

Lewis Acid-Mediated Ring Opening of Propargylic Epoxides : A Stereospecific Synthesis of 1,2-Disubstituted Homopropargylic Alcohols.

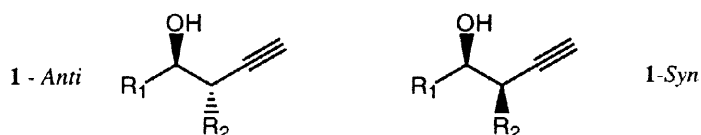
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Abstract : The $\text{BF}_3\text{-Et}_2\text{O}$ -mediated ring opening of propargylic epoxides by organometallic nucleophiles gives in a completely regio- and stereospecific fashion 1,2-disubstituted homopropargylic alcohols in good to excellent yields. © 1998 Elsevier Science Ltd. All rights reserved.

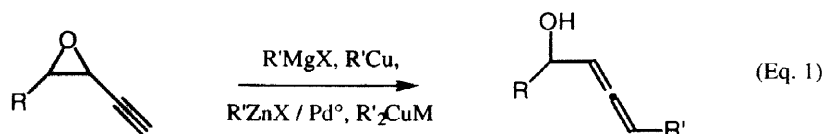
In the course of our studies toward allylzincation of vinylmetals¹, we were in need of a good, stereospecific and simple method to prepare various 1,2-disubstituted homopropargylic alcohols of the general formula **1** in a defined *syn* or *anti* relationship :



Generally, these products are prepared by the reaction of allenylmetals on aldehydes². However, this approach requires a good regiochemical control (allenyl vs propargyl alcohol formation) as well as a good stereochemical control (*syn* vs *anti* attack): Whereas the use of allenylzinc reagents leads to *anti* propargylic products with excellent yields and diastereoselection levels³, the formation of *syn* propargylic products involves generally the reaction of allenylstannanes with aldehydes under Lewis acid catalysis⁴.

Another possible way to prepare these products could be the nucleophilic attack of an organometallic species onto a propargylic epoxide. However, very little is known about ring opening of propargylic epoxides by carbon nucleophiles on the propargylic position. The main observed reaction with organometallics (Grignard reagents without⁵ or with^{5,6} copper salts, organozinc reagents under palladium catalysis⁷, organoalanes⁸) is the $\text{S}_{\text{N}}2'$ ring-opening reaction, leading to allenols (Eq. 1).

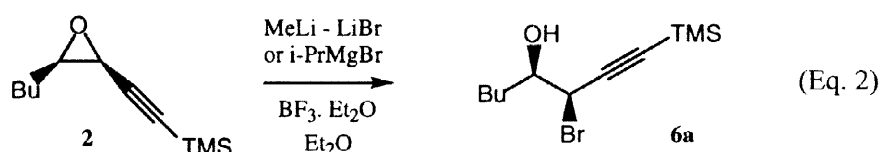
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To the best of our knowledge, only two examples of reaction at the propargylic site are reported: the reaction of Grignard reagents on an enyne-epoxide⁹, and the reaction of organotitanium reagents on propargylic epoxides reported by Krause and Seebach¹⁰.

When we tried to open the propargylic epoxide **2** by MeLi or iPrMgCl, no reaction was observed. This is consistent with the report of a very slow process⁵. We thought then that the reaction could be activated by the presence of a Lewis acid. Ring-opening of simple or allylic epoxides with carbon nucleophiles in the presence of a Lewis acid such as BF₃·Et₂O¹¹ is well-known. However, propargylic epoxides have never been employed. We were pleased to see that the presence of BF₃·Et₂O considerably activates the reaction: ring-opening occurs at low temperature (-78°C) in less than one hour exclusively at the propargylic position. Moreover, *the reaction is completely stereospecific*, with total inversion of configuration at the propargylic carbon atom, leading to the *syn* homopropargylic alcohols **4a-e** from the *cis* epoxide **2** or to the *anti* homopropargylic alcohols **5a-c** from the *trans* epoxide **3**. The results with various nucleophiles are reported in the Table 1.

Under these conditions, we could observe that the presence of LiBr or MgBr₂ leads to the competitive reaction of bromide ion to give bromohydrin **6** again in a remarkable regio- and stereospecific fashion (Eq. 2) and in a 50 % yield. Then the use of “salt-free” organolithium species or Grignard reagents of the RMgCl-type was necessary.



The use of ether as a solvent was also necessary since in THF, no reaction was observed at a temperature below 0°C.

The inversion of configuration at the propargylic carbon atom was proved by the comparison of ¹H and ¹³C NMR spectral data of compound **5a** with those reported in the literature¹².

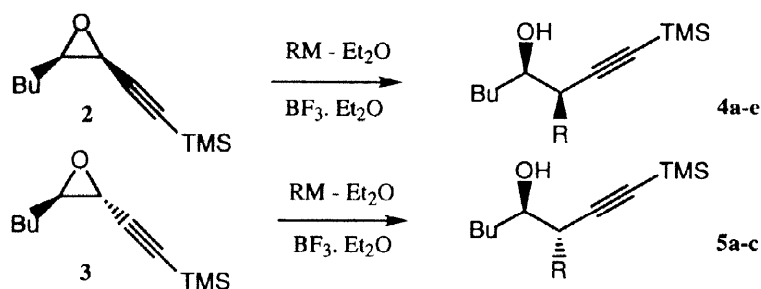


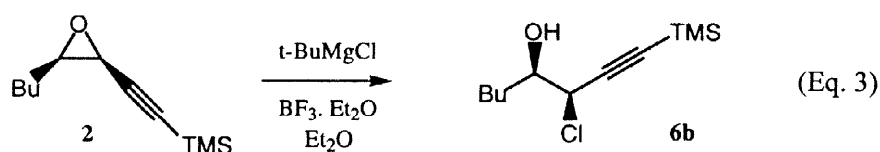
Table 1. Stereospecific Formation of Homopropargylic Alcohols **4**, **5** from Epoxides **2**, **3**.

Entry	Starting material	RM*	Product	Yield
1	2	MeLi	4a	90 %
2	2	EtMgCl	4b	75 %
3	2	i-PrMgCl	4c	70 %
4	2	BnMgCl	4d	65 %
5	2	BuLi**	4e	35 %
6	3	MeLi	5a	60 %
7	3	EtMgCl	5b	62 %
8	3	i-PrMgCl	5c	65 %

* All the used organometallic species were in solution in ether, except for entry 5.

** Used as a solution in hexane.

As can be seen in the Table 1, the use of primary as well as secondary organolithium or organomagnesium species is allowed. In the case of tertiary organometallics, the use of $t\text{-BuMgCl}$ leads to the chlorohydrin **6b** (Eq. 3), whereas the use of $t\text{-BuLi}$ gives numerous unidentified products.



The synthesis of the starting materials **2** and **3** was performed following the described procedure, by oxidation of the corresponding (*Z*) or (*E*)-enynes⁵.

In conclusion we have disclosed a new and highly stereospecific synthesis of *syn* or *anti* disubstituted homopropargylic alcohols. Further results in this field will be reported in due course.

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References

1. Bähr, A.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1996**, *37*, 5873-5876.
2. Yamamoto, H. Propargyl and Allenyl Organometallics, in: *Comprehensive Organic Synthesis*, Trost, Fleming eds. ; Pergamon Press: London, 1991; pp 81-98.
3. Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565-4567.
Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377-11390.
4. Marshall, J.A.; Wang, X. *J. Org. Chem.* **1990**, *55*, 6246-6248; Marshall, J.A.; Wang, X. *J. Org. Chem.* **1992**, *57*, 1242-1252; Marshall, J.A.; Perkins, J. *J. Org. Chem.* **1994**, *59*, 3509-3511.
5. Alexakis, A. *Pure & Appl. Chem.* **1992**, *64*, 387-392; Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron* **1991**, *47*, 1677-1696.
6. Ortiz de Montellano, P.R. *J. Chem. Soc., Chem. Commun.* **1973**, 709-710; Vermeer, P.; Meijer, J.; deGraaf, C.; Scheurs, H. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 46; Tigchelaar, M.; Meijer, J.; Kleijn, H.; Bos, H.J.T.; Vermeer, P. *J. Organomet. Chem.* **1981**, *221*, 117-221; Oehlschlager, A.C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587-5590; Doutheau, A.; Sartoretti, J.; Goré, J. *Tetrahedron* **1983**, *39*, 3059-3065; Marshall, J.A.; Pinney, K.G. *J. Org. Chem.* **1993**, *58*, 7180-7184.
7. Kleijn, H.; Meijer, J.; Overbeek, G.C.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 97-101.
8. Trost, B.M.; Tour, J.M. *J. Org. Chem.* **1989**, *54*, 484-486.
9. Perveev, F.Y.; Kudryashova, N.I. *Zhur. Obshch. Khim.* **1953**, *23*, 348-351; *Chem. Abstr.* **1954**, *48*, 2566d.
10. Krause, N.; Seebach, D. *Chem. Ber.* **1988**, *121*, 1315-1320.
11. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391-394; Eis, M.J.; Wrobel, J.E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693-3694.
12. Hoffmann, R.W.; Giesen, V.; Fuest, M. *J. Liebigs. Ann. Chem.* **1993**, 629-639.