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REACTIVITY OF RCu,BF_3 AND R_2CuLi,BF_3 TOWARDS THE ETHER LINKAGE. EPOXIDES, ACETALS AND ORTHOFORMATES

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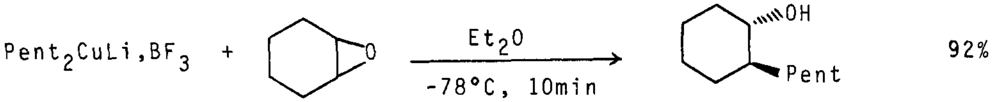
Summary : The association of BF_3 to organocopper and cuprate reagents increases dramatically their reactivity towards epoxides. The same reagents cleave acetals to afford the product of substitution of one alkoxy group, whereas orthoformates lead to acetals under conditions where no further attack occurs.

Acetals are, by far, the most used protective group of aldehydes and ketones. This protective group is usually stable towards various organometallic reagents, such as organolithium and Grignards reagents although in the latter case cleavage of the acetal may occur under drastic conditions[1] (toluene at reflux). On the other hand,aluminum hydrides (DIBAH,$LiAlH_4/AlX_3$) are known to cleave them[2], as well as some organoboron derivatives[3]. Also, association of a Lewis acid ($TiCl_4$,BF_3,$SnCl_4$,$AlCl_3$ etc...) with a silicon derivative effects the replacement of an alkoxy group of the acetal by an organic group[4]. More pertinently, a Grignard reagent cleaves mixed alkoxy-aryloxy acetals in the presence of $TiCl_4$[5] and alkynyl lithium reagents react with epoxides in the presence of BF_3[6]. These examples point to the synthetic potential of "classical" organometallic derivatives when associated with a strong Lewis acid. The limitation of this concept arises with the possible transmetallation ($RLi + TiCl_4 \longrightarrow RTiCl_3 + LiCl$ for example).

Yamamoto et al[7], followed by other authors[8,9] have demonstrated the enhanced reactivity of a combination of a Lewis acid and organocopper or cuprate reagents (RCu or R_2CuLi and BF_3,BR_3,$TiCl_4$ or $AlCl_3$) in S_N2' displacements and conjugate addition . Yet, there is no report on their reactivity towards the ether linkage of epoxides, acetals or orthoesters. We report in this preliminary note our first results in this field, using the following reagents in Et_2O or THF[10] :

RCu,LiX,BF_3 <u>A</u> R_2CuLi,BF_3 <u>B</u>

Although Bu_2CuLi or BuLi + 5% CuX are known to cleave tetrahydrofuran[11], we only observed the decomposition of reagents <u>A</u> and <u>B</u> in this solvent. Smaller cyclic ethers, such as epoxides, however, are readily opened by reagent B at low temperatures (-78°C).

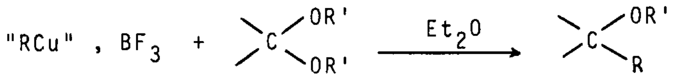


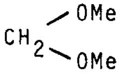
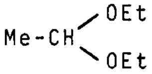
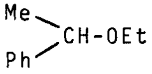
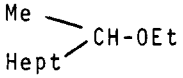
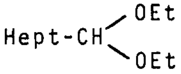
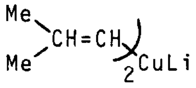
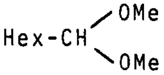
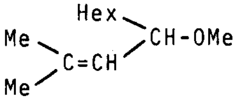
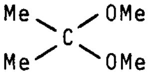
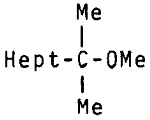
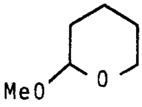
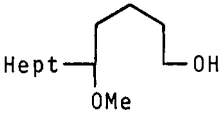
The reaction is exceedingly fast. This dramatic increase of reactivity is obtained without the use of an excess of organocopper reagent and has to be compared with more conventional reagents (5 R_2CuLi[12] : 0°, 2 h, 97% ; $R_2CuCNLi$[13] : -20°, 2 h, 95%). Only the anti substitution product is observed though accompagnied by 4% of 2-bromo-1-cyclohexanol. This last product is, however, the main one when the reaction is done with reagent A. Reagent B also reacts with isoprene monoepoxide (-78°C, 10min) with the same regio- and stereo-selectivity as R_2CuLi alone[14,15]). The study of the scope and limitations of this reaction is presently under way.

The acetal functionality is normally stable towards organocopper and cuprate reagents[16]. In contrast we found that reagents A or B are highly reactive towards acetals with[17] substitution of one alkoxy group by the organocopper reagent (see table). The reaction is quite fast (10 - 60min), even at low temperatures and, as expected, organocuprate reagents B are more reactive than organocopper reagents A (compare entries 4 and 5, and 7 and 8), although raising the temperature usually allows complete conversion of the starting acetal. Variously substituted acetals react as well, no matter the steric congestion (entry 8). In the case of tetrahydropyranyl acetal (entry 9) we only obtained the product of ring opening with <1% of substitution of the methoxy group. It should be recalled that RMgX alone affords both products in refluxing toluene[1] and that RMgX/$TiCl_4$ in THF reacts with THPOAr with only substitution of the aryloxy group[5]. The solvent has a dramatic influence on the reactivity of acetals. In THF solvent no reaction occurs at all.

Finally, it should be also noted that various organic groups in A and B may be used in this reaction : Me, n-alkyl, aryl or alkenyl.

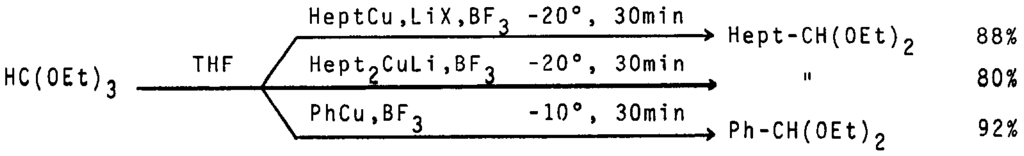
Orthoesters are more susceptible to cleavage by organometallic reagents[18]. Their reaction with Grignard reagents is commonly used for the synthesis of aldehydes (after hydrolysis of the obtained acetal), although heating is sometimes necessary[19,20]. On the other hand, we found that orthoformates are highly reactive towards reagents A and B in Et_2O and also in THF solvents. However, in Et_2O, the reaction may proceed further and the resulting acetal is, in turn, attacked by the organometallic reagent. A simple way to avoid such a reattack is to switch to THF, and high yields of acetal are, now, obtained.



Entry	"RCu"	Acetal	Temp.	Time	Product[a]	Yield
1	HeptCu,LiX		-60°	30min	Hept-CH$_2$-OMe	81%
2	PhCu,LiX		-30°	30min		89%
3	HeptCu,LiX	"	-40°	20min		84%
4	MeCu,LiX		-30°	30min	"	58%[b]
5	Me$_2$CuLi	"	-30°	30min	"	93%
6			-30°	30min		93%
7	HeptCu,LiX		-30°	30min	 $\text{Hept-}\overset{\text{Me}}{\underset{\text{Me}}{\text{C}}}\text{-OMe}$	70%
8	Hept$_2$CuLi	"	-30°	30min	"	94%
9	Hept$_2$CuLi		-50°	15min		83%

a. These products are fully characterized by GLPC, I.R., ^1H and ^{13}C NMR

b. A gummy precipitate prevents the reaction to proceed further



It must be pointed out that all these reactions are performed with stoechiometric amounts of reactants and that the yields correspond to distilled products. Such a high reactivity towards acetals and orthoformates is almost unknown in ethereal solvents and may found high synthetic utility for the easy and rapid preparation of acetals or ethers, starting with easily available organolithium reagents.

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10. The formulation of reagents A and B does not imply the formation of a new complex. In fact the reaction may be run in either of the following two manners, with the same experimental result :
    - RCu,LiX or R_2CuLi is premixed with BF_3 at -78°C for 10min and the electrophile is added thereafter
    - RCu,LiX or R_2CuLi is premixed with the electrophile and 1 eq. of $BF_3 . Et_2O$ is slowly added at low temperature (-78°)
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17. Such acetals are reported to afford intractable mixture when reacted with $RMgX/TiCl_4$ in THF. We also obtained such a mixture with RMgX or RLi in the presence of BF_3,Et_2O in Et_2O.
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