Stereospecific Reactions Leading to Allylboronic Esters in Acyclic Systems: Implications for Chiral Drug Synthesis with Remote Stereocontrol

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Abstract: We hereby report the preparation of acyclic molecules featuring congested stereocenters in a 1,4-relationship in only three catalytic steps from commercially available building blocks. Our approach involves a diastereoselective diboration of alkenyl cyclopropyl methanol derivatives followed by a regioselective exergonic ring fragmentation. As the starting materials can be prepared enantiomerically enriched and all substituents can be interconverted, this strategy allows a large variety of diversely functionalized allylboronic esters possessing distant tetrasubstituted stereocenters with high diastereoselectivity.

Since the discovery of the first enantioselective transformation,[1] extensive efforts have been directed towards the development of strategies allowing the creation of stereogenic centers of defined stereochemistry.[2] Despite these extensive efforts, the efficient and straightforward preparation of all possible enantio- and diastereomers of a given molecular scaffold possessing multiple stereocenters at distant positions along a acyclic hydrocarbon chain is still a difficult task.[3] For two distant stereocenters, one of the problems reside in that the first stereocenter might have intrinsically a low stereochemical impact on the creation of the second, requiring the transformation to be mediated by an external reactant (Figure 1).[4]

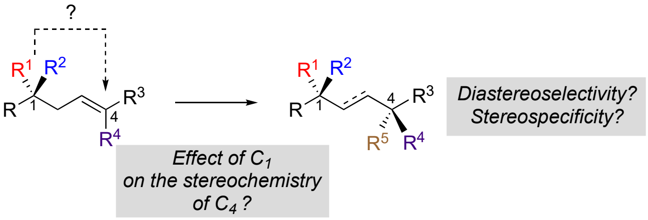
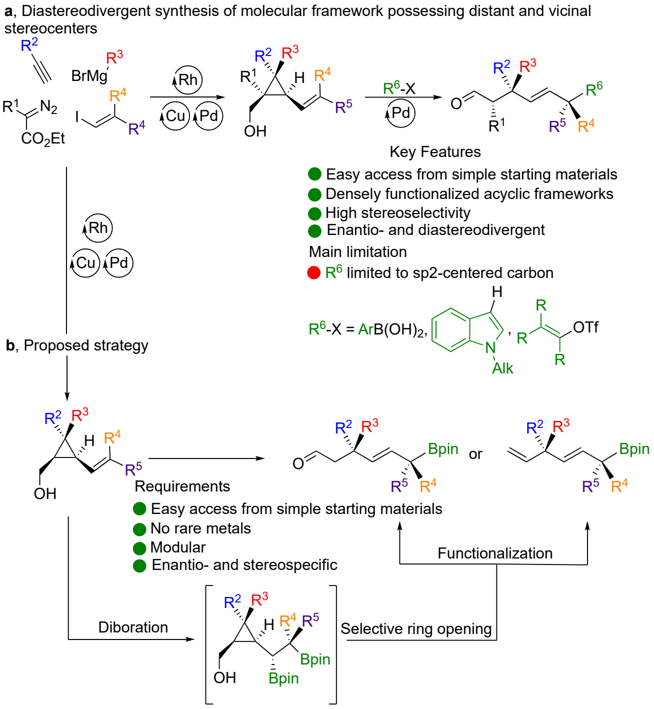


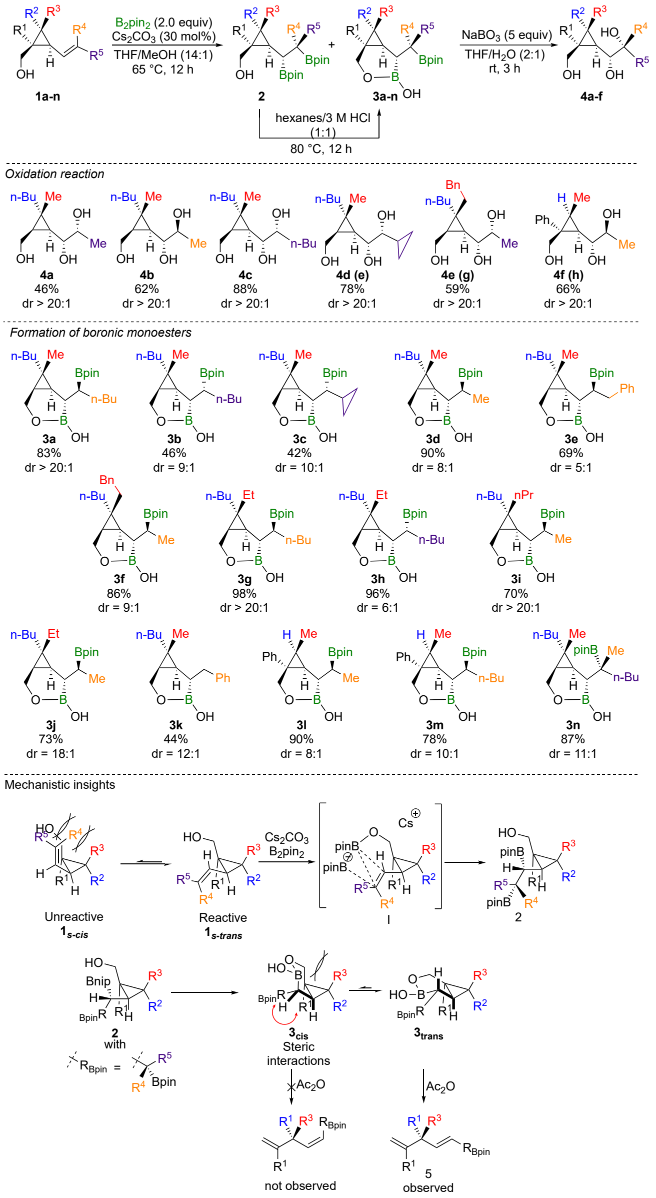
Figure 1. Potential problems of stereochemical induction at long-distance

The development of new stereospecific approaches are still in need[5] but it requires the stereoselective formation of each stereocenter independently and simultaneously. In this context we have recently disclosed the diastereodivergent synthesis of enantiomerically enriched acyclic molecular backbones presenting up to two quaternary stereocenters in a 1,4-relationship in only three catalytic steps from commercially available alkynes (Scheme 1a).[6]



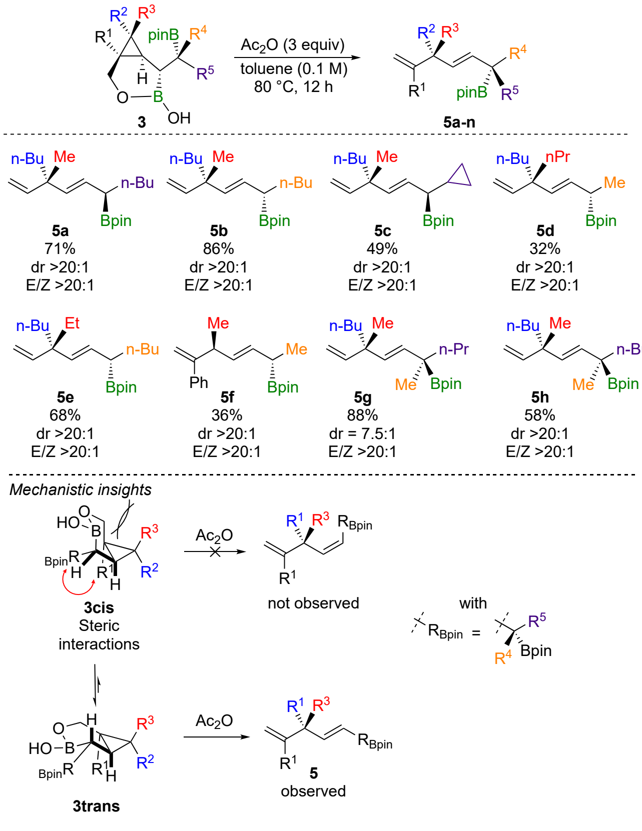
Scheme 1. Stereoselective synthesis of acyclic molecules containing distant (1,4) congested stereocenters

This methodology was based on a stereospecific domino reaction involving a substrate-directed diastereo- and regioselective carbopalladation, followed by a regioselective cyclopropane ring fragmentation and a final Pd-walk to produce the expected acyclic products. The presence of the hydroxyl group was crucial to direct the diastereoselectivity of the carbopalladation as well as the regioselectivity of the fragmentation. Although clearly efficient, one limitation was the restriction to sp^2 carbon-bounded nucleophiles arising from the addition of arylboronic acid, indole or vinyl triflate derivatives (R^6 group, Scheme 1a). Since boronic esters are versatile precursors to various functionalities,[7-9] we hypothesized a selective borametalation reaction of alkene coupled with a subsequent ring-opening as a new entry to acyclic compounds possessing distant congested stereocenters (Scheme 1b). We hereby report the rapid and modular synthesis of allylboronic esters bearing up to two stereodefined tetrasubstituted stereocenters in a 1,4-position within an acyclic chain (Scheme 1b) from stereodefined alkenyl cyclopropyl methanol, easily accessible in 2 catalytic steps from commercially available alkynes. Although the proposed strategy is appealing, a complete control of each elementary step is required to obtain good chemical yields and diastereomeric ratios. Our initial concern was therefore the diastereocontrol of the diboration reaction and we took inspiration from the pioneering reports of Fernández[10] and Morken.[11] We started our study by performing the diboration of alkenyl cyclopropyl methanol derivative **1a** (R^1 = H, R^2 = *n*-Bu, R^3 = Me, R^4 = H, R^5 = Me), and the desired diborylated product **2a** was formed as a single diastereomer accompanied by the cyclized product **3a** arising from the reaction of the hydroxyl moiety with the closest boronic ester. This initial result shows that, in sharp contrast to the diboration of acyclic 1,4-alkenol providing two diastereomers,[11] the presence of a cyclopropyl ring drastically improve the selectivity. Even though **2a** could not be easily separated by column chromatography from **3a**, they were both convergently oxidized, under mild conditions, to a unique triol **4a** as a single diastereomer (Scheme 2).[12,13] When the corresponding (*Z*)-alkenyl cyclopropyl methanol derivative **1b** (R^1 = H, R^2 = *n*-Bu, R^3 = Me, R^4 = Me, R^5 = H) was subjected to the same reaction conditions, the opposite diastereomer **4b** was obtained (Scheme 2), showcasing that the diboration/oxidation sequence was stereospecific. The nature of the substituents on the double bond R^4 and R^5 (Scheme 2, **4c** and **4d**) could be varied as well as the nature on the cyclopropyl core (Scheme 2, **4e** and **4f**) allowing a general access to triols **4a-f** (Scheme 2) without affecting selectivities. The presence of the quaternary stereocenter on the three-membered ring can also be on the carbon C_2 (Scheme 2, R^1 = Ph, **4f**). The relative stereochemistry was established by X-Ray diffraction analysis of **4d** (from an *E*-olefin) and **4f** (from a *Z*-olefin), respectively confirming the *syn*-diboration reaction.[14,15] Configurations of all other products were determined by analogy. It should be noted that the diastereoselectivity of the diboration reaction decreases with the distance between the olefin and the cyclopropyl methanol core (*i.e.* allyl cyclopropyl methanol gave lower diastereoselectivity, not reported in Scheme 2, see Supporting Information for details). Independent of the nature of the intermediates **2** or **3**, in variable ratio according to the nature of the substrate, the mild oxidation reaction provides a wide range of triols **4a-f** with an excellent diastereocontrol. Based on the available experimental data, we postulate that the high diastereoselectivity with which **2** (or **3**) is generated might be due to the combination of the following two factors: i) the alkenyl cyclopropyl methanol preferentially adopts the conformer $\mathbf{1}_{\boldsymbol{s\text{-}trans}}$ over $\mathbf{1}_{\boldsymbol{s\text{-}cis}}$ to minimize steric interactions, especially when $R^4 \neq H$; ii) B_2pin_2 proceeds through a *syn*-diboration directed reaction by the hydroxyl moiety (mechanistic insights, Scheme 2, **I**) leading to a single diastereomer **2**.



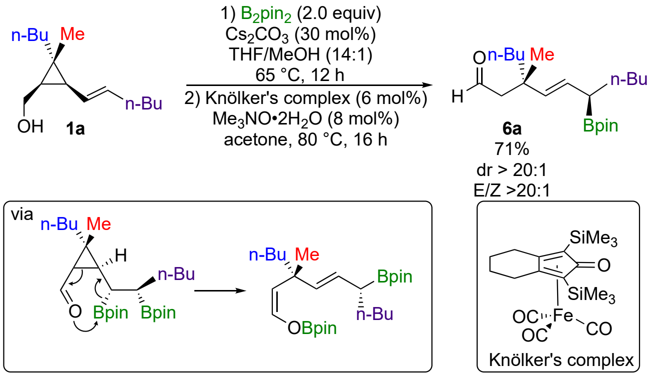
Scheme 2. Synthesis of triols **4a-f** and access to boronic monoesters **3a-n** from alkenyl cyclopropyl methanol derivatives

We surmised that the presence of these two intermediates (**2** and **3**) might have a different behaviour for the subsequent selective ring-fragmentation reaction and we became interested to converge the presence of these two products into a single one.[16] We were pleased to observe a clean transformation of **2** into **3**, by refluxing the mixture of these two diborylated species in a 1:1 mixture of 3 M aqueous HCl and hexanes (formation of boronic monoesters, Scheme 2).[17,18] It should be highlighted that this transformation could be realized in a one pot sequence directly from **1** to **3**. In addition, it appears to be much more diastereoselective starting from *Z*-olefins than from *E*-olefins (compare **3a** to **3b** and **3g** to **3h**). Nevertheless, boronic monoesters **3** were obtained in good to excellent yields and diastereoselectivities providing an access to both diastereomer by simply permuting the nature of the substituents R^4 and R^5. The nature of the substituents R^1 to R^3 on the cyclopropyl core has also no effect on the transformation and **3** were always obtained in good to excellent yields and selectivities (Scheme 2). A particular reactivity was observed for the formation of **3k**, possessing an initial styrenyl cyclopropyl methanol structure (R^4 = Ph, R^5 = H), as the monoborylated species was solely observed (presumably generated by protodeboration of the labile benzylic boronic ester). Notably, the present methodology could also be used on a trisubstituted alkene to regioselectively produce **3n** albeit with lower diastereomeric ratio. The relative stereochemistry was unambiguously confirmed by X-Ray analysis of **3n** (see supporting information).[14, 19] An important aspect of the diboration reaction is, at the opposite of the Pd-catalysed instantaneous ring-opening of alkenyl cyclopropyl methanol,[6] the boronic monoester unit **3** doesn't rearrange spontaneously and could be used as a handle for delayed β-fragmentation reaction. In this context, the chemoselective *on-demand* activation of the boronic monoester **3**, triggering the ring fragmentation to form the desired skipped dienes possessing tetrasubstituted stereocenters, could be achieved by simple addition of an excess of acetic anhydride to **3** at 80 °C. Allylboronic esters **5a-h** were formed as single *E*-diastereomers (Scheme 3). The reaction scope was investigated with different substitution patterns on both stereocenters and proved to be rather general. Opposite diastereomers could be obtained at will (Scheme 3, compare **5a** with **5b**) with similar yields and selectivities.



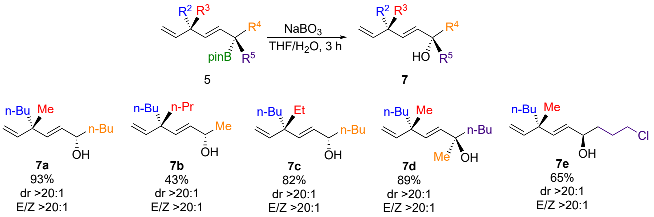
Scheme 3. Rearrangement of boronic monoesters **3** into skipped dienes **5**

It is noteworthy that the ring-opening is selective towards the C-C bond cleavage of the cyclopropyl group in β-to the boronic monoester and not from the one β-to the Bpin unit as the cyclopropyl unit of **5c** remained intact.[20] Our hypothesis is that the conformer **3**$_{\text{trans}}$ is predominant over **3**$_{\text{cis}}$ to minimize again steric interactions leading exclusively to the (*E*)-allylboronic ester **5**. Two distant tri- or tetrasubstituted stereocenters could therefore be produced in decent yields as unique diastereomers (Scheme 3, **5f**, **5g** and **5h**, respectively) illustrating the power of this strategy to prepare distant encumbered stereocenters. The transformation could also be performed directly from **1** without any purification steps to provide **5d** or **5f** with similar results (see Supporting Information for details). As was initially suspected, when **2** was treated under the same experimental conditions, the ring-fragmentation was not observed underlining the necessity to converge the diboration into the single product **3** for subsequent transformation. In addition, we surmised that a push-pull effect could favour a new type of fragmentation of the mixture of **2a** and **3a** if the alcohol moiety could be *in-situ* oxidized into an aldehyde. After an extensive screening, the use of Knölker's complex[21] in acetone delivered efficiently the aldehyde **6a** as a single *E*-isomer with an excellent diastereocontrol (Scheme 4).[22]



Scheme 4. Direct conversion of alkenyl cyclopropyl methanol derivative **1a** into acyclic allylboronic ester **6a**

As the aldehyde before fragmentation was not observed in the crude reaction mixture, we believe that the fragmentation was spontaneous through the concerted mechanism depicted in Scheme 4. Finally, the allylboronic esters **5** could be derivatized into the corresponding alcohols with complete retention of configuration under oxidative conditions (Scheme 5, **7a-7e**) to produce skipped dienol derivatives as single *E*-isomer possessing the requested distant stereocenters.



Scheme 5. Oxidation of allylboronic esters **5**

7e Could even be obtained in this three-step sequence from the corresponding alkenyl cyclopropyl methanol derivative underlining the possibility to have functional groups. Additional attempts to functionalize **5** have been tested by engaging the allylboronic ester in aldehyde or nitroso allylations, or in various metal-catalyzed cross-coupling, but the bulky allylboronic ester species showed poor reactivity and low regio- and diastereoselectivities indicating that further studies are necessary to extend the scope of functionalization. In conclusion, a 3-step stereospecific synthesis of stereodefined allylboronic esters within acyclic systems bearing two distant stereocenters from simple reagents could easily be achieved. As the alkenyl cyclopropyl methanol derivatives can be prepared enantiomerically enriched,[23] and all substituents can be interconverted,[6] the proposed strategy should similarly provide a wide variety of diversely functionalized allylboronic esters enantiomerically enriched. In the course of our study, we unravelled two new selective cyclopropane ring fragmentations leading to skipped dienyl molecular backbones. We are currently focussing our efforts to various functionalization of the allyl boronic ester.

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Keywords: alkenyl cyclopropyl methanol • diboration • fragmentation • allylboronic esters • stereocenters

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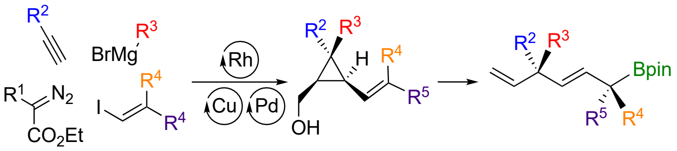

A 3-step stereospecific synthesis of stereodefined allylboronic esters within acyclic systems bearing two distant stereocenters from simple reagents could easily be achieved