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Single-Pot Asymmetric Approach toward Enantioenriched Quaternary Stereocenter-Containing Alkylidenecyclobutanes

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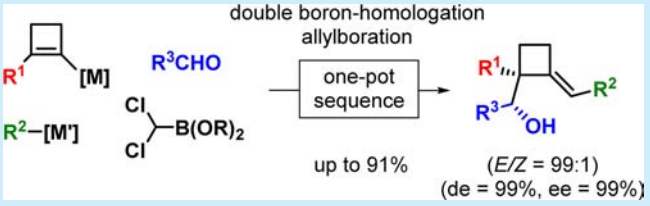
Supporting Information

ABSTRACT: Enantioenriched alkylidenecyclobutanes possessing a quaternary stereogenic center, usually difficult to access, have been synthesized by combining a double boron-homologation and an allylboration through a highly efficient and diastereoselective one-pot process. Starting from commercially available substrates, this protocol represents a simple way of accessing chiral unsaturated four-membered ring systems with excellent stereoisomeric ratios.



Small, unsaturated ring systems have received great interest in organic chemistry due to their fascinating and blossoming panel of reactivity.[1−6] Among them, alkylidenecyclobutanes (ACBs) are important synthons and core patterns that can be found in various natural architectures.[2] Only a few reports relate their accessibility via cycloadditions,[3] rearrangements,[4] or other transition-metal-assisted processes.[5] However, their synthesis is often limited by the lack of efficient and selective methodologies. Possessing a relatively higher ring strain than alkylidenes of larger cycloalkanes, ACBs have been studied for their exceptional reactivity toward the synthesis of substituted cyclopentenes, cyclopentanones, or eight-membered-ring derivatives.[6]

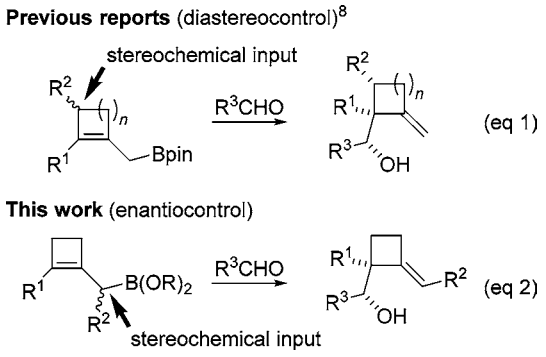
We recently reported a highly diastereoselective sequence to allow for accessing methylenecyclopropanes[7] and -butanes[8] in their racemic forms (Scheme 1), starting from simple substrates or commercially available materials. We wish to report herein efficient one-pot diastereo- and enantioselective sequences for the construction of unsaturated four-membered ring systems containing a quaternary stereocenter (Scheme 1, eq 1).

We based our study on the interesting work of Matteson about boron-homologation and establishments he made on the asymmetric formation of α-chiral boronic esters.[9] While enantiomerically pure diols as ligands for allylboron species usually lead to an incomplete transfer of chirality for allylboration reactions,[10] boron-homologations have proven to furnish α-chiral boronic esters with a perfect control of the new stereocenter.[11] We envisioned combining asymmetric homologations with allylborations to synthesize chiral alkylidenecyclobutanes.

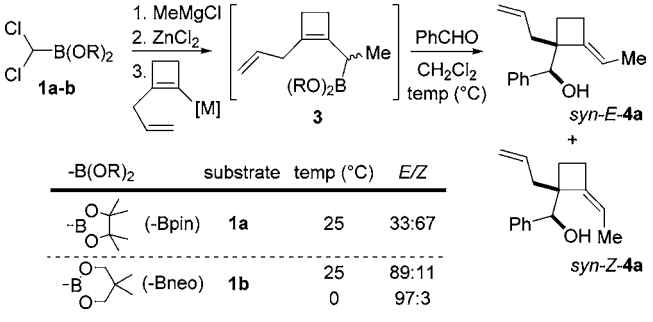
The stereochemical information would then be relayed by the newly generated stereocenter (Schemes 1, eq 2), α to the boronic ester moiety, to the allylic position when preforming the final allylation reaction, controlled by the transition state.

First, we optimized the conditions for the synthesis of racemic alkylidenecyclobutanes, starting from α,α-dichloromethylboronic esters (Scheme 2). One equivalent of nucleophile (MeMgCl) was added to perform the first boron-homologation, in the presence of zinc chloride, followed by the addition of a preformed cyclobutenyl metal species, to allow for the formation of **3**, through a second, in situ, boron homologation. After the solvent was switched to dichloromethane, benzaldehyde was added to allow the allylboration to proceed.

Scheme 1. Access to ACBs via One-Pot Sequences



Scheme 2. Optimization of the One-Pot Sequence



-B(OR)$_2$		substrate	temp (°C)	*E*/*Z*
	(-Bpin)	**1a**	25	33:67
	(-Bneo)	**1b**	25	89:11
			0	97:3

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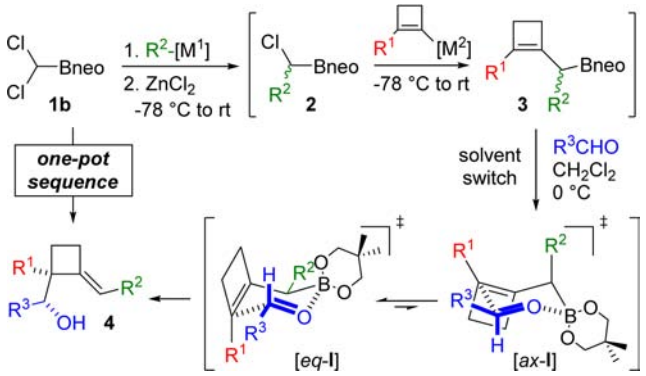
When pinacol was used as a ligand, a mixture of ACBs *syn-E*-**4a** and *syn-Z*-**4a** (33:67, respectively) was obtained. This ratio was further improved to 89:11 (with *syn-E*-**4a** as the major isomer) by employing neopentyl glycol as a ligand. As a matter of fact, it has been previously shown that the *E*/*Z* ratio can easily be changed by modifying the composition of the allylboronate.[12] Lowering the temperature to 0 °C gave the best results in terms of *E*/*Z* ratio (>97:3).

Such a difference in the stereoselectivity can be explained by steric effects of methyl groups in the case of pinacol ligands, hindering the pseudoequatorial position and forcing the R^2 chain to adopt the pseudoaxial position. Less hindered diols (**1b**) (Scheme 3) do not shield the pseudoequatorial position,

Scheme 3. Diastereoselective Approach to ACBs



balancing the equilibrium toward *eq*-**I**, leading to the exclusive formation of (*E*)-**4** derivatives. This same transition state also allows us to explain the diastereoselectivity observed in the allylation reaction for the relative *syn* configuration of the two new stereocenters following the model proposed by Hoffmann,[13] giving *syn*-(*E*)-**4** as the major product.

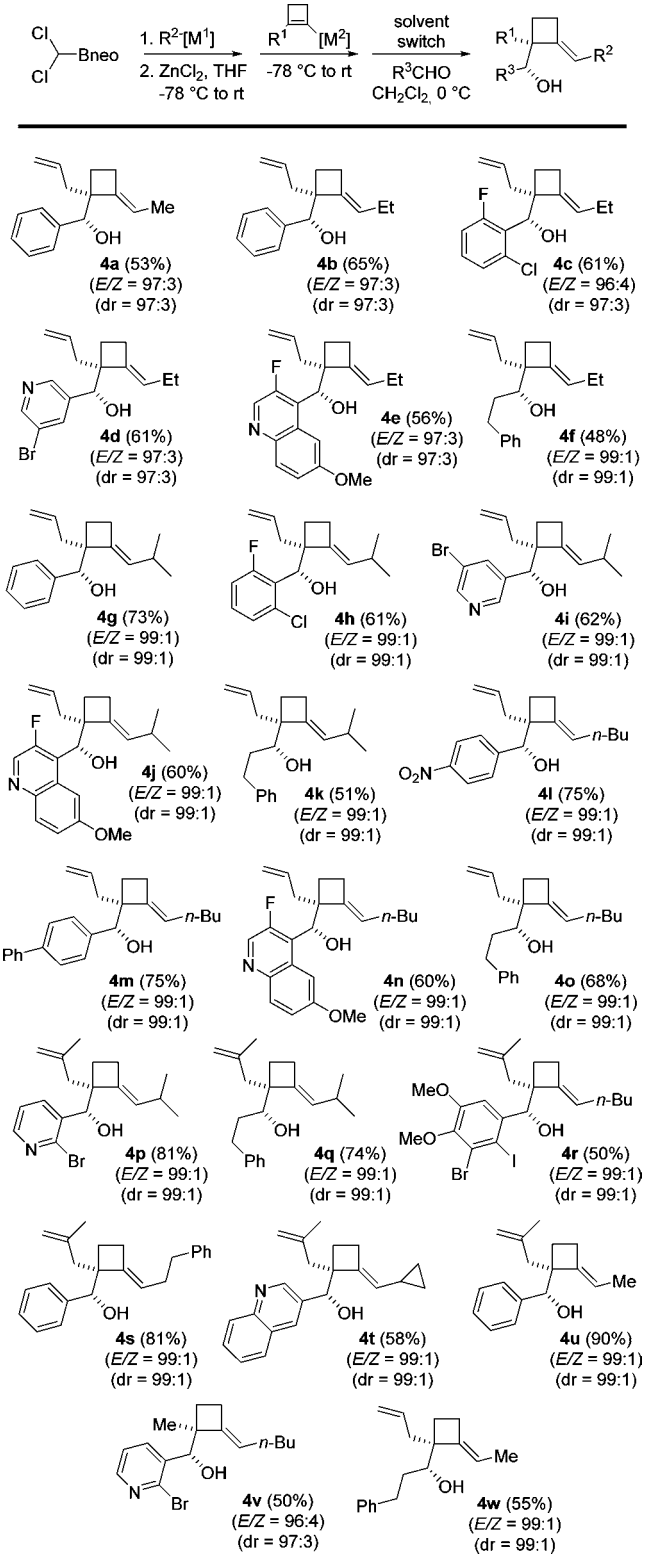
On the strength of this successful experiment, different racemic α-chiral cyclobutenylmethylboronic esters made of neopentyl glycol were generated in situ to explore the synthetic scope of such a methodology for the formation of alkylidenecyclobutanes containing a quaternary stereocenter. The scope of the double-homologation/allylation sequence is depicted in Scheme 4.

Employing various organometallic nucleophiles (R^2-[M^1]) for the first homologation could furnish α-chloro boronic esters **2**, to which was subsequently added the ex situ generated cyclobutenylmetal species, leading to the formation of **3**.

The first boron-homologation was performed by introduction of MeMgCl (**4a,u,w**), EtMgCl (**4b−f**), *i*-PrMgCl (**4g−k** and **4p−q**), *n*-BuLi (**4l−o,r,v**), $PhCH_2CH_2MgBr$ (**4s**) or *c*-PrMgBr (**4t**), affording the respective α-chloroboronic ester. In parallel, cyclobutenylmetal species were generated ex situ by addition of allylzinc bromide (**4a−o**), (2-methylallyl)zinc bromide (**4p−u**), or Me_3Al/Cp_2ZrCl_2 (**4v**) to the commercially available 4-bromobutyne after deprotonation and were subsequently added to **2**, leading to a large panel of chiral cyclobutenylmethylboronic esters **3**. Allylation reactions were then performed, furnishing alkylidene cyclobutanes **4a−v** in exceptionally high levels of diastereoselectivity (dr up to 99:1, *E*/*Z* ratio up to 99:1) (Table 1) and in good to high yields (up to 90%).

In the case of **4u** (90%), the solvent was not switched to dichloromethane and allylation was performed in THF, leading

Scheme 4. Scope of the Method[a]



[a]dr (*syn*/*anti*) and *E*/*Z* ratios were determined by GC and ^{13}C NMR.

to similar results in terms of diastereoselectivity and 83% yield. However, the reaction reached its completion only after 18 h at room temperature, when 30 min was usually necessary for allylation in dichloromethane at 0 °C. We attributed this difference of reactivity to a possible competition of the solvent with the aldehyde in the coordination to the boron atom.

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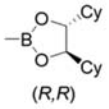
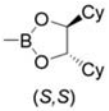
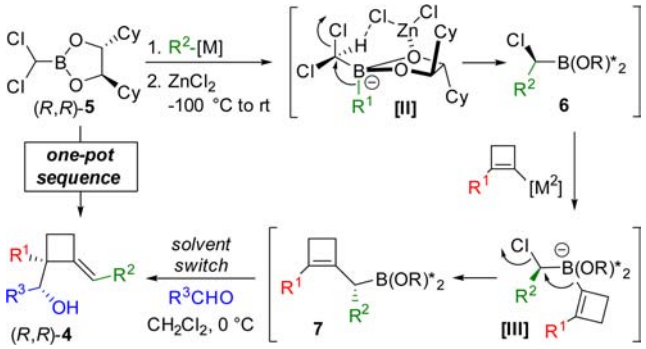
Table 1. Access to ACBs in Their Enantiopure Form

-B(OR)$_2$	product	yield (%)[a]	de (%)[b]	E/Z[b]	ee (%)[c]
 (*R*,*R*)	(+)-**4l**	58	99	99:1	99
	(-)-**4r**	62	99	99:1	99
	(+)-**4q**	58	99	99:1	99
	(-)-**4p**	91	99	99:1	97
 (*S*,*S*)	(-)-**4l**	47	99	99:1	99
	(+)-**4r**	55	99	99:1	99
	(-)-**4q**	79	99	99:1	99
	(+)-**4p**	88	99	99:1	97

[a]Isolated yields. [b]Determined by GC. [c]Determined by HPLC utilizing a chiral stationary phase.

To push the method further, we envisioned that a chiral ligand for the formation of the organoboronic ester would ultimately lead to the formation of enantiomerically enriched ACBs. Pioneered by Matteson, the introduction of 1,2-dicyclohexylethanediols (Cy = cyclohexyl) has proven to efficiently promote a transfer of chirality to the α-position when performing a boron-homologation of an organoboron derivative **5** by addition of a nucleophile R^2-[M] (Scheme 5).[11] (*R*,*R*)-**5** was then submitted to homologation, furnishing the boronate species **II**.

Scheme 5. Substrate-Controlled Synthesis of Enantiopure ACBs

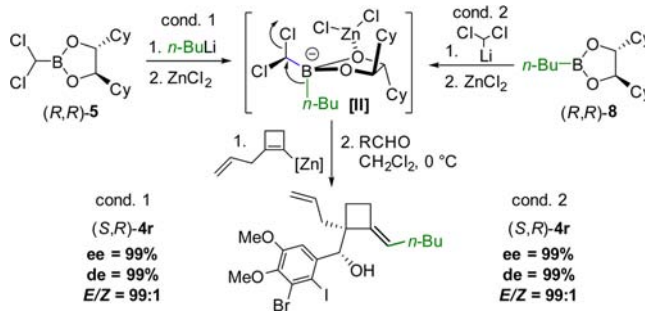


According to the literature, the presence of $ZnCl_2$ is necessary for the stereoselectivity to be maximal. In the proposed model, coordination of $ZnCl_2$ by an oxygen atom of the diol helps the positioning of the dichloromethyl side chain, with one of the diastereotopic chlorides being antiperiplanar to R^1 and the other one away from the salt **II**. Moreover, a H-bonding between a chloride atom ($ZnCl_2$) and the residual H of the dicholoromethyl chain reinforces the diastereoselectivity of the 1,2-metalate rearrangement. A diastereoselective intramolecular substitution takes place, leading to the formation of **6**. A cyclobutenylmetal species was subsequently added, giving stereospecifically the α-chiral allylboronic ester **7**, through the intermediate **III**, in which the substitution occurs antiperiplanary. Finally, allylborations were performed after the solvent was switched to dichloromethane and the appropriate electrophile was added.

As previously proposed, a Zimmermann−Traxler model could explain the diastereoselective formation of ACBs **4**, obtained as their pure enantiomeric forms (ee up to 99%).[14] The results are described in Table 1. Through this highly diastereoselective one-pot process, organoboron derivatives, cyclobutenylmetal species, and aldehydes of different natures could furnish ACBs with excellent diastereo- and enantiomeric ratios (up to >99:1) and good to excellent yields. Ultimately, both enantiomers (*R*,*R*)-**5** and (*S*,*S*)-**5** were used to obtain isomers of **4l**, **4p**, **4q**, and **4r** of opposite absolute configurations.

Importantly, we finally show that starting from either (*R*,*R*)-**5**, possessing the dichloromethyl moiety, or from (*R*,*R*)-**8**, having the *n*-butyl chain preinstalled, followed by addition of dichloromethyllithium led to obtaining (*S*,*R*)-**4r** (after subsequent introduction of the appropriate aldehyde) in comparably high levels of enantio- and diastereoselectivities (ee = 99%, de = 99%). This observation supports the involvement of the intermediate boron−ate complex **II** (Scheme 6) in the diastereoselective 1,2-metalate rearrangement.

Scheme 6. Comparison between (*R*,*R*)-5 and (*R*,*R*)-8 as Substrates for the Sequence Leading to (*S*,*R*)-4r



In conclusion, we have assembled an efficient route for the preparation of ACBs through highly diastereoselective one-pot sequences involving boron-homologation and allylboration strategies. Moreover, a powerful tool involving chiral auxiliaries for rapidly accessing enantiomerically pure ACBs was developed using commercially available starting material.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01432.

Experimental procedures and spectroscopic characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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