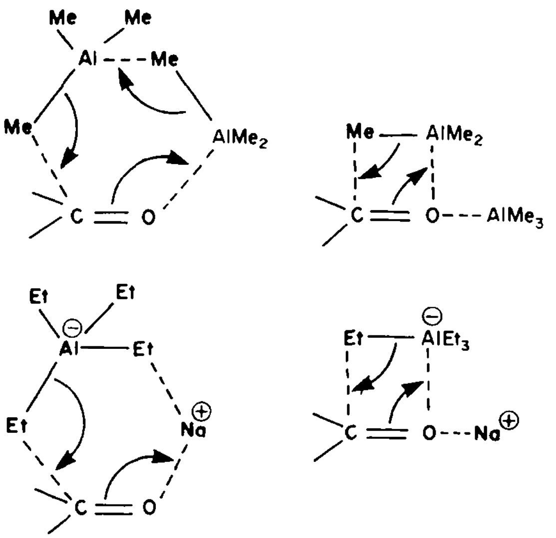


Scheme 7.

Table 10. Reaction of 4-t-butylcyclohexanone with $NaAlEt_4$.

Exp.	Solvent (catalyst)	E %	A %	Ratio E/A
1	T H F	0	0	
2	Et_2O	23	21	1,10
3	Et_2O ($NiCl_2$)	40	35	1,14
4	Hexane	19	20	0,95
5	Hexane ($NiCl_2$)	38	26	1,46

Reaction time at 35 : 4 hr; Ratio $NaAlEt_4$/ketone: 1.



Scheme 8.

epoxides, these ate complexes are more reactive than the corresponding dialkylmagnesiums in diethylether.

In the case of the aliphatic epoxides the sodium and lithium tetraalkylaluminates lead mainly to alkylation of the least substituted carbon of the epoxide ring. In the case of epoxides with a C–O bond in the benzyl position, this carbon is alkylated exclusively.

The reaction always proceeds by total inversion of the configuration of the carbon in the epoxide ring, namely the site of the alkylation.

Thus, since recent work has shown that it is easy to prepare a large variety of tetraalkylaluminates starting with a terminal ethylenic group,[1–9] these organometallics present a certain interest for the synthesis of alcohols formed by direct opening of the epoxide ring. We believe that in some cases they may be more interesting than the cuprates derived from the corresponding Grignard reagent (the most easily accessible cuprates) which, because of the presence of magnesium halides, involve a risk of isomerisation of certain epoxides.

Finally, in their reaction with bifunctional compounds the ate complexes seem to be extremely selective: thus, with *trans*-ethyl 3-phenylglycidate the only alcohol obtained is the result of alkylation of the benzyl carbon with total inversion of its configuration, whereas dialkylmagnesiums and alkyllithium give resins.

$NaAlEt_4$ is a good agent for alkylating carbonyl compounds when used in solvents of low basicity such as diethylether, or in totally noncoordinating solvents such as the hydrocarbons. The yield of the addition alcohol are greatly improved by using $NiCl_2$. In a more basic solvent such as THF we have not observed the alkylation of these carbonyl compounds, even in the presence of $NiCl_2$.

The behaviour of $NaAlEt_4$ with 2-phenylpropanal in diethyl ether gives predominantly the pair of enantiomers predicted by Cram's rule, and this with better stereoselectivity than ethylmagnesium bromide, while in pentane the reaction is no longer stereoselective.

Finally, with a cyclic ketone, 4-t-butylcyclohexanone, $NaAlEt_4$ in diethylether and in hexane in the presence of $NiCl_2$ gives predominantly the equatorial alcohol resulting from an axial attack, which is generally not favoured at all.

Thus, with the ate complexes of aluminium it seems possible to alkylate the cyclic ketones in the axial position. It is known that the trialkylaluminiums too effect alkylation predominantly in the axial position, but except for the trimethylaluminium, they unfortunately give mixtures of the addition and reduction alcohols.

EXPERIMENTAL

Solvents. THF, diethylether and toluene were distilled from LAH. Pentane, hexane and cyclohexane were distilled from Na. All solvents were stored in dry box under N_2 atmosphere.

Organometallic compounds. Manipulation of organometallic compounds were performed whenever possible in a dry box under pure N_2.

$LiAlnBu_4$ was prepared by mixing equimolar amounts of nBuLi dissolved in hexane and pure nBu_3Al. The white powder formed was filtered off, washed three times with pentane and dried under vacuum (3 hr 50°, 0,1 mm Hg).[52]

$NaAlEt_4$ was prepared according to method Frey *et al.* by heating at 110° during 2 hr dispersed sodium and Et_3Al in toluene.[51, 52]

Epoxides. 1-phenyl-2,3-epoxypropane was prepared by the method of Tiffeneau and Fourneau.[53]

$IR_{(cm^{-1})}$: 700, 740, 1260, 3011, 3060; ^1H NMR δ 2.2 to 3.1 (m, 5) δ 7.15 (m, 5 aromatic).

1-phenyl-2,3-epoxybutane (*trans*) was prepared by expoxodation of mixture of 1-phenyl-2,3 butene (*cis* + *trans*) with *p*-nitroperbenzoic acid and separation by preparative gc.[24] ^1H NMR δ 1.2 (d, 3), δ 2.4 to 2.8 (m, 4) δ 7.1 (m, 5 aromatic).

Styrene oxide and cyclohexene oxide were commercial products, purified by distillation before use.

trans-2,3-Epoxybutane was prepared by the method of Winstein and Lucas[55] from commercial *trans*-2-butene.

trans-Ethyl 3-phenylglycidate

At room temp, 0.25 mole ethyl choracetate was added to a flask containing 0.25 mole NaH in 100 ml N,N-dimethylformamide. 0.25 mole of benzaldehyde were then added. The mixture was allowed to stand over night then hydrolysed, and extracted with diisopropyl ether. After distillation, the *trans* isomer (major product) was separated by preparative gc. 20% Carbowax 20M Chromosorb W (60 80 a.w.). ^1H NMR δ: 1.3 (t, 2, OCH_2 $C\underline{H}_3$), δ: 3.35 (d, 1, $-\underline{C}H \cdot CO_2Et$) δ: 4, (d, 1, $C_6H_5 \cdot \underline{C}\underline{H}$) J = 1.5 Hz δ: 4.21 (q, 2, $-O-\underline{C}H_2-CH_3$) δ: 7.3 (m, 5, aromatic).

cis Ethyl 3-phenylglycidate

(Coupling constant for hydrogens on eppxide bridge was J = 6 Hz).

General procedure. In a dry box under pure N_2 g, 0.005 mole of solid ate complex was introduced into a 50 ml flask fitted with rubber septum, 10 ml of the solvent was added through the septum with a syringe. The flask was then immersed in a thermostatic bath, and the organic compound (epoxide or carbonyl compound) was added with a syringe. The hydrolysis was performed with 20% NH_4Cl aq, internal standard was added and after extraction analysis of organic layer was effectuated by gc.

Identification of alcohols. Alcohols resulting of the alkylation of various epoxides were identified by cg with authentic samples generally obtained by reaction of the epoxide with Et_2Mg or nBu_2Mg in Et_2O.[23,24,31,57] Furthermore we verified that the alcohols obtained had a retention time different from that of the alcohols which could result from isomerisation of the epoxide to carbonyl compound. The analyses by cg were performed on the following columns: 17% carbowax 20 M on chromosorb W (60 80) a.w.; 17% JXR on chromosorb W (60 80) a.w.; 12%

carbowax 20 M + 5% apiezon on chromosorb W (60–80) a.w.

Ethyl 3-phenyl-2-hydroxypentanoate (2R, 3S) (2S, 3R) *and ethyl 3-phenyl-2-hydroxyheptanoate* (2R, 3S) (2S, 3R)

These compounds were identified by gc as one of the hydroxyesters obtained by reaction of Et_3Al or nBu_3Al with *trans*-ethyl 3-phenylglycidate.[54]

The configuration of the hydroxyesters was determined after the transformation of ester group into a Me group.[56]

The alcohols obtained by this transformation were identified by gc by comparison of their retention time with alcohols obtained by reduction of 3-phenyl-2 pentanone and 3-phenyl-2 heptanone with LAH. The preponderant diastereomeric product was given by Cram's rule.

Reactions with carbonyl compounds. Acetophenone, 1-phenyl-2 propanone, 2-phenyl propanal and 4-terbutylcyclohexanone were commercial products purified by distillation or crystallisation before reaction.

Identification of alcohols. Alcohols obtained were identified by gc by means of reference alcohols by comparison of their retention times on two columns: 17% carbowax 20 M on chromosorb W (60–80 a.w.). 12% carbowax 20 M + 5% Apiezon on chromosrob (60–80 a.w.).

The absence of addition alcohol in the reaction of $NaAlEt_4$ with benzophenone in the THF was verified by ^1H NMR on the crude product of reaction.

4-*Phenyl*-3 *pentanols.* A mixture of diastereomeric alcohols *erythro* and *threo* was prepared by reaction of Grignard reagent of EtBr with 2-phenylpropanal. In this reaction diastereomeric "*Erythro*" alcohol was the preponderant product.[44]

4-*ter Butyl*-1-*ethylcyclohexanols.* A mixture of alcohols was prepared by reaction of Grignard reagent of EtBr with 4-t-butyl-cyclohexanone. In this reaction, the alcohol *A* with the OH group in the axial position was the preponderant product.[37]

REFERENCES

[1] E. C. Ashby and J. J. Lin, *Tetrahedron Letters* 4481 (1977).

[2] F. Sato, S. Sato, H. Kodama and M. Sato, *J. Organometal. Chem.* **142,** 71 (1977).

[3] F. Sato, H. Kodama and M. Sato, *Chem. Letters* 789 (1978).

[4] F. Sato, K. Oguru and M. Sato, *Ibid.* 805 (1978).

[5] K. Isagawa, M. Ohige, K. Tatsumi and Y. Otsuji, *Ibid.* 1155 (1978).

[6] F. Sato, H. Kodama, Y. Tomuro and M. Sato, *Ibid.* 623 (1979).

[7] S. Baba, D. E. Van Horn and E. Negishi, *Tetrahedron Letters* 1927 (1976).

[8] E. Negishi, S. Baba and A. O. King, *J. Chem. Soc. Chem. Comm.* 17 (1976).

[9] G. Zweifel, R. A. Lynd and R. E. Murray, *Synthesis* 52 (1977).

[10] A. Shaap and J. F. Arens, *Recl. Trav Chim. Pays-Bas* **87,** 1249 (1968).

[11] G. Boireau, J. L. Namy and D. Abenhaim, *Bull. Soc. Chim. Fr.* 1042 (1972).

[12] C. R. Johnson, R. W. Herr and D. M. Wieland, *J. Org. Chem.* **38,** 4263 (1973).

[13] R. D. Acker, *Tetrahedron Letters* 3407 (1977).

[14] R. Wolfrum, G. Sauermann and E. Weiss, *J. Organomet. Chem.* **18,** 27 (1969).

[15] J. L. Atwood and D. C. Hrncir, *Ibid.* **61,** 43 (1973).

[16] K. Mach, *Ibid.* **2,** 410 (1964).

[17] R. L. Gerteis, R. E. Dickerson and T. L. Brown, *Inorganic Chem.* **3,** 872 (1964).

[18] J. Yamamoto and C A. Wilkie, *Ibid.*, **10,** 1129 (1971).

[19] T. D. Westmoreland, J. R., N. S. Bhacca, J. D. Wander and M. C. Day, *J. Organomet. Chem.* **38,** 1 (1972).

[20] Naseer Ahmad and M. C. Day, *J. Am. Chem. Soc.* **99,** 941 (1977).

[21] J. L. Wuepper and A. I. Popov, *Ibid.* **92,** 1493 (1970).

[22] J. F. Ross and J. P. Oliver, *J. Organomet. Chem.* **22,** 503 (1970).

[23] J. L. Namy, G. Boireau and Abenhaim, *Bull. Soc. Chim. Fr.*, 3191 (1971).

[24] G. Boireau, J. L. Namy and D. Abenhaïm, *Ibid.* 1042 (1972).

[25] G. Boireau and D. Abenhaïm, *J. organomet. Chem.* **92,** 131 (1975).

[26] E. C. Ashby and G. Heinsohn, *J. Org. Chem.* **39,** 3297 (1974).

[27] E. A. Jeffery, A. Meisters and T. Mole, *Aust. J. Chem.* **27,** 2569 (1974).

[28] L. Bagnell, E. A. Jeffery, A. Meisters and T. Mole, *Ibid.* **27,** 2577 (1974).

[29] L. Bagnell, E. A. Jeffery, A. Meisters and T. Mole, *Ibid.* **28,** 801 (1975).

[30] K. Fischer, K. Jonas, P. Misbach, R. Stabba and G. Wilke, *Angew. Chem.* Internat. Ed. **12,** 943 (1973).

[31] J. Deniau, E. Henry-Basch and P. Fréon, *Bull. Soc. Chem., Fr.* **12,** 4414 (1969).

[32] J. D. Morisson, R. L. Atkins and S. E. Tomaszewski, *Tetrahedron Letters* 4635 (1970).

[33] D. J. Pasto and R. Snyder, *J. Org. Chem.* **30,** 1634 (1965).

[34] D. Abenhaïm and J. L. Namy, *Tetrahedron Letters* 1001 (1972).

[35] G. Boireau, D. Abenhaïm, C. Bernardon, E. Henry-Basch and B. Sabourault, *Ibid.* 2521 (1975).

[36] E. C. Ashby, L. C. Chao and J. Laemmle, *J. Org. Chem* **39,** 3253 (1974).

[37] E. C. Ashby and J. Y. Laemmle, *Chem. Rev.* **75,** 521 (1975).

[38] H. Felkin and G. Swierczewski, *Tetrahedron* **31,** 2735 (1975).

[39] E. Colomer, R. P. J. Corriu and B. Meunier, *J. Organometal. Chem.* **71,** 197 (1974).

[40] J. L. Pierre and H. Handel, *Tetrahedron Letters* **2,** 2317 (1974).

[41] J. L. Pierre, H. Handel and R. Perraud, *Tetrahedron* **31,** 2795 (1975).

[42] H. Handel and J. L. Pierre, *Ibid.* **31,** 2799 (1975).

[43] H. Handel and J. L. Pierre, *Tetrahedron Letters* 2029 (1976)

[44] D. J. Cram and F. A. Abd El Hafez, *J. Am. Chem. Soc.* **74,** 5828 (1952).

[45] E. C. Ashby and S. Yu, *J. Chem. Soc.* D, 351 (1971).

[46] J. L. Namy, *C.R. Acad. Sci.* Série *C*, **272,** 1334 (1971).

[47] E. C. Ashby, S. Yu and P. V. Roling, *J Org. Chem.* **37,** 1918 (1972).

[48] P. R. Jones, E. J. Goller and Q. J. Kauffman, *Ibid.* **34,** 3566 (1969).

[49] M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Letters* 2199 (1968).

[50] M. Cherest and H. Felkin, *Ibid.* 2205 (1968).

[51] F. W. Frey, P. Kobetz, G. C. Robinson and T. O. Sistrunk *J. Org. Chem.* **26,** 2950 (1961).

[52] G. Boireau, D. Abenhaïm and E. Henry-Basch, *Tetrahedron* **35,** 1457 (1979).

[53] M. Tiffeneau and E. Fourneau, *Bull. Soc. Chim. Fr.* **43,** 456 (1928).

[54] J. L. Namy, D. Abenhaïm and G. Boireau, *Bull. Soc. Chim. Fr.* 2943 (1971).

[55] S. Winstein and H. S. Lucas, *J. Am. Chem. Soc.* **61,** 1576 (1939).

[56] H. L. Goering and C. Serres Jr., *Ibid.* **74,** 5908 (1952).

[57] G. Boireau and D. Abenhaïm, *J. Organometallic Chem.* **92,** 131 (1975).