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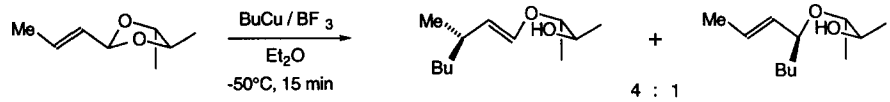
Asymmetric Cleavage of Chiral α,β-Ethylenic Acetals by Organolithium Reagents

Alexandre Alexakis*, Farida Mhamdi, Franz Lagasse and Pierre Mangeney

Laboratoire de Chimie des Organo-Eléments, CNRS UA 473, case 183
Université P. et M. Curie, 4, Place Jussieu , F-75252 Paris Cedex 05, France
Fax 33 (1) 44 27 75 67

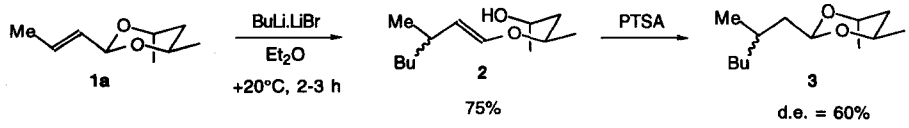
Abstract : *α,β-Ethylenic chiral acetals react regio- and stereoselectively with organolithium reagents. The obtained enol ether may be hydrolyzed into a chiral β-disubstituted aldehyde.* Copyright © 1996 Elsevier Science Ltd

Chiral acetals are powerful tools in asymmetric synthesis[1]. They may be stereoselectively cleaved by several reagents or combination of reagents. Particularly, α,β-ethylenic acetals are regio- and diastereoselectively cleaved by triorganoaluminum[2] (R_3Al) or organocopper reagents associated with a Lewis acid[3] (RCu/BF_3). In this latter case the regioselectivity is total (γ-attack) only with aryl[3a] or alkenyl[3b] groups; with alkyl groups it is at best 4:1 :



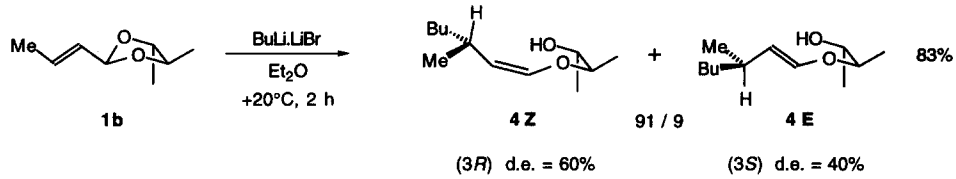
Organolithium reagents are known to react in S_N' manner with α,β-ethylenic acetals[4]. We report herein our strange results on the diastereoselective cleavage of such chiral acetals with these reagents.

Crotonaldehyde acetal **1a**, prepared with (*R,R*) 2,4-pentanediol, reacts at room temperature, in a few hours (2-3 h) , with nBuLi.LiBr, in Et_2O, to afford, in 75% isolated yield, the E enol ether **2**. The E stereochemistry of the double bond indicates that acetal **1a** reacted in its transoïd conformation (as drawn on the scheme) :

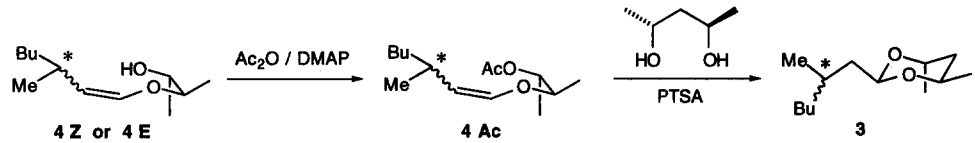


As for the diastereoselectivity, it cannot be ascertained at this stage and recyclization of enol ether **2** into the new acetal **3** is needed (cat. PTSA). For acetal **3**, two diastereomers, in a 50 : 50 ratio, are clearly distinguished by NMR or GC which means that the reaction of **1a** in the transoïd conformation is completely non-diastereoselective.

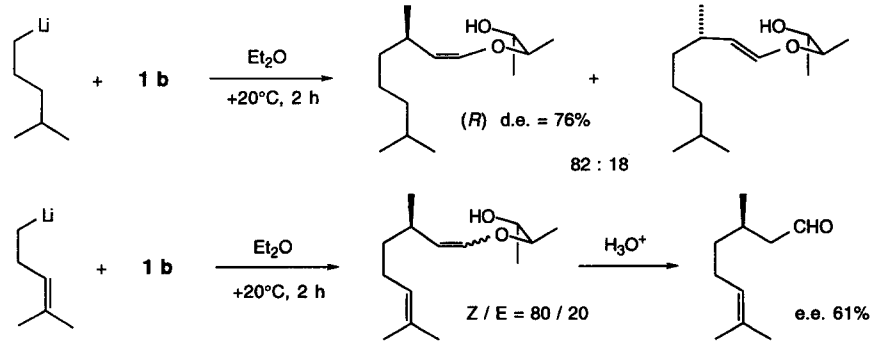
The corresponding homochiral five membered ring acetal **1b**, prepared with (*R,R*)-2,3-butanediol, reacts analogously with the same reagent. However, the stereochemical results are completely different. Two enol ethers are, now, obtained (in 91 : 9 ratio), with the Z isomer, **4Z**, predominating. This is quite unexpected since RCu/BF_3, as well as Me_3Al always gave the E enol ether whatever the ring size of the chiral acetal.[2,3]



The two isomers **4Z** and **4E** could be seperated by silicagel column chromatography, and the diastereomeric excess could be evaluated after a two steps process : *1)* acetylation (Ac_2O, DMAP in Et_2O) and *2)* transacetalisation with (*R,R*)-2,4-pentanediol which gives the chiral acetal **3**. Enol ether **4Z** shows a (3*R*) configuration (d.e. 60%) whereas **4E** is of (3*S*)-configuration (d.e. 40%).



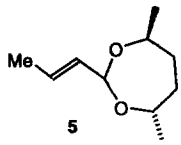
A short synthetic application of this reaction is shown below with the synthesis of non-racemic chiral dihydrocitronellal and of citronellal :



It should be noted that the solvent has a strong influence on the feasability of this reaction : in THF no reaction takes place and in pentane the reaction rate is slighly faster (1.5 h) ; two equivalents of TMEDA slow down the reaction rate (5-6 h) and the diastereoselectivity is much lower. Finally, the stereochemical outcome of this reaction is the same if salt-free commercial BuLi/hexane is used.

The reaction with other organolithium reagents and other chiral acetals, listed below, is shown in the Table. Phenyl lithium (entry 1) reacts very sluggishly, even in pentane, and gave, in 65% yield a mixture of both enol ethers (Z/E = 64/36 ; d.e. on Z : 50% *S* configuration[5] and d.e. on E : 50% *R*[5]). The reaction of tBuLi was fast (2h) but was very sensitive to the solvent ; in pentane (entry 3) excellent diastereoselectivity was attained but

poor Z/E selectivity : 36/64 (d.e. on Z : 95% *S*[5]; d.e. on E : 88% *R*[5]) whereas in Et_2O (entry 2) the E enol ether was largely the major one but with poor stereoselectivity (Z/E = 15/85 ; d.e. on Z : 58% *S*; d.e. on E : 18% *R*).



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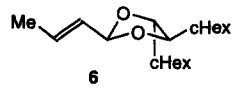

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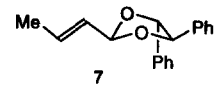

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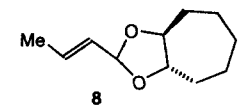

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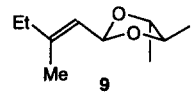

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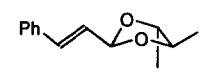

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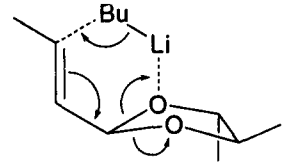
On the other hand, various acetals obtained from diols and crotonaldehyde have also been tested. The seven membered ring acetal **5**, from 2,5-hexane diol, gave exclusively the E enol ether without any diastereoselection (entry 4) . Among the other *d,l* 1,2-diols tested, dicyclohexyl ethane diol, acetal **6** (entry 5), gave a low Z/E ratio of 2.2/1 ; diphenyl ethane diol, acetal **7** (entry 6), was deprotonated by BuLi on the benzylic position with destruction of the molecule by β-elimination ; however 1,2-cycloheptane diol,acetal **8** (entry 7), afforded a Z/E ratio (9/1) as good as 2,3-butanediol but with a higher diastereoselectivity (d.e.72% on the Z enol ether). Finally we should add that two other acetals were tried, **9** and **10**. The reaction of nBuLi with **9** (entry 8) resulted in 1-4 elimination by abstraction of an allylic proton cis to the acetal.[6] As for acetal **10** (entry 9), it reacted to give the product of reverse regioselectivity[4a] and with a low diastereoselectivity.[7]

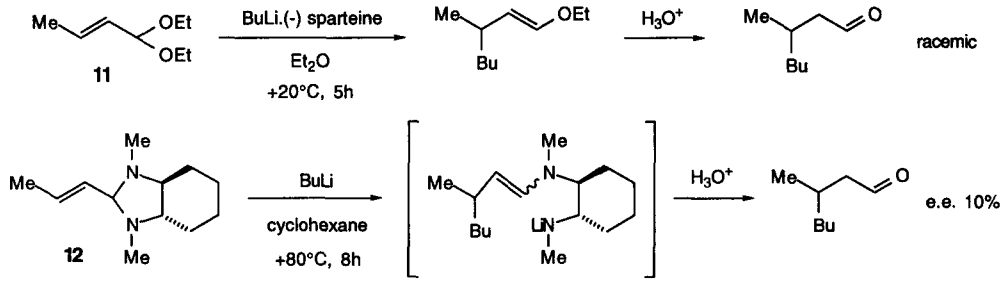
Table : Reaction of various organolithium reagents with various chiral acetals

Entry	Chiral Acetal	Organolithium reagent	Solvent	Yield %	Z / E ratio	d.e. % conf. of Z	d.e. % conf. of E
1	**1b**	PhLi.LiBr	Et_2O	65	64 / 36	50% *S*[5]	50% *R*[5]
2	"	tBuLi	Et_2O	62	15 / 85	58% *S*[5]	18% *R*[5]
3	"	tBuLi	pentane	65	36 / 64	95% *S*[5]	88% *R*[5]
4	**5**	BuLi	Et_2O	78	0 / 100	-	0
5	**6**	BuLi	Et_2O	83	69 / 31	not determined	
6	**7**	BuLi	Et_2O	0	decomposition		
7	**8**	BuLi	Et_2O	81	90 / 10	72 *R*	-
8	**9**	BuLi	Et_2O	0	1,4 elimination		
9	**10**	BuLi	Et_2O	73	reverse regioselectivity		

Speculations about the mechanism of this reaction are scarce.[4] It probably involves an addition-elimination process, since carbolithiation of ethylenic acetals are known.[8] That explains the usual obtention of the E enol ether. However, the formation of the Z enol ether indicates that the main reaction path is more or less concerted and occurs through a cisoïd conformation of **1b** :



Two additional atempts were made to perform asymmetrically the above reaction. Precomplexation of BuLi with (-)-sparteine and reaction with diethoxy butene **11** gave the completely racemic E enol ether. On the other hand, reaction of chiral aminal **12** with BuLi, in refluxing cyclohexane, gave the desired aldehyde with about 10% e.e. :



It seems hard to explain which are the factors playing the crucial role on the observed selectivities. Steric aspects are not negligeable in view of the result with tBuLi. However the aggregation state of the organolithium reagent seems also very important as is, of course, the structure of the acetal itself.

References and notes.

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   c) Bailey, W.F.; Zartun D.L. : *J. Chem. Soc , Chem. Comm.* **1984**, 34
5. The inversion of configuration as compared to **4Z** and **4E** is only due to the C.I.P. rules.
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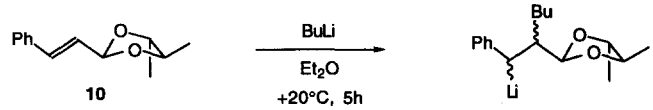

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