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DIASTEREOSELECTIVE β-ELIMINATION. SYNTHESIS OF CHIRAL ALKOXY-ALLENES

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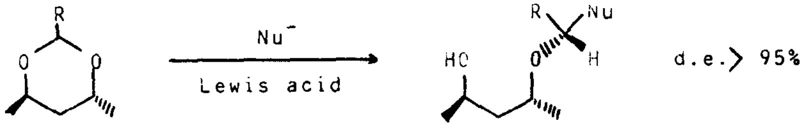
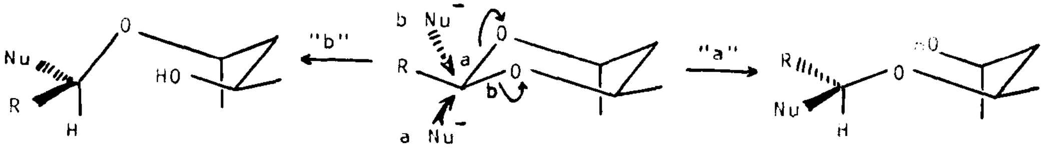
Summary : Chiral alkoxy-allenes are obtained by reaction of chiral acetylenic acetals with Grignard reagents in the presence of catalytic amount of copper salt. The crucial step is a highly diastereoselective β-elimination reaction of the transient alkenyl organometallic species.

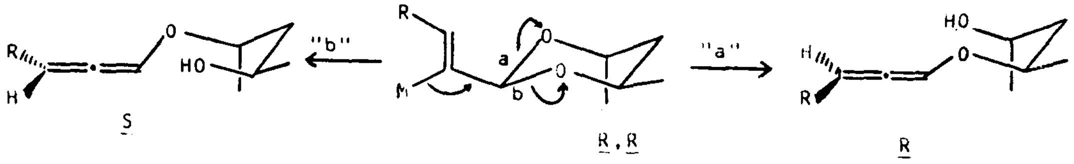
We recently reported[1] the diastereoselective substitution of an alkoxy group, in chiral acetals, by an organocopper reagent in the presence of BF_3. Such diastereoselective ring openings had also been described using silylated reagents in the presence of various Lewis acids[2].



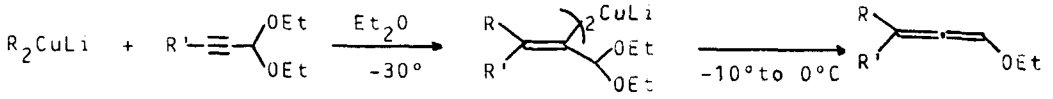
This high selectivity was mainly attributed to the H,Me 1,3 diaxial interaction which favors, in the transition state, the cleavage of the "a" C-O bond, the one which best releases these strains[3].



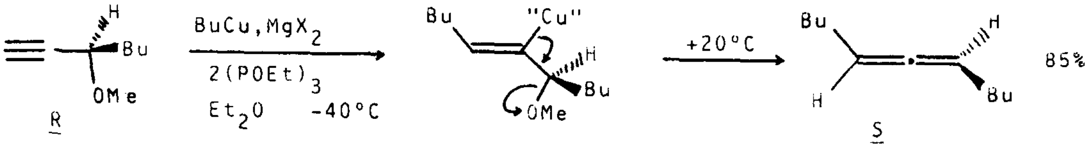
Based on the same arguments we anticipated that the β-elimination of the following organometallic derivative should also be diastereoselective, thus generating an allenic chirality : path "a" should be therefore favored. (the following scheme postulates an anti elimination process)



Such organometallic species are easily obtained through the carbocupration of acetylenic acetals by lithium dialkyl cuprates in Et$_2$O[4] :



However, even with the highest diastereoselection, the above elimination process, would be of no value if it was not of pure syn or anti type. To get more insight into this β-elimination reaction we studied an analogous reaction, *viz* the carbocupration of a propargylic ether of R configuration[5] which affords an allene (after allowing the stable alkenyl copper intermediate to decompose) of S configuration.

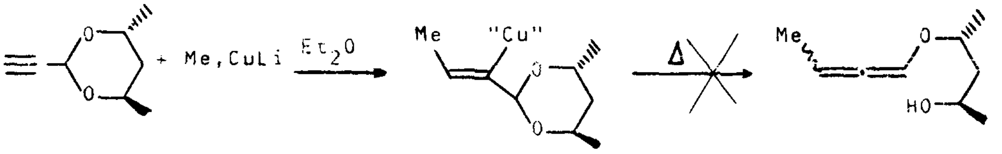


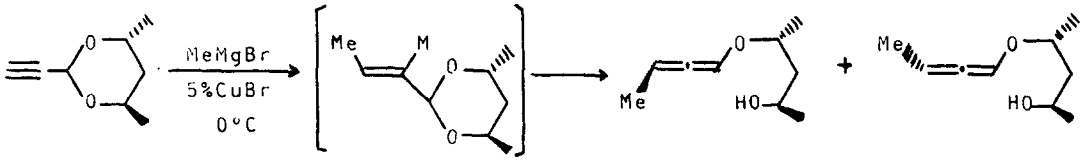
Data of the corresponding alcohol
$[\alpha]_D^{25}$: +15.3°(c=3,diox) e.e. 75%

$[\alpha]_D^{25}$=43.6°(c=10,CHCl$_3$) e.e. 66%
optical yield : 88%

This reaction provided the key answer to the above question : the β-elimination process is of anti type and it occurs with very high selectivity (88%).

The diastereoselective elimination reaction on chiral acetylenic acetals could therefore be tested :





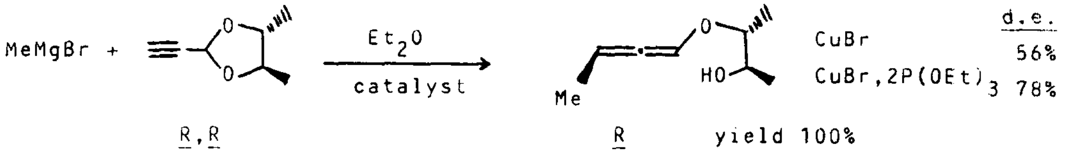
R,R

R 64%

S 36% d.e. 28%

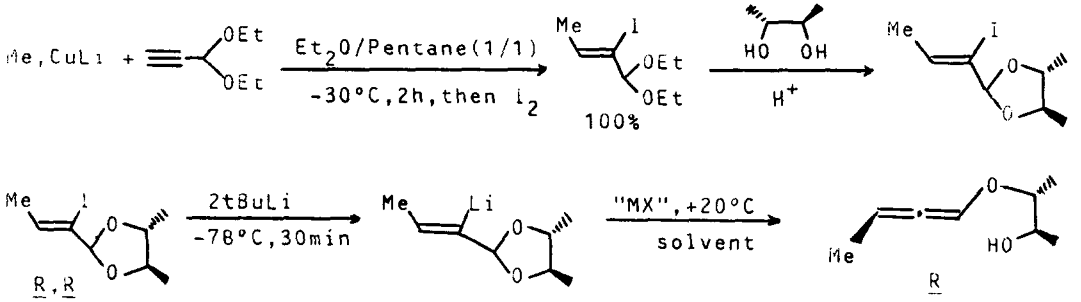
The first surprise came from the exceptional thermal stability of the alkenyl cuprate bearing a cyclic acetal system, which did not β-eliminate, even at reflux temperature (+35°C) ! However, the catalytic process[4,6] (RMgX + 5% CuX) did provide the expected alkoxy allenes, in quantitative yield, and probably via the same mechanistic pathway. Unfortunately, the diastereomeric excess[8] was quite low, although the stereochemical course of the reaction was exactly the one anticipated (see below).

Turning to the dioxolan ring instead of the dioxan proved more rewarding :



This result is quite unexpected since six membered rings were considered more efficient than the five membered ones in the diastereoselective substitution reaction[2]. Another factor which has to be taken into account is the known tendency of chiral allenes to be racemised by organocopper reagents[7]. We found that this racemisation is almost suppressed when the copper reagent is complexed by σ donnor ligands such as P(OEt)$_3$. Under these conditions the d.e. raises to 78%.

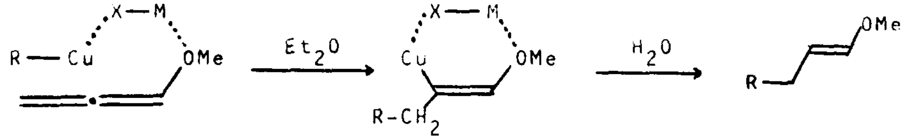
This diastereoselective β-elimination can also be examined in the total absence of copper metal through the following reactions :

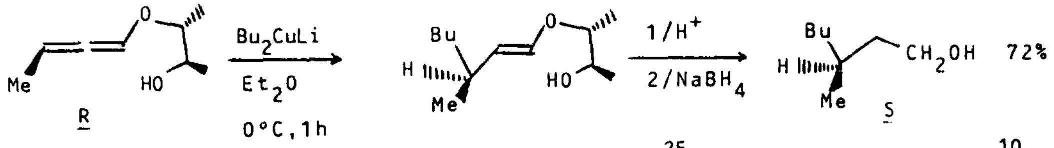


Et$_2$O,Li d.e.= 86% Et$_2$O,MgX d.e. = 92%
THF,Li 0% Et$_2$O,ZnX 14%

The highest diastereomeric excess is obtained by either the lithium or the Grignard reagent in Et$_2$O, with the same major isomer as in the above copper catalyzed reaction.

The absolute configuration of these chiral alkoxy-allenes was determined through the known <u>syn</u> addition reaction of lithium dialkyl cuprates to them[9] :

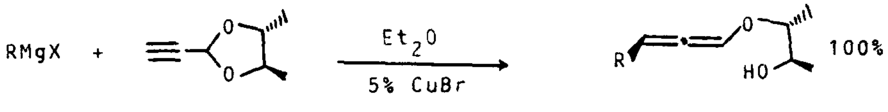




d.e. 56% d.e. 24% $[\alpha]_D^{25}$:-0.72°(c=29,Et$_2$O)e.e. 23%[10]

This syn addition to a chiral allene generates an asymmetric carbon, which in the present case was of <u>S</u> configuration[10]. This result implies that the alkoxy-allene was of <u>R</u> configuration, and since the chiral auxiliary diol was of <u>R,R</u> configuration, this fact implies that, indeed, the elimination process occured with selective cleavage of the C-O bond next to the axial (or pseudoaxial) methyl group of the dioxan (or dioxolan) ring (path "a" in the above mentioned scheme).

The degree of this diastereoselectivity seems to depend also upon the nature of the organic group of the organometallic reagent.



R =	d.e.
Me	56%
nBu	70%
tBu	100%
Ph	46%

These last results are unoptimised and should be improved by using the two step procedure (via the alkenyl iodide). Further work is in progress to get more insight into this new type of diastereoselective reactions.

Aknowledgements :

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