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BORON TRIFLUORIDE ASSISTED OPENING OF EPOXIDES BY LITHIUM ALKENYL ALUMINATE REAGENTS

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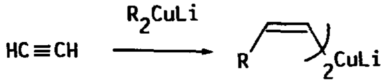
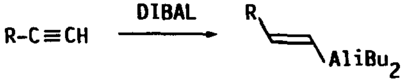
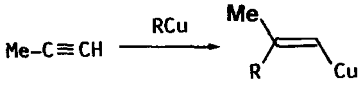
Summary *- Alkenyl aluminate reagents, obtained by hydroalumination of terminal alkynes followed by ate complexation with MeLi, react readily with poorly reactive cyclic ethers such as cyclohexene oxide and oxetane, in the presence of* $BF_3.Et_2O$. *Alkenyl aluminate reagents obtained by reaction of an alkenyl lithium reagent and* Me_3Al *behave similarly.*

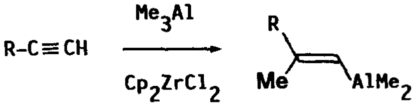
INTRODUCTION -

We have recently demonstrated that organocuprate reagents react very rapidly with poorly reactive epoxides, in the presence of boron trifluoride etherate[1]. Thus various alkyl, alkenyl and aryl groups are efficiently transferred. On the other hand, alkyl, alkenyl and phenyl lithium reagents[2], are well as alkynyl lithium reagents[3], are known to react in an analogous manner with epoxides under the electrophilic assistance of $BF_3.Et_2O$[4].
The hydroalumination and carboalumination reactions of alkynes are convenient ways to obtain alkenyl aluminum derivatives[5]. In this respect they are complementary to the carbocupration of alkynes[6], giving generally the opposite stereochemistry around the double bond.





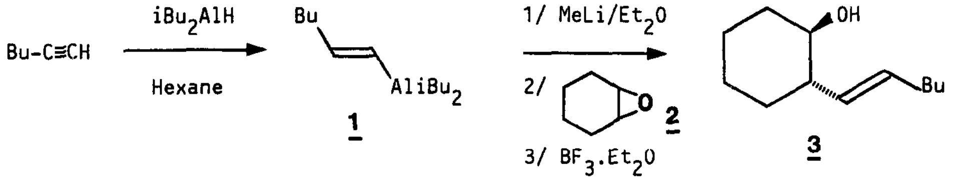




Unfortunately, alkenyl aluminum reagents react very slugishly with epoxides[7]. Even after ate complexation with MeLi, they only react with unhindered ones[5]. It is noteworthy, for example, that they do not open cyclohexene oxide in more than 5% yield[8]. We report herein that the electrophilic assistance of $BF_3.Et_2O$ permits, now, such a reaction.

RESULTS AND DISCUSSION -

Alkenyl aluminum reagent 1 was prepared in the usual manner[5], by hydroalumination of 1-hexyne with diisobutyl aluminum hydride (DIBAH) in hexane as solvent. This aluminum derivative 1 is totally unreactive towards cyclohexene oxide 2 in hexane, Et_2O or THF, at room temperature or at reflux. Upon addition of one eq. of $BF_3.Et_2O$ at -78°C, in hexane or Et_2O, only polymerization products were obtained. Thus, reagent 1 is not enough a good nucleophile to react even with electrophilically activated cyclohexene oxide. It is already known that organoaluminum ate complexes are much superior nucleophiles[5,7]. For example reagent 1, reacts after ate complexation, with MeLi[5], with monosubstituted epoxides (but not with cyclohexene oxide 2). Therefore we added halide free MeLi (1M in Et_2O) to reagent 1, then cyclohexene oxide in Et_2O and finally one equivalent of $BF_3.Et_2O$, at -78°C. Immediatly, an exothermic reaction took place, and after work up a 60% isolated yield of 2-(E)-hexenyl cyclohexanol 3 was obtained (entry 1).

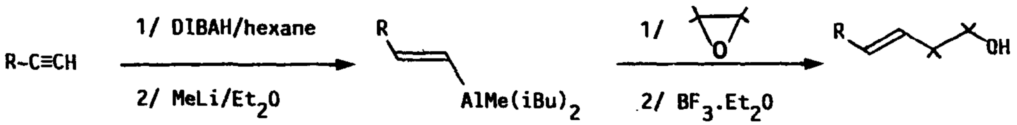


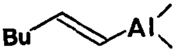
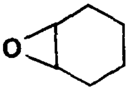
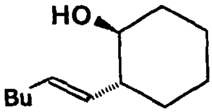
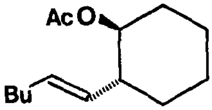
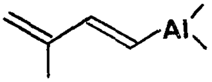
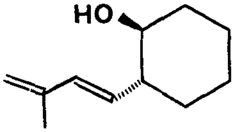
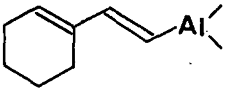
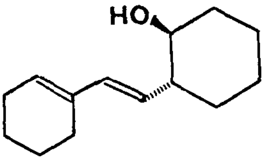
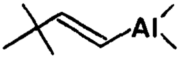
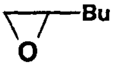
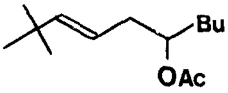
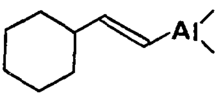
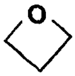
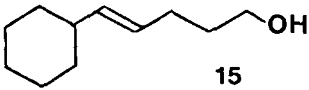
This result demonstrates the effectiveness of this procedure for the reaction of organoaluminum reagent with poorly reactive epoxides.

It is remarkable that no cationic rearrangement of cyclohexene oxide took place and that only a single stereoisomer of 3 was observed, having a trans relationship between the two substituents on the cyclohexane ring.

When the same reaction was performed with MeLi containing LiBr (entry 2), a slightly better yield of 3 was obtained but contaminated with 2-bromo cyclohexanol 4 (3/4 : 80/20). Thus nucleophilic competition between the alanate reagent of 1 and Br^- ion is a problem which has to be taken into account[4]. Nevertheless base treatment of the crude product destroys the halohydrin 4 and acetylation permits the isolation of 5 the acetate of 3, by distillation. It should be noted, that the isolation of the products shown in the table is best performed by flash column chromatography. Attempts to distill the crude product generally gave poor yields, due to some boron impurities in the crude mixture. However, when this crude mixture is acetylated (Ac_2O, pyridine) these impurities disappear and distillation of the acetate is not any more troublesome.

As shown in the table, the reaction works well also with monosubstituted epoxide 11 (entry 5). Only one regioisomer 12 is observed, the one arising from attack at the less hindered side of the epoxide. It should be recalled that all the reactions mentioned in the table are performed under stoichiometric conditions. No optimization studies were done with an excess of either reagent. Oxetane 14 reacts smoothly and gives high yield of alkenol 15 (entry 6). This is the first report on opening of oxetane by alkenyl-aluminum reagents. Attempts to open epoxysilane 16 were however unsuccesful[9], as well as the reaction of the silicon bearing organoalanate 17 with cyclohexene oxide.



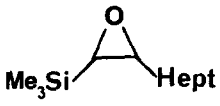
Entry	Alkenyl Aluminum reagent	Epoxide	Product	Yield
1	 **1**	 **2**	 **3**	60%^{a}
2	″	″	 **5**	68%^{b}
3	 **6**	″	 **7**	61%^{a,c}
4	 **8**	″	 **9**	67%^{a,d}
5	 **10**	 **11**	 **12**	75%^{b}
6	 **13**	 **14**	 **15**	72%^{a}

a/ Isolated by flash column chromatography

b/ Isolated by distillation after acetylation (see experimental part)

c/ Accompanied, in 11% yield, by the parent alkynol (see text)

d/ Accompanied, in 9% yield, by the parent alkynol (see text)



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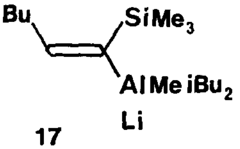

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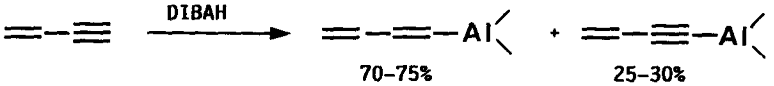
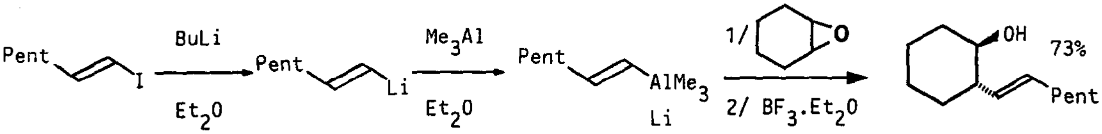
Of particular interest are the examples shown in entries 3 and 4, with dienic organoaluminum reagents 6 and 8. The latter are easily prepared in situ by hydroalumination of 1-enynes. The obtained dienols 7 and 9 are interesting substrates for further synthetic elaboration as examplified by the intramolecular Diels-Alder reaction described in the next paper. It should however be pointed out that the formation of dienic aluminum reagents is plagued by alkynyl aluminum reagents arising from metallation[5].



The latters react also quite well with epoxides so that 2-alkynyl cyclohexanols are also formed, which are difficult to remove completely either by distillation or column chromatography.

Another way to prepare an alkenyl alanate reagent is to start with an alkenyl lithium reagent according to :



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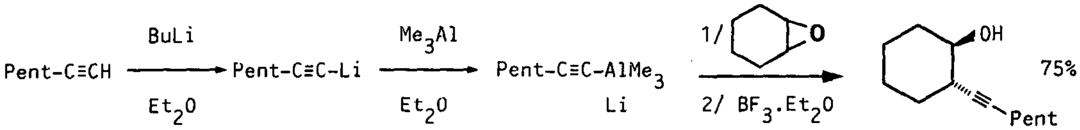
Such an approach generalizes the reaction of organoaluminate reagents with epoxides to any alkenyl lithium reagents. Although the latter reagents react already with epoxides in the presence of $BF_3.Et_2O$, an excess of usually 3 equivalents RLi is needed[2]. The same argument holds also for organocuprate reagents which need 2 equivalents RLi to form one eq. of a cuprate reagent[1]. The above reaction with alanates was performed under strictly stoichiometric conditions. Thus an alkenyl aluminum approach seems quite competitive with respect to the number of equivalents of organolithium reagent needed.

Alkynyl alanates also undergo the reaction :



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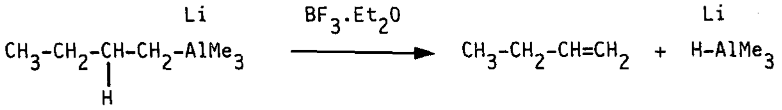
However, in this case, alkynyl lithium reagents are known to react similarly (with $BF_3.Et_2O$) without excess reagent[3], so the organoaluminum approach seems less competitive. Finally, we also have tried the reaction with n-butyl trimethyl alanate and cyclohexene oxide (with $BF_3.Et_2O$). 2-Butyl cyclohexanol was produced in less than 10% yield, the major product being cyclohexanol itself. Its presence arises from a hydride species formed in situ by BF_3 promoted ß-elimination according[7] to :



$$CH_3\text{-}CH_2\text{-}\underset{\displaystyle H}{\overset{\displaystyle Li}{CH}}\text{-}CH_2\text{-}\bar{A}lMe_3 \xrightarrow{BF_3.Et_2O} CH_3\text{-}CH_2\text{-}CH{=}CH_2 + \overset{\displaystyle Li}{H\text{-}AlMe_3}$$

Such a hydride species may be generated with diisobutyl alkenyl alanates if the selectivity of the alkenyl transfer is not total (as it is usually the case[5]). However we did not detect cyclohexanol itself is these experiments.

In conclusion it is evident that BF_3 promoted opening of epoxides works well not only with organolithium and organocuprate reagents, but also with organoaluminate reagents. Its extension to heteroatom nucleophiles is presently under way in order to widen even more the scope of this reaction.

EXPERIMENTAL -

^1H NMR spectra were recorded on a Jeol MH100 apparatus ($CDCl_3$; δ ppm from TMS).
^{13}C NMR on a Jeol FX90Q ($CDCl_3$; δ ppm from TMS).
IR spectra were obtained on a Perkin Elmer model 457 spectrometer (neat, cm^{-1}).
GLPC analyses were performed on a Carlo Erba chromatograph model G1 and 2150 using a 3m glass column (10% SE30 on silanized chromosorb G 80/100 mesh or Carbowax 20M) and 25m capillary glass column (OV 101).
The gas chromatograph was coupled to an integrator Hitachi D2000.

The hydroalumination of alkynes is performed exactly as described in ref. 5. To the alkenyl aluminum (35 mmol) solution in hexane (90 ml) is added halide free MeLi (35 mmol, 1M in Et_2O) at -20°C. After stirring for 10 min at 0°C, the epoxide (or oxetane) (30 mmol) in Et_2O (20 ml) is added. The mixture is then cooled to -78°C and $BF_3.Et_2O$ (3.8 ml, 30 mmol) in Et_2O (30 ml) is slowly introduced while the temperature rises to -50°C. After 15 min, the reaction is quenched with MeOH (20 ml) and, after 10 min at -30°C, with 1N HCl (50 ml). The salts are filtered off, the aqueous layer extracted with Et_2O (3 x 50 ml) and the combined organic phases washed once with aqueous $NaHCO_3$ (50 ml) then dried over $MgSO_4$. After evaporation of the solvents, the crude product is chromatographied on SiO_2 (eluent Hex/EtOAc : 95/5) or acetylated in the following manner : the crude product is dissolved in pyridine (50 ml), acetic anhydride (5.7 ml, 60 mmol) is added, and the mixture stirred overnight at room temperature. Then, MeOH (10 ml) is added and, after 1 h, the reaction mixture is partitioned in Et_2O (200 ml) and aqueous $NaHCO_3$ (100 ml). The organic layer is washed with 1N HCl (3 x 50 ml) then dried over $MgSO_4$. After evaporation of the solvent, the crude product is distilled through a 10 cm Vigreux column.

2-(E,1-hexenyl)-1:cyclohexanol 3 :**I.R.** : 3330, 970. ^1H **NMR** : 5.67(dt,1H), 5.34(dd,1H), J : 16Hz, 3.22(m,1H), 1.0-2.2(m,16H), 0.91(t,3H). ^{13}C **NMR** : 133.1, 132.3(-CH=), 73.1(-CHOH), 50.1(CH), 33.9, 32.4, 31.7, 25.4, 24.9, 22.3(CH_2)n 13,9(CH_3). Anal. : $C_{12}H_{22}O$: 182.30 ; calc. : C : 79.05, H : 12.16 ; found : C : 79.11, H : 12.11.
2-(E,1-hexenyl)-1-cyclohexyl acetate 5 : **B.p.** : 72-73°C/0.05 mmHg. **I.R.** : 1735, 965.
^1H **NMR** : 5.0-5.6(m,2H), 4.55(m,1H), 1.93(s,3H), 1.1-2.0(m,15H), 0.86(t,3H).
^{13}C **NMR** : 169.9(-COO-) 131.9, 131.2(-CH=), 75.4(-CH-OAc), 46.8(CH), 32.3, 32.0, 31.8, 31.7, 25.1, 24.7, 22.2(CH_2), 21.1, 13.9(CH_3). Anal. $C_{14}H_{24}O_2$: 224.34 ; calc. C : 74.95, H : 10.78 ; found C : 74.91, H : 10.84.
2-(3-methyl-1,3-butadienyl)-1-cyclohexanol 7 : **I.R.** : 3330, 3010, 965. ^1H **NMR** : 6.28(d,1H), 5.56(dd,1H), J-16Hz, 4.92(s,2H), 3.25(m,1H), 2.60(m,1H), 1.84(s,3H), 1.0-2.0(m,9H)
^{13}C **NMR** : 141.9(-C=), 134.2, 132.8(-CH=), 115.1$(=CH_2)$, 73.5(-CHOH), 49.9(-CH-), 34.7, 31.8, 25.6, 25.1(CH_2), 18.7(CH_3).

2-|2-(1-hexenyl)-E,1-ethenyl|-1-cyclohexanol 9 : I.R. : 3330, 3010, 965. ^{1}H **NMR** : 6.15(d,1H), 5.35(dd,1H), J : 16Hz, 5.18(t,1H), 3.19(m,1H), 1.1-2.2(m,18H). ^{13}C **NMR** : 135.7 (-CH=), 135.4(-C=), 128.6, 127.8(-CH=), 73.5(-CHOH), 50.4(-CH-), 34.0, 31.8, 25.8, 25.4, 24.9, 24.7, 22.7, 22.6(CH$_2$).
2-Dimethyl-E,3-decen-6-yl acetate 12 : B.p. : 71-72°C/0.05 mmHg. **I.R.** : 1730, 965 ^{1}H **NMR** : 5.48(d,1H), 5.24(dt,1H), J : 16 Hz, 4.80(m,1H), 2.16(dd,2H), 1.96(s,3H), 1.0(s,9H), 0.90-1.6(m,9H). ^{13}C **NMR** :170.3(-COO-), 144.7, 119.8(-CH=), 73.7(-CH-OAc), 37.8, 33.4, 32.9, 29.7, 27.6, 22.6, 21.1, 14.0. Anal. C$_{14}$H$_{26}$O$_2$: 226.36 ; calc. C : 74.29, H : 11.58 ; found C : 74.22, H : 11.65.
6-Cyclohexyl-E,4-penten-1-ol 15. I.R : 3330, 970. ^{1}H **NMR** : 5.38(m,2H), 3.58(t,2H), 1.1-2.15(m,16H). ^{13}C **NMR** : 137.2, 127.0(-CH=), 62.3(-CH$_2$OH), 40.7, 33.4, 32.7, 29.1, 26.4, 26.2. Anal C$_{11}$H$_{20}$O : 168.28 ; calc. C : 78.51, H : 11.98 ; found C : 78.58, H : 11.92.
The two following compounds were obtained starting with an alkenyl or alkynyl lithium compound : to an ethereal solution (100 ml) of E,1-Iodo-1-heptene[10] (7.84 g, 35 mmol) is added *n*-BuLi (1.6N solution in hexane) (21.8 ml, 35 mmol) at -78°C. After 10 min at -50°C, Me$_3$Al (2.38 M in hexane) (14.7 ml, 35 mmol) is added. The mixture is stirred 10 min at 0°C and then the aluminate is treated as described in the general procedure (epoxide, BF$_3$.Et$_2$O etc...).
2-(E,1-heptenyl)-1-cyclohexanol 18 : B.p. : 64-65°C/0.05 mmHg. **I.R.** : 3330, 970 ^{1}H NM : 5.70(dt,1H), 5.32(dd,1H), J = 16 Hz, 3.15(m,1H), 1.0-2.3(m,18H), 0.88(t,3H) ^{13}C **NMR** : 132.7, 132.4(-CH=), 73.2(-CHOH), 50.0(-CH-), 34.1, 32.8, 31.8, 31.5, 29.3, 25.5, 25.0, 22.6(CH$_2$), 14.1(CH$_3$. Anal. C$_{13}$H$_{24}$O : 196.33 ; calc. C : 79.53, H : 12.32 ; found C : 79.58, H : 12.29.
To an ethereal solution (100 ml) of 1-heptyne (3.84 g, 40 mmol) is added n-BuLi (1.6N in hexane) (21.8 ml, 35 mmol) at -10°C. The mixture is stirred 30 min at room temperature (milky precipitate), then cooled to -50°C. Me$_3$Al (2.38 M in hexane)(14.7 ml, 35 mmol) is added and the solution stirred at 0°C for 10 min. The alkynyl alanate is ready for further reaction as described in the general procedure.
2-(1-heptynyl)-1-cyclohexanol 19 : B.p. : 72-74°C/0.05 mmHg. I.R. : 3350, 2250 ^{1}H **NMR** : 3.35(m,1H), 1.1-2.3(m,18H), 0.89(t,3H). ^{13}C **NMR** : 82.5, 81.5(-C≡C-), 73.6(-CHOH), 39.0(-CH-), 33.1, 31.4, 31.2, 28.9, 25.0, 24.3, 22.3, 18.8(CH$_2$), 14.0(CH$_3$).Anal. C$_{13}$H$_{22}$O : 194.32 ; calc. C : 80.36, H : 11.41 ; found C : 80.44, H : 11.39.

Acknowledgments -
The authors thank Professor J.F. Normant for fruitful discussions and the C.N.R.S. for financial support (U.A. 473).

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