VIP Copper Catalysis Very Important Paper

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Regio- and Diastereoselective Copper-Catalyzed Carbomagnesiation for the Synthesis of Penta- and Hexa-Substituted Cyclopropanes

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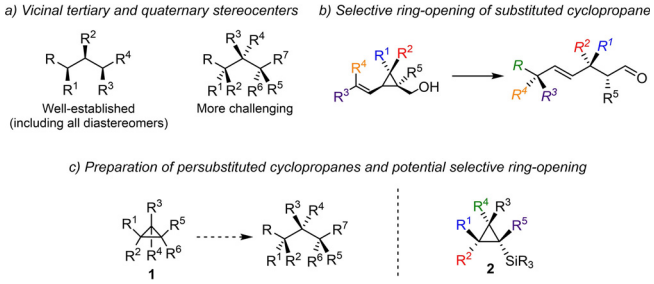
Abstract: *Despite the highly strained nature of cyclopropanes possessing three vicinal quaternary carbon stereocenters, the regio- and diastereoselective copper-catalyzed carbomagnesiation reaction of cyclopropenes provides an easy and efficient access to these novel persubstituted cyclopropyl cores with a complete regio- and diastereoselectivity.*

Modern stereoselective synthesis relies on the efficient and straightforward development of strategies that allow the rapid preparation of complex molecular architectures from simple starting materials.[1] In the last decade, numerous approaches have been reported in the literature to construct aliphatic chains possessing vicinal stereocenters[2] but the synthetic difficulty drastically rises on increasing the degree of substitution. For instance, the diastereoselective formation of three vicinal tertiary stereocenters is nowadays moderately well established,[3] but the equivalent formation of two or three vicinal quaternary carbon stereocenters still represents an important chemical challenge (Scheme 1a).[4] In recent years, we have been particularly interested in the development of new strategies allowing the preparation of vicinal stereocenters within acyclic systems by selective ring-opening of polysubstituted cyclopropanes[5] (see Scheme 1b for a recent representative example).[6] Nevertheless, none of our approaches reported so far allowed the formation of vicinal quaternary stereocenters.[7] One of the reasons was the lack of methods to selectively prepare persubstituted cyclopropanes **1** as unique diastereomers. Despite a few reports of the synthesis of polysubstituted cyclopropanes,[8] persubstituted analogs were still inaccessible. Such stereodefined persubstituted strained rings are potential substrates for subsequent selective carbon-carbon bond cleavage (Scheme 1c).[5] From the onset, it was clear that the selective formation of three vicinal quaternary carbon stereocenters in a cyclopropane should generate much torsional strain, as all bonds are eclipsed.[9] Based on these combined torsional and ring strain constraints, we initially restricted our efforts to the selective formation of persubstituted silyl cyclopropanes **2**, hoping that the longer carbon-silicon bond would allow an easier preparation.[10] In addition, the formation of **2** might serve as a source of vicinal carbon-persubstituted cyclopropanes after subsequent Hiyama-type cross-coupling reactions.[11] Although we were pleased to report the preparation of compounds **2** as single diastereomers,[12] all our attempts to engage them in cross-coupling reactions were unsuccessful.



Scheme 1. Formation of vicinal stereocenters and persubstituted cyclopropanes.

As we were seeking a diastereoselective access to persubstituted cyclopropanes possessing only carbon-based side chains, we then reconsidered the copper-catalyzed carbomagnesiation reaction of persubstituted cyclopropenes as a potential method.[13]

To control the regioselectivity of the carbometallation reaction, we hypothesized that the presence of a π-hybridized carbon center linked to the sp^2 carbon center of the cyclopropene should not only increase the reactivity of the addition reaction of the organometallic species but also control the regioselectivity. The diastereoselectivity would then be steered, in non-polar solvents, by the chelation of the organometallic species by the ester (Scheme 2).[14] We started our investigation by preparing various arylated cyclopropenes **3a**–**m**, easily accessible by the well reported Rh-catalyzed decomposition of diazoacetate with arylated alkynes.[15] The copper-catalyzed carbomagnesiation of **3a** then proceeded smoothly at −25 °C to yield **4a** in excellent yield as a single diastereomer. As expected, the preferred regioisomer originates from the formation of the stabilized benzylic organometallic intermediate; importantly, the formation of a single diastereomer indicates that the in situ formed benzyl cyclopropyl magnesium species is configurationally stable under the experimental condition. As the copper-catalyzed carbo-

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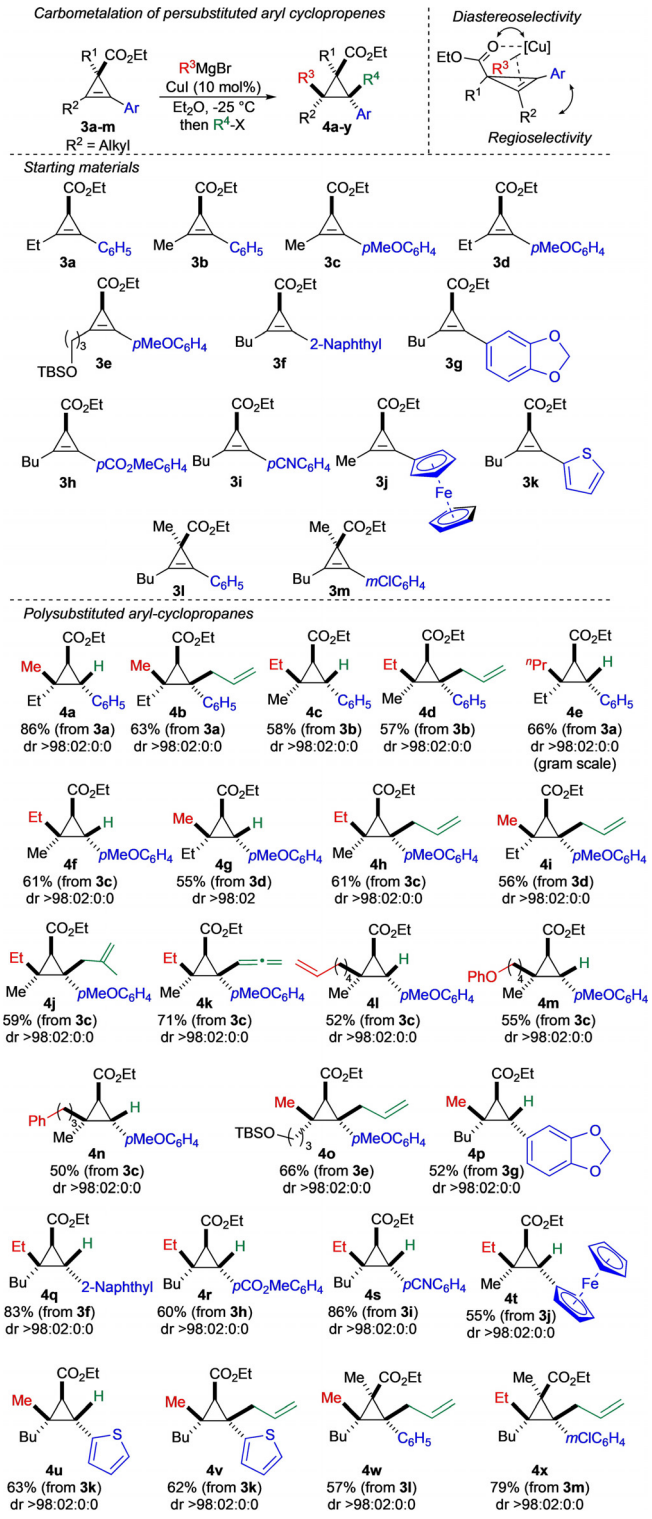
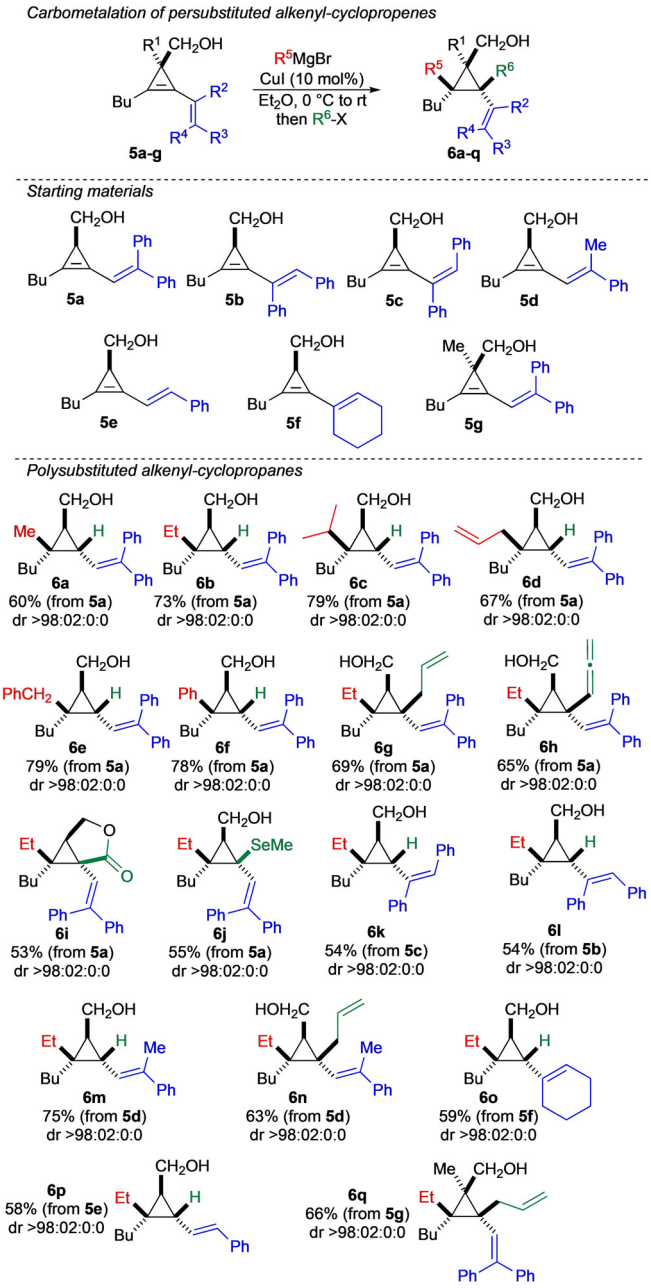


Scheme 2. Copper-catalyzed carbomagnesiation of aryl-substituted cyclopropenyl esters.

magnesiation is a *syn*-addition across the double bond,[13] the relative configuration was easily established by determining the coupling constant of the two hydrogens of **4a** (J = 5.97 Hz).[16] Cyclopropyl copper reacts smoothly with an electrophile, for example, allyl bromide as representative example, to provide **4b**, possessing two vicinal quaternary carbon centers with similar diastereoselectivity. The complementary diastereomeric pair was also prepared, by formally exchanging the alkyl substituent at the cyclopropenyl core and the alkyl group of the Grignard reagent (compare **4a** and **4b** with **4c** and **4d**, Scheme 2), formed as a single diastereomer in all cases. Scaling up the reaction to gram scale did not affect the overall outcome of the reaction (**4e**, Scheme 2). The nature of the alkyl group of the cyclopropenes and also of the Grignard reagent can be varied (**4l–o**, Scheme 2). Changing the electronic properties of the aromatic ring from electron-rich (**4f–p**, Scheme 2) via electron-neutral (**4q**) to electron-poor (**4r** and **4s**, Scheme 2) altered neither the reaction nor the selectivity. In addition, a few heteroaromatics, such as ferrocene or thiophene, as aromatic groups also allowed the transformation and delivered the desired products with similarly high regio- and diastereomeric ratios (**4t–v**, Scheme 2). It should also be noted that the copper-catalyzed carbomagnesiation proceeds fast enough at the strained double bond, while functional groups such as ester or nitriles remain intact. However, secondary Grignard reagents could not be satisfactorily added, and the presence of secondary alkyl side chains on the cyclopropenes drastically decreases the yield of the transformation. Finally, when the persubstituted cyclopropenes **3l** and **3m** were used as starting materials, the transformation proceeded similarly to provide, after reaction of the resulting cyclopropyl magnesium intermediate with allyl bromide, persubstituted cyclopropanes **4w** and **4x** as unique diastereomers. These promising results confirm that our proposed strategy does indeed allow the formation of three vicinal quaternary carbon stereocenters at all three carbons of the three-membered ring.

Having established the protocol for a regio- and diastereoselective carbometallation of polysubstituted cyclopropenes possessing an aromatic group, we then turned our attention to the reactivity of alkenyl cyclopropenes **5** (for all preparative details, see Supporting Information) as this should provide a new approach to the important molecular motif of polysubstituted alkenyl cyclopropanes **6**.[17] Although the carbometallation of alkenyl-cyclopropenyl esters was not very conclusive, we were able to observe that the copper-catalyzed carbomagnesiation of alkenyl cyclopropyl carbinols **5a–g** proceeded smoothly in only 2 h at room temperature to provide the corresponding alkenyl-cyclopropanes **6a–q** as single diastereomers.

The products of the copper-catalyzed carbomagnesiation of **5** were obtained with a wide variety of Grignard reagents. Primary (Scheme 3, **6a** and **6b**), secondary (Scheme 3, **6c**), allyl (Scheme 3, **6d**), benzyl (Scheme 3, **6e**) and aryl (Scheme 3, **6f**) Grignard nucleophiles were all successfully added, with good yields and selectivities. Tertiary alkyl Grignards, however, failed to react with the corresponding alkenyl cyclopropyl carbinol **5a**. The regioselectivity and relative configuration were confirmed by X-ray analysis of **6f**,[18] and the configurations of all other products were assigned by analogy. The in situ formed cyclopropyl Grignard intermediate could then react with various electrophiles (such as allyl and propargyl bromide, CO_2 or elemental selenium followed by MeI) to provide the allylated, allenylated, lactone

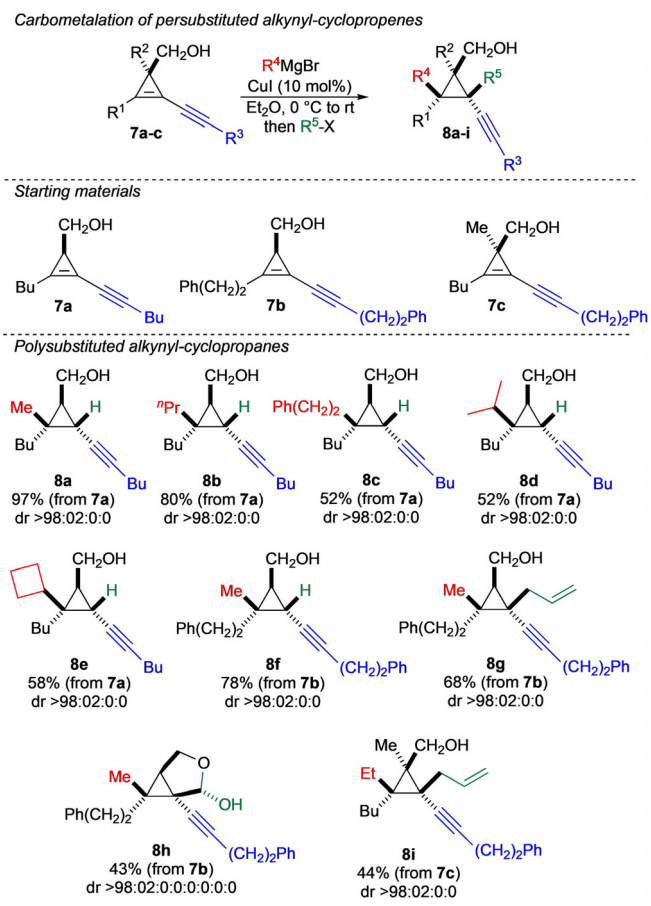


Scheme 3. Copper-catalyzed carbomagnesiation of alkenyl-substituted cyclopropenyl carbinols.

or SeMe products, respectively, in good yields and as unique diastereomers (Scheme 3, **6g–j**). In addition, various substitution patterns of the alkenyl fragments are compatible with our experimental conditions, as the initial stereochemistry of the external double bond is preserved in the products (Scheme 3, **6k–p**). Finally, this approach also allows the preparation of persubstituted alkenyl cyclopropane **6q** in 66% yield as a unique diastereomer, underlining, once again, the power of this strategy for the formation of fully (hexa)-substituted alkenyl cyclopropanes as a single isomer.

Having successfully synthesized stereodefined polysubstituted aryl- and alkenyl-cyclopropanes, we wondered whether we could extend this concept of carbometallation to the formation of alkynyl-cyclopropanes **8**. However, the selectivity of the carbometallation reaction could become a problem, because the carbocupration of alkynes is a well-known reaction and usually proceeds at similar temperature.[19]

We did indeed observe that the copper-catalyzed carbomagnesiation of alkynyl-cyclopropenyl carbinol **7a** was completely stereo- and regioselective, providing, at room temperature, the corresponding alkynyl cyclopropane carbinol **8a** as a single product with an outstanding diastereoselectivity (Scheme 4). Various Grignard nucleophiles were added, such as primary (Scheme 4, **8a–c**) and secondary (Scheme 4, **8d** and **8e**) alkyls, with similar efficiency. The intermediate cyclopropyl Grignard reacts efficiently with electrophiles such as allyl bromide or dimethylformamide to afford **8g** and **8h** as single diastereomers (Scheme 4). In the latter case, a single lactol is formed because of steric constraints in the final product. The regioselectivity and relative configuration was confirmed by X-ray analysis of **8h** (Scheme 4).[20] Finally, when the reaction was performed on the persubstituted alkynyl-cyclopropenyl carbinol **7c**, the resulting alkynyl persubstituted cyclopropane derivative **8i** was obtained in 44% yield as a unique diastereomer, together with its allenyl counterpart, the latter resulting from equilibration of the propargyl Grignard intermediate with the allenylmagnesium bromide intermediate (see Supporting Information).



Scheme 4. Copper-catalyzed carbomagnesiation of alkynyl-substituted cyclopropenyl carbinols.

In conclusion, we have developed, for the first time, an efficient and broadly applicable approach to the synthesis of polysubstituted and stereodefined cyclopropyl rings possessing vicinal quaternary carbon stereocenters. Despite the highly strained nature of these ring systems, the regio- and diastereoselective copper-catalyzed carbomagnesiation reaction of persubstituted cyclopropenes represents an excellent access to persubstituted cyclopropane derivatives as single diastereomers. We are currently investigating the selective ring-opening of these molecular backbones as a new route to vicinal quaternary stereocenters in acyclic systems.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbon quaternary stereocenters · copper-catalyzed carbomagnesiation · diastereoselectivity · persubstituted cyclopropanes

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