Some Aspects of the Reactivity of RCu/BF$_{3}$ Reagents towards the Ether Linkage [and Discussion]

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Phil. Trans. R. Soc. Lond. A 1988 **326**, 557-564
doi: 10.1098/rsta.1988.0106

Phil. Trans. R. Soc. Lond. A **326**, 557–564 (1988)
Printed in Great Britain

Some aspects of the reactivity of RCu/BF_3 reagents towards the ether linkage

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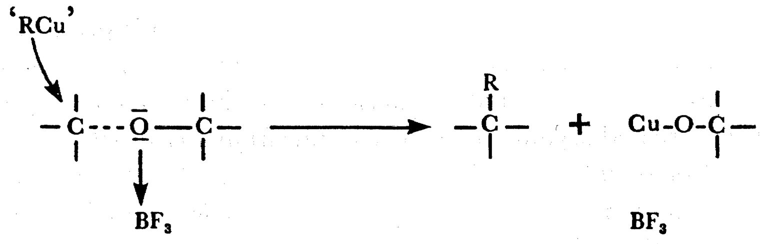
Organocopper reagents associated with a strong Lewis acid such as BF_3 react with the C—O single bond of orthoesters, acetals and epoxides. The diastereoselective cleavage of chiral acetals opens a new way of obtaining chiral secondary alcohols or chiral β-substituted aldehydes. A partial synthesis of the pheromone of the California red scale uses this approach. The opening of hindered epoxides is also very efficient with R_2CuLi/BF_3 reagents. Thus reaction with epoxy-silane gives rise to conjugated dienes as illustrated with the synthesis of the pheromones of Lobesia botrana and of Bombyx mori. Cyclohexene oxide reacts in the same way with R_4AlLi/BF_3 and the dienyl substituted cyclohexanols, thus obtained, can be used in highly stereoselective intramolecular Diels–Alder reactions.

INTRODUCTION

Among the various organometallic compounds introduced in organic synthesis these past 20 years, organocopper reagents are probably the most popular ones because of the unique and useful transformations they promote: substitution reactions (Posner 1975; Normant 1972; Jukes 1974), conjugate addition reactions (Normant 1972; Jukes 1974; Posner 1972) and carbometallation reactions (Normant & Alexakis 1981). The range of their applications was widened recently with the introduction of the higher order organocuprates (Lipshutz *et al.* 1984) (R_3CuLi_2, $R_2CuCNLi_2$...) and with the combination of RCu and R_2CuLi reagents with strong (Yamamoto 1986) or weak (Corey & Boaz 1985; Alexakis *et al.* 1986; Nakamura *et al.* 1986; Johnson & Marren 1987) Lewis acids (BF_3, Me_3SiX...). This report deals with our results with this last class of reagents.

Unlike organolithium or Grignard reagents, which undergo trans-metallation reactions with BF_3, organocopper reagents are inert (at least at the usual reaction temperature of −20 to 0 °C). Thus, the Lewis acid acts as an electrophilic activator of the substrate, which is, then, more easily attacked by the nucleophile: RCu or R_2CuLi. The reactions shown in scheme 1 concern the cleavage of the C—O single bond of ethers.



Scheme 1

Cleavage of acetals

Grignard reagents react with orthoesters at high temperature (Bodroux 1904; Tschitschibabin 1904) (refluxing benzene, for example). Organoaluminium reagents, which are considered as 'amphophilic' reagents (nucleophilic as well as Lewis acidic) react more easily with them (Mole & Jeffery 1972; Negishi 1980). The combination RCu/BF_3, which also represents a nucleophile and a Lewis acid, reacts even more easily. In Et_2O solvent and with triethyl orthoformate, the reaction occurs already at −60 °C and proceeds even further with cleavage of the resulting acetal!

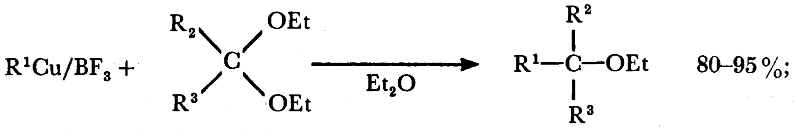
$$RCu/BF_3 + HC(OEt)_3 \xrightarrow[Et_2O]{} R{-}CH(OEt)_2 \xrightarrow[Et_2O]{RCu/BF_3} R_2CH{-}OEt.$$

However, in THF solvent, the reaction stops at the acetal stage (Ghribi *et al.* 1984*a*):

$$RCu/BF_3 + HC(OEt)_3 \xrightarrow[-30\,^{\circ}C,\ 30\ mn]{THF} R{-}CH(OEt)_2;$$

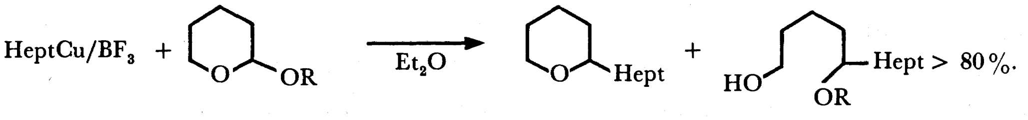
$$R = Hept\ (88\,\%);\quad Ph\ (92\,\%);\quad Bu{-}\overset{Z}{CH{=}CH}{-}\ (65\,\%).$$

On the other hand, the reaction with acetals, in Et_2O solvent, is quite general (Ghribi *et al.* 1984*a*) with respect to the nature of the R group of RCu and to the degree of substitution of the acetal carbon:



R^1 = Me, Hept, Ph, $Me_2C{=}CH{-}$
$R^2 = R^3$ = H or R^2 = H, R^3 = Hept or $R^2 = R^3$ = Me.

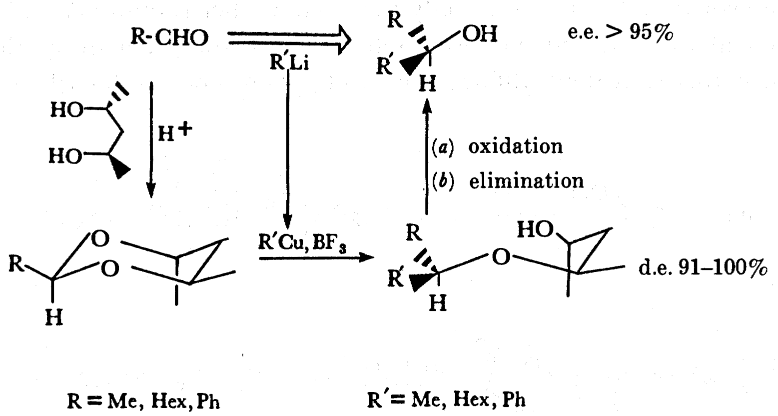
In the particular case of alkoxy substituted tetrahydropyrans, cleavage of the endocyclic C—O bonds is the main process (Ghribi *et al.* 1984*a*; A. Alexakis & D. Jachiet, unpublished results):



R = Me, Et, iPr	5 %	95 %
R = Ph	100 %	0 %

The exocyclic C—O bond is broken only when a phenoxy group is present.

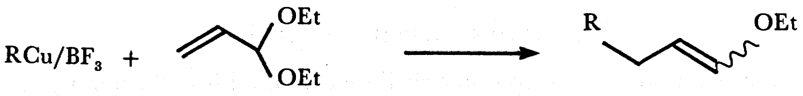
This concept of acetal cleavage takes its full synthetic interest when one considers chiral acetals with a C2 axis of symmetry and the diastereoselectivity they may provide (Ghribi *et al.* 1984*b*). The newly created asymmetric centre results from an *anti* attack on the C—O bond that is near the axial or pseudoaxial Me group of the ring. The absolute configuration was determined by an oxidation–elimination sequence, which leads to known chiral alcohols without any loss of enantiomeric purity (scheme 2).



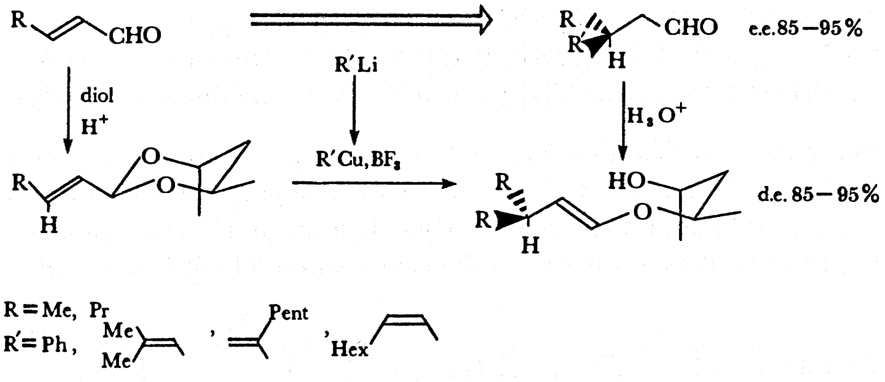
Scheme 2

Thus, the overall result of the above process may be viewed as the enantioselective addition of any kind of organolithium reagent to any kind of aldehyde.

Organocopper reagents associated with BF$_3$ are known to undergo preferential *anti* S_N2' reaction with allylic chlorides, and other leaving groups. (Yamamoto 1986). Thus, the reaction with allylic acetals should lead to enol ethers according to:



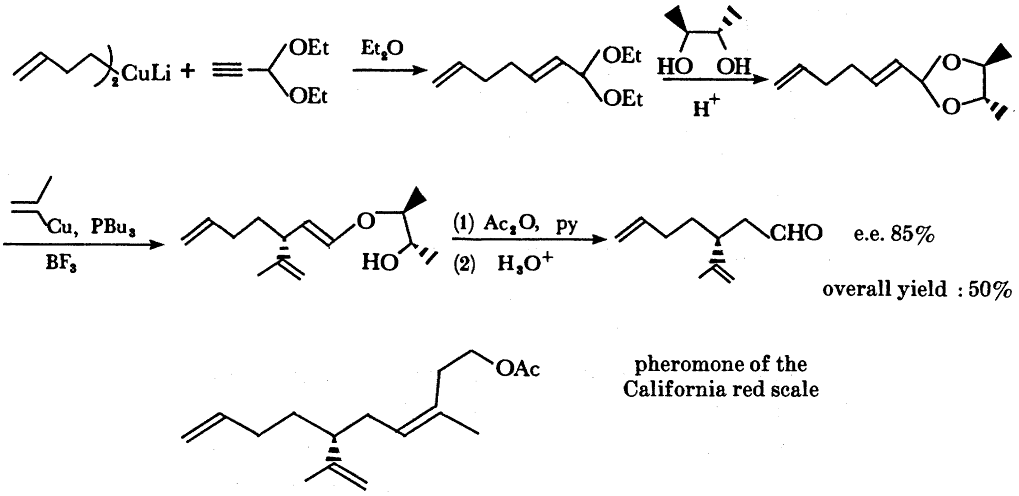
Indeed, this is true with 'soft' organocopper reagents aryl–Cu and vinyl–Cu (where an sp^2 carbon is bound to the metal), whereas with alkyl–Cu mixture of S_N2 and S_N2' products are obtained (Ghribi *et al.* 1984*c*). The reaction of chiral α,β-ethylenic acetals with the former organocopper reagents (with BF$_3$) affords, after hydrolysis of the obtained enol ether, chiral β-substituted aldehydes with recovery of the auxiliary diol. The overall process may be viewed as a conjugate addition of ArLi or vinyl–Li to a substituted α,β-ethylenic aldehyde (Mangeney *et al.* 1986, 1987) (scheme 3).



Scheme 3

The stereochemical outcome of this reaction 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_N2'

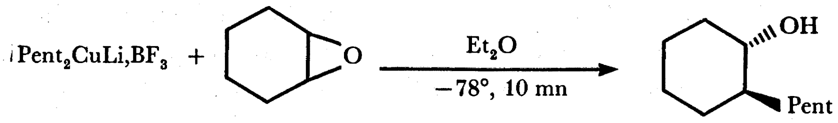
substitution. Noteworthy is the fact that only the *E*-enol ether is obtained indicating that the reaction occurred in the transoid conformation. A short and efficient synthesis of the key aldehyde for the synthesis of the California red scale pheromone is described in scheme 4.



SCHEME 4

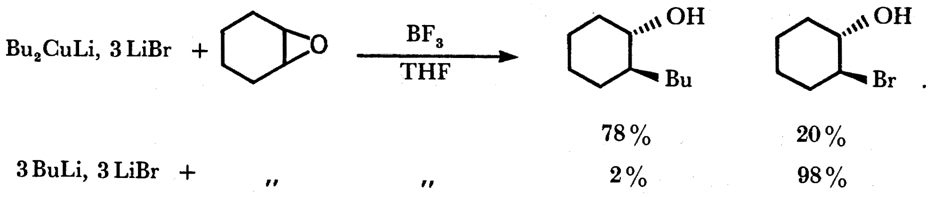
REACTIONS WITH EPOXIDES

Organocopper reagents are known to react easily with epoxides (Posner 1975). However, in some cases, such as with cyclohexene oxide, the reaction is sluggish and low yielding. We found that electrophilic activation with $BF_3 \cdot Et_2O$ improves dramatically the rate of the reaction as well as its yield (Ghribi 1984*a*), as shown below in a comparison with some literature data.

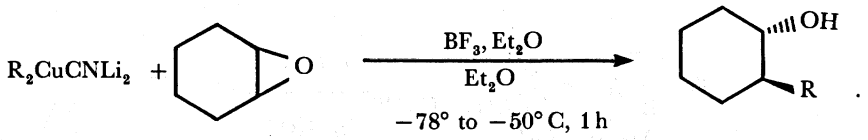


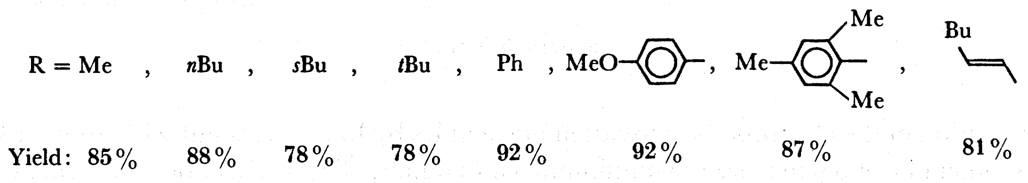
10 BuLi/5 CuI/Et_2O; 4 h; 25 °C: 65% (Johnson *et al.* 1975)
2 BuLi/2 CuCN/Et_2O; 5 h; 0 °C: 66% (Acker 1977)
1.5 BuMgCl/0.15–CuI/THF; 2 h; 0 °C: 58% (Huynh *et al.* 1979)
1.1 PrLi/1.1 thienylCu/THF; 1 h; 0 °C: 55% (Lipshutz *et al.* 1985)

A systematic study revealed that the best suited reagents are lithium cyanocuprates $R_2CuCNLi_2$ associated with BF_3,Et_2O (Alexakis 1986). The presence of halide ions has sometimes deleterious effects because a few percent of halohydrins (5–15%) are produced; but this effect is not as pronounced as in the case of the combination RLi–BF_3 (Eis *et al.* 1984):



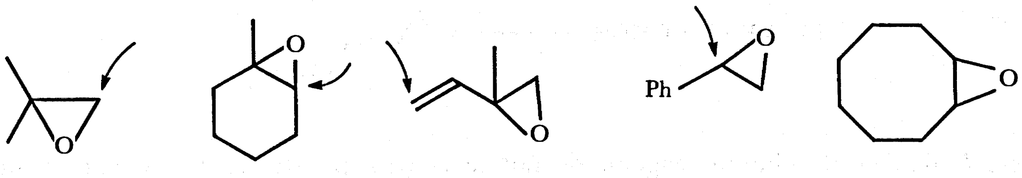
Cyclohexene oxide, chosen as a model epoxide, reacts with a great variety of organic groups (in $R_2CuCNLi_2$) such as primary, secondary or tertiary alkyl groups and various aryl and alkenyl groups, whatever their steric bulk (mesityl cuprate, for example):





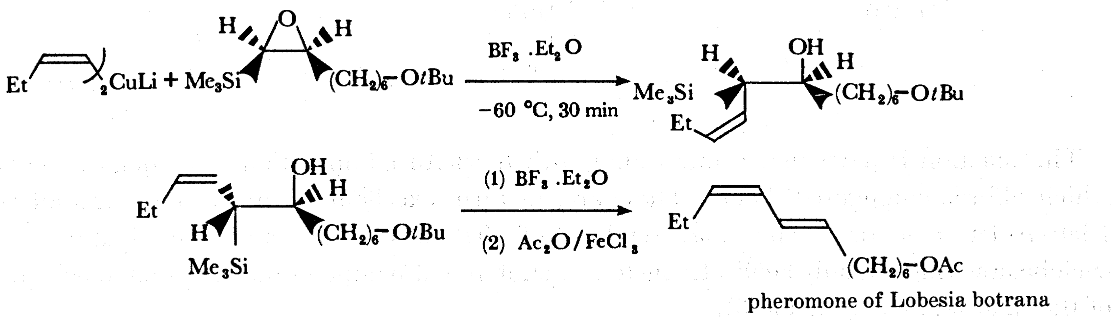
In all the above examples, only the *trans* substituted cyclohexanol is obtained. Such a high stereoselectivity rules out any purely cationic process and favours a quasi-concerted mechanism in which the nucleophile ($R_2CuCNLi_2$) attacks *anti* to the C—O bond whereas the role of the Lewis acid should be restricted to a simple electrophilic activation of the epoxide.

Various other epoxides (and oxetane) have also been tested, showing the generality of this reaction.

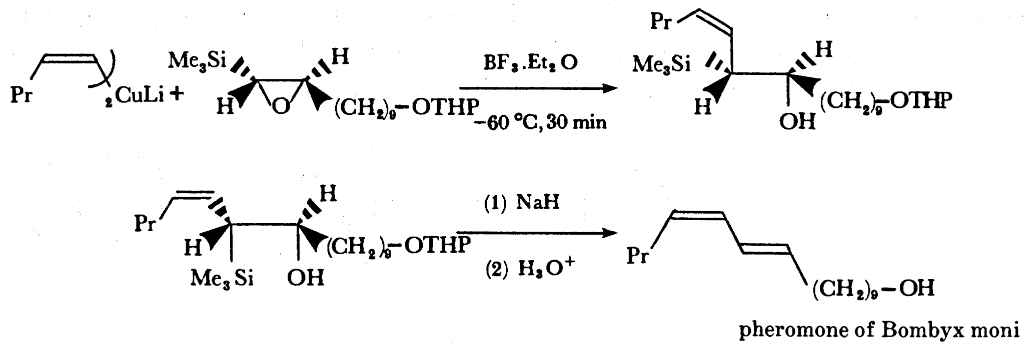


It is clear, from the above examples, that the presence of BF_3 does not alter the regioselectivity of the attack of the cuprate reagent at the less substituted side of the epoxide. For styrene oxide the benzylic position is chosen and with allylic epoxides, S_N2' attack is preferred. As for the chemoselectivity, a total selectivity for the epoxide is observed in the presence of an ester functionality whereas a 5:1 selectivity occurs with ketones.

This enhanced reactivity of $R_2CuCNLi_2/BF_3$ reagents towards epoxides was exploited in their reaction with epoxy-silanes for the synthesis of insect pheromones having a conjugated diene system (Alexakis & Jachiet 1988) (scheme 5).

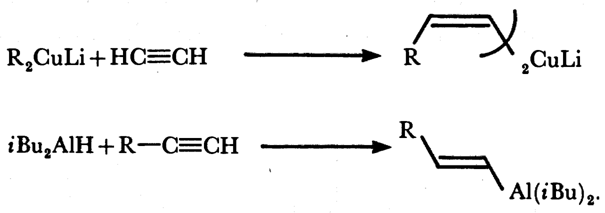


Scheme 5

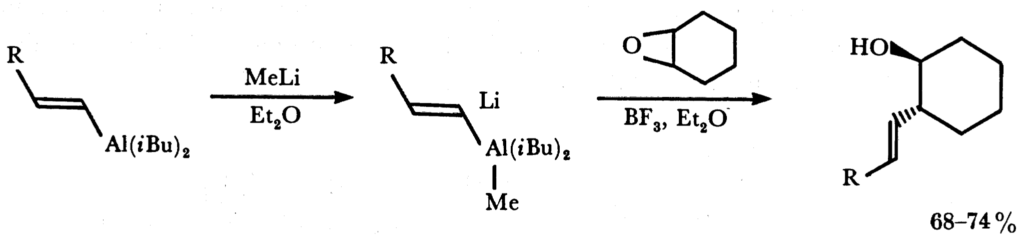


SCHEME 5 (*cont.*)

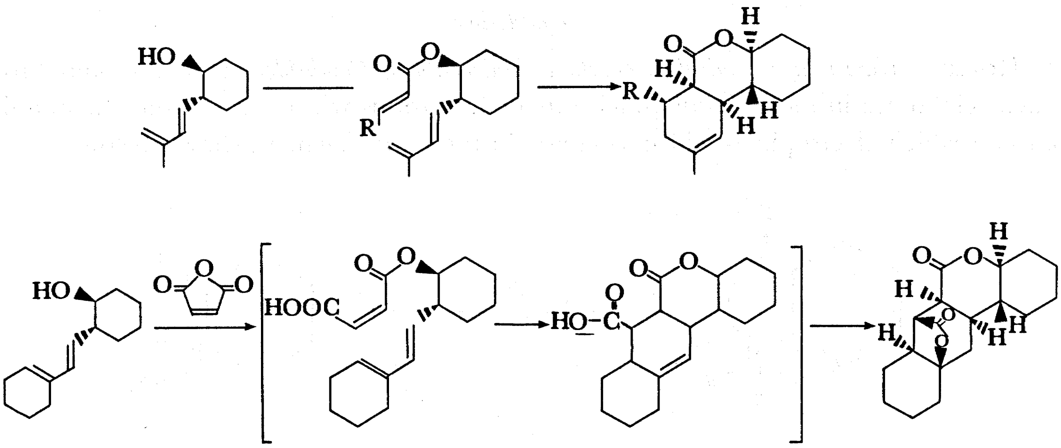
An extension of the electrophilic activation of epoxides by BF_3 was sought with another kind of organometallic reagent: organoaluminium compounds. The carbocupration reaction of acetylene affords *Z*-alkenyl metallic species (Normant & Alexakis 1981), whereas the hydroalumination reaction of mono-substituted alkynes affords, complementarily, *E*-alkenyl metallic species (Zweifel 1984):



These *E*-alkenyl aluminium reagents do not react with poorly reactive epoxides, such as cyclohexene oxide, even after transformation into the more nucleophilic aluminum *ate* complexes. (Negishi *et al.* 1976). We found that, in the presence of BF_3 they do react, giving rise to *E*-alkenyl substituted cyclohexanols. Again, the stereoselectivity is total with an *anti* opening of the oxirane ring:



The reaction is particularly interesting with the hydroalumination of conjugated enynes, which affords conjugated dienes. These are, in turn, excellent substrates for intramolecular Diels–Alder reactions. The *trans* relation of the substituents and the rigidity of the cyclohexane ring not only facilitates such a reaction but also imposes the unique stereochemistry of the final adducts (scheme 6).



SCHEME 6

From all the above results it seems clear that the electrophilic activation of acetals and epoxides is a useful means to enhance their reactivity. The application of these reactions in enantio- and diastereoselective synthesis opens new ways to the chemist for a short and efficient preparation of many target molecule.

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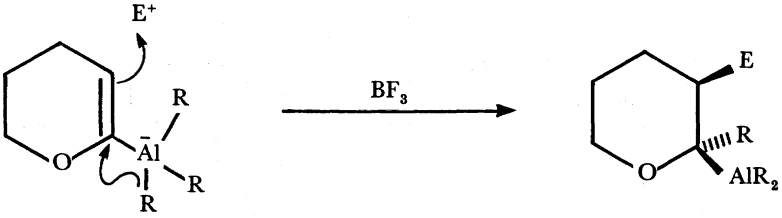
Discussion

A. B. Holmes (*University Chemical Laboratory*, *University of Cambridge*, *U.K.*). Would Professor Alexakis elaborate in more detail which functional groups will migrate from the aluminium atom and which electrophiles will participate in the rearrangement shown below?



A. Alexakis. The electrophiles E^+ tried up to now are epoxides and aldehydes. As for the R group that migrates, it follows the usual order of transferability in aluminium chemistry i.e.

 > Me— > iBu— .