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CARBOCYCLIZATION OF δ-ACETYLENIC PROPARGYLIC ZINC REAGENTS

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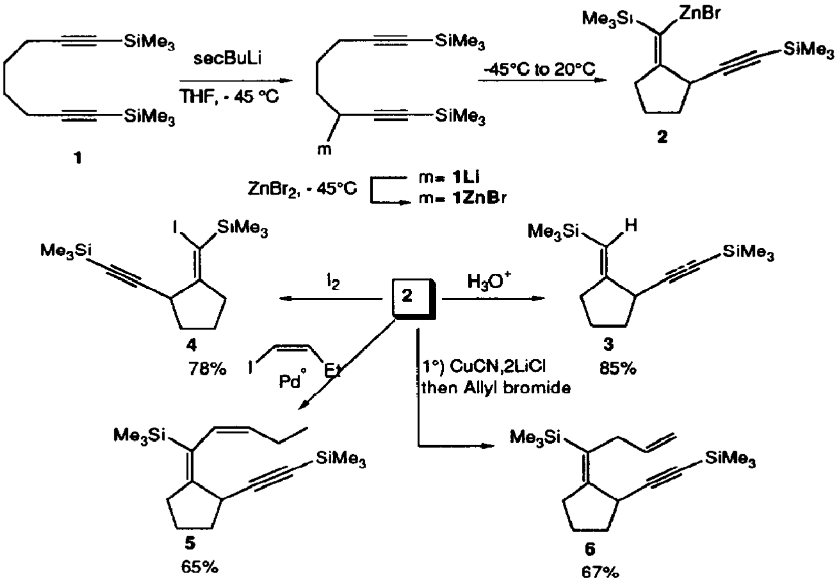
Abstract: δ- acetylenic metallated propargylic derivatives undergo an easy cyclisation to afford stereodefined exomethylene cyclopentanes with a total diastereoselection

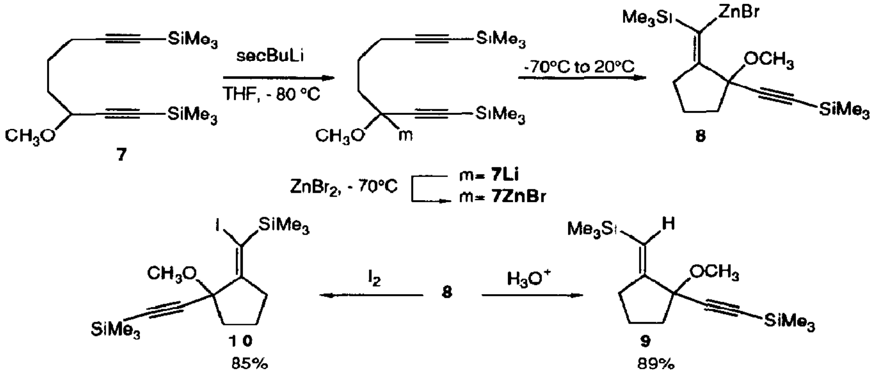
Intramolecular addition of alkyl organometallic species to an alkyne is of great interest and the use of a variety of metals including Li[1], Mg[2], Al[3], Cu[4], Zn[5], Ti[6], Pd[7] and Ni[8], has been investigated for this carbocyclization. During our study on the carbocyclization of organozinc reagents[9], we observed that some ω-ethylenic metallated propargylic ethers undergo an easy cyclization[10]. We now report, that this simple methodology can be extended to the intramolecular carbometallation of ω-acetylenic metallated propargylic derivatives.



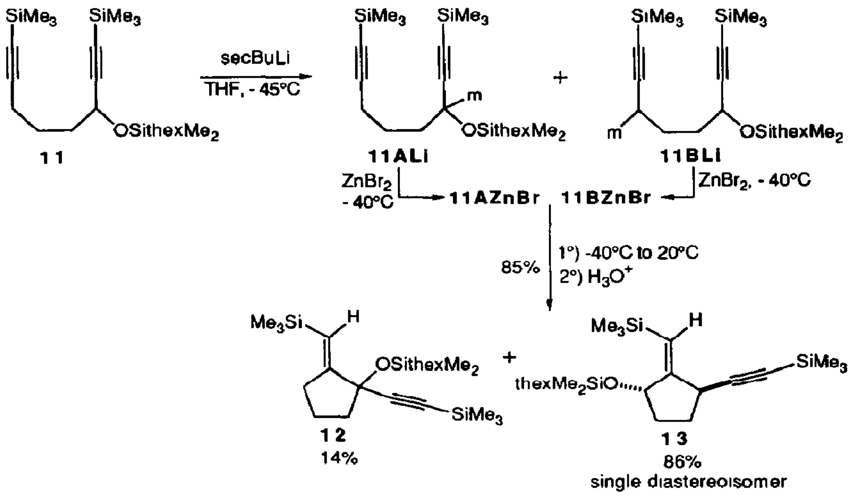
1,8-Bistrimethylsilyloctadiyne **1**, the most simple substrate for this study, is easily metallated in THF to give the allenyl-propargyl organolithium **1Li**, which is unable to cyclize at room temperature, whereas its zinc derivative **1ZnBr** cyclizes rapidly at 20°C within 5 to 10 min prior to the addition of various electrophiles.

The transmetallation of **1Li** to **1ZnBr** can be checked before cyclization, by hydrolysis of an aliquot, at low temperature and analysis by gas chromatography : the 60/40 allenyl-propargyl ratio arising from protonation of **1Li** becomes < 5/95 after transmetallation into the organozinc bromide **1ZnBr** (and protonation). The pure (E) stereochemistry of the vinyl silane **3**, determined by a nuclear Overhauser effect, clearly shows that the carbocyclization proceeds in a totally stereoselective fashion to give, in this condition (20°C, 5 to 10 min), the configurationally stable (Z)-alkenylzinc bromide **2**[11] via a *syn* addition of the propargylic-allenic zinc bromide to the acetylenic moiety. This carbocyclization represents a new desymmetrization of diynes **1** which serves to deliver functionalized exomethylene cyclopentanes.

We tested it on more functionalized molecules. Thus, introduction of a propargylic methoxy group is possible, if one starts from **7**, metallated as quoted above :



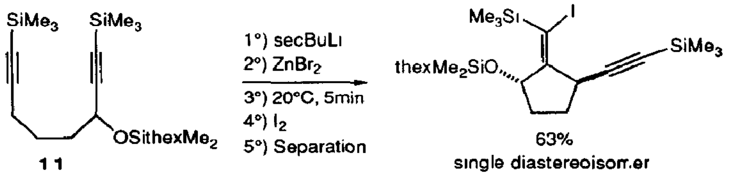
The organozinc bromide **7ZnBr** undergoes a regiospecific 5-exo-Dig cyclization to give **8**. The cyclic product has been characterized by hydrolysis to **9** or iodinolysis to **10** with good chemical yields. Both **9** and **10** are single isomers. In order to get access to the free alcohol, we have studied the metallation of **11**, which is effected as described before, but now, the carbocyclization leads, after hydrolysis, to a mixture of products.Although the more acidic proton is still in the propargylic ether position and leads to **11ALi**, the bulky protecting group of the ether function impedes the metallation in this position. Then, the kinetic metallation occurs on the less hindered propargylic position leading to **11BLi**.



After transmetallation to the corresponding organozinc derivatives and warm-up to room temperature, for 5 to 10 min, the cyclic products **12** and **13** are respectively obtained in a 14/86 ratio. Nevertheless, the two derivatives are very well separated by chromatography on silica gel (eluent : pentane/ether : 99/1) and the major product **13** is isolated with a 68% chemical yield as a single isomer. The relative configurations of sp^3 and sp^2 carbons in **13** were established by nuclear Overhauser effect.

Thus, indirectly, we have determined for the first time the effect of an oxygenated substituent in propargylic position during the carbocyclization of metallated propargylic derivatives. The stereochemistry can be explained by a chair-like transition state complex accounting for the preferred 5-exo-Dig cyclization of 5-hexynyl metals[1e].

In summary, this promising carbocyclization of propargylic derivatives allows us to construct stereodefined multifunctional exomethylene cyclopentanes with a total diastereoselection :



We are currently exploring the construction of polysubstituted carbocycles along these lines, particularly in cases where the alkyne moieties are substituted by groups other than silicon.

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