

Chiral acetals in enantio- and diastereoselective substitution or elimination reactions

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Abstract - The dioxolane or dioxane ring of chiral acetals is diastereoselectively cleaved in two types of organometallic reactions. 1/ Substitution in an SN₂ or SN₁ manner by organocopper reagents associated with BF₃. 2/ β-elimination of an alkenyl organometallic reagent. These reactions provide, in the first case, chiral secondary alcohols (ee > 95%) or β,β-disubstituted carbonyl compounds (ee > 90%) whereas in the second case chiral alkoxy-allenes (d.e. > 90%) are obtained.

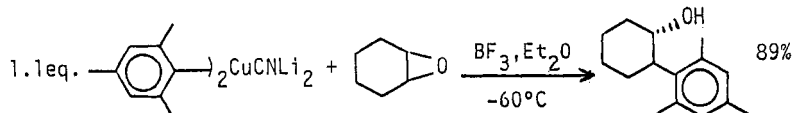
INTRODUCTION

Cyclic chiral acetals with a C₂ axis of symmetry have widely been used recently as chiral auxiliaries in asymmetric synthesis. They may act, by their directive effect, on the differentiation between the *si* and *re* face of a proximal prochiral function (ref. 1), or alternatively they may participate in the reaction itself by diastereoselective cleavage of the chiral acetal ring (ref. 2). The work we report herein (ref. 3) belongs to this latter category and is subdivided into two parts corresponding to two different ways of ring cleavage :

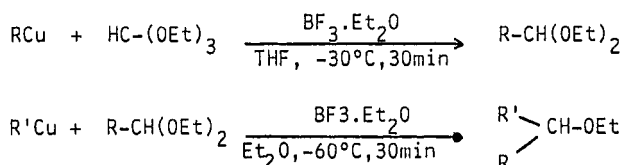
- 1/ Direct nucleophilic attack of the acetal ring by organometallic reagents such as RCu, BF₃ or RLi, which ultimately produce chiral secondary alcohols or β-substituted aldehydes or ketones.
- 2/ β-Elimination of an adequate organometallic reagent (M=Cu, Li, Mg, Zn) which produces a chiral alkoxy-allene, a useful and versatile chiron.

SUBSTITUTION REACTIONS

We have shown recently that organocopper and cuprate reagents (RCu and R₂CuLi) associated with a strong Lewis acid, such as BF₃.Et₂O, are able to cleave the C-O single bond of activated ethers. Thus poorly reactive epoxides react cleanly and very rapidly with R₂CuLi/BF₃ reagent, even if R is a quite large group (ref. 4,5) :

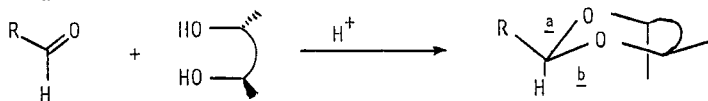


In THF solvent, RCu, BF₃ reagents react with triethyl orthoformate to afford the corresponding acetal. However, in Et₂O solvent, the reaction may proceed further and acetals are cleaved to ethers (ref. 4) :



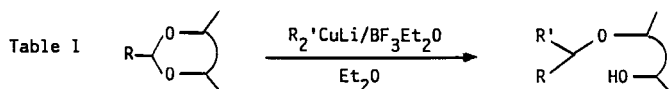
This last reaction takes its full synthetic interest when one considers chiral cyclic acetals and the diastereoselectivity they might provide.

These chiral acetals are easily prepared from an aldehyde or its dialkyl acetal and a chiral diol with a C_2 axis of symmetry :



Thus, in the ground state, the two sides *si* and *re* of the aldehyde are, now, differentiated having an equatorial (*si* face) or an axial (*re* face) Me group on the acetal ring. The diastereoselectivity of the reaction with RCu, BF_3 (as well as with $R-SiMe_3/TiCl_4$ according to W.S. Johnson (ref 2a) or R_2Al according to H. Yamamoto (ref. 2b) will depend, now, on which C-O bond, a or b, will be broken and what type of substitution will occur, a syn or anti one.

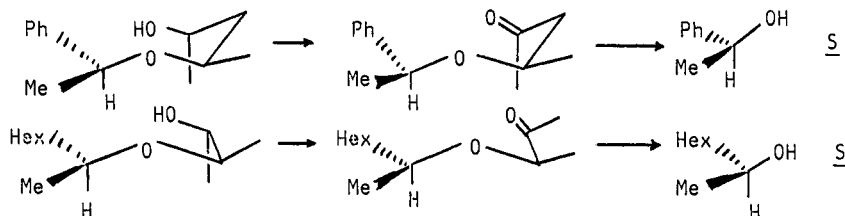
The results of the reaction of various R_2CuLi/BF_3 with various acetals are shown in table I.



Entry	Acetal	Cuprate	Yield	Major product	d.e.	Entry	Acetal	Cuprate	Yield	Major product	d.e.
1		Me_2CuLi	95%		67%	5		Me_2CuLi	96%		100%
2		"	93%		91%	6		Hex_2CuLi	89%		100%
3		"	92%		86%	7	"	Ph_2CuLi	94%		100%
4		"	96%		72%						

Acetals of aliphatic aldehydes and R,R -2,3-butanediol (entries 5, 6, 7) afford only one detectable diastereoisomer, whereas the same acetal of benzaldehyde gives two diastereoisomers with a 67% diastereoisomeric excess (entry 1). As reported by W.S. Johnson (ref. 6) and by H. Yamamoto (ref. 7), a much better stereocontrol is achieved with the less flexible dioxane system (entry 2). Even the seven membered cyclic acetal (entry 3) is very diastereoselective. The dioxane acetal with 1,3-butanediol (entry 4) is cleaved only on the non substituted side of the molecule (ref. 8) ; however the d.e. is lower than the one obtained with the disubstituted dioxane (entry 5). Nevertheless the stereochemistry of the obtained product clearly shows that an anti substitution takes place.

The absolute configuration of the newly created asymmetric center was determined by an oxidation-elimination sequence (ref. 6), which leads to known chiral alcohols without any loss of enantiomeric purity :

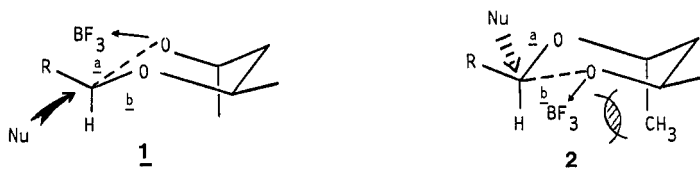


Such a high diastereocontrol is better accounted by a concerted mechanism rather than by a cationic one (ref. 8), even though a strong Lewis acid is present in the reaction medium.

The anti nucleophilic attack of the cuprate reagent should be very fast once the electrophilic assistance of BF_3 has weakened one of the two C-O bonds, a or b, of the acetal



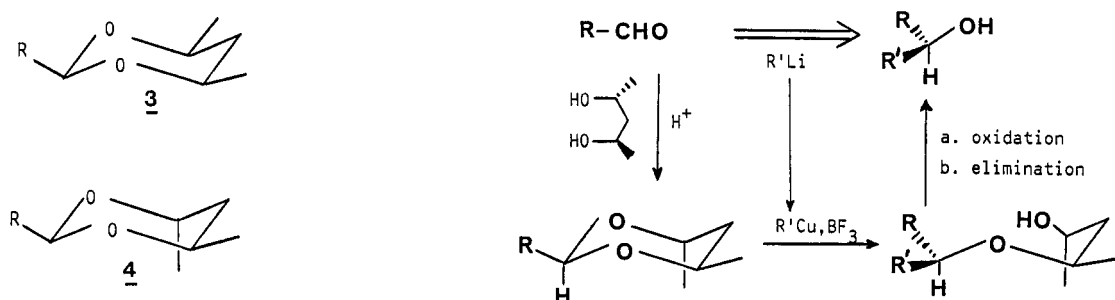
Our stereochemical results which are the same as those of W.S. Johnson (ref. 2a) and H. Yamamoto (ref. 2b), suggest an anti nucleophilic attack from the si face with concomitant cleavage of the a C-O bond, the one which is on the side of the axial Me group on the ring. The preferential cleavage of the a C-O bond may be attributed to the 2-4 diaxial interaction (H-Me) which is released when the bond is cleaved as shown in the transition state 1. This is not the case when the b C-O bond is broken, thus disfavoring the transition state 2 (ref. 8).



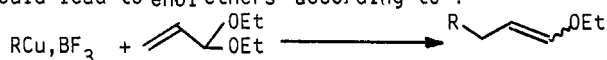
The site of complexation of the Lewis acid is also noteworthy (ref. 9). The complexation with the oxygen next to the axial Me group is preferred for steric as well as for electronic reasons: in this case the b C-O bond will be shortened due to the anomeric effect while in transition state 2 the shortening of the a C-O bond increases the steric 2-4 (H ↔ Me) diaxial interaction.

This preferential complexation of the Lewis acid on an oxygen next to an axial Me group can also be substantiated by the fact that the meso acetal 3 is much less reactive than the d,l one 4 with RCu, BF_3 (ref. 10).

The overall result of the above process may be viewed as the enantioselective addition of any kind of organolithium reagent with any kind of aldehyde:



Organocopper reagents associated with BF_3 are known to undergo preferential anti SN' reaction with allylic chlorides and other leaving groups (ref. 11). Thus, the reaction with allylic acetals should lead to enol ethers according to:



Indeed this is true with "soft" organocopper reagents Ar-Cu, BF_3 and Vinyl-Cu, BF_3 whereas with BuCu, BF_3 mixture of SN'_2 and SN_2 products are obtained (ref. 12).

The reaction of PhCu, BF_3 with various chiral acetals (ref. 3c) of crotonaldehyde are shown in table II. The acetal obtained from R,R-2,3-butanediol is among the best ones and more importantly, it is the less expensive of all the other auxiliary diols (it is also commercially available).

The acetates of the obtained enol ethers are easily hydrolysed to the corresponding β -disubstituted aldehydes with recovery of the auxiliary diol. The overall process may be viewed as a conjugate addition of an ArLi to a substituted α, β -ethylenic aldehyde:

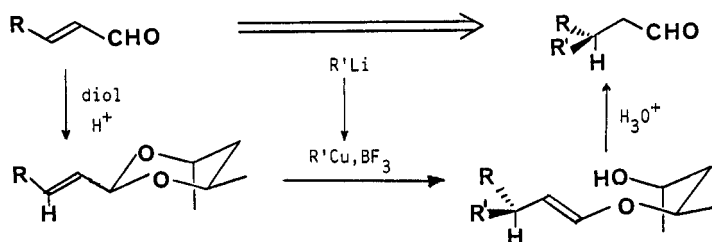
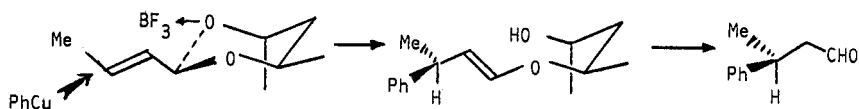


Table II

Entry	Acetal	Yield %	Ligand	d.e. enol ether%	e.e. aldehyde	Stereo-chemist.
8		70	Me ₂ S	76	73	<u>S</u>
9		75	PBu ₃	95	a	<u>S</u>
10		75	-	69	a	<u>R</u>
11		71	PBu ₃	91	a	<u>S</u>
12		70	Me ₂ S	77	73	<u>S</u>
13		50	Me ₂ S	76	75	<u>S</u>
14		76	Me ₂ S	58	b	b
15		67	Me ₂ S	35	34	<u>S</u>
16		70	Me ₂ S	29	29	<u>S</u>

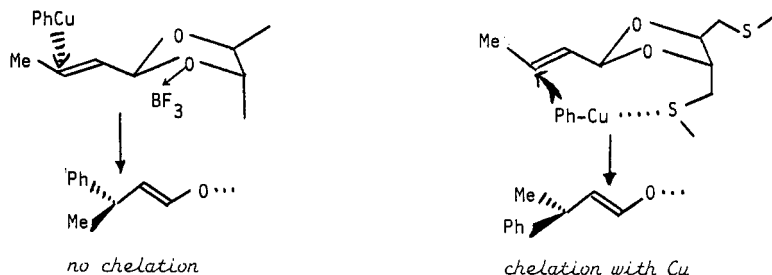
a : Enol ether not hydrolysed into the aldehyde
 b : The racemic d,l diol was used

The stereochemical outcome of this reaction (ref. 13) is easily understood in the same manner as the direct substitution (S_N2) of the previously seen acetals. In the present case it is an anti S_N' substitution :



Noteworthy is the fact that only the E enol ether is obtained indicating that the reaction occurred in the transoid conformation.

In the case of some functionalised acetals (entries 15, 16) the stereochemical outcome of the reaction is reversed. Although in these cases the e.e. of the final aldehyde is not very high it is interesting to note the dramatic effect of the chelation factor :



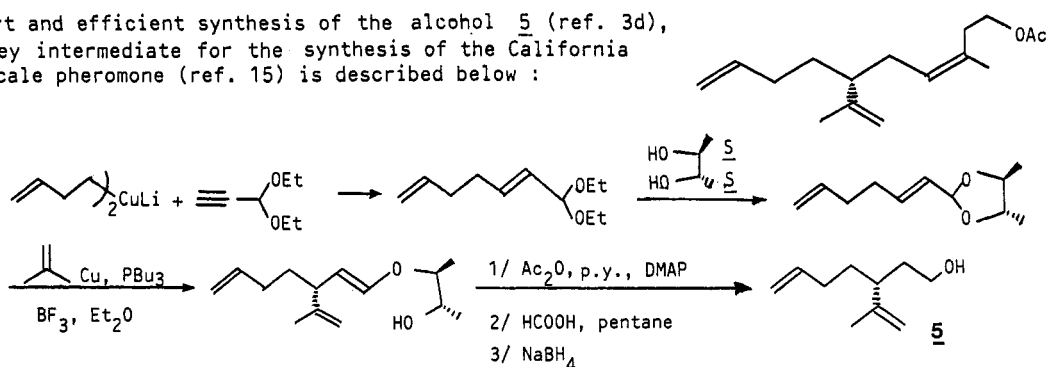
This effect interferes with the steric hindrance and this fact can account for the low d.e. observed. Another factor which has to be taken into account is the ligand around the copper atom. The highest e.e.'s are obtained with PBu₃, one of the best ligands of organocopper reagents (ref. 14) (compare entries 8 and 9, table II and all entries in table III).

Alkenyl copper reagents behave like ArCu ones in that only S_N' reaction is observed (ref. 3d) and also excellent diastereo- and enantioselectivities are attained (see table III).

Table III

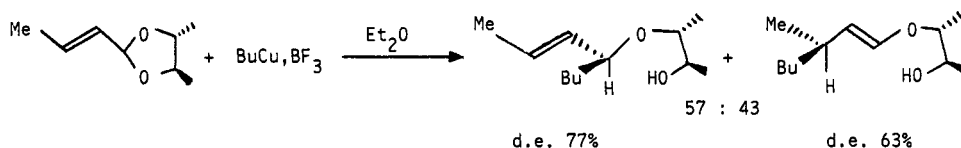
Entry	Organocopper reagent	Ligand	Yield %	d.e.%
17		-	69	24
18		Me ₂ S	72	67
19		PBu ₃	70	85
20		-	75	50
21		Me ₂ S	71	60
22		PBu ₃	69	85
23		Me ₂ S	70	73
24		PBu ₃	68	85

A short and efficient synthesis of the alcohol **5** (ref. 3d), the key intermediate for the synthesis of the California red scale pheromone (ref. 15) is described below :

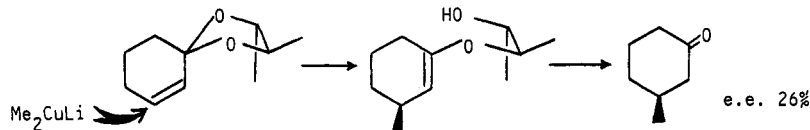


overall yield : 50% e.e. : 85% from MTPA ester

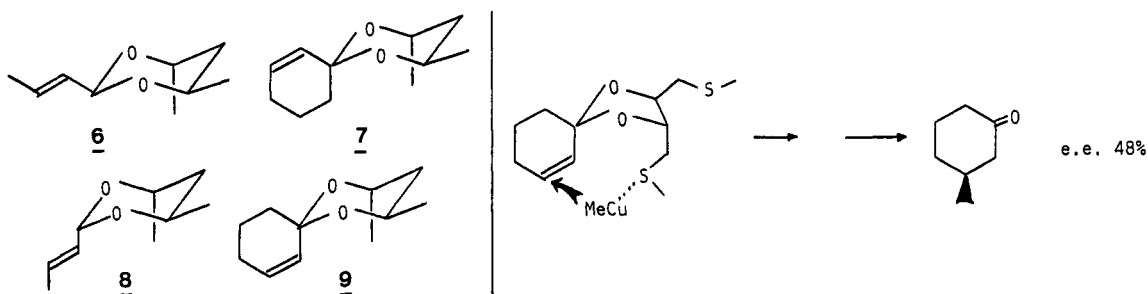
The reaction of alkyl copper reagents is not regioselective, affording a mixture of both SN_2 and SN' products. However the d.e. of both products is usually very high (ref. 16) :



The reaction with ketals is always regioselective affording only the SN' adduct whatever the organocopper reagent used (ref. 17). However, the diastereoselectivity is, now, poor with the ketal of cyclohexenone and R,R-2,3-butanediol (ref. 3a) :



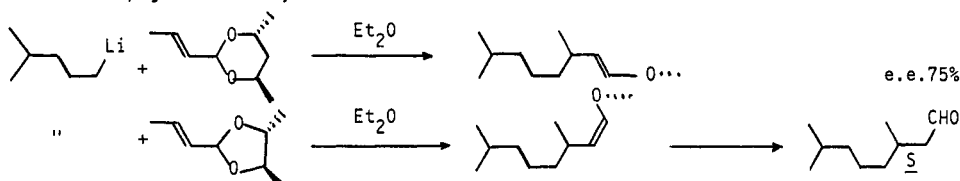
This poor diastereoselectivity may be due to the fact that ketals may adopt two conformations **7** and **9** whereas acetals adopt only conformation **6** and not **8**. Chelation effects, however, have a more dramatic influence in the case of ketals, since only one conformer (**9**) has an appropriate geometry to allow such a chelation (ref. 18)



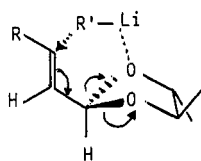
Thus, by chelation, the organocopper reagent comes from the side of the axial (or pseudoaxial) substituent, whereas without chelation it comes from the opposite side.

The overall process is, here again, a formal conjugate addition of an organolithium reagent to an enone, with recovery of the chiral auxiliary diol.

It was reported that ethylenic acetals react with alkyl lithium reagents in an SN' manner, affording an enol ether (ref. 19). The reaction with chiral cyclic acetals follows the same way (ref. 20). Crotonaldehyde acetal, with R,R-2,4-pentanediol reacts at room temperature in a regioselective manner but not in a diastereoselective one. The stereochemistry of the obtained enol ether is almost exclusively *E*. By contrast, a dioxolane, the acetal with R,R-2,3-butanediol, gives mainly the *Z* enol ether (*Z*:*E* = 4.2:1).

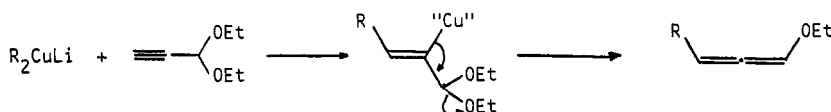


The stereochemistry of the enol ether indicates that a *cisoid* conformation is adopted in the transition state, while the final configuration (*S*) shows that the nucleophile entered from the side of the pseudoaxial Me group on the ring :

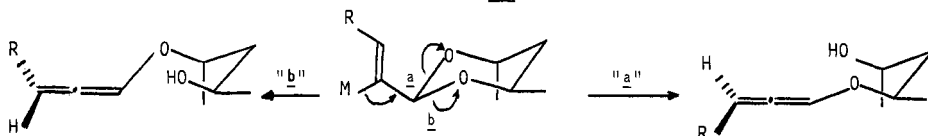


ELIMINATION REACTIONS

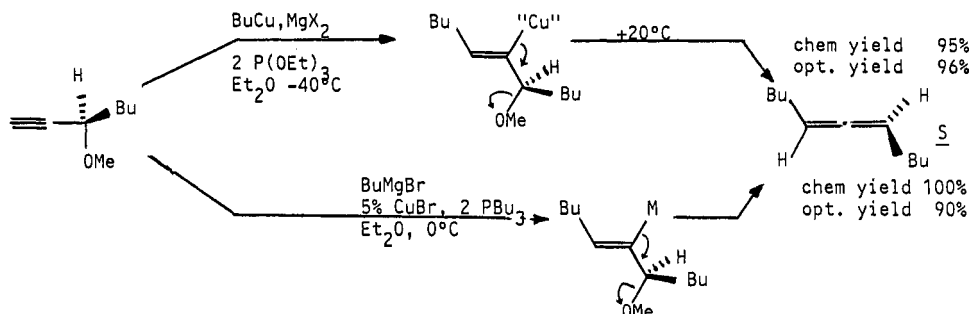
We have shown some years ago that lithium diorganocuprate reagents add across the triple bond of propargylic acetals to afford a stable and reactive alkenyl cuprate intermediate (ref. 21). However, if the reaction temperature is sufficiently high (-20° to 0°C) a β -elimination occurs leading to an alkoxy allene.



If, now, the acetal is a cyclic and chiral one this reaction may deliver a chiral alkoxy allene (ref. 3b). We have shown in the first part that, in cyclic chiral acetals, the *a* C-O bond which is nearby the axial substituent, is the most prone to be broken, thus releasing the $\text{H} \rightarrow \text{Me}$ 2,4 diaxial steric interaction. Path "*a*" should be therefore favored :

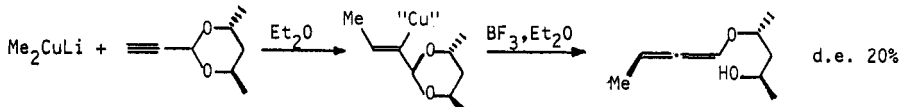


In this scheme an *anti* elimination is postulated. However, this fact needs to be ascertained since even with the highest diastereoselection, the above elimination process would be of no value if it is not of pure *syn* or *anti* type. To get more insight into this β -elimination process a very close reaction was examined, *viz* the carbocupration of propargylic ethers (ref. 22). These compounds also undergo addition of organocopper reagents to afford an alkenyl copper intermediate, which also collapses into an allene. The reaction proceeds in the same manner with a Grignard reagent and a catalytic amount of copper halide (ref.17., 23) :



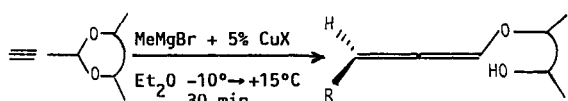
Both reactions give the same chiral allene of *S* configuration when starting with a propargylic ether of *R* configuration. This result indicates that the β -elimination process is of *anti* type and it occurs with a very high selectivity.

Assuming that with propargylic chiral acetals the elimination follows the same way, we reacted them with Me_2CuLi . However, to our surprise, the intermediate lithium alkenyl cuprate bearing a *cyclic* acetal did not eliminate even at reflux temperature ($+35^{\circ}\text{C}$). The elimination product, the alkoxy allene, was only obtained upon addition of a Lewis acid, $\text{BF}_3 \cdot \text{Et}_2\text{O}$



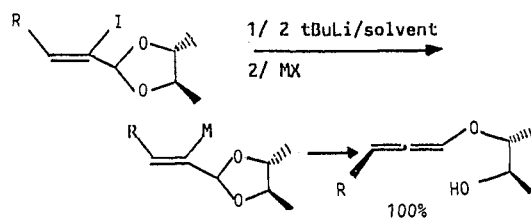
On the other hand, the catalytic process ($\text{RMgX} + 5\% \text{CuX}$) did provide the expected alkoxy allenes, in quantitative yield but also with a low diastereomeric excess (same major isomer as above). In fact the d.e. is highly dependent on the size of the ring of the acetal, and also on the type of substituents on it (see table IV). Dioxolanes are clearly superior to dioxane in this reaction (compare entry 25 with all others). The nature of the diol used as chiral auxiliary is also important and cycloheptanediol (entry 29) or cyclooctanediol (entry 30) seem to be among the best examined thus far (ref. 24).

Table IV



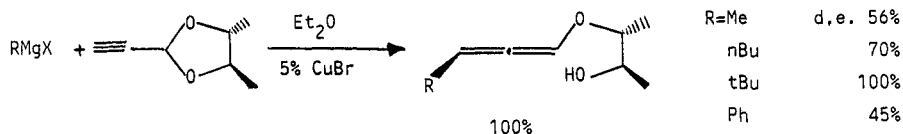
Entry	Acetal	CuX	d.e. %
25		CuBr	28
26		CuBr	56
27		CuBr CuBr, 2P(OEt) ₃	59 78
28		CuBr	30
29		CuBr	74
30		CuBr CuBr, 2 P(OEt) ₃	66 85

Table V



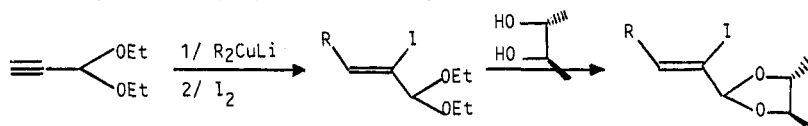
Entry	Acetal	M	Solvent	d.e. %
31		Li	Et ₂ O	80
32	"	Li	THF	0
33	"	MgBr	Et ₂ O	92
34		ZnBr	"	14
35		Li	"	60
36		Li	"	96
37		Li	"	87
38		Li	"	40
39	"	MgBr	"	58

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



Another factor which has to be taken into account is the known tendency of chiral allenes to be racemised by organocopper reagents²⁵. Indeed in the reaction shown in entry 26, the d.e. dropped to 12% after letting the reaction stand overnight at room temperature. We found that this racemisation is partly suppressed when the copper reagent is complexed with σ donor ligands such as P(OEt)₃ (see entries 27 and 30).

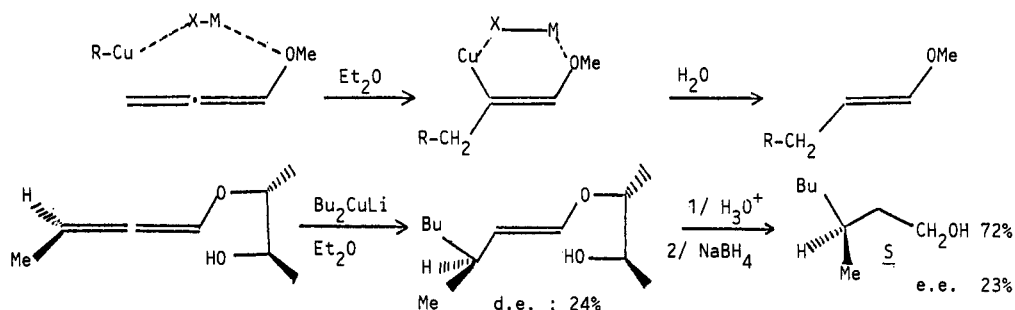
The diastereoselective β -elimination can also be examined in the total absence of copper metal from an alkenyl iodide prepared according to



Metal-halogen exchange with tBuLi affords an alkenyl lithium reagent, which also β -eliminates to give an alkenyl acetal, of the same stereochemistry as the one obtained through the copper catalysed process.

The results shown in table V indicate that the best d.e. are obtained with lithium or the Grignard reagents in Et₂O. Diphenylethanedione is the best choice in this approach. In THF solvent, there is no diastereoselectivity at all. The monosubstituted dioxolane (entries 38, 39) is remarkably selective; only the unsubstituted C-O bond is cleaved. In this case a strong influence of the nature of the metal is observed, Mg being quite more diastereoselective than Li.

The absolute configuration of these chiral alkenyl acetals was determined through the known *syn* addition reaction of lithium dialkyl cuprates to them (ref. 26).



This syn addition to a chiral allene generates an asymmetric sp^3 carbon, which in the present case is of *S* configuration. This result implies that the alkoxyallene is of *R* configuration, and since the chiral auxiliary diol is of *R,R* configuration, this fact implies that, indeed, the elimination process occurred with selective cleavage of the C-O bond next to the axial (or pseudoaxial) Me group of the dioxane (or dioxolane) ring (path "a" in the above mentioned scheme).

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