

Cyclic Stereocontrol via Organobismetallic Reagents. Part V. Diastereoselective Synthesis of Substituted Cyclopropyl Zinc Reagents by the Metalla-Claisen Reaction

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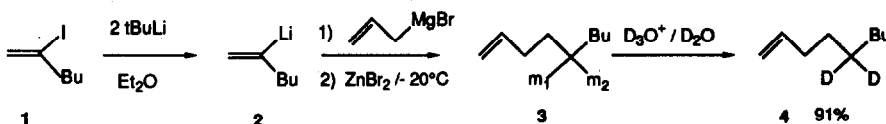
Abstract: The tandem "Metalla-Claisen - Cyclization" reaction of a functionalized vinyl lithium derivative allows the preparation of a single isomer of a metallated cyclopropyl ring.

Cyclopropanes play an important role in many aspects of organic chemistry¹. They are found in a number of significant natural products², and diastereoselectively substituted cyclopropanes have proven to be useful synthons for further transformations to stereodefined cyclic and acyclic compounds³. The most common methods for preparation of stereodefined cyclopropanes are 1,3-elimination⁴ from carbanions bearing a leaving group in β -position, the Simmons-Smith reaction⁵, and its various modifications⁶, and other methods based on carbene⁷ and carbenoid⁸ chemistry.

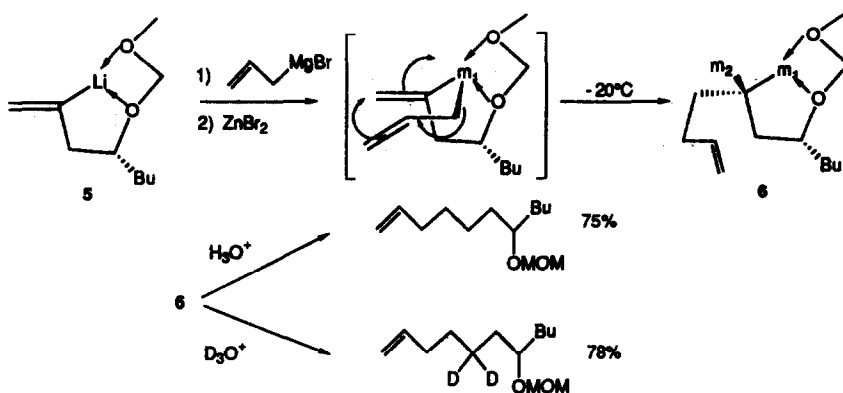
We have reported that the carbozincation of alkenyl magnesium⁹ and lithium¹⁰ organometallics is a unique approach to the preparation of 1,1-dimetallalkanones of zinc and this methodology can be used for achieving stereocontrol in the construction of acyclic systems¹¹.

We have already pointed out that ether, a less basic solvent than THF, accelerates such addition reactions. Even more, the vinyl metals used so far in THF solutions^{9,10} were of type $R-CH=C(Z)metal$ ($Z = H$ or $SiMe_3$), since when Z is an alkyl moiety the addition of allyl zinc bromide requires higher temperatures, and formation of the gembismetallics is accompanied by loss of metal hydride. A notable exception¹² is the case of $Z = phenyl$.

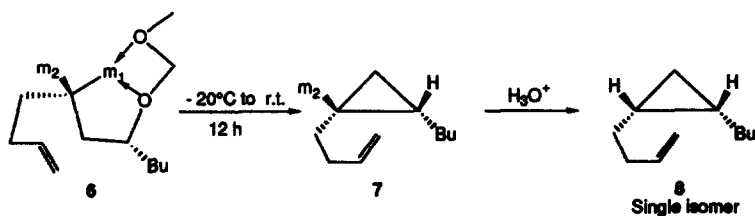
Here, we show that the addition of an ethereal solution of allyl magnesium bromide and zinc dibromide to an ethereal solution of 1-hexen-2-yl lithium **2** (generated via metal-halogen exchange from the corresponding iodo derivative **1**), leads to the fast formation (2-3 h at $-20^\circ C$) of the stable organogembimetallic **3**. After treatment with D_3O^+/D_2O , **3** gives the corresponding 5,5-dideutero-non-1-ene **4** in 91% yield (100% deuteration):



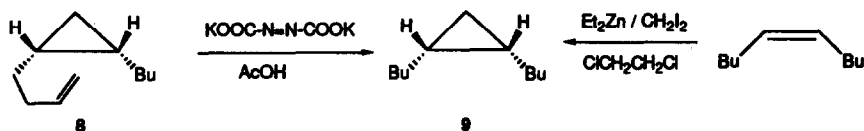
The same experiment can be done with a functionalized vinyl lithium¹³ compound :



These stable organogembimetallics were generated at -20°C , as evidenced by the fact that quenching of the reaction mixture with HCl or DCl afforded respectively the hydrogeno or deuterio alkenes in good yield (scheme 1). By warming very slowly the reaction mixture to room temperature (overnight), **6** undergoes a diastereoselective 1,3-elimination to give a single isomer of a metallated cyclopropane¹⁴.



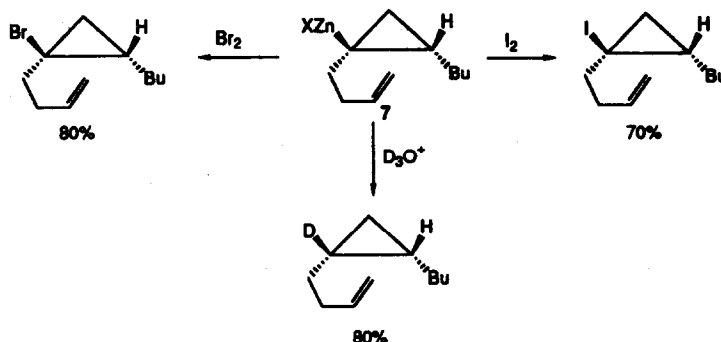
The stereochemistry of the cyclopropane **8** has been determined, after reduction of the terminal double bond¹⁵ into **9**, by comparison with an authentic sample, prepared by an independent way^{6c,16}.



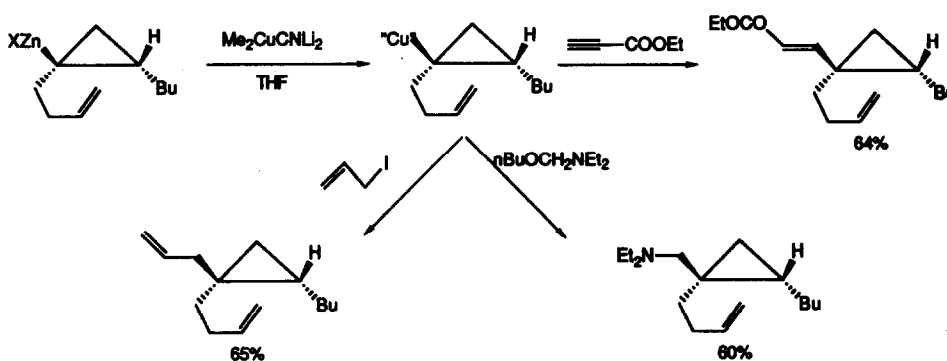
The stereochemical course of this transformation (**6** to **7**) is puzzling and awaits further experimentation since:

(i) This intramolecular $\text{S}_{\text{N}}2$ displacement may result from a double inversion process at C-m and C-O which is considered more likely^{17,18} than a double retention if the leaving group is a halogen or a tosyl group. (ii) However, in our case, we are dealing with a bad and chelating leaving group favoring double retention, and (iii) two diastereotopic metals have to be considered. Thus, scheme 1 and 2 are merely working hypotheses at this stage. Whatsoever, from a synthetic point of view, it is very important to be able to generate an organozinc reagent ($m = \text{Zn}$) **7** in which the cyclopropyl ring carbons are stereoselectively substituted¹⁹. The cyclopropyl zinc derivative serves as a unique nucleophilic reagent bearing a quaternary chiral carbon. For instance,

electrophilic trapping of this organometallic with iodine or bromine gave the corresponding iodo or bromo-cyclopropanes as single products :



Another major advantage of this new methodology is the easy metal-metal exchange to a copper reagent²⁰ (obtained from the alkylzinc 7 by transmetalation with Me₂CuCNLi₂)



This copper reagent²¹ can react by 1,4-addition with ethyl propiolate to afford the corresponding vinyl cyclopropane, or by alkylation with allyl iodide to give the allylated product, but also in a formal S_N2 fashion with an amino ether to give the corresponding aminomethylcyclopropane derivative.

In conclusion, this tandem "one pot Metalla-Claisen - cyclization" of a functionalized vinyl lithium derivative, allows a very easy and straightforward preparation of metallated (zinc or copper) cyclopropyl rings which can react with different electrophiles. We are currently exploring the mechanism as well as the scope and limitations of this reaction.

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The trans-1,2-dibutyl cyclopropane has been also prepared. $^1\text{H NMR}$: 0.11 to 0.14 (dd, 2H, J = 6.6 ; 5.5) 0.34 to 0.37 (dd, 2H, J = 6.6 ; 5.5) ; 0.86 to 0.89 (t, 6H, J = 7.15) ; 1.1 to 1.4 (m, 12H)
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