

Stereochemical aspects on the formation of chiral allenes from propargylic ethers and epoxides

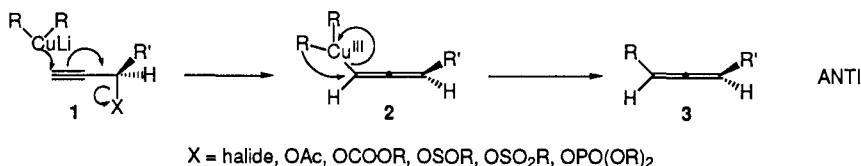
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Abstract - Chiral propargylic ethers react with organocopper reagents to afford optically active allenes by a *syn* addition to the triple bond followed by an *anti* β -elimination of the resulting alkenyl copper species. However, the same reaction, run with a Grignard reagent and a catalytic amount of copper (I) salt affords allenes through an *anti* or *syn* process. The crucial step is the β -elimination of the intermediate alkenyl metal species, which is of *anti* type with RMgI and of *syn* type with RMgCl . Propargylic acetates, which also afford allenes in this reaction, but through a Cu(III) intermediate, are not sensitive to this "halogen effect". By close analogy to ethers, propargylic epoxides react with Grignard reagents and catalytic amount of Cu(I) salt, leading to α -allenic alcohols. The reaction is highly diastereoselective and its stereochemical outcome can be fully controlled. The *syn* diastereomer, probably arising through an addition-elimination mechanism, is better obtained with RMgCl and copper (I) bromide, whereas the *anti* diastereomer is best obtained with RMgBr and a complexed copper (I) salt.

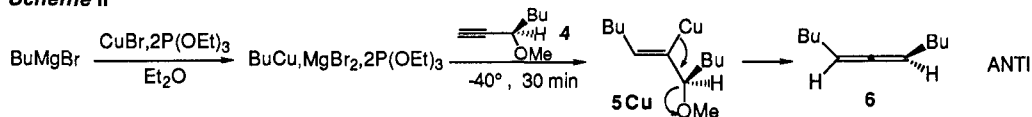
The synthesis of chiral allenes **3** is often done by reaction of an organocopper derivative with a chiral propargylic substrate **1** (where X is a good leaving group) (ref 1). Mechanistically, these reactions are thought to proceed through a Cu^{III} intermediate **2** resulting from an *anti* $\text{S}_{\text{N}}2$ nucleophilic attack of the Cu^{I} atom. This intermediate collapses by reductive elimination to allene **3** with retention of configuration. (ref 2) The overall result is an *anti* process (Scheme I) :

Scheme I



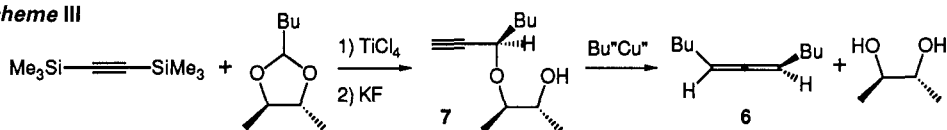
During our work on the carbocupration of alkynes (ref 3), we had the opportunity to demonstrate that the formation of dibutyl allene **6** from propargylic ether **4** follows a different path. A *syn* addition first takes place producing an alkenyl copper reagent **5Cu**, which can be trapped by various electrophiles. This alkenyl copper species undergoes, then, a β -elimination to afford allene **6** (ref 4) (Scheme II). The nature of this β -elimination was studied with a chiral substrate **4** and was found to be *anti* (ref 5). The overall process occurred with >96% chirality transfer (or optical yield) :

Scheme II

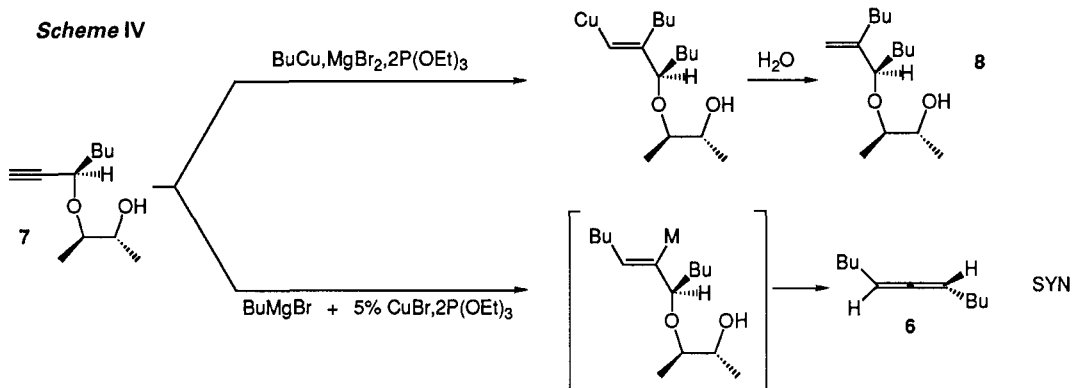


Some years later, we needed to prepare large amounts of chiral dibutyl allene **6** and we thought more convenient to use another optically pure propargylic ether. Indeed, Johnson et al (ref 6), reported an elegant synthesis of propargylic ethers, such as **7**, bypassing the need of preparing first an optically active propargylic alcohol (Scheme III). Such an approach is particularly attractive since it allows also the recovery of the chiral diol, used as auxiliary.

Scheme III



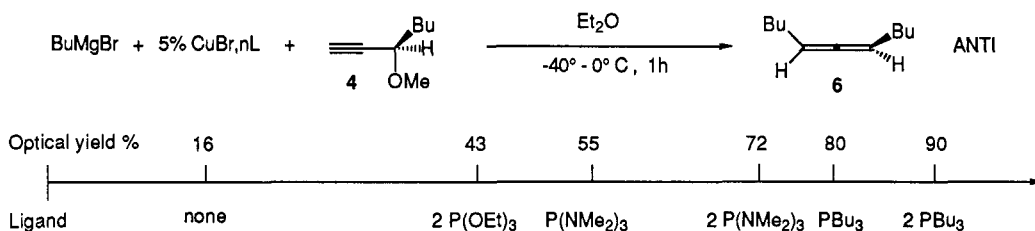
However, repetition of the experiment described in Scheme II, gave, largely, the undesired regioisomer **8** instead of the expected allene (Scheme IV). Since Gaudemar et al (ref 7) have shown that the same allene synthesis can be carried out with a Grignard reagent and a catalytic amount of copper salt, we also tried this procedure. Indeed, we obtained, this time, the desired dibutyl allene **6** but, surprisingly, through a syn overall process ! (Scheme IV) :



Thus, the catalytic process, seems to be sensitive to various factors which not only affect the regioselectivity of this reaction but also its stereoselectivity. In order to have a closer view of these factors, we studied in more details all the parameters of this reaction on a more simple substrate : propargylic ether **4** .

It was reported, in 1979, by Claesson et al (ref 8), that the catalytic version of the reaction shown in Scheme II occurred with a low chirality transfer, giving an allene of 16% optical purity, through an overall anti process. It was also postulated that extensive racemization took place, by the organocopper reagent (ref 9) or copper (0) (ref 10), also found in these reactions, through a SET process. Our first idea was that stabilization of the reacting organocopper species by appropriate ligands should avoid such racemization. Indeed, as shown in Scheme V, on the scale, trivalent phosphorus ligands allow, now, an excellent chirality transfer with an optical yield of 90% for the anti process. Tributyl phosphine is known to be a better ligand than triethyl phosphite (ref 11) and the results corroborate this fact. Thus, the catalytic procedure allows, now, a very efficient synthesis of optically active allenes through an anti process.

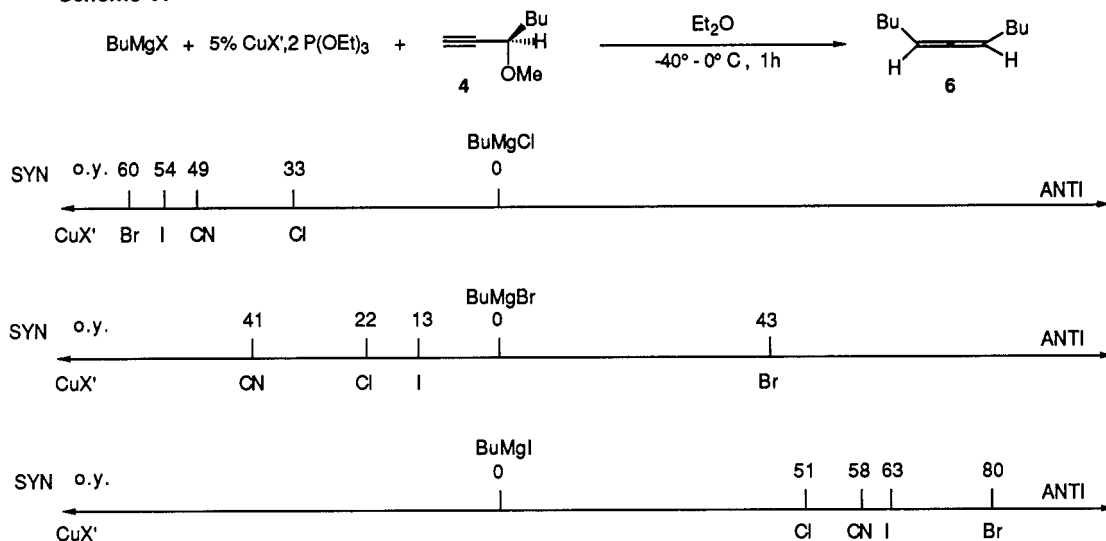
Scheme V



The surprise came when we varied the nature of the copper salt and most strikingly, when we changed the halogen of the Grignard reagent. We found that BuMgI always lead to the anti allene **6**, whereas BuMgCl allways lead to the syn allene **6** ! More impressively, as shown in Scheme VI, BuMgBr gave highly variable results, depending only upon the catalytic amount (5%) of the copper (I) salt, giving the syn allene **6** with CuCN (o.y. 41%) or the anti one with CuBr (o.y. 43%). These results are summarized on the three scales in Scheme VI

All these reactions proceed through an addition-elimination mechanism, as in the stoichiometric case (Scheme II) since it is possible to isolate, after hydrolysis at an intermediate stage of the reaction, ~30% of 5-methoxy-E,6-undecene. The addition step is still a syn carbocupration ; it is, therefore, the type of β -elimination of the alkenyl-metal intermediate that determines the overall stereochemistry. The amount, of this

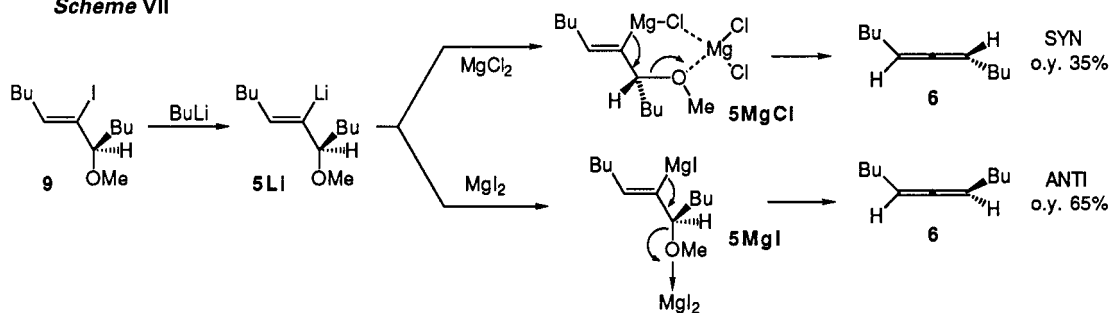
Scheme VI



intermediate (30%) compared with the 5% of CuX, indicates that this intermediate should be mainly an alkenyl Grignard reagent. We were, thus, led to study the nature of the β -elimination of alkenyl Grignard reagents of type **5Mg** in the absence of any copper salt.

As shown in Scheme VII, the iodination of alkenyl copper reagent **5Cu** (Scheme II) gave, in 70% yield, the iodide **9** (ref 4), which, after metal-halogen exchange, affords the lithium reagent **5Li**. Transmetalation to the Grignard reagent by addition of MgI_2 or MgCl_2 salts lead respectively to the *anti* or to the *syn* allene **6**. In a simplified view it may be admitted that the small size and the electronegativity of the chlorine atom allow a cyclic transition state where the greater Lewis acidity of MgCl_2 (ref 12) plays a role in favor of a *syn* elimination. On the other hand, the size of the iodine atom does not allow such a cyclic arrangement and the elimination becomes predominantly *anti* (Scheme VII).

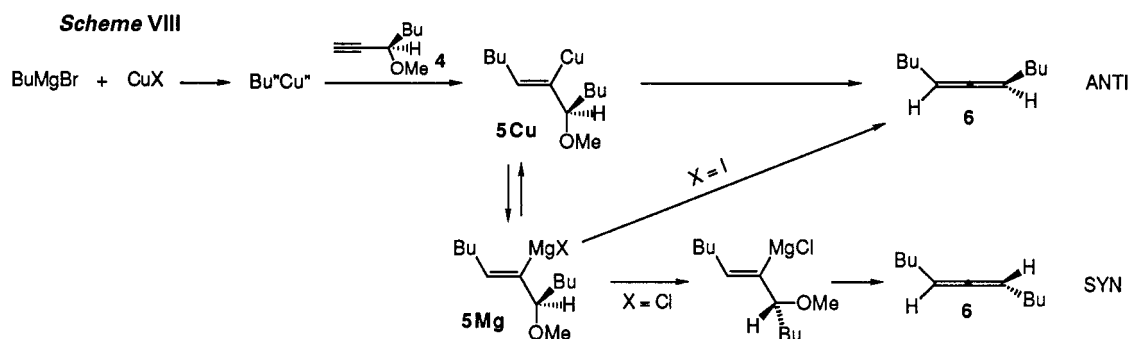
Scheme VII



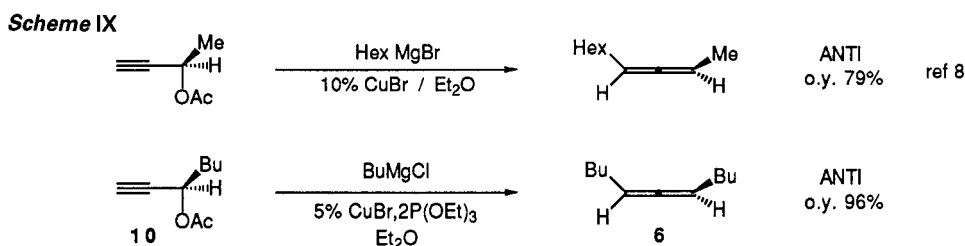
Whatever the case, it is synthetically important to be able, with the same substrate, to change the stereochemical course of this reaction. Improvement of the optical yield of the *syn* process was, thus, required. Reaction of BuMgCl with propargylic ether **4**, under 5% CuBr catalysis, gave the *syn* allene **6** with 41% optical yield. When $\text{CuBr} \cdot 2\text{P}(\text{OEt})_3$ was used, the optical yield climbed to 60%. However, a better ligand such as PBU_3 gave worse results (o.y. 24%). Thus, the effect of PBU_3 was not, as we initially thought, to prevent racemization of the formed allene; it intrinsically favors an *anti* elimination. Finally we found that *in situ* generation of more MgCl_2 has a strongly beneficial effect. Thus, when the reaction was run with 5% CuBr , 1 eq. of TMSCl and in a mixture of Et_2O /pentane (50/50), a 76% optical yield of *syn* allene **6** could be attained.

Considering the various aspects of all the factors that affect the stereochemical course of this reaction, the following general explanation may account for all the above results. The Grignard reagent undergoes, first, a transmetalation to a copper species which adds to the triple bond of the propargylic ether leading to an alkenyl copper complex **5Cu** (Scheme VIII). This copper intermediate **5Cu** may undergo a β -elimination

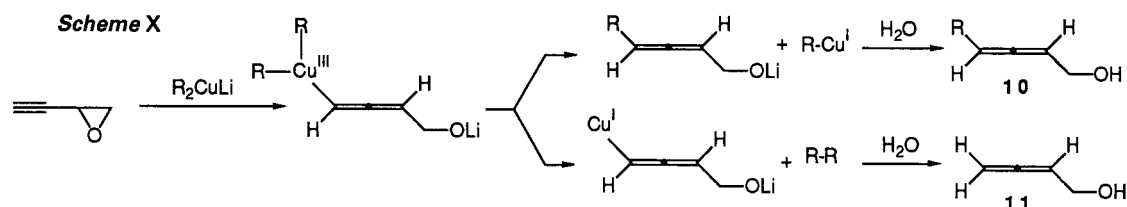
which is of *anti* type as shown in the stoichiometric case (Scheme II). However, **5Cu** must transmetallate also to an alkenyl Grignard species **5Mg** since at an intermediate stage of the reaction **5Cu** + **5Mg** amount to 30% of the reaction products with only 5% Cu(I) salt present. According to the nature of the halogen of the Grignard intermediate **5Mg** a *syn* or an *anti* β -elimination takes place (Scheme VIII). The rate of the exchanges **5Cu** \rightarrow **5Mg** and the kinetics of the β -elimination (the irreversible step) of **5Cu** or **5Mg** determine the final proportion of the *syn* or the *anti* allene **6**. We have already noted the accelerating effect of a good ligand in the β -elimination of the alkenyl copper intermediate **5Cu** (ref 4). Thus, a good ligand such as PBu₃ will favor the β -elimination of **5Cu** and therefore the *anti* process, rather than the transmetallation to **5Mg** which, with Cl as halogen, would favor the *syn* process.



It was of interest to check if this intriguing "halogen effect" of the Grignard reagent was operative in other organocopper reaction, particularly those involving a different mechanistic pathway. Propargylic acetates, as well as other propargylic substrates having a good leaving group, are known to afford allenes through a Cu(III) intermediate following an overall *anti* process (Scheme I). The reaction was also known to occur with a catalytic amount of Cu(I) salt (ref 8). When we performed this reaction with acetate **10**, under our best *syn* conditions, we obtained the *anti* allene **6** with an excellent optical yield (Scheme IX). Thus, a reaction that proceed through a Cu(III) intermediate is always an *anti* substitution, whatever the halogen of the Grignard reagent RMgX.



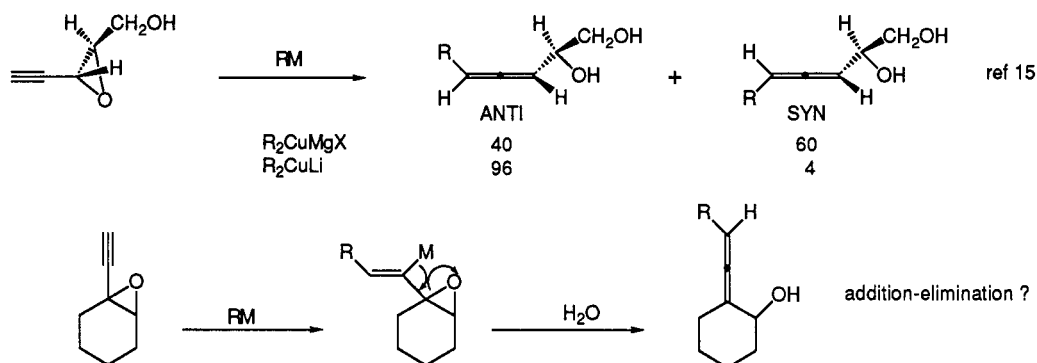
This different behaviour of the two mechanisms (addition-elimination or Cu(III) intermediate) can be used for the determination of the mechanism of other reactions in organocopper and organomagnesium chemistry. One such interesting case is that of propargylic epoxides. Ortiz de Montellano (ref 13) has shown, first, that these compounds react with lithium diorganocuprates to afford *anti* α -allenic alcohols **10** (ref 14). As major by-product he obtained an unsubstituted allenol **11**. Such reduction by-products are typical of a Cu(III) intermediate (Scheme X).



On the other hand, Oehlschlager (ref 15) reported that the metal counterion of the cuprate reagent may strongly affect the stereoselectivity of this reaction (Scheme XI), a result which is more compatible with an

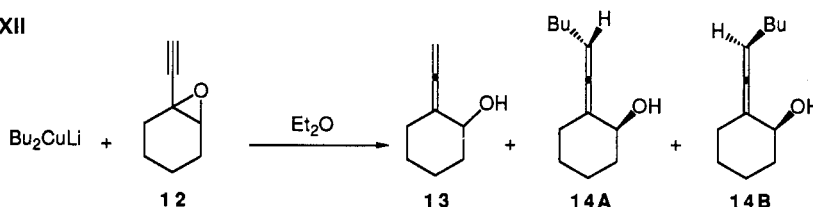
addition-elimination process instead. If one considers that epoxides are a special kind of *ethers*, then a "halogen effect" could influence the steric course of the reaction.

Scheme XI



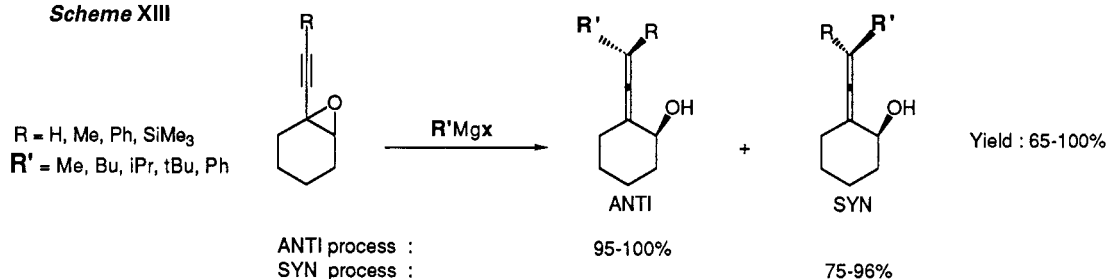
Our first experiments were done with ethynyl cyclohexene oxide **12** as model epoxide. Reaction with Bu_2CuLi , under the conditions described by Ortiz de Montellano (ref 13) gave three allenols: the reduction product **13** (33%), and two alkylation products **14A** and **14B** (54% ; 81/19) distinguishable by ^{13}C NMR or by G.C. after acetylation. In view of the known propensity of organocopper reagents to promote preferential *anti* S_{N}' (ref 16) substitution, we ascribed to the major isomer **14A** the *anti* configuration (Scheme XII).

Scheme XII



Next, the catalytic procedure (ref 17) was examined under our best *anti* conditions. Optimization studies allowed us to obtain the *anti* allenol **14A** in 74% yield without any trace of the *syn* allenol **14B**. These conditions ($\text{RMgBr} + 5\% \text{CuBr} \cdot 2\text{PBu}_3 + \text{epoxide}$ in Et_2O) were then applied to a variety of propargylic cyclohexene oxides and different Grignard reagent with an almost equal success (Scheme XIII). On the other hand, the *syn* process was also optimized to give the *syn* allenol **14B** in quantitative yield and 88% selectivity. These conditions ($\text{RMgCl} + 5\% \text{CuBr} + 1 \text{ eq. TMSCl} + \text{epoxide}$ in $\text{Et}_2\text{O}/\text{pentane}$) were also very effective on a variety of epoxides and different Grignard reagents (Scheme XIII).

Scheme XIII

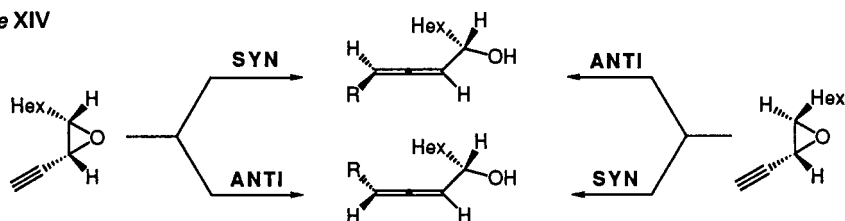


We also found that monosubstituted propargylic epoxides such as **12** can react with a Grignard reagent without copper salt (!), although the reaction becomes very slow. With RMgCl and RMgBr the reaction is highly *syn* selective. This procedure is the preferred one for the transfer of Me and Ph groups.

It was of interest to check if this stereochemical control was also operative in the acyclic series. To this end, we synthesized the isomeric epoxides **15E** and **15Z** in a very high state of purity (>99%). These two epoxides were expected to give the same diastereomer when reacted under respectively *anti* and *syn* conditions. The same should be true if we reverse the experimental conditions as summarized in Scheme XIV. The

results are in complete agreement with our expectations. In all cases high selectivities (>85%) and yields (>84%) are obtained. It should, however, be noted that, with trans epoxide **15E** the selectivities are higher, particularly for the syn process.

Scheme XIV



Allenic alcohols, such as the ones shown above, are quite interesting synthons in that they contain highly condensed stereochemical information (ref 1). Thus, they may be oxidized on the allenic skeleton to afford, among others, cyclopentenone derivatives (ref 18), or stereoselectively alkylated (ref 19). Beyond the synthetic interest of being able to obtain highly selectively either diastereomer starting from the same propargylic substrate, these reactions reveal the subtlety of behaviour of "classical" organometallics such as Grignard reagents.

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