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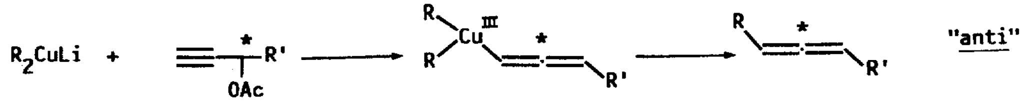
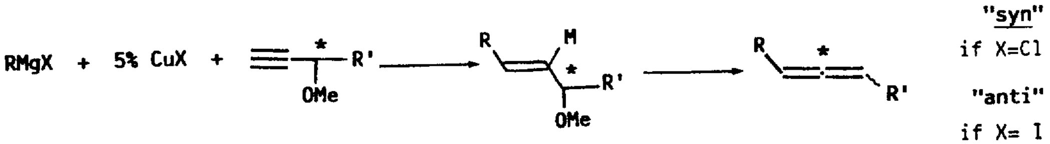
DIASTEREOSELECTIVE SYNTHESIS OF α-ALLENIC ALCOHOLS FROM PROPARGYLIC EPOXIDES

A. Alexakis*, I. Marek, P. Mangeney, J.F. Normant
Laboratoire de Chimie des Organoéléments, Université P. et M. Curie
4 Place Jussieu, 75252 Paris Cedex 05

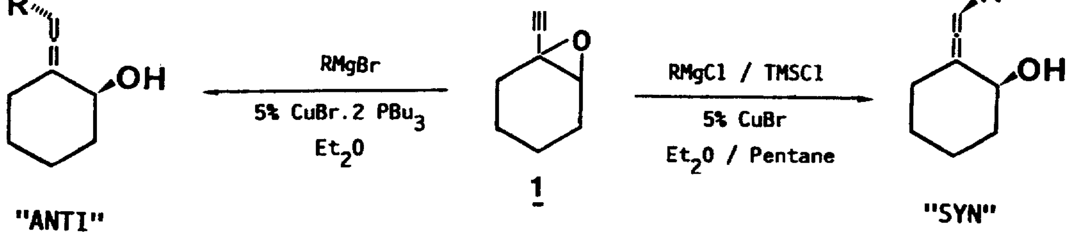
Summary. *The cuprocatalyzed reaction of a Grignard reagent with propargylic epoxides proceed through an addition-elimination mechanism. By changing the reaction conditions, particularly the halogen atom of RMgX it is possible to control the diastereoselectivity of the reaction. Both diastereoisomers of an allenic alcohol can thus be obtained at will.*

Propargylic epoxides are known to react with organocopper reagents[1], leading to allenic alcohols, by an anti overall, process[2], through a postulated Cu^{III} intermediate based on the analogy with propargylic acetates or tosylates[3]. If one considers that propargylic epoxides are a special kind of propargylic ethers, then an addition-elimination mechanism could be operative as well[4]. We have recently shown that, with the latter mechanism, the stereochemical course of the reaction varies with the nature of the halogen of RMgX[5] :

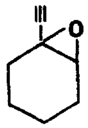
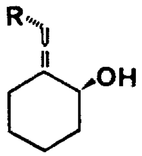
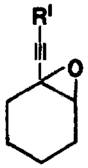
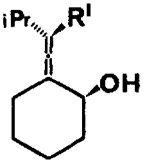




In this letter, we demonstrate that propargylic epoxides are sensitive to such a "halogen effect", leading, at will, to the "ANTI" or "SYN" allenol :

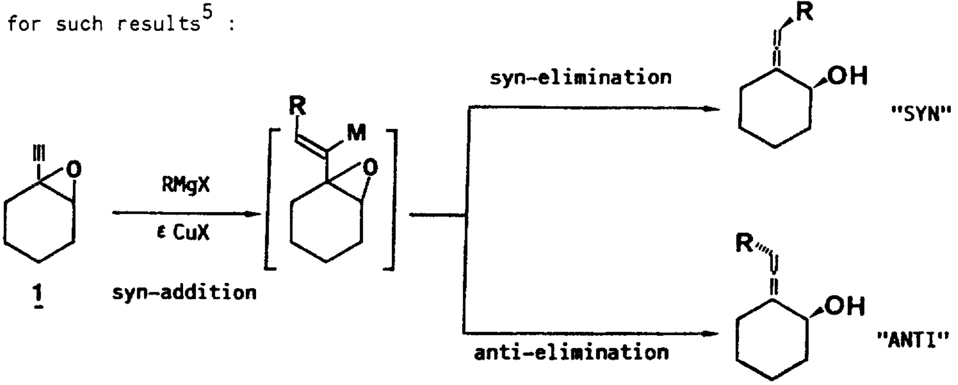


$$\text{Epoxide} + \text{RMgBr} + 5\%\ (\text{CuBr}, 2\text{PBu}_3) \xrightarrow{\text{Et}_2\text{O}} \text{"ANTI" allenol}$$

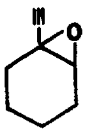
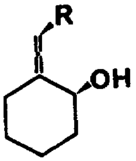
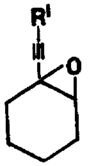
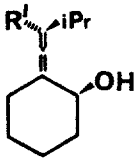
Epoxide	RMgBr	Allenol[a]		yield[b] %	diastereo-selectivity[c]
 1	Bu		R = Bu	78	100%
"	iPr	"	R = iPr	72	100%
"	tBu	"	R = tBu	100	96%
"	Ph	"	R = Ph	60	95%
 2 R' = Me	iPr		R' = Me	80	100%
" 3 R' = $SiMe_3$	"	"	R' = $SiMe_3$	91	95%
" 4 R' = Ph	"	"	R' = Ph	50	100%

a) : all the products were fully characterized
b) : yield of isolated product
c) : the diastereoisomers are easily distinguished by ^{13}C NMR. They are also separated by G.C., after acetylation.

Our preliminary studies were done with ethynyl cyclohexene oxide 1. Contrary to an early report[1b], this epoxide reacts smoothly with various Grignard reagents, under copper[1] catalysis, in Et_2O solvent. The reaction is also regioselective affording mainly, and even exclusively in many cases, the S_N2' product viz the α-allenic alcohol. As for the stereoselectivity, it varies greatly according to the R group and the halogen of the Grignard reagent and the nature of the ligand[6]. Only an addition-elimination mechanism can account for such results[5] :



Epoxide + RMgCl + 5% CuBr + TMSCl $\xrightarrow{Et_2O/Pentane}$ "SYN" allenol

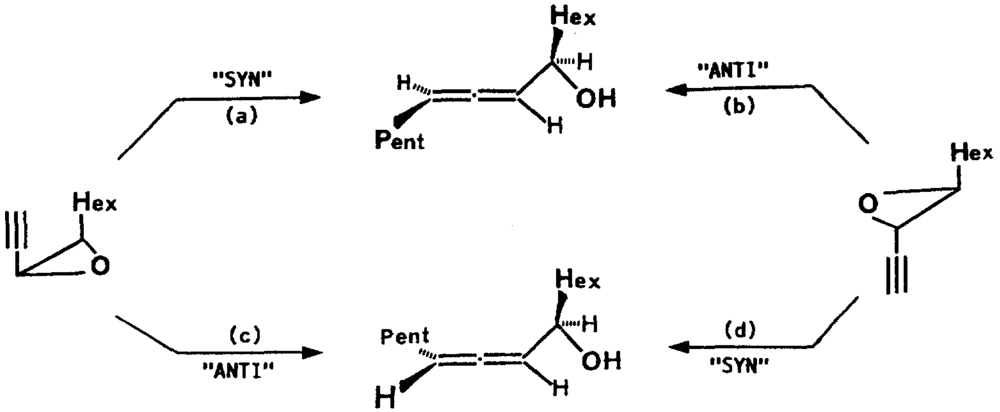
Epoxide	RMgCl	conditions[a]	Allenol	yield%	diastereo-selectivity
 1	Me	B	 R = Me	91	95%
"	Bu	A	" R = Me	100	88%
"	Ph[b]	B	" R = Ph	90	96%
 2 R' = Me	iPr	A	 R' = Me	100	84%
" 3 R'=$SiMe_3$	"	A	" R' = $SiMe_3$	95	96%
" 4 R' = Ph	"	A	" R' = Ph	84	76%

a) Conditions A : 2RMgCl + 5% CuBr + 1TMSCl/Et_2O
" B : 2RMgCl/Et_2O
b) PhMgBr, in Et_2O, was used

The optimized ANTI conditions involve a Grignard reagent derived from an alkylbromide (RMgBr) and a copper salt complexed (and solubilized) with two equivalents of a strong ligand, PBu_3, in Et_2O solvent. The reaction occurs already at - 50°C, (and at - 30°C with the substituted alkynyl cyclohexene oxides).

On the other hand the optimized SYN conditions involve the use of RMgCl in mixture of Et_2O and pentane (50/50). The copper catalyst, CuBr, is uncomplexed. The presence of 1 eq. of Me_3SiCl also increases the syn selectivity, although its role cannot be explained unequivocally[7]. More unexpectedly, in the case of ethynyl epoxides, the copper salt seems to be unnecessary !! However the reaction rate is then strongly slowed down. By this latter way the methyl and phenyl groups are best introduced. In the absence of copper salt a different mechanism might be operative, such as a direct S_N' reaction where a syn selectivity is usually observed[8].

The above control of diastereoselectivity was also extended to the case of acyclic propargylic epoxides :



(a) Pent MgCl/Et_2O : 92% (syn/anti : 81/19)
(b) Pent MgBr + 5% CuBr, $2PBu_3/Et_2O$: 90% (syn/anti : 10/90)
(c) Pent MgBr + 5% CuBr, $2PBu_3/Et_2O$: 80% (syn/anti : 4/96)
(d) Pent MgCl/Et_2O 94% (syn/anti : 96/4)

Thus, the addition-elimination mechanism allows us to control the diastereoselectivity of the reaction toward the threo or erythro isomer.

Acknowledgments:

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References and Notes.

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   b) P. Vermeer, J. Meijer, C. de Graaf, H. Schreurs : Rec. Trav. Chim.,Pays-Bas, 93, 46 (1974)
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6. A variation of the diastereoselectivity was already noted according to the nature of the cuprate reagent (R_2CuLi or R_2CuMgX) and the ligand (Me_2S or not) : A.C. Oehlshlager, E. Czyzewska, Tetrahedron Lett., 24, 5587 (1983)
7. TMSCl may act as an alcoholate scavenger, a Cl^- donnor (RMgCl + TMSCl → RTMS + $MgCl_2$) or as a d electron acceptor
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