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ARE ALLENES FORMED FROM PROPARGYLIC ETHERS THROUGH A SYN OR ANTI DISPLACEMENT ?

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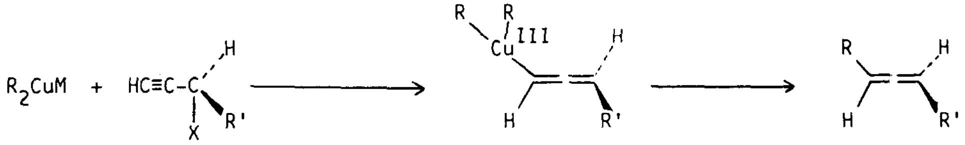
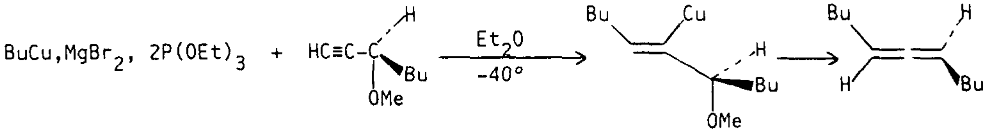
Summary : *The copper catalyzed reaction of Grignard reagents with asymetric propargylic ethers leads to chiral allenes, with very high optical yield. This reaction proceeds through a syn addition to the triple bond followed by a syn or anti β-elimination, according to the nature of the halogen of the Grignard derivative.*

Organocopper and cuprate reagents react with propargylic functional derivatives to afford allenes[1]. This highly efficient chemo- and stereoselective entry to allenes has already found many applications in organic synthesis[2]. The stereochemical outcome of this reaction has also been scrutinely investigated with chiral propargylic derivatives. It turns out that an overall anti SN' process is involved, probably via a copper^{III} intermediate[3-7].



X = halogen, -OCOR, -OCOOR, -OCONR$_2$, -OSOR, -OSO$_2$R, -OPO(OR)$_2$

Yet, an alternative mechanism has been shown to operate in the case of propargylic ethers, where the alkoxy functionality is a poorer leaving group. A syn addition of the organocopper reagent across the triple bond leads to a stable (below -35°C) alkenyl copper intermediate which collapses, by anti β-elimination, to an allene[8,9]. The overall process is again an anti SN' displacement.

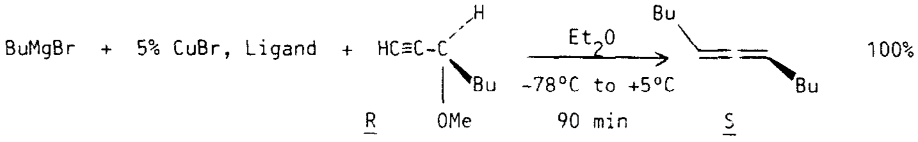


chem. yield : 95%
optical yield : 96%

Propargylic ethers also react with Grignard reagents, under copper^{I} catalysis[7,10]. Although no intermediate of any type was trapped, the overall process was shown to be an anti substitution despite a very low optical yield (~16%)[7].

When we run the catalytic reaction (5% CuX) under standard conditions (-78°C to +5°C, 90 min) the intermediate alkenyl metallic species can be quenched at -40°C in 30% yield after hydrolysis of an uncomplete reaction. This allylic ether is exclusively of E geometry, indicating that, as in the case of the stoichiometric reaction, the addition to the triple bond is of syn type. This result also shows that (at least to an extent of 30%) the catalytic reaction proceeds by an addition-elimination mechanism rather than through a Cu^{III} intermediate.

When the catalytic reaction is performed with a chiral propargylic ether, a chiral allene is obtained in quantitative yield. However, once formed, this chiral allene may be partly racemized by the organocopper or cuprate catalytic species[11]. We thought that a complexation of the copper salt could prevent such a racemisation. And indeed, as shown in the table, the better the ligand, the higher the optical yield. In all these cases the overall process is an anti substitution. Thus, the syn addition is followed by an anti β-elimination, exactly as in the stoichiometric reaction.

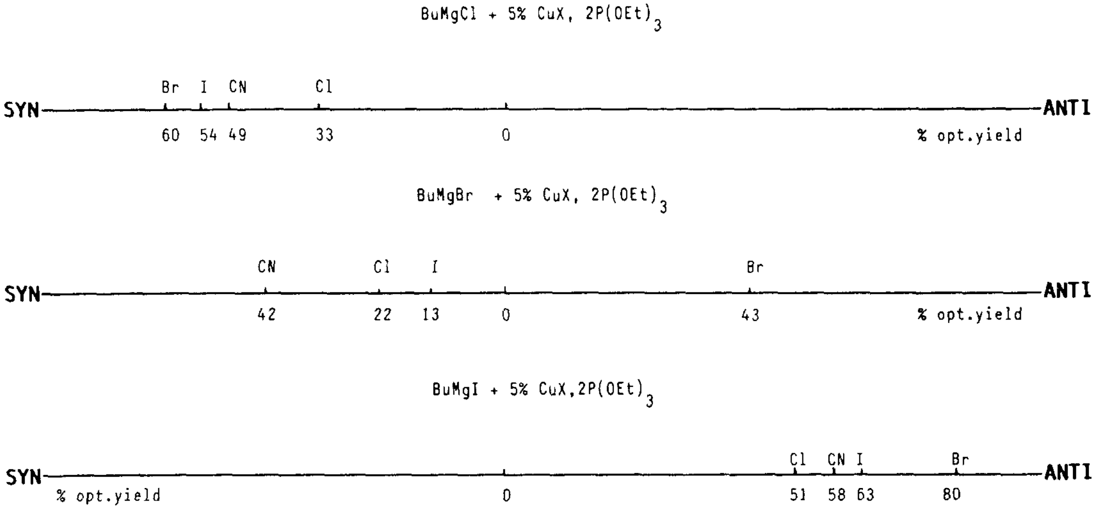


$[\alpha]_D^{25}$, deg(c,Et_2O) of the alkyne[a]	Ligand (per Cu)	$[\alpha]_D^{25}$, deg(c,$CHCl_3$) of the allene[b]	optical yield
+ 35.17 (3.34)	none	+ 3.92 (1.50)	16%
"	2P(OEt)$_3$	+ 10.70 (2.13)	43%
+ 46.13 (5.28)	P(NMe$_2$)$_3$	+ 17.90 (3.02)	54.5%
"	2P(NMe$_2$)$_3$	+ 23.70 (4.01)	72%
"	P(Bu)$_3$	+ 26.2 (2.88)	80%
"	2P(Bu)$_3$	+ 29.6 (2.64)	90%

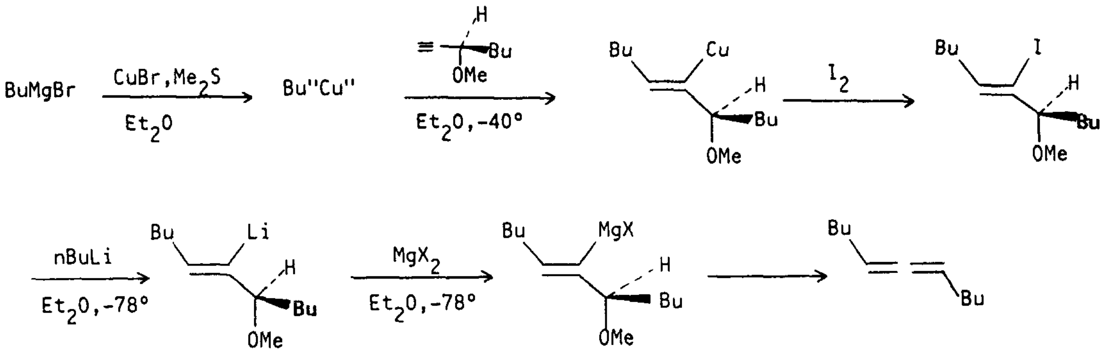
a : [α] max = ± 95.5°[12]
b : [α] max = ± 68°[13]

In search of even higher optical yields, we have also undertaken a systematic investigation of the influence of the copper salt and of the type of the Grignard reagent. To our surprise, we observed in many cases, that the allene was formed via an overall syn substitution process. In these cases, we have checked that the alkenyl metallic intermediate was arising from a syn addition exclusively. Therefore, the second step, the syn or anti β-elimination is responsible of the observed variation of absolute configuration of the allene.

As shown in the following scheme, BuMgCl always leads to the allene by a syn overall substitution, whereas with BuMgI an anti substitution is always observed.



The question which arises therefore, is that of the nature of the alkenyl metal intermediate. Since only 5% of copper halide is used and 30% of this intermediate are isolated, it seems that part of this intermediate is an alkenyl magnesium halide. From the stoichiometric reaction we know that an alkenyl copper intermediate undergoes an anti β-elimination. What kind of β-elimination undergoes an alkenyl magnesium halide ? The answer to this question is summarized in the following scheme.



X = I ----------→ anti elimination, optical yield 68%

X = Cl ----------→ syn elimination, optical yield 35%

These results are in accordance with the above ones, indicating that RMgI shows a propensity to β-eliminate by an anti process whereas RMgCl β-eliminates via a syn one.

Starting with a study on mechanistic considerations on organocopper chemistry, we are left with a problem on stereoselective elimination of a simple Grignard reagent which has not been already studied to our knowledge.

It is thus possible to obtain, at will, allenes of reverse configuration, in high optical yields, starting with only one propargylic ether. Further work is in progress and will be reported in due time.

Typical experimental procedure -

160 µl of an ethereal 1N solution of CuX, ligand (160 µmol) is added to a stirred solution of 400mg of 3-methoxy-1-heptyne (3.17mmol), in 30ml anhydrous ether, at room temperature. After cooling to -78°C an ethereal solution of BuMgX (6.34mmol) is rapidly introduced into the reaction flask. The cooling bath is removed and the stirred solution is allowed to warm up to +5°C (90mn), temperature at which the reaction is complete, as shown by aliquots taken every 30mn. The mixture is hydrolyzed with 10ml NH_4Cl aqueous sol., the organic layer separated and dried over $MgSO_4$. The crude product is filtered through 30g silica (elution with pentane) to afford 480mg of pure dibutylallene (100% yield).

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