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Regio- and Diastereoselective Copper-Catalyzed Carbometalation of Cyclopropenylsilanes

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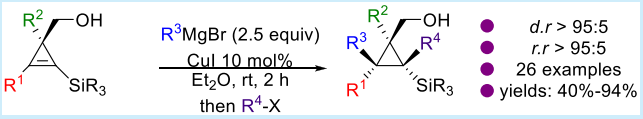
Supporting Information

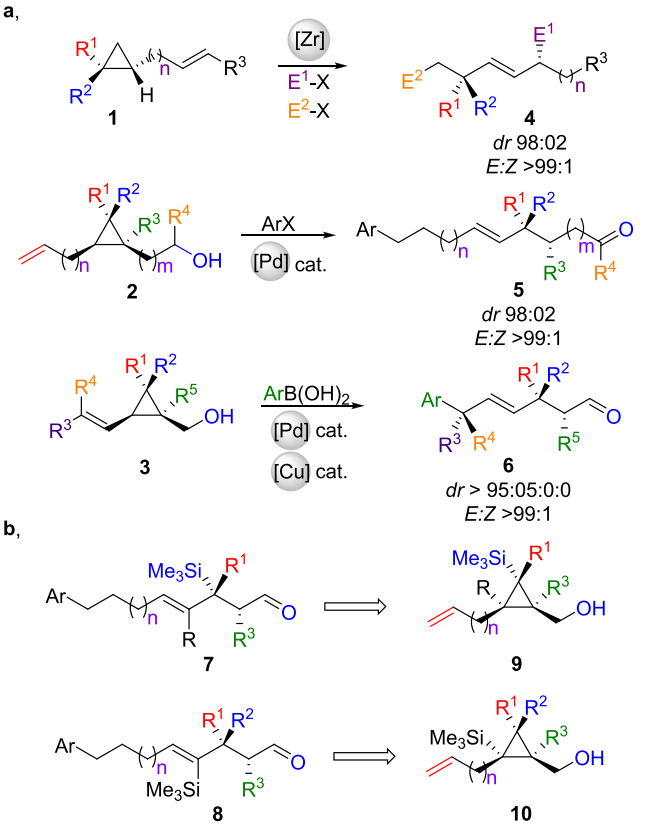
ABSTRACT: We therein report a regio- and diastereoselective copper-catalyzed carbometalation of enantioenriched readily available cyclopropenylsilanes as a synthetic tool to access a large family of stereodefined fully-(hexa)-substituted cyclopropanes.



In the past few decades, we have witnessed tremendous progress in controlling quaternary carbon stereocenters within acyclic molecular backbones.[1] In this context, our group has been particularly interested in the direct[2] or remote[3] stereocontrolled metal-induced ring fragmentation of polysubstituted cyclopropanes as a synthetic tool to reach these skeletons. For instance, ω-alkenyl cyclopropanes **1**[3a,b] or alkenyl cyclopropyl alcohols **2**[3c] or **3**[2] were excellent substrates for Zr- or Pd-triggering cyclopropane ring-opening. These remote functionalization reactions resulted in the efficient production of acyclic molecular skeletons **4**−**6** possessing several stereogenic centers including the expected quaternary center as a unique diastereoisomer (path a, Scheme 1). To further extend the complexity of our final products, we were interested to develop strategies with the presence of either a stereodefined quaternary allylsilane **7** or vinylsilane **8** for potential subsequent transformations. However, at this point, we were more concerned by the preparation of the required starting materials (**9** and **10**) than that by the metal-mediated ring-opening reactions *per se*. Indeed, we have already observed that the selective ring-opening triggered by Pd-catalyzed Heck reaction is rather insensitive to the nature of the substituents at the quaternary stereocenter.[2,3] On the other hand, the straightforward preparation of fully substituted cyclopropanes **9** and **10** as a single diastereoisomer represented an interesting synthetic challenge (path b, Scheme 1). The elaboration of congested systems on a small ring adds a level of complexity as exemplified by the difficulty to selectively construct contiguous quaternary carbon stereocenters.[1a−d,4] Two ambitious tasks would entail the preparation of these cyclopropyl rings: first, the preparation of these fully substituted three-membered rings diastereoisomerically pure and enantiomerically enriched; then, the use of a single and unique precursor for the synthesis of **9** and **10** at will.

Any new strategy answering all these criteria would certainly be highly desirable and would represent a powerful addition to the field of small ring chemistry.[5] Based on our recently acquired experience on the catalytic enantioselective 1,2-bisalkylation of cyclopropenes[5d,g] and previous publications by Nakamora, Fox, and Lautens,[6] we surmised that fully substituted cyclopropyl carbinols **9** and **10** could be synthesized diastereo- and enantioselectively starting from a common cyclopropene precursor **11** (Scheme 2).

Scheme 1. Selective Ring-Opening of Three-Membered Rings



Indeed, cyclopropenes **11** may be accessed through a Rh-catalyzed decomposition of diazoesters in the presence of terminal alkynes. Key to the success of our plan was that an enantioselective version of this [2 + 1] cycloaddition process

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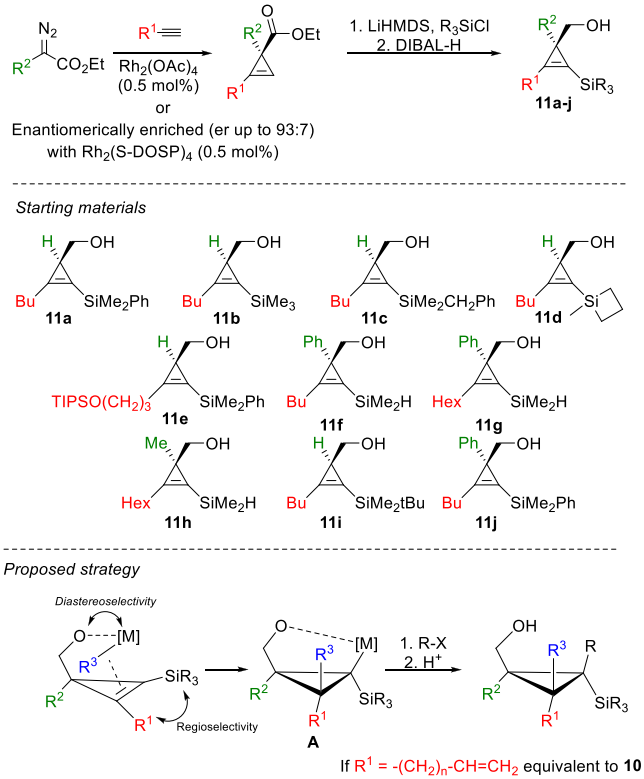
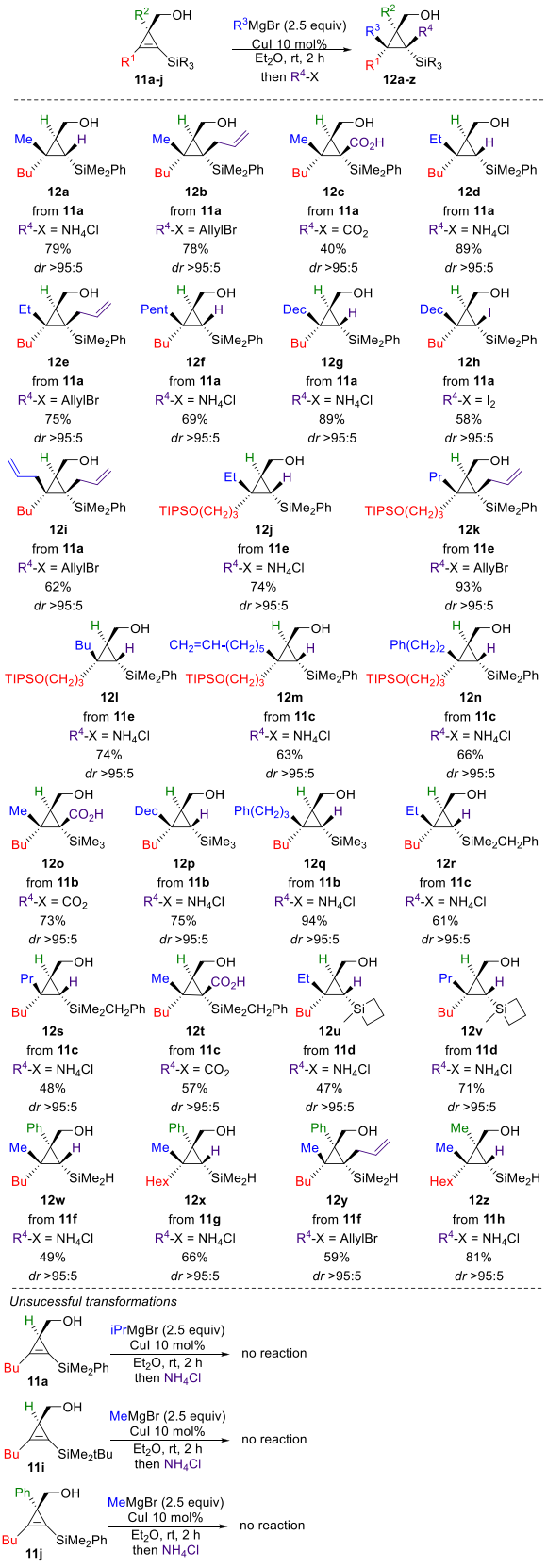
Scheme 2. Straightforward Preparation of the Starting Materials



has been reported (Scheme 2).[7] Cyclopropenyl esters were thus engaged in a subsequent metalation−silylation sequence[8] before reduction to lead to the unique required precursors **11**.

Based on the stabilization of carbanion α to silicon,[9] we were confident that the regioselectivity of the carbometalation should be controlled; the diastereoselectivity should result from a chelated intermediate (Scheme 2). Although the chelated nature of the metalated cyclopropyl species **A** should also control the configurational stability of the resulting carbanion, α-metalated silylated species are subject to epimerization into thermodynamically more stable entities.[10] Only complete control of the configurational stability could lead to a single diastereoisomer. Based on these assumptions, we performed the copper-catalyzed carbomagnesiation reaction of **11a** in Et_2O at room temperature. We were delighted to observe a smooth and completely regio- and diastereoselective carbometalation. The corresponding product **12a** was isolated as a single regio- and diastereoisomer after hydrolysis in less than 1 h as summarized in Scheme 3. At the outset, a scale-up experiment established our confidence in the robustness of the current method, as **12a** could be prepared on a 1.5 g scale. Scaling up this reaction showed no loss of regio- and diastereoselectivity. Despite the steric hindrance around the tertiary organometallic species, we were pleased to see that the intermolecular reaction with an electrophile was possible. The products of electrophile incorporation were obtained as a single diastereoisomer in moderate to good yields (**12b** and **12c**, Scheme 3). The relative configuration was established by X-ray analysis of **12c** (CCDC 1942906; see Supporting Information) and confirmed our assumptions regarding the selectivity of the reaction. The configuration of all other products was assigned by analogy. It should be noted that

Scheme 3. Copper-Catalyzed Carbomagnesiation of Cyclopropenylsilanes 11a−j



aldehyde could also be added but without any diastereoselectivity at the carbinol center (not shown in Scheme 3). A large variety of primary alkyl and allyl Grignard reagents could

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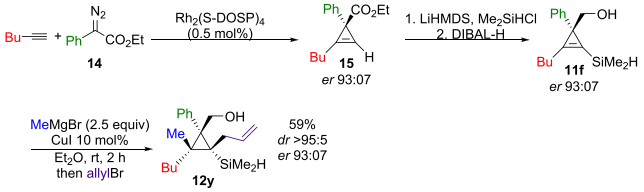
be added on the cyclopropenyl ring with similar yields and selectivities (**12c−m**, Scheme 3); however, secondary Grignard reagents failed to react most probably for steric reasons (Scheme 3, bottom).

Products possessing a remote double bond for subsequent Pd-catalyzed isomerization could also be easily achieved either through the double bond incorporated as a nucleophilic species (**12m**, Scheme 3) or as electrophiles (**12b,e,k,y**, Scheme 3), or both (**12i**, Scheme 3). The nature of the substituents on the silicon atom could also be varied ($PhMe_2Si$, Me_3Si, $PhCH_2Me_2Si$, $Me(CH_2)_3Si$, Me_2HSi) without again changing the overall outcome of the reaction (**12a** and **12o−z**, Scheme 3).

However, the bulky tBuMe$_2$Si group on the cyclopropene (**11i**, Scheme 3, bottom) does not allow the carbometalation to proceed.

Finally, we were interested to apply our strategy to the preparation of fully substituted cyclopropanes, and although **11j** could not lead to the addition product (Scheme 3, bottom), **11f−h** possessing less sterically hindered substituents on the silicon could lead to the expected products. For instance, when MeMgBr was added to an ethereal solution of **11f,g,h**, in the presence of CuI (10 mol %), the carbometalated products **12w,x**, and **z** were respectively obtained in good yields as a unique diastereoisomer. Addition of allyl bromide to the resulting cyclopropylmagnesium bromide remarkably provides the fully substituted cyclopropane **12y**. It should be emphasized that, in all examples investigated in this study, the corresponding α-silylated cyclopropylmagnesium species showed remarkable configurational stability and no epimerization was observed. Using this strategy, enantiomerically enriched fully substituted cyclopropane can therefore be easily prepared in relatively a few chemical steps as described in Scheme 4. The Rh^{II}-catalyzed enantioselective addition of ethyl

Scheme 4. Preparation of a Diastereo- and Enantiomerically Enriched Fully Substituted Cyclopropane



diazoacetate **14** to 1-hexyne was initially performed and gave **15** in an excellent 93:07 enantiomeric ratio.[7b] Then, **15** was treated with a base followed by Me_2SiHCl and the ester was subsequently reduced to provide **11f** with the same enantiomeric ratio. The latter was first engaged in a copper-catalyzed methylmagnesiation reaction followed by reaction with allyl bromide to furnish **12y** in 59% yield as a single diastereoisomer with an enantiomeric ratio of 93:07.

In conclusion, the copper-catalyzed carbomagnesiation of cyclopropenylsilanes was successfully developed. This reaction provides an interesting entry to a wide range of variously substituted cyclopropylsilanes as single isomers. Although this reaction suffers from few limitations mainly due to the difficulty to introduce contiguous sterically hindered groups, examples of fully (hexa)-substituted cyclopropane are reported. We are currently further exploring the reactivity of these cyclopropylsilanes in the Pd-catalyzed remote ring opening reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03531.

Experimental procedures, characterization data for all new compounds, and crystallographic data (PDF)

Accession Codes

CCDC 1942906 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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