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Communication

Borylated Cyclopropanes as Spring-Loaded Entities: Access to Vicinal Tertiary and Quaternary Carbon Stereocenters in Acyclic Systems

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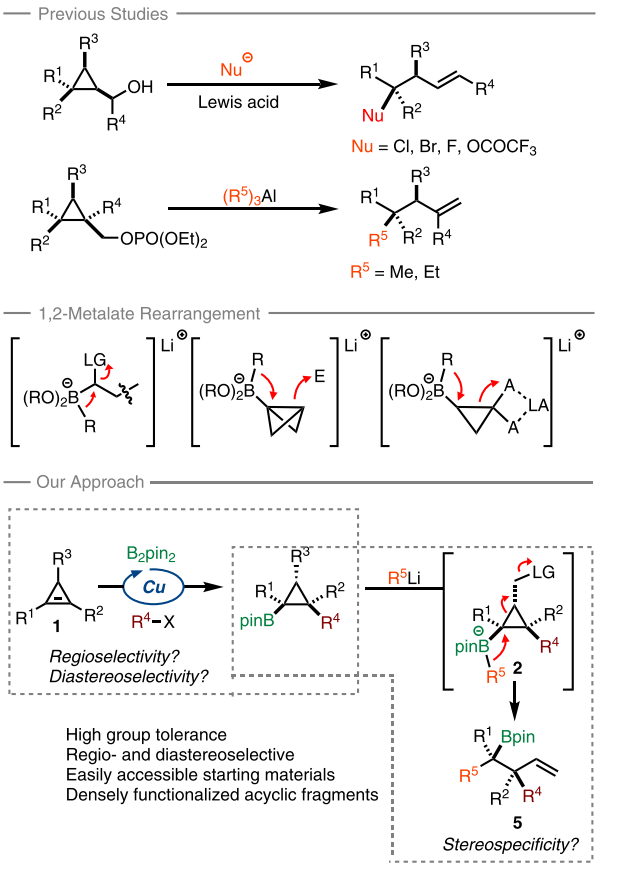
ABSTRACT: Herein, we present the formation of acyclic frameworks bearing two consecutive stereocenters of either tertiary or quaternary nature starting from easily accessible cyclopropenes. This holistic approach involves a regio- and diastereoselective hydro- or carboborylation of substituted cyclopropenyl esters. Formation of boronate complexes of the latter via the addition of nucleophiles and subsequent stereospecific 1,2-migration with carbon−carbon bond cleavage delivered the title compounds.

The growing demand for complex molecular architectures, especially acyclic fragments bearing multiple stereocenters, is contrasted by the challenging nature of their stereoselective synthesis generated by rotational freedom as well as distorted geometries.[1] Thus, the discrimination between two seemingly similar alkyl side chains is still complex to achieve in acyclic systems. Even though various strategies have appeared over the years,[2] protocols for the selective formation of vicinal stereocenters of either tertiary or quaternary nature are still rather limited.[3] In this context, the carbon−carbon bond cleavage of densely functionalized cyclopropanes as a new approach of molecular editing has gained increased momentum over the past few years,[4] as it provides an innovative solution for the creation of well-defined stereocenters along acyclic hydrocarbon architectures from an easily accessible cyclopropyl platform.[5] We have recently reported a nucleophilic substitution reaction at the quaternary carbon center of cyclopropyl carbinol derivatives, with a pure inversion of configuration, to access tertiary alkyl halides and esters as a single diastereomer (Scheme 1, top).[6] Furthermore, organoaluminum species could be successfully implemented as nucleophiles when using polysubstituted cyclopropyl methyl phosphates, again with a complete inversion of configuration at the most substituted carbon center (Scheme 1, top).[7] Although our previous reports showed a high degree of stereoselectivity and a broad scope with respect to the cyclopropyl unit, the nature of the nucleophilic counterpart was mainly restricted to halogens and Me_3Al.[8] Considering this serious limitation, we were interested in developing an alternative approach to broaden the scope of the resulting acyclic fragments. From all considered possibilities, the Matteson 1,2-metalate rearrangement seemed to be a promising starting point to overcome this restriction, as it allows the use of various organolithium reagents and their stereospecific transfer to the α-position next to the boron moiety (Scheme 1, middle).[9] In this respect, Aggarwal and co-workers showed recently the application of this chemistry to small rings by accessing either stereodefined cyclobutane systems by breaking the central C−C σ-bond of

Scheme 1. Stereoselective Synthesis of Acyclic Compounds Bearing Vicinal Stereocenters



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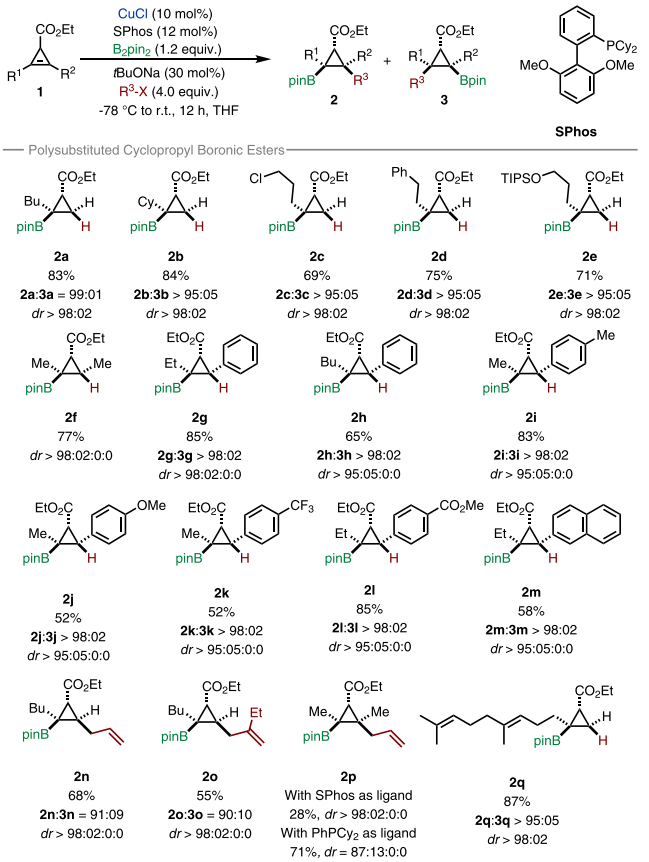
bicyclo[1.1.0]butyl boronic esters[10] or by using the strain release of doubly activated donor−acceptor cyclopropyl boronate complexes (Scheme 1, middle).[11]

Inspired by these reports, we surmised that polysubstituted cyclopropyl boronic esters might undergo a stereospecific ring-opening when decorated with a proper leaving group to deliver acyclic fragments bearing up to two adjacent fully substituted stereocenters (Scheme 1, bottom).[12] Although several diastereo- and enantioselective protocols for the formation of borylated cyclopropanes have been reported,[13] the formation of their polysubstituted analogues was still missing. Therefore, we first focused on devising a convergent approach to polysubstituted cyclopropyl boronic ester **2** through the copper-catalyzed hydro- and carboboration of cyclopropenyl esters **1**. At the outset of our studies, we used the original conditions reported by Tortosa [B_2pin_2 (1.2 equiv), CuCl (10 mol %), *t*BuONa (30 mol %) in THF][14] on our model substrate, namely, cyclopropenyl ester **1a** (R^1 = Bu, R^2 = H),[15] with MeOH as electrophile, and we screened various phosphine ligands to obtain **2** with high regio- and diastereoselectivity. We were delighted to observe that when SPhos was used as ligand (12 mol %), from the two possible constitutional isomers (**2a** and **3a**), the product **2a** was formed in a 99:01 ratio in excellent yield as a single diastereomer (Scheme 2; for all ligands tested and variation of experimental conditions, see the Supporting Information).

Under the optimized set of conditions, the scope of the regio- and diastereoselective copper-catalyzed hydro- and carboboration was examined using a broad range of cyclopropyl esters **1**, which are easily accessible by the well-known Rh-catalyzed decomposition of diazoacetates in the presence of an alkyne (Scheme 2). It should be noted that cyclopropenyl esters **1** could easily be prepared enantiomerically enriched by using dirhodium tris(diphenyltriflylimidazolidinone)-(acetate).[16] Besides a primary alkyl group on the cyclopropenyl core, the reaction proceeds smoothly in the presence of a cyclohexyl substituent (**2b**), whereas a bulky *tert*-butyl group completely inhibited the reaction (not shown in Scheme 2). In all cases, the boracupration proceeds *anti* to the ester group and could be rationalized by the steric hindrance of the boracopper species ligated to SPhos combined with the polar nature of the solvent that should prevent intramolecular chelation.[17] Functional groups on the side chain, such as chloride or silyl ether (**2c** and **2e**, respectively), do not hamper the transformation, nor does a phenyl group tethered to the three-membered ring (**2d**). To further test the generality of our protocol, we subsequently investigated the reactivity of sp^2-disubstituted cyclopropenyl esters **1f−m**. When symmetrical cyclopropene **1f** (R^1 = R^2 = Me) was treated under the same experimental condition, **2f** was obtained as a single diastereomer in 77% yield. When the cyclopropene has now two different sp^2-substituents (i.e., **1g−m**, R^1 = alkyl, R^2 = aryl), the constitutional selectivity leaned on inherently two different substituents on the two sp^2 carbon centers of the double bond, leading, after boracupration, to the formation of the electronically stabilized cyclopropyl copper species.[18] Indeed, in all these cases, only the isomers **2g−m** were obtained with an outstanding selectivity as a single diastereomer. The relative configuration was determined by X-ray analysis of **2f**, **2g**, **2h**, **2j**, **2k**, and **2p**, unambiguously confirming the *anti*-addition relative to the ester. All other relative configurations were assigned by analogy and eventually further corroborated by analysis of the coupling constant of the two vicinal hydrogen atoms of the cyclopropyl unit ($^3J_{HH}$ = 8−9 Hz for *cis*-coupling).[19] Variation of the electronic nature of the aromatic core with either electron-donating or electron-withdrawing groups had no effect on the selectivity of addition, nor did the use of an extended π-system. Next, we were interested in further extending our approach to more substituted cyclopropyl boronic esters and in situ trapping the resulting cyclopropyl copper species with a carbon electrophile. To our delight, allyl phosphate (1.2 equiv) proved to be an excellent coupling partner, as it reacted smoothly with the parent cyclopropenyl ester **1a** to furnish the allylated compound **2n** in 68% as a single diastereomer (accompanied with minor amounts of the opposite constitutional isomer). Similar results were observed when using branched allyl phosphate, delivering compound **2o** in 55% yield. When **1p** was treated similarly, **2p** was obtained in excellent diastereomeric ratio but in lower yield (28%). However, by using slightly modified experimental conditions with $PhPCy_2$ as ligand instead of SPhos, the formation of **2p** was successfully achieved (71% yield) albeit with a lower diastereoselectivity. As both diastereomers could be independently isolated by purification by column chromatography, we have opted for this modified condition for this particular case. Finally, we prepared geraniol-derived cyclopropenyl ester **1q** and subjected it to our standard reaction conditions. Gratifyingly, desired product **2q** was obtained in 87% yield without any interference of the additional double bonds in the reaction process. Therefore, through this unified strategy, an assortment of bench-stable polysubstituted cyclopropyl bor-

Scheme 2. Cu-Catalyzed Hydro- and Carboborylation of Substituted Cyclopropenyl Esters



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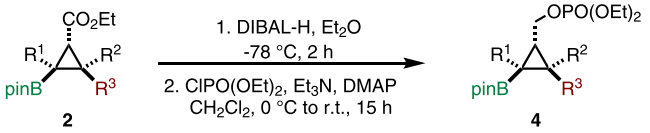
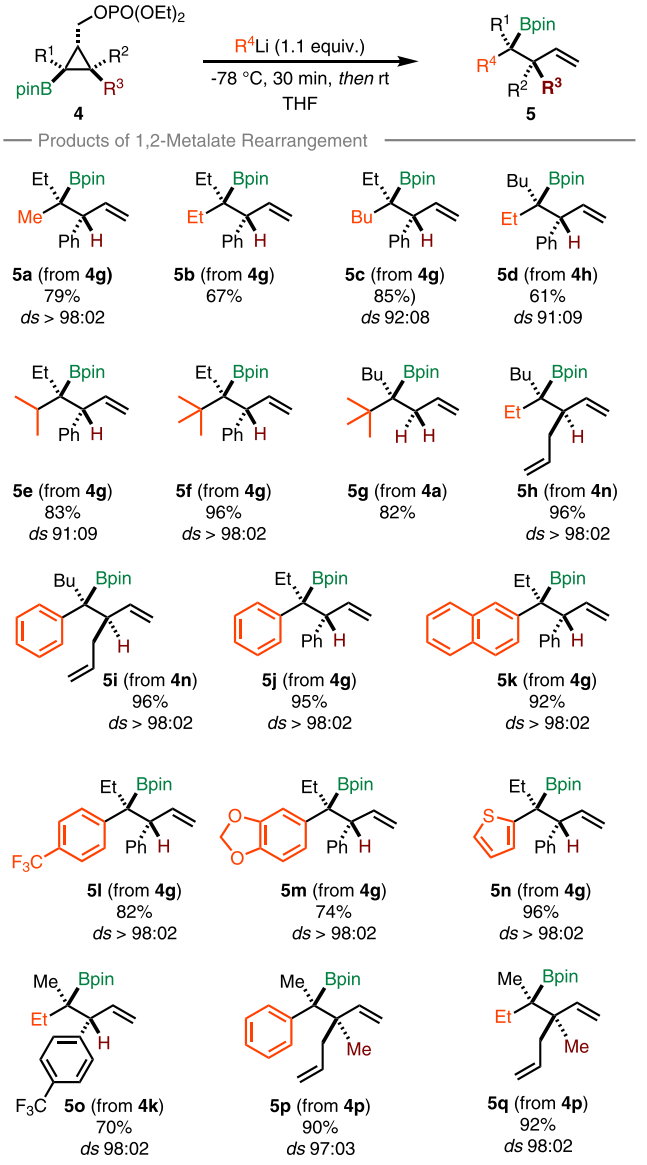
onic esters was prepared expeditiously by a predictable route in high stereoisomeric purity in only two catalytic steps from alkynes. The reaction could also be scaled up, as 1 g of **1g** could be transformed into **2g** with an identical selectivity. The next step for the 1,2-metalate rearrangement is based on our previous research on molecular editing by carbon−carbon bond cleavage.[7] To promote this ring-fragmentation, the ester moiety had to be transformed into a good leaving group. Thus, polysubstituted cyclopropyl boronic esters **2a**, **2g**, **2h**, **2k**, **2n**, and **2p** were transformed in an efficient two-step procedure to phosphates **4** as shown in Scheme 3 (for all details, see the Supporting Information). Having various boronic ester-substituted cyclopropyl phosphates in hand, we then investigated the anticipated 1,2-migration reaction with subsequent carbon−carbon bond cleavage.

Scheme 3. Sequence of Reduction−Phosphorylation



When phosphate **4g** (R^1 = Et, R^2 = Ph, R^3 = H) was subjected to the addition of methyllithium in THF at −78 °C, the formation of the ate-complex was obtained. Simply warming the reaction mixture to room temperature triggered the rearrangement to occur and provided the acyclic product **5a** in good yield as a single diastereomer (Scheme 4). Pleasingly, the transformation proceeded with a complete stereospecificity. Based on this promising result, we then explored the scope of the potential nucleophile for the 1,2-migration. Adding commercially available primary alkyllithium reagents of various lengths gave the desired acyclic fragments in good yields (**5a−c**, Scheme 4), although a slight erosion of stereospecificity for **5c** was observed. Both diastereomers at the tertiary carbon center holding the pinacol boronic ester could be prepared by permuting the nature of the alkyl group on the original cyclopropene and of the alkyllithium reagent (compare **5c** and **5d**, Scheme 4). Similar results were also observed when secondary and tertiary alkyllithium reagents, such as isopropyl- and *tert*-butyllithium (**5e** and **5f**) were employed. In the latter case, the transformation proceeds in quantitative yield with excellent diastereospecificity. The stereochemistry of the allylic substituent has no effect on the overall process (compare **5a−f** with **5h**, Scheme 4). Indeed, when we applied our procedure to the phosphate **4n** bearing an allyl group in a *cis* fashion to the pinacol boronic ester (R^1 = Bu, R^2 = H, R^3 = allyl), ethyllithium furnished the desired acyclic fragment **5h** in excellent yield as a single diastereomer. We then focused on the use of sp^2-carbon nucleophiles starting with phenyllithium, which was found to be an excellent coupling partner, delivering boronic ester **5i** and **5j** in nearly quantitative yield, irrespective of the stereochemistry of the adjacent stereocenter. Extending the π-system by introducing a naphthyl group (**5k**) does not change the stereochemical outcome neither by decorating the aromatic core with either electron-withdrawing or electron-rich groups (**5l** and **5m**, Scheme 4). In all cases, a smooth transformation was observed. In addition, a heteroaromatic ring as nucleophile, such as a thienyl derivative, performed extremely well to produce **5n** with an excellent selectivity. The same holds when the electronic nature of the allylic substituent is different (**5o**, Scheme 4).

Scheme 4. 1,2-Metalate Rearrangement of Cyclopropyl Boronic Esters



Spurred by these results, we then decided to evaluate the behavior of pentasubstituted cyclopropyl boronic ester **2p** (R^1 = R^2 = CH_3, R^3 = allyl), which would potentially lead to the vicinal formation of tertiary and quaternary carbon stereocenters. The addition of phenyllithium proceeded smoothly to provide **5p** with high stereospecificity and 90% yield. The relative configuration of **5p** was determined by X-ray analysis, confirming that the intramolecular nucleophilic substitution at the most substituted carbon center proceeded with inversion of configuration. The same holds for the preparation of **5q**.

In conclusion, we have developed an efficient method to construct acyclic architectures bearing up to two adjacent stereocenters of either tertiary or quaternary nature. Starting from simple cyclopropenyl esters, highly strained and densely functionalized cyclopropyl boronic esters were synthesized in a regio- and diastereoselective fashion. Formation of the corresponding boronate complexes with various carbon nucleophiles delivered, after 1,2-migration and carbon−carbon bond cleavage, the desired acyclic fragments with high degrees of stereospecificity.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c07394.

Experimental procedures, characterization data for all new compounds, optimizing tables, crystal structures along with copies of spectra (PDF)

Accession Codes

CCDC 2173683−2173687 and 2175547 contain 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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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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