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A Stereospecific Synthesis of 1,2-Disubstituted Homopropargylic Protected Alcohols from Bromoallenols.

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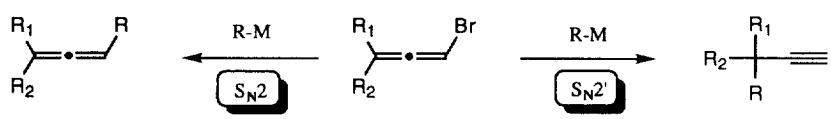
Abstract : Bromoallenols derived from propargylic epoxides are transformed in two steps and in a stereospecific fashion into 1,2-disubstituted homopropargylic protected alcohols with Grignard reagents with or without copper salts.

Having recently developed a new and stereospecific method for the preparation of bromoallenols from propargylic epoxides[1], we would like to report our results concerning the transformation of these compounds into 1,2-disubstituted homopropargylic alcohols. The substitution reactions of bromoallenes have been studied[2]; whereas nitrogen- and sulfur-centered nucleophiles are known to displace bromide in a S_N2' fashion[3], the results with carbon-centered nucleophiles are less clear-cut. The most commonly employed nucleophiles are organocopper species. The regiochemistry of the nucleophilic displacement (S_N2 *vs* S_N2') is highly dependent on the nature of the organocopper species as well as of the structure of the substrate (Scheme 1) :



Scheme 1

The S_N2 displacement, leading to the allene, was observed with organocuprates R_2CuLi[4], and with $RCu\text{-}MgBr_2$ and Grignard reagents under Cu(I) catalysis[5]. On the other hand, the S_N2' displacement, leading to the alkyne, was reported with lower order cuprates R_3Cu_2Li[6], heterocuprates $RCu(CN)Li$[5-7], as well as with Vermeer-type[8] organocopper species $RCu\text{-}MgBr_2\text{-}LiBr$[5,9]. However, steric hindrance was shown to cause

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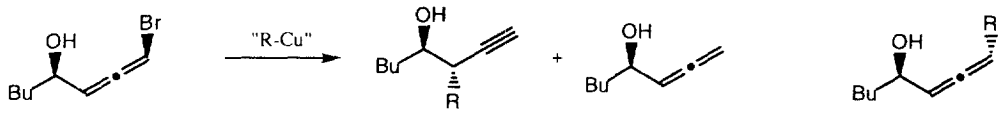
deviations to this regioselectivity pattern[5,6]. The stereochemistry of the S_N2' process was found to be purely *anti*; this was attributed to an addition-elimination mechanism[5] or to a Cu(III) species intermediacy[10].

However, the presence of an heteroatom in the α position of the allenyl moiety was shown by Mann and Taddei to overcome these regioselectivity problems, by directing the nucleophilic attack and then favouring the S_N2' process[11]. This encouraged us to examine the behaviour of our previously prepared[1] bromoallenols toward carbon-centered nucleophiles. The bromoallenol **1** was exposed to different organocopper reagents (3 eq.). According to Mann's results, we never obtained any S_N2 product (substituted allenol **4**); the substitution reaction gave us only the S_N2' product (homopropargylic alcohol **2**), accompanied by an important quantity of the reduction product (unsubstituted allenol **3**), as depicted on the scheme 2. The results are summarized in the table 1. The structure of compounds **2** was unambiguously attributed by comparison of ^1H and ^{13}C data with those obtained from direct ring-opening of epoxides with organometallics that we have recently described[12].



1 **2** **3** **4**

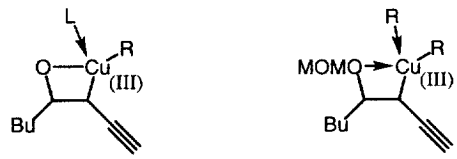
Scheme 2

Table 1. Substitution Products of Bromoallenol **1** with various Organocopper Reagents.

Entry	"R-Cu"	Yield of **2**	Yield of **3**
1	MeCu(CN)Li	35 %	35 %
2	$Me_2Cu(CN)Li_2$	0 %	40 %
3	i-PrMgBr / CuBr 5%	20 %	40 %
4	MeCu / LiBr	30 %	30 %

We thought that the large amount of reduction product **3** was due to the great stability of the supposed Cu(III) intermediate; this surprisingly high stability could be attributed to a O-Cu binding stronger than a simple chelation (intermediate **A** on Scheme 3). Then we decided to protect the alcohol as a MOM ether, in order to diminish this interaction (intermediate **B** on Scheme 3). This was effected under standard conditions in high yield (90 %) and the resulting bromoalleneacetal **5** was allowed to react with various organocopper reagents (3 eq.). We were pleased to see that no more reduction product was observed; the homopropargylic

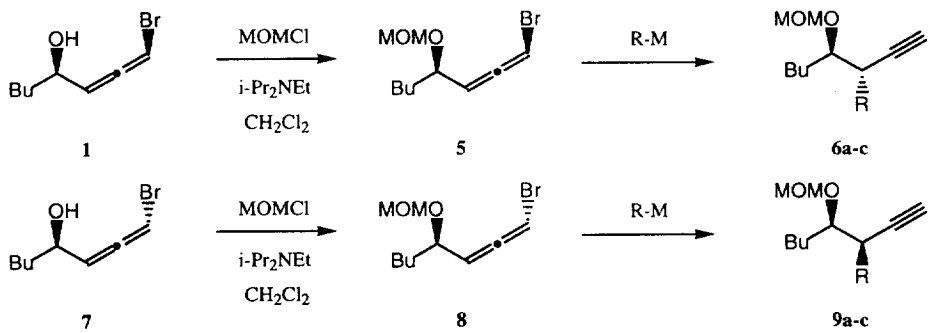
acetals **6** were obtained in high yields and in a totally stereospecific manner (except in one case, see entry 6 on table 2), resulting from the desired *anti* S_N2' reaction.



A **B**

Scheme 3

The same result was obtained when the reaction was performed on the diastereomeric bromoallenacetal **8** prepared from the bromoallenol **7**[1], as depicted on the scheme 4. The results for various organometallic reagents are summarized in the table 2.



Scheme 4

Table 2. Protected Homopropargylic Alcohols from Protected Bromoallenols **5**, **8** and Organometallics.

Entry	Starting material	R-M	Product	Yield
1	**5**	MeCu(CN)Li	**6a**	95 %
2	**5**	i-PrMgBr / CuBr 5 %	**6b**	85 %
3	**5**	i-PrCu / $MgBr_2$ / Me_2S	**6b***	42 %
4	**5**	BuCu(CN)Li	**6c**	95 %
5	**5**	i-PrMgBr	**6b**	90 %
6	**5**	allylMgBr / CuBr 5%	**6b****	53 %
7	**8**	MeCu(CN)Li	**9a**	90 %
8	**8**	i-PrMgBr	**9b**	83 %

* The product of a S_N2 reaction was also obtained in a 28 % yield.

** The other diastereoisomer was also obtained in a 13 % yield.

Moreover, we were very surprised, in a control experiment, to see that the same substitution reaction proceeded very cleanly from both the regio- and the stereochemical standpoints with Grignard reagents *in the absence of any copper salt !* This is contradictory with some previously reported results[13]. Apparently the presence of the heteroatoms in the α position of the allenyl moiety not only directs the substitution reaction on the S_N2' way, but also considerably enhances the reaction rate of Grignard reagents.

Concerning the reaction mechanism, it can be deduced from the presence of the reduction product **3** that the reaction of bromoallenol **1** with copper reagents proceeds through a mechanism involving a Cu(III) intermediate. It seems likely to be the same for the reaction of bromoallenacetals **5** and **8**. However, the mechanism of the reaction of Grignard reagents remains uncertain. Both regioselectivity (pure S_N2' reaction) and stereoselectivity (pure *anti* reaction) are, to the best of our knowledge, unprecedented in the literature[14].

In conclusion we have disclosed a new and highly stereospecific synthesis of homopropargylic protected alcohols starting from easily available bromoallenols[1], leading to *syn* or *anti* disubstituted homopropargylic alcohols starting from propargylic epoxides *cis* or *trans* respectively. Further results in this area will be reported in due course.

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