Tetrahedron Letters, Vol. 34, No. 47, pp. 7575-7578, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Cyclic Stereocontrol via Organobismetallic Reagents[1]. Part VI. Stereodefined Substituted Cyclopropyl Zinc Reagents

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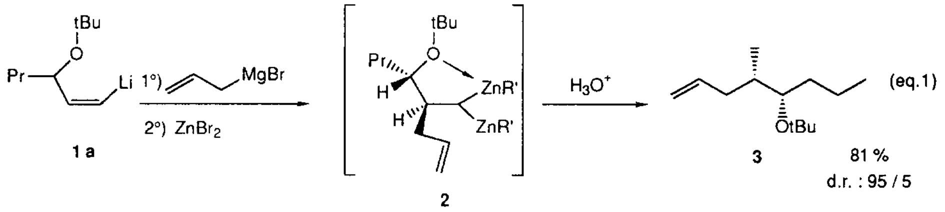
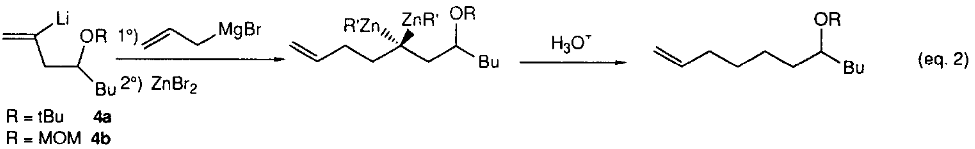
Abstract:The Metalla Claisen reaction followed by a 1,3-elimination generates a diastereoselectively substituted metallated cyclopropane.

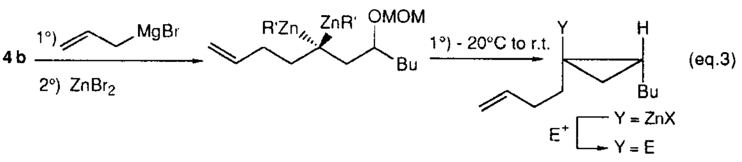
We have recently reported[2], that the Metalla Claisen rearrangement of (*Z*)-lithio vinylic ether **1a** with one equivalent of allyl zinc bromide affords the corresponding 1,1-dimetallic species **2**[3],which is hydrolyzed to the ethylenic ether **3**, with a very high diastereoselectivity (eq. 1):



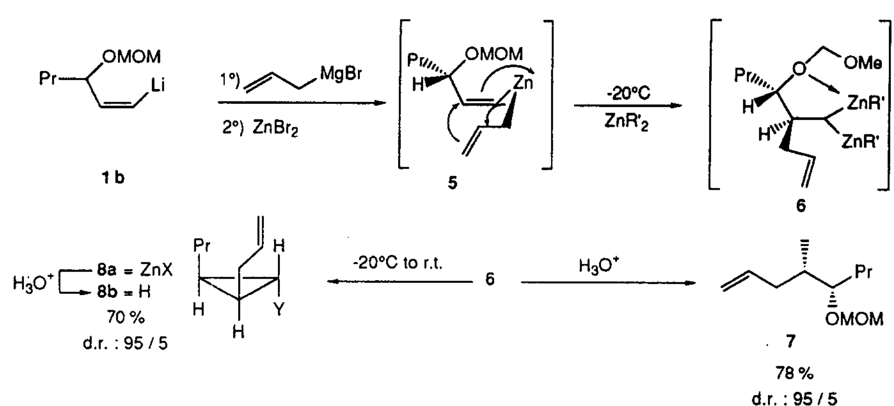
In the case of 2-lithio-4-*ter*-butoxy-1-alkene **4a**, the reaction is also straightforward[4] (eq.2) but, of course, no diastereoselection can be put to evidence by hydrolysis:



However, in the case of **4b**, switching from the *ter*-butoxy group to a methoxymethyl group (MOM), and warming the reaction mixture to room temperature, promotes a cyclization and delivers a metallated cyclopropane as a *unique* isomer[4] (eq.3), and hence a way to 1,1,2-trisubstituted cyclopropanes.

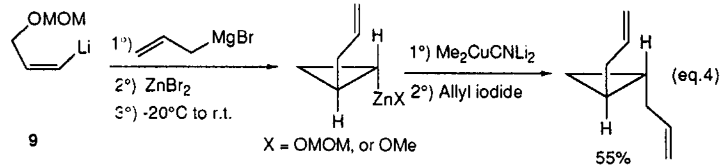


We now report that this simple methodology can be applied to the synthesis of 1-*metallated 2,3-disubstituted* cyclopropanes[5]. Thus, starting from the (Z)-lithio allylic ether[6] **1b**, (MOM instead of *ter*-butoxy) and treating it with allyl zinc bromide, leads to the intermediate allyl vinyl zinc derivative **5**, which undergoes a [3,3] sigmatropic rearrangement to give the 1,1-dimetallic species **6**[2d,3], which is hydrolyzed to the corresponding ether **7**[7]. But, warming slowly the reaction mixture to room temperature, promotes a diastereoselective 1,3-elimination to give, after hydrolysis, a cis cyclopropane **8b**.

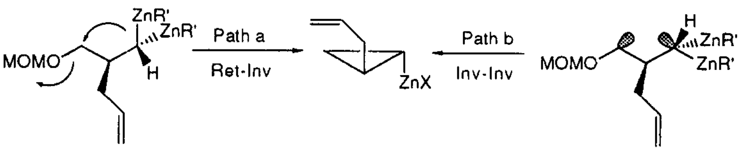


Scheme 1

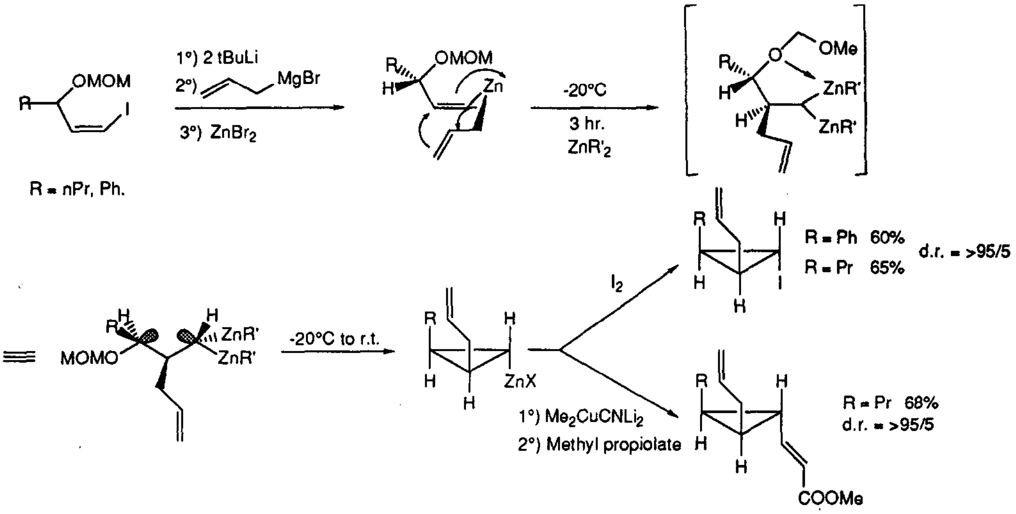
Knowing the stereochemistry of the organogembismetallics **6** (from the corresponding known ether **7**[7]) and the cis stereochemistry of the cyclopropane **8b**, we can conclude that the intramolecular S$_N$2 displacement results from an inversion at the electrophilic center[8]. Concerning the carbanionic center, it has been established by several authors, that such 1,3-eliminations involve either inversion[9] or retention of configuration[10] at the carbon-metal center. In the present case, the same tandem "one pot Metalla Claisen-cyclization" reaction of the (Z)-lithio allylic ether **9** has been carried out and the resulting cyclopropyl zinc has been transmetallated to a copper reagent[11], then allylated to furnish the pure trans bisallyl cyclopropane[12] of C$_2$ Symmetry, (eq. 4).



If we postulate, that the zinc to copper transmetallation operates with retention of configuration, as is the usual case for metallated cyclopropanes[13], we show here, that the intermediate organogembismetallic species leads to a unique monometalallated cyclopropane: We are dealing with two diastereotopic metals which can enter either an inversion-inversion at both carbon centers (path b), or a retention-inversion process (path a), and we cannot presently solve this dilemna.

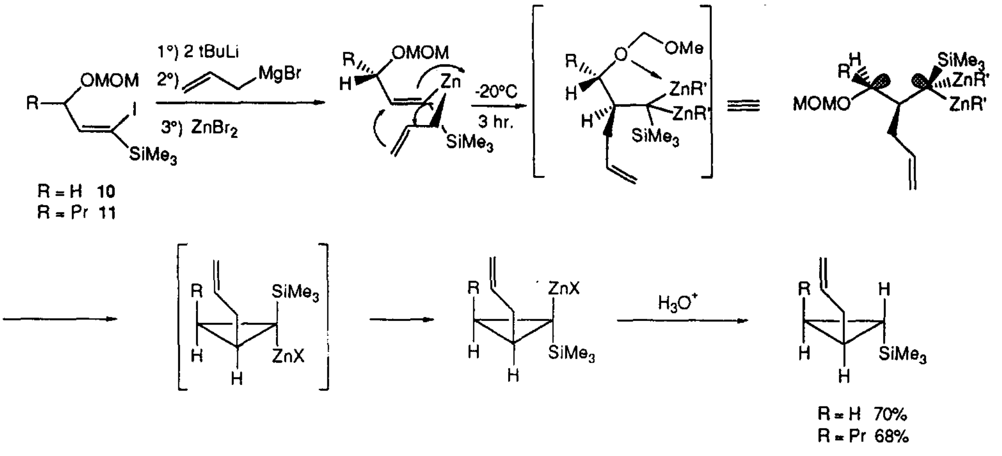


Whatsoever, if now we combine the diastereofacial selectivity of the Metalla Claisen rearrangement, shown in scheme 1, with the preceding selectivity arising from the 1,3-elimination[14] (eq.4), we are able to generate stereoselectively a 1-*metallated 2,3-disubstituted cyclopropane* which has been quenched by iodine, or submitted to conjugated additions, (after zinc to copper exchange[11]), on a propiolic ester.



The stereochemistry of these cyclopropanes has been determined without ambiguity by the analysis of the corresponding coupling constants[15] of the cyclopropyl protons (500 MHz) and by Nuclear Overhauser Effects (NOE). The same stereochemical result has been obtained when the R group is either alkyl or phenyl.

Finally, we wish to report that some mono or *disubstituted cyclopropyl trimethylsilanes*[16] can be successfully prepared by this tandem reaction. The conversion of **10** or **11**[17] into the 1,1-diorganometallics[2], followed by a diastereoselective cyclization step, leads to the formation of a *unique* isomer of the corresponding cyclopropyl trimethylsilylzinc reagents.



The NMR analysis of the stereochemistry[15] of these cyclopropyl silanes indicates that, now, the zinc metal is, before hydrolysis, in a *syn* relationship with the two alkyl groups. This result is compatible with the known isomerisation of the α-substituted cyclopropyl *gem* silyl-metals[18] to the more thermodynamically favorable form (where the silyl group lies trans to the alkyl moiety). In conclusion, this new tandem "Metalla Claisen-cyclization" reaction allows a very easy preparation of metallated trisubstituted cyclopropyl rings with a very high diastereoisomeric purity.

Acknowledgments : We thank Mrs M. Baudry and F. Grojean for the synthesis of various starting materials.

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(Received in France 5 September 1993; accepted 17 September 1993)