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ON THE REGIOCHEMISTRY OF CYCLIALKYLATION OF REGIODEFINED 4-HALO-1-ALKENYLMETALS PRODUCING CYCLOBUTENES

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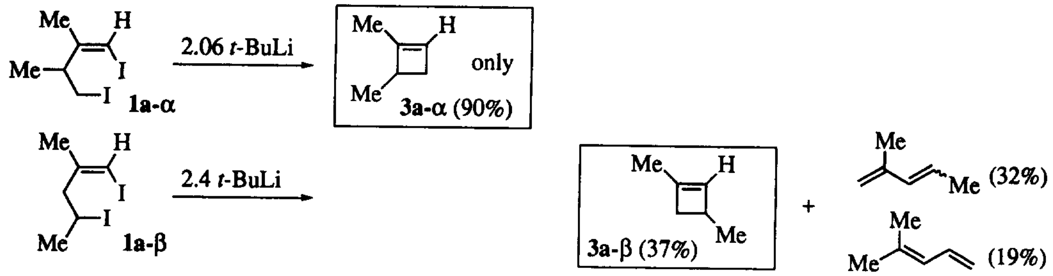
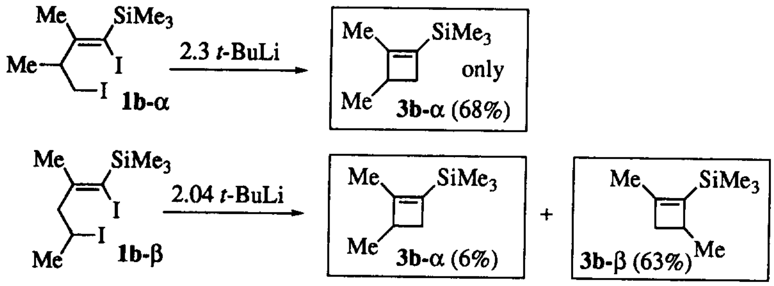
Abstract: A combination of recently developed *anti*-carbometallation of homopropargyl alcohols and cyclialkylation of 4-halo-1-alkenyllithiums of appropriate stereochemistry and regiochemistry provides, for the first time, a regiospecific procedure for the synthesis of regiodefined cyclobutenes presumably via σ-type cyclialkylation, whereas carboalumination of 4-halo-1-alkynylmetals containing Si or Al leads to regioconvergent cyclobutene formation. © 1997, Elsevier Science Ltd. All rights reserved.

We have previously reported some novel cyclialkylation reactions of 4-halo-1-alkenylmetals to give cyclobutenes.[1-4] The required alkenylmetal precursors were generated either via halogen-lithium exchange reaction of the corresponding alkenyl iodides (**1**) or *in situ* carbo- or hydrometallation of 4-halo-1-alkynylmetals (**2**) containing Si, Al, Zn, and other metals. For the conversion of these precursors into cyclobutenes (**3**), both σ- and π-type cyclization processes[1-3] are conceivable. The latter reaction involving 4-halo-1,1-dialuminoalkenes has been applied to an efficient and elegant synthesis of sterpurene (**4**)[5] via 1–iodo-2-methylcyclobutene (**5**). We recently further extended the synthetic scopes of these reactions,[6] and this cyclialkylation methodology promises to provide collectively a highly general route to cyclobutenes.[7] And yet, virtually all of the cyclobutenes prepared to date are 1-mono- and 1,2-disubstituted derivatives, the preparation of which does not require regiodefined precursors, and the regiochemistry of the cyclobutenylation reactions mentioned above has not been adequately clarified.

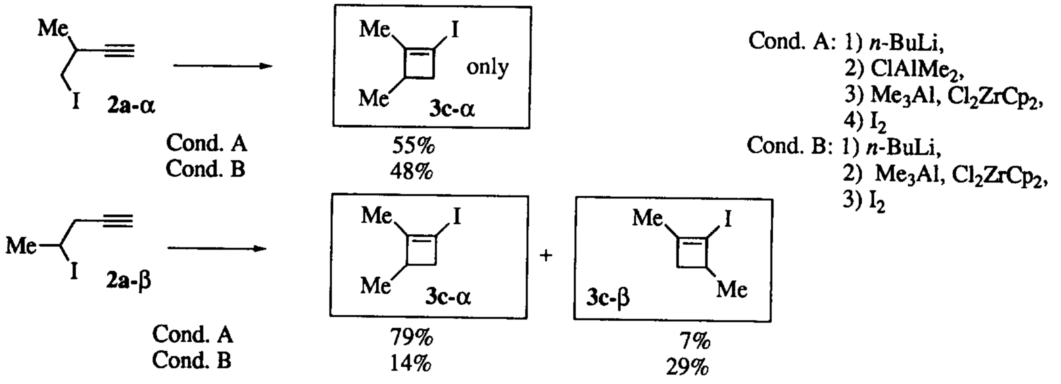
We now report experimental details of four representative pairs of reactions summarized in Schemes 1-4, which not only have clarified regiochemical details of these specific reactions but also have provided some insights into regiochemical trends and reaction mechanisms. Although prediction of the reaction courses in quantitative terms remains to be difficult in some cases, the courses of various reactions may be accommodated by a general mechanistic scheme shown in Scheme 5. In short, the cyclialkylation reaction of (Z)-4-halo-1-alkenyllithiums which do not contain the second metal is regiospecific (Scheme 1). If they contain a Me_3Si group in the C-1 position, regiochemical scrambling may occur to a minor extent, but the reaction is still largely regiospecific (Scheme 2). In sharp contrast, the cyclobutenylation reaction of 4-halo-1-alkynylsilanes with $Me_3Al–Cl_2ZrCp_2$ is regioconvergent, producing only one of the two possible regioisomers regardless of the regiochemistry of the starting material (Scheme 4). Interestingly, the corresponding reaction of 4-halo-1-alkynylalanes is largely regioconvergent, whereas that of the corresponding alanates proceeds predominantly with retention of the regiochemistry of the starting compounds (Scheme 3).



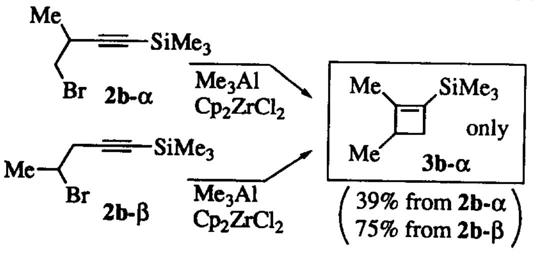
Scheme 1



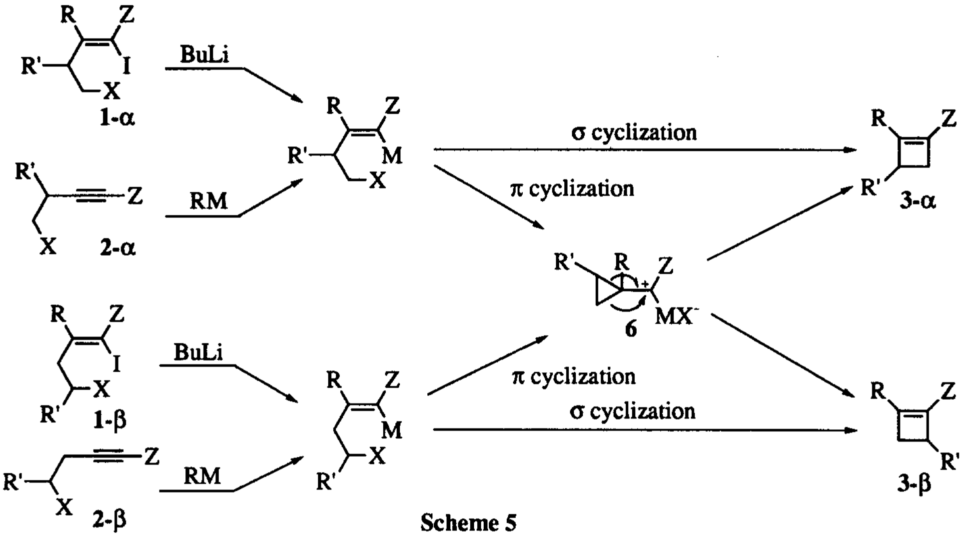
Scheme 2



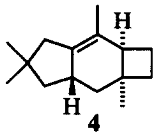
Scheme 3



Scheme 4



Scheme 5



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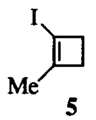

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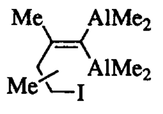
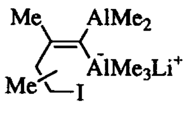


7-α and 7-β



8-α and 8-β

The stereo- and regiodefined 1,4-diiodo-1-alkenes (**1a** and **1b**) were prepared by recently developed chelation-controlled *anti*-methylalumination reactions of homopropargyl alcohol derivatives followed by iodination.[8] As expected on the basis of the essentially 100% regiospecificity observed in the formation of cyclohexenes via cyclialkylation of (Z)-6-bromo-1-alkenyllithium derivatives,[2] treatment of **1a-α** with 2 equiv of *t*-BuLi provided exclusively **3a-α** in 90% yield. The corresponding reaction of **1a-β** afforded **3a-β** albeit only in 37% yield (Scheme 1). No trace of **3a-α** was detectable, but 2- and 4-methyl-1,3-pentadienes were formed as byproducts in 32 and 19% yields, respectively. We may conclude that the cyclialkylation reaction of (Z)-4-halo-1-alkenyllithiums is virtually 100% regiospecific, even though cyclization of 4-alkyl-substituted derivatives is complicated by competitive β elimination. We further conclude that this reaction must follow the σ cyclization paths shown in Scheme 5. The courses of the corresponding reaction of silylated alkenyllithiums derived from **1b-α** and **1b-β** are similar but somewhat different. While **1b-α** was converted selectively into **3b-α** in 68% yield, **1b-β** gave **3b-β** and **3b-α** in 63 and 6% yields, respectively (Scheme 2). So, a skeletal rearrangement indicative of the π cyclization path occurs to the extent of 10%, although the reaction is still largely regiospecific. Introduction of the 1-silyl group must boost the nucleophilicity of the π-bond. On this basis, a partial mechanistic switch from σ cyclization to π cyclization is not surprising in cases where the desired σ process is sluggish due to steric and/or other reasons.

We have previously prepared a regioisomeric pair **2b-α** and **2b-β** and observed that their reaction with Me_3Al and Cl_2ZrCp_2 would give a single regioisomer to which we assigned **3b-β** mainly on the basis of NMR chemical shift values.[2,3] The sense of regiochemistry represented by **3b-β** was opposite to that observed in the corresponding hydroalumination of **2b**-α and **2b**-ß,[2,3] which did make our assignment of **3b**-ß somewhat suspicious. More detailed NMR analyses including the use of GHMQC and GHMBC techniques,[9] indeed clearly indicate that our previous regiochemical assignment was erroneous and that **3b**-α is the exclusive cyclobutene product obtained in 39 and 75% yields from **2b**-α and **2b**-ß, respectively. Thus, the sense of regiochemistry is the same as in hydroalumination. As we concluded earlier,[2,3] the observed regio-convergency is consistent with the π cyclization process via a common intermediate **6**. The reaction of alkynylaluminum derivatives derived from **2a**-α and **2a**-ß with $Me_3Al—Cl_2ZrCp_2$ is most intriguing. When **2a**-α was successively treated with *n*-BuLi (1.05 equiv, -78 °C, 0.5 h), Me_2AlCl (1.05 equiv, -78 °C, 0.5 h) and a mixture of Me_3Al (2 equiv) and Cl_2ZrCp_2 (1 equiv) in CH_2Cl_2 first at -78 °C and then at 23 °C for 22 h (Conditions A), **3c**-α was obtained upon iodinolysis in 55% yield as the exclusive cyclobutene product. The corresponding reaction of **2a**-ß also gave, after iodinolysis, **3c**-α in 79% yield, but its regioisomer **3c**-ß was also obtained in 7% yield. So, the reaction is largely regioconvergent, and it must largely proceed via π cyclization. When **2a**-α was treated with *n*-BuLi and then a 2:1 mixture of Me_3Al and Cl_2ZrCp_2 (Conditions B), **2a**-α produced **3c**-α as the only cyclobutene product in 48% yield. Unexpectedly, the corresponding reaction of **2a**-ß gave **3c**-α and **3c**-ß in 14 and 29% yields, respectively. So, it proceeds predominantly with retention of the regiochemistry of the starting compounds. Even though the exact origin of the significantly increased level of retention of regiochemistry attained through mere omission of Me_2AlCl is not clear, it is tempting to speculate that, under Conditions A employing Me_2AlCl, **2a**-α and **2a**-ß are converted first to the corresponding alkynyldimethylalanes and then to 1,1-bis(dimethylalumino)alkene derivatives (**7**-α and **7**-ß) which undergo π cyclization to the extent of >90%, while omission of Me_2AlCl (Conditions B) converts **2a**-α and **2a**-ß first to the corresponding alkynyltrimethylalanates and then to **8**-α and **8**-ß, respectively, in which one of the C—Al bonds is sufficiently nucleophilic to undergo σ cyclization. However, some other alternatives involving π cyclization cannot be ruled out at this time.

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