Synthetic Methods

International Edition: DOI: 10.1002/anie.201507444
German Edition: DOI: 10.1002/ange.201507444

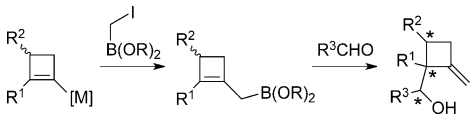
Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies

*Michael Eisold and Dorian Didier**

Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

Abstract: *A highly diastereoselective synthesis of methylenecyclobutanes possessing a quaternary stereocenter is reported, in which boron homologation of an easily-generated cyclobutenylmetal species is performed, followed by an allylation reaction. Combining three steps in a one-pot process further optimized the method, which afforded the expected adducts in excellent yields and stereoselectivity, starting from commercially available 4-bromobutyne.*

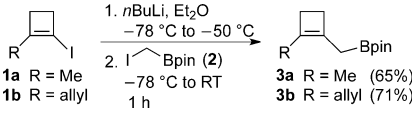
Possessing a unique geometry, alkylidenecyclobutanes (ACBs) are fascinating motifs that are encountered in natural compounds[1] and found as key intermediates in their syntheses.[2] Moreover, ACBs can undergo valuable ring-expansion reactions towards the synthesis of substituted cyclopentanones, cyclopentenes, or eight-membered-ring derivatives.[3] Despite several reports reviewing stereoselective access to substituted cyclobutanes,[4] the chemistry of alkylidenecyclobutanes remains a relatively unexplored and challenging domain among strained systems.[5] Commonly generated through gold(I)-catalyzed [2+2] cycloadditions between an allene and an unsaturated system,[6] ACBs have recently been accessed by other transition-metal-mediated processes.[7] On the other hand, if one could access a cyclobutenylmetal species, boron homologation could lead to in situ formation of the desired methylenecyclobutane (MCB) through a simple allylation reaction (Scheme 1). Following pioneering work by Matteson et al.,[8] Aggarwal et al. showed the high synthetic potential of such a method for the construction of elaborated structures[9] by applying a reagent-controlled asymmetric homologation using Hoppe's carbamates.[10]



Scheme 1. Unprecedented approach to MCBs containing quaternary stereocenters.

We report herein the results of our successful investigation of unprecedented boron allylation reactions based on cyclobutenylmethylboronic esters for the sequential one-pot diastereoselective synthesis of MCBs possessing a quaternary stereocenter.

Cyclobutenylmethylboron derivatives (**3a** and **3b**; Scheme 2) were identified as key units of this study. Since they would directly undergo an allylation reaction in the presence of an electrophile, their synthesis was undertaken first. Performing an iodine–lithium exchange on **1a**[11a] or **1b**[11b] at −50 °C, followed by introduction of the boronic ester **2** led to formation of the desired cyclobutenylmethylboronic esters **3a** and **3b** (65 % and 71 % respectively).



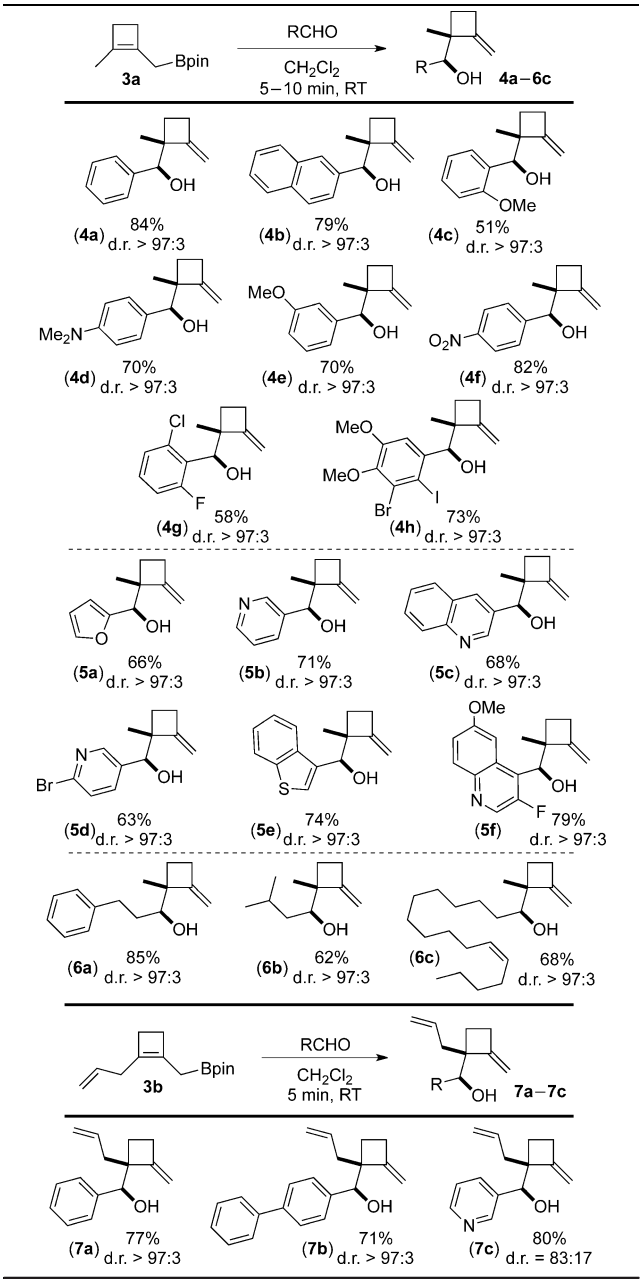
Scheme 2. Synthesis of cyclobutenylmethylboronic esters **3a** and **3b**.

Next, we investigated the allylation reaction of benzaldehyde in the presence of **3a**. The reaction was carried out at room temperature in dichloromethane and completion was reached in less than five minutes. Surprisingly, low-temperature conditions were not required to achieve high levels of diastereoselectivity, and the alkylidenecyclobutane **4a** was isolated in good yield and stereoselectivity (84 %, d.r. > 97:3, Table 1). Aromatic aldehydes possessing an electron-donating group (*o*-OMe, *m*-OMe, *p*-NMe_2) or an electron-withdrawing group (*p*-NO_2) also led to the desired products (**4c**–**4f**) with comparable levels of stereoselectivity. Halogenated aromatic aldehydes also underwent boron allylation to form MCBs **4g** and **4h** in moderate to good yields (58–73 %). Interestingly, heteroaromatic aldehydes also reacted quickly with **3a**, leading to the synthesis of MCBs with greater functionalization. Oxygen-, nitrogen-, and sulfur-containing heterocycles were introduced in the same way, furnishing MCBs **5a**–**5f** in good yields and excellent diastereoselectivity (d.r. > 97:3). To further extend the reaction scope, we employed aliphatic aldehydes: dihydrocinnamal, isovaleraldehyde, and 11-hexadecenal gave products **6a**–**6c** to good yields and excellent diastereoselectivity. However, even using reported methods for the enhancement of allylation reactions, ketones and imines did not lead to the expected products.[12]

[*] M. Eisold, Dr. D. Didier
Department of Chemistry and Pharmacy
Ludwig-Maximilians-University Munich
Butenandtstrasse 5–13, 81377 Munich (Germany)
E-mail: dorian.didier@cup.uni-muenchen.de

Supporting information (experimental procedures and spectroscopic characterization (IR, HRMS, and ^1H and ^{13}C NMR data) of all new compounds) and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201507444.

Table 1: Diastereoselective synthesis of MCBs from **3a**.

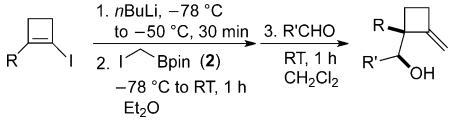


Promising results obtained with **3a** encouraged us to explore the potential and versatility of **3b** in allylation reactions towards the synthesis of more diverse MCBs. Gratifyingly, the reaction with benzaldehyde was complete within five minutes and **7a** was isolated in 77% yield with a high diastereoisomeric ratio (d.r. > 97:3). 4-Biphenylcarboxaldehyde led to similar results (**7b**, 71% yield, d.r. > 97:3). 3-Pyridine-carboxaldehyde afforded the MCB **7c** with a lower diastereoisomeric ratio (d.r. = 83:17).

The relative configuration of MCBs was assigned by analogy with **4f**, which could be crystallized as a single diastereoisomer (d.r. > 99:1 by GC) and analyzed by X-ray diffraction (see the Supporting Information).[13]

We additionally investigated the possibility of merging the different steps of the sequence into a one-pot process to facilitate the production of MCBs from commercially available materials. Cyclobutene iodides **1a** and **1b** were evaluated first. After carrying out lithium–iodine exchange, iodomethylboronic ester **2** was subsequently introduced to perform the boron homologation. Dichloromethane was added to the reaction mixture along with the electrophile (Table 2) to

Table 2: One-pot synthesis of MCBs starting from **1a** and **1b.**



Entry	Substrate	Product	Yield[a]	d.r.[b]
1	**1a**	**4a**	68%	> 97:3
2	**1a**	**5b**	55%	> 97:3
3	**1b**	**7a**	56%	> 97:3

[a] Yield of isolated product. [b] Determined by ^{13}C NMR.

allow the allylation reaction to proceed directly on the in situ generated allylboron intermediate. In these cases, completion of the reaction was only observed after one hour, thus indicating a possible competitive interaction of the coordinative solvent (diethyl ether) with the substrate. Similar results were obtained in terms of diastereoselectivity (d.r. > 97:3), but the yields of isolated product were lower compared to the two-step procedure (Table 1). Addition of benzaldehyde led to **4a** and **7a** (61% and 56%, respectively), and 3-pyridinecarboxaldehyde furnished **5b** in 55% yield.

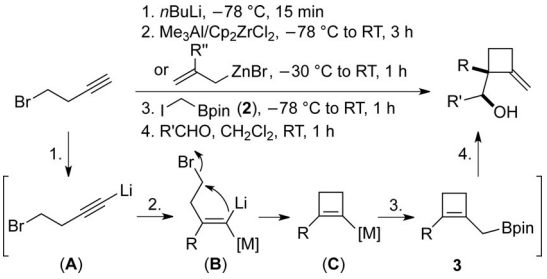
Having successfully performed the two-step, one-pot procedure, we took on the challenge of forming the metalated cyclobutene in situ, starting the sequence directly from commercially available 4-bromobutyne (Table 3).

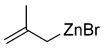
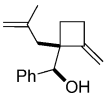
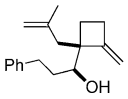
Deprotonation of the alkyne with *n*-butyllithium is followed by a carbometallation reaction (Me_3Al/Cp_2ZrCl_2 or allylzinc bromide), which leads to the formation of *gem*-bimetallic intermediate **B**.[14] Nucleophilic substitution of the bromide takes place at 20°C, giving the desired metalated cyclobutene species of Al or Zn (**C**). The homologation is performed by adding **2** to the reaction mixture to furnish the intermediate **3**. After diluting the solution with dichloromethane, the allylation reaction proceeds after the addition of aldehydes to give the product with high diastereoselectivity (d.r. > 97:3) and in good yields (78 to 85%), which demonstrates the efficiency of this four-step, one-pot sequence. Different allylzinc species were also used to promote the formation of a wider range of compounds (**7a**, **7d** and **7e**) with the same stereoselectivity and in good yields (52 to 72%).

More elaborate chiral substrate were further studied. Iodocyclobutene **8** was synthesized according to Negishi's procedure,[11] from which the chiral cyclobutenylmethylboronic ester **9** (Table 4) was generated in situ through the procedure described above (Table 2).

The addition of aldehydes to achieve the formation of MCBs possessing three consecutive stereocenters, with one

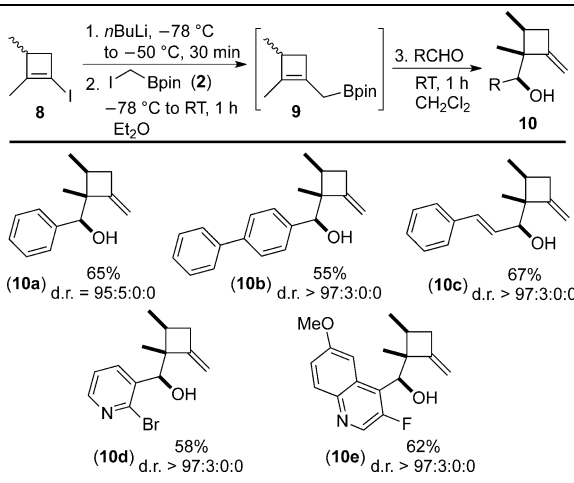
Table 3: One-pot synthesis of MCBs starting from 4-bromo-1-butyne.



Entry	R-[M][a]	Product	Yield[b]	d.r.[c]
1	Me_3Al/[Zr]	**4a**	85%	>97:3
2	Me_3Al/[Zr]	**5b**	78%	>97:3
3	Me_3Al/[Zr]	**6a**	84%	>97:3
4	Allyl-ZnBr	**7a**	52%	>97:3
5		 **7d**	72%	>97:3
6		 **7e**	66%	>97:3

[a] See the Supporting Information. [b] Yield of isolated product. [c] Determined by ^{13}C NMR.

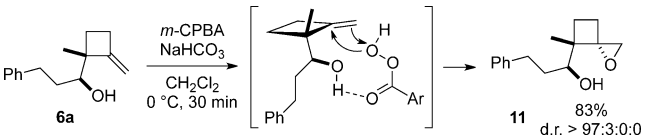
Table 4: One-pot synthesis of MCBs starting from **8**.



being quaternary, was then pursued with the crude mixture after changing the solvent system to dichloromethane. A selection of aldehydes was used, leading to the formation of **10a**–**10e** with high diastereoselectivity and 55–67% yield.

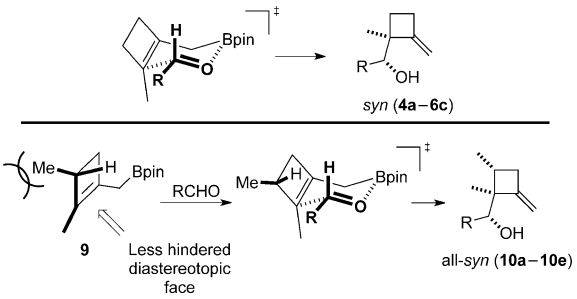
Since allylation reactions could be performed within short periods of time, the specific cyclobutane geometry plays an incontestable role. In fact, only a few boron allylation processes have been described in which tetrasubstituted olefins were used. Up to 24 h and/or the presence of a catalyst were needed to achieve good yields.[15] The particularly good reactivity of our cyclobutenylmethyl boron system could be attributed to strain release when going from cyclobutene to an ACB.[16]

To highlight the synthetic utility of the method, we considered the transformation of **6a** into a substituted 1-oxaspiro[2.3]hexane. The epoxidation of **6a** was performed in the presence of *m*-CPBA to furnish **11**, which possesses three stereocenters, two of which are quaternary, in high yield and diastereoisomeric ratio (Scheme 3).



Scheme 3. Further transformation of MCB into chiral 1-oxaspiro-[2.3]hexane.

A Zimmermann–Traxler transition state is proposed to explain the stereochemical outcome of the allylation reaction (Scheme 4).[17] The chain of the aldehyde preferentially adopts the pseudo-equatorial position, thereby minimizing the energy of the system. In the cases of achiral substrates **3a** and **3b**, the proposed model furnishes a *syn* relative configuration, which correlates with the configuration observed by X-ray diffraction. Concerning the chiral substrate **9**, the attack from one or the other diastereotopic faces has to be considered. We assume that the methyl group shields one of the two faces, thereby orienting the approach of the aldehyde from the opposite face, which leads to formation of the "all-*syn*" MCB based on a Zimmermann–Traxler transition state.



Scheme 4. Zimmerman–Traxler models explain the *syn*-diastereoselectivity in MCBs.

In conclusion, we have reported an unprecedented and straightforward way of approaching methylenecyclobutanes possessing up to three adjacent stereocenters through multistep one-pot sequences, starting from either easily synthesized or commercially available starting materials. Perfect diastereocontrol of the allylation process is achieved under mild conditions, in short periods of time, and without the addition of a catalyst.

Acknowledgments

We thank the Chemical Industry Fund (FCI Liebig-fellowship) for financial support, Prof. Dr. Konstantin Karaghiosoff and Prof. Dr. Paul Knochel for moral support.

Keywords: allylboration · boron homologation · diastereoselectivity · methylenecyclobutanes · one-pot reactions

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15884–15887
Angew. Chem. **2015**, *127*, 16112–16115

[1] a) J. D. White, S. Jana, *Org. Lett.* **2009**, *11*, 1433–1436; b) S. A. Ruider, T. Sandmeier, E. M. Carreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 2378–2382; *Angew. Chem.* **2015**, *127*, 2408–2412; c) M. Kögl, L. Brecker, R. Warrass, J. Mulzer, *Angew. Chem. Int. Ed.* **2007**, *46*, 9320–9322; *Angew. Chem.* **2007**, *119*, 9480–9482.

[2] a) Y. Yang, X. Fu, J. Chen, H. Zhai, *Angew. Chem. Int. Ed.* **2012**, *51*, 9825–9828; *Angew. Chem.* **2012**, *124*, 9963–9966; b) J.-B. Farcet, M. Himmelbauer, J. Mulzer, *Org. Lett.* **2012**, *14*, 2195–2197.

[3] a) P. Boontanonda, R. J. Grigg, *Chem. Soc. Chem. Commun.* **1977**, 583–584; b) Y. Tobe, T. Kishida, T. Yamashita, K. Kakiuchi, Y. Odaira, *Chem. Lett.* **1985**, 1437–1440; c) S. P. Samuel, T.-q. Niu, K. L. Erikson, *J. Am. Chem. Soc.* **1989**, *111*, 1429–1436; d) M. Jiang, M. Shi, *Org. Lett.* **2008**, *10*, 2239–2242; e) D. Crépin, J. Dawick, C. Aïssa, *Angew. Chem. Int. Ed.* **2010**, *49*, 620–623; *Angew. Chem.* **2010**, *122*, 630–633.

[4] a) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052–1103; b) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, *103*, 1449–1483; c) T. Bach, *Synthesis* **1998**, *5*, 685–703; d) M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453–1473.

[5] M. Shi, J.-M. Lu, Y. Wei, L.-X. Shao, *Acc. Chem. Res.* **2012**, *45*, 641–652.

[6] a) S. M. Kim, J. H. Park, Y. K. Kang, Y. K. Chung, *Angew. Chem. Int. Ed.* **2009**, *48*, 4532–4535; *Angew. Chem.* **2009**, *121*, 4602–4605; b) J.-F. Zhao, T.-P. Loh, *Angew. Chem. Int. Ed.* **2009**, *48*, 7232–7235; *Angew. Chem.* **2009**, *121*, 7368–7371; c) S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2012**, *51*, 11552–11555; *Angew. Chem.* **2012**, *124*, 11720–11723; d) H. Faustino, I. Alonso, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.* **2013**, *52*, 6526–6530; *Angew. Chem.* **2013**, *125*, 6654–6658.

[7] a) L. Chen, M. Shi, C. Li, *Org. Lett.* **2008**, *10*, 5285–5288; b) J. P. Markham, S. T. Staben, D. F. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708–9709; c) M. Iwazaki, H. Yorimitsu, K. Oshima, *Synlett* **2009**, *13*, 2177–2179; d) T. Kurahashi, A. de Meijere, *Angew. Chem. Int. Ed.* **2005**, *44*, 7881–7884; *Angew. Chem.* **2005**, *117*, 8093–8096; e) A. Innitzer, L. Brecker, J. Mulzer, *Org. Lett.* **2007**, *9*, 4431–4434; f) T. Fujiwara, N. Iwasaki, T. Takeda, *Chem. Lett.* **1998**, 741–742.

[8] a) D. S. Matteson, R. H. W. Mah, *J. Am. Chem. Soc.* **1963**, *85*, 2599–2603; b) D. S. Matteson, R. Ray, *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.

[9] a) M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183–188; b) S. Roesner, D. J. Blair, V. K. Aggarwal, *Chem. Sci.* **2015**, *6*, 3718–3723.

[10] E. Beckmann, V. Desai, D. Hoppe, *Synlett* **2004**, 2275–2280.

[11] a) L. D. Boardman, V. Bagheri, H. Sawada, E.-i. Negishi, *J. Am. Chem. Soc.* **1984**, *106*, 6105–6107; b) F. Liu, E.-i. Negishi, *Tetrahedron Lett.* **1997**, *38*, 1149–1152.

[12] a) M. Althaus, A. Mahmood, J. R. Suárez, S. P. Thomas, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 4025–4028; b) M. Raducan, R. Alam, K. J. Szabó, *Angew. Chem. Int. Ed.* **2012**, *51*, 13227–13230; *Angew. Chem.* **2012**, *124*, 1305–13053; c) J. L.-Y. Chen, H. K. Scott, M. J. Hesse, C. L. Willis, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 5316–5319; d) J. L.-Y. Chen, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 10992–10996; *Angew. Chem.* **2014**, *126*, 11172–11176.

[13] CCDC 1417504 (**4 f**) contains the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] I. Marek, *Chem. Rev.* **2000**, *100*, 2887–2900.

[15] J. W. J. Kennedy, D. G. Hall, *J. Org. Chem.* **2004**, *69*, 4412–4428.

[16] K. B. Wiberg, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312–322; *Angew. Chem.* **1986**, *98*, 312–322.

[17] a) R. W. Hoffmann, H.-J. Zeiss, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 306–307; *Angew. Chem.* **1979**, *91*, 329–329; b) R. W. Hoffmann, H.-J. Zeiss, *J. Org. Chem.* **1981**, *46*, 1309–1314; c) R. W. Hoffmann, *Pure Appl. Chem.* **1988**, *60*, 123–130; d) R. W. Hoffmann, G. Niel, A. Schlapbach, *Pure Appl. Chem.* **1990**, *62*, 1993–1998.

Received: August 10, 2015
Revised: September 21, 2015
Published online: November 13, 2015

