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Highly diastereoselective approach to methylenecyclopropanes *via* boron-homologation/allylboration sequences†

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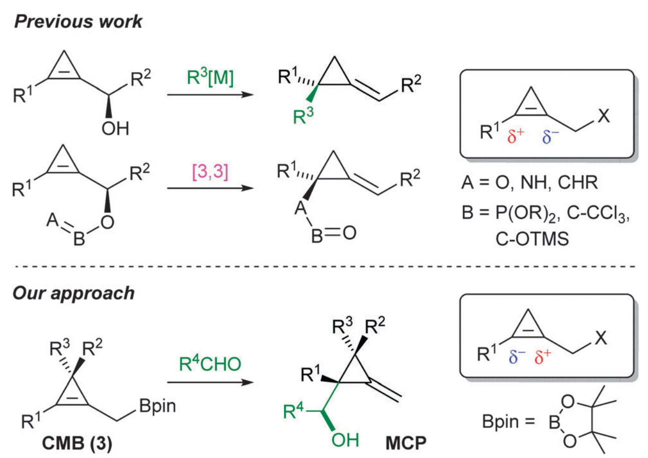
A simple and efficient diastereoselective synthesis of methylenecyclopropanes is described, in which boron-homologation and allylboration are merged into a one-pot process, starting from *in situ* generated cyclopropenyllithium species. This unprecedented methodology opens a new route to strained alkylidenecycloalkanes containing a quaternary stereocenter, in high yields and excellent diastereomeric ratios.

Alkylidenecyclopropanes (ACPs) possess a fascinating reactivity which continues to spark curiosity among the organic chemistry community, as they are candidates for a wide range of transformations.[1] These structures have been recently employed to undergo ring expansion reactions in the presence of Lewis acids,[2] or in acyclic stereocontrol through hydrometallations[3] or zirconium-promoted C–C bond cleavage.[4] Besides, ACPs represent valuable precursors of chiral cyclopropanes,[5] architectures that can be found in a number of biologically active substrates.[6]

Among different diastereoselective routes for their preparation, Marek[7] and Fox[8] independently developed an easy and straightforward access to ACPs by using cyclopropenylcarbinol derivatives in a S_N2' reaction (Scheme 1). Cossy recently demonstrated the potential of secondary cyclopropenylcarbinol to undergo an Ireland–Claisen rearrangement, leading to ACPs by C–C bond formation.[9] [3,3]-Sigmatropic rearrangements have also proven their efficiency in C–O[10] and C–N[11] bond forming reactions, resulting in heterosubstituted ACPs in high diastereoisomeric ratios.

We hypothesized that a thoroughly designed allylic system embedded in the cyclopropyl core could allow for a nucleophilic allylation to proceed. Having recently reported the diastereoselective one-pot synthesis of methylenecyclobutanes using allylboronate derivatives,[12] we envisioned that an easily prepared cyclopropenylmethyl boronic ester (CMB) would undergo the corresponding

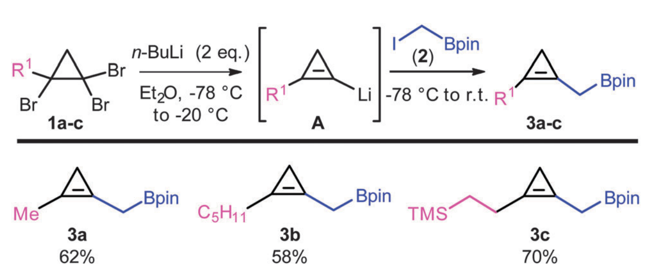


Scheme 1 Synthetic routes towards ACPs.

stereoselective allylboration[13] reaction leading to the formation of challenging methylenecyclopropanes (MCPs) (Scheme 2).

As CMBs (**3**) were identified as key intermediates in this study, their synthesis was undertaken first. Performing a double lithium-bromide permutation on a tribromocyclopropane afforded the intermediate cyclopropenyllithium species **A**.[14] Subsequent addition of iodomethylboronic ester **2** resulted in a boron-homologation reaction[15] through a 1,2-metallate rearrangement, and derivatives **3a–c** were isolated in 58–70%.

With new allylic systems in hands, we investigated allylborations of aldehydes by first using the methyl derivative **3a**. Interestingly, the



Scheme 2 Access to CMBs **3** from corresponding tribromocyclopropanes **1**.

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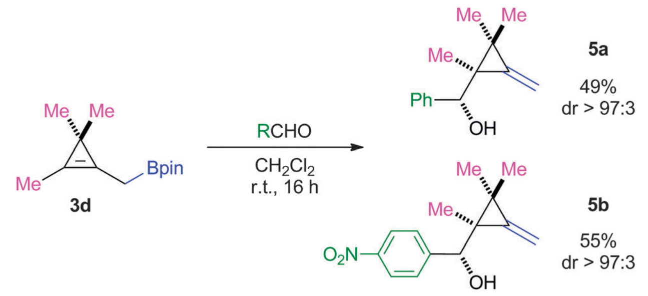
reaction with benzaldehyde was completed within 15 min, leading to the expected methylenecyclopropane **4a** in 76% yield and excellent diastereoselectivity (dr > 97 : 3). Such a fast reaction time can be explained by strain release when displacing the double bond from the *endo* to the *exo* position.[16] As a matter of fact, similar results were obtained for the synthesis of methylenecyclobutanes from cyclobutenylmethyl-boronic esters, with reaction times below 10 min.[12] Reaction with aromatic and heteroaromatic aldehydes furnished the expected products in high yields (up to 89%) and excellent diastereoselectivities in all cases (dr > 97 : 3), as depicted in Scheme 3. Starting from **3a**, methylcyclopropanes **4a–j** were isolated with up to 89%. Slightly lower yields were obtained in cases of pyrrole and indole derivatives (**4g**, 58% and **4e**, 52% respectively). An α,β-unsaturated aldehyde furnished the desired product **4d** in good yield and excellent diastereoisomeric ratio.[17]

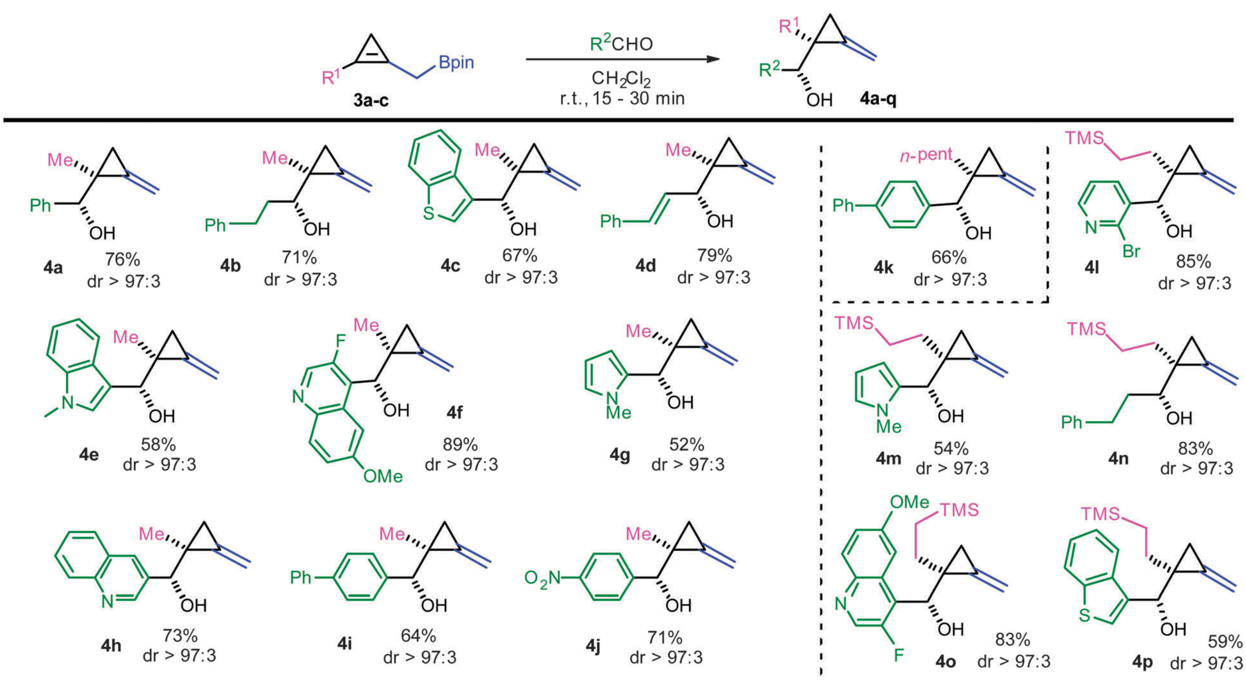
Changing the substituent at the vinylic position of the starting CMB to a pentyl chain (**3b**) did not affect the reactivity of the system nor the stereoselectivity of the allylation, and **4k** was isolated in 66% yield after reaction with biphenylcarboxaldehyde. Allylboration was further performed by employing the silylated substrate **3c**. With similarly high diastereomeric ratios, the introduction of nitrogen- or sulfur-containing heteroaromatic and aliphatic aldehydes resulted in building blocks of higher functionality (**4l–p**) in good to excellent yields (up to 85%) in only 15 min (Scheme 3).

To further expand the scope, CMB **3d** bearing two methyl substituents was synthesized from the corresponding tribromocyclopropane.[14] However, a notable difference of reactivity was observed when comparing to the previous systems **3a–c**, and acceptable levels of starting material conversion were reached only after 16 h at room temperature. Despite comparable strained patterns, the presence of two additional substituents on **3d** must play an undeniable role in lowering the reactivity of the allylic system. Such a sterically hindered moiety could partially inhibit the approach of the aldehyde, consequently increasing the reaction time (Scheme 4).

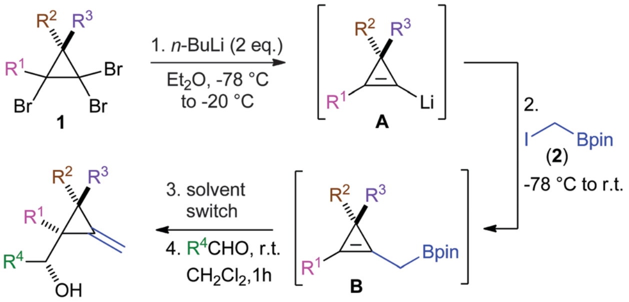


Scheme 4 Allylboration of aldehydes using CMB **3d**.

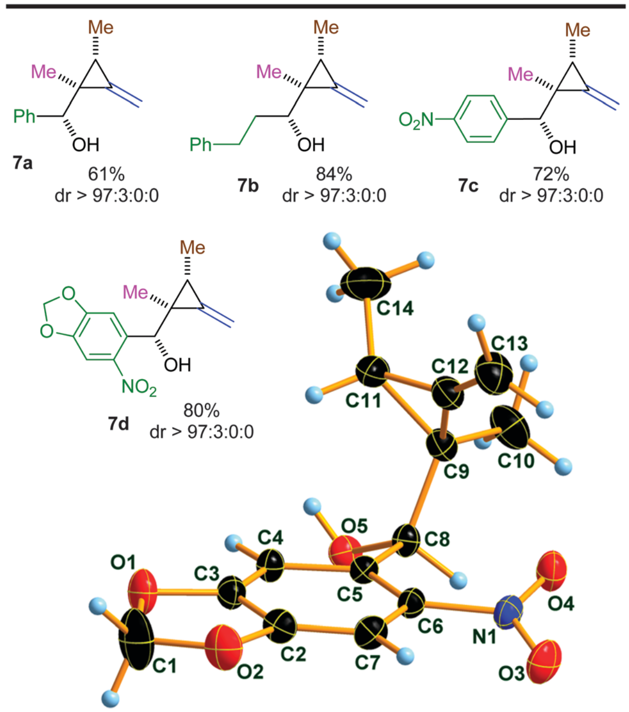
Having successfully demonstrated a new diastereoselective way of accessing MCPs, we took on the challenge of performing all the steps in a one-pot process, starting directly from tribromocyclopropanes **1**. Addition of two equivalents of *n*-butyllithium to **1** leads to the intermediate lithium species **A**. Subsequent addition of **2** triggers a 1,2-metallate rearrangement, furnishing CMB **B**. At this point, changing the solvent of the reaction from THF to dichloromethane was detrimental for the reaction to be completed within 1 hour. THF was found to be competing with the aldehyde for coordination to the boron atom. Finally, the introduction of aldehydes allowed for the allylboration to proceed, leading to MCPs described in Scheme 5. Starting the sequence with **3a** (R^1 = Me, entries 1–3) furnished the expected MCPs **4a**, **4i** and **4j** in good yields, while **3c** furnished **4n** (R^1 = $(CH_2)_2$TMS, entry 4). In these cases, the diastereoisomeric ratios continued to be excellent



Scheme 3 Diastereoselective synthesis of methylenecyclopropanes **4a–p** through allylboration of aldehydes from **3a–c**.



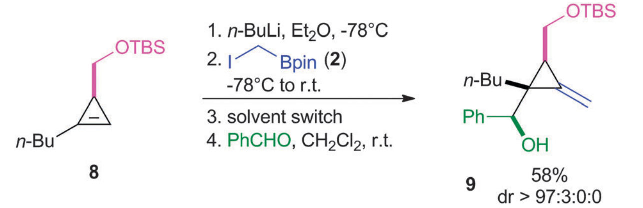
Entry	R^1	R^2	R^3	R^4	product	yield	dr
1	Me	H	H	Ph	**4a**	62%	97:3
2	Me	H	H	p-PhC_6H_4	**4i**	65%	97:3
3	Me	H	H	p-$NO_2C_6H_4$	**4j**	64%	97:3
4	$(CH_2)_2TMS$	H	H	$(CH_2)_2Ph$	**4n**	70%	97:3
5	Me	H	H	2-benzo-thiophenyl	**4q**	75%	55:45



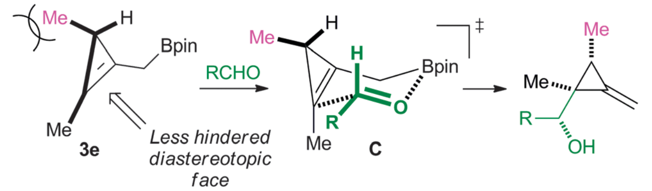
Scheme 5 Three-step-one-pot sequence for the diastereoselective synthesis of MCPs.

and the yields were comparable to the step by step procedure. The use of 2-benzothiophene carboxaldehyde in the sequence involving **3a** (entry 5) resulted in a full conversion, but a drastic drop of diastereoselectivity was observed.[18]

With optimal conditions in hands for the one-pot formation of MCPs, we envisioned that using chiral tribromocyclopropanes (possessing an additional methyl group) could allow for the diastereocontrolled synthesis of MCPs containing three consecutive stereocenters. Aromatic and aliphatic aldehydes furnished expected "all-*syn*" adducts **7a–d** in excellent yields and stereoselectivities (dr up to 97 : 3 : 0 : 0). The relative configuration of afore mentioned MCPs was attributed by analogy with **7d** that could be crystallized and analysed by X-ray diffraction.[19]



Scheme 6 Chiral cyclopropene for the one-pot synthesis of MCP.



Scheme 7 Proposed Zimmerman–Traxler model for allylboration reactions involving CMBs.

Next, we investigated the possibility of starting from a chiral cyclopropene **8** (Scheme 6). In this specific case, the lithium species was simply generated by deprotonation of the three-membered ring in the presence of *n*-BuLi. The subsequent introduction of **2** to undergo a boron-homologation was then followed by the addition of benzaldehyde, after switching the solvent to dichloromethane. Through an allylboration, the homoallylic alcohol **9** was obtained as a single diastereoisomer, in 58% yield.

Interestingly, low temperatures were not required to observe an excellent diastereochemical outcome. We propose to explain this high diastereoselectivity by a pseudo-chair transition state involving a Zimmerman–Traxler model (Scheme 7). The chain of the aldehyde would then preferencially adopt the pseudo-equatorial position.[20] When starting from chiral CMB **3e** possessing a methyl group, one face of the cyclopropenyl derivative is shielded and the aldehyde approaches then from the opposite side, leading to the all-*syn* relative configuration.

In conclusion, we demonstrated the high potential of boron-homologation and allylboration to promote the simple synthesis of MCPs in excellent diastereoisomeric ratios. A wide variety of aldehydes was used in this unprecedented approach, showing the tolerance of the reaction towards sensitive functional groups. Ultimately, a one-pot process was elaborated, in which boron-homologation and allylboration were merged to simplify the procedure, and leading to MCPs containing up to three consecutive stereocenters.

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