Synthetic Methods Hot Paper

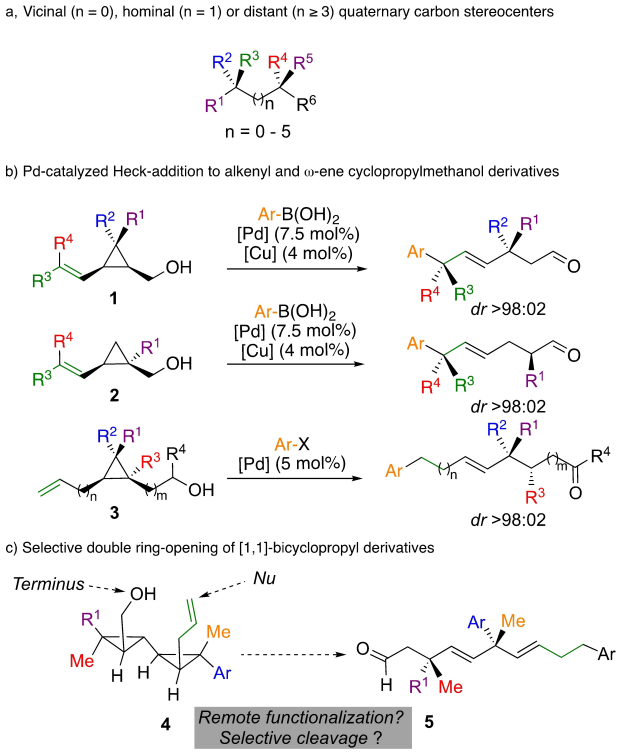
How to cite: *Angew. Chem. Int. Ed.* **2022**, *61*, e202203652
International Edition: doi.org/10.1002/anie.202203652
German Edition: doi.org/10.1002/ange.202203652

Preparation of Distant Quaternary Carbon Stereocenters by Double Selective Ring-Opening of 1,1-Biscyclopropyl Methanol Derivatives

*Yogesh Siddaraju, Juliette Sabbatani, Anthony Cohen, and Ilan Marek**

Abstract: The diastereoselective double carbometalation reaction of cyclopropenes provides, in a single-pot operation, two ω-ene-[1,1]-bicyclopropyl ester derivatives. One regioisomer then undergoes a Pd-catalyzed addition of aryl iodide to provide skipped dienes possessing several distant stereocenters including two congested quaternary carbon centers with excellent diastereoselectivity.

Controlling stereogenic centers in acyclic systems have always been at the heart of organic synthesis.[1] Despite outstanding achievements reported in the past few decades, the creation of several distant and congested stereocenters with a perfect selectivity remains a difficult challenge.[2] In this context, the diastereoselective preparation of vicinal ($n=0$), hominal ($n=1$) or distant ($n\geq2$) stereocenters possessing at least one quaternary carbon stereocenter within acyclic systems is scarce (Scheme 1a),[3] to become rare when two quaternary are concerned.[4] In this context, and based on our expertise for selective cleavage of carbon–carbon bond embedded into a cyclopropyl ring,[5] we have recently described the Pd-catalyzed remote functionalization of different stereodefined polysubstituted alkenyl cyclopropylmethanol derivatives[6] as a new approach to generate vicinal and distant stereocenters with high selectivities (Scheme 1b). For instance, alkenyl cyclopropyl carbinol **1** led to the formation of two distant (1,4) quaternary stereocenters[6] whereas the same reaction applied to alkenyl cyclopropylmethanol **2** provided 1,5-distant stereocenters (Scheme 1b).[7] Alternatively, the double bond triggering the entire process can be remote as in **3** and different molecular scaffolds are obtained possessing now adjacent stereocenters.[8] An alternative and hypothetically interesting approach to reveal distant stereocenters would be the control of the selectivity for the ring opening of two adjacent cyclopropyl units (Scheme 1c). We were thus wondering if

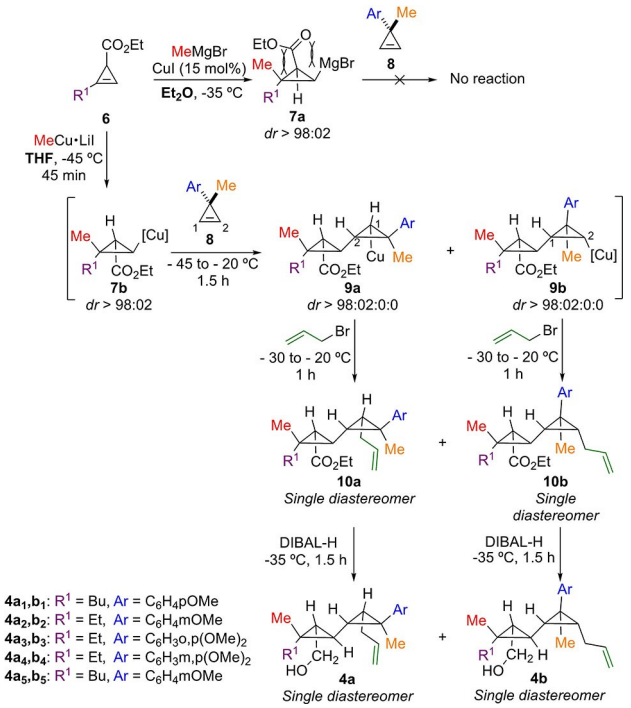


Scheme 1. Preparation of vicinal, hominal and distant stereocenters.

polysubstituted ω-alkenyl-[1,1]-bicyclopropyl methanol **4** could potentially serve as a new starting material for an initial remote functionalization triggering a selective double ring-opening of the two adjacent three-membered rings (Scheme 1).[9] Although the proposed strategy is synthetically appealing as a convergent approach to potentially prepare skipped dienes possessing distant (1,4) quaternary carbon stereocenters within acyclic systems (i.e., **4** into **5**), an easy and efficient initial preparation of the desired starting materials **4** as a single diastereomer was required.

At the outset, we were aware that the convergent preparation of highly substituted alkenyl-[1,1]-bicyclopropyl methanol derivative **4** as single diastereomer might pose a synthetic challenge, we were nevertheless hoping that the various strategies of functionalization of cyclopropenes,[10] previously developed in our research group, could bring a straightforward solution to this problem. We therefore initially focused our attention to the diastereoselective and convergent preparation of the molecular scaffold **4** from simple cyclopropenyl ester **6** (Scheme 2). The latter was easily accessible through a rhodium-catalyzed decomposi-

[*] Dr. Y. Siddaraju, Dr. J. Sabbatani, A. Cohen, Prof. Dr. I. Marek
Schulich Faculty of Chemistry, Technion—Israel Institute of Technology
Technion City, 3200009 Haifa (Israel)
E-mail: chilanm@technion.ac.il



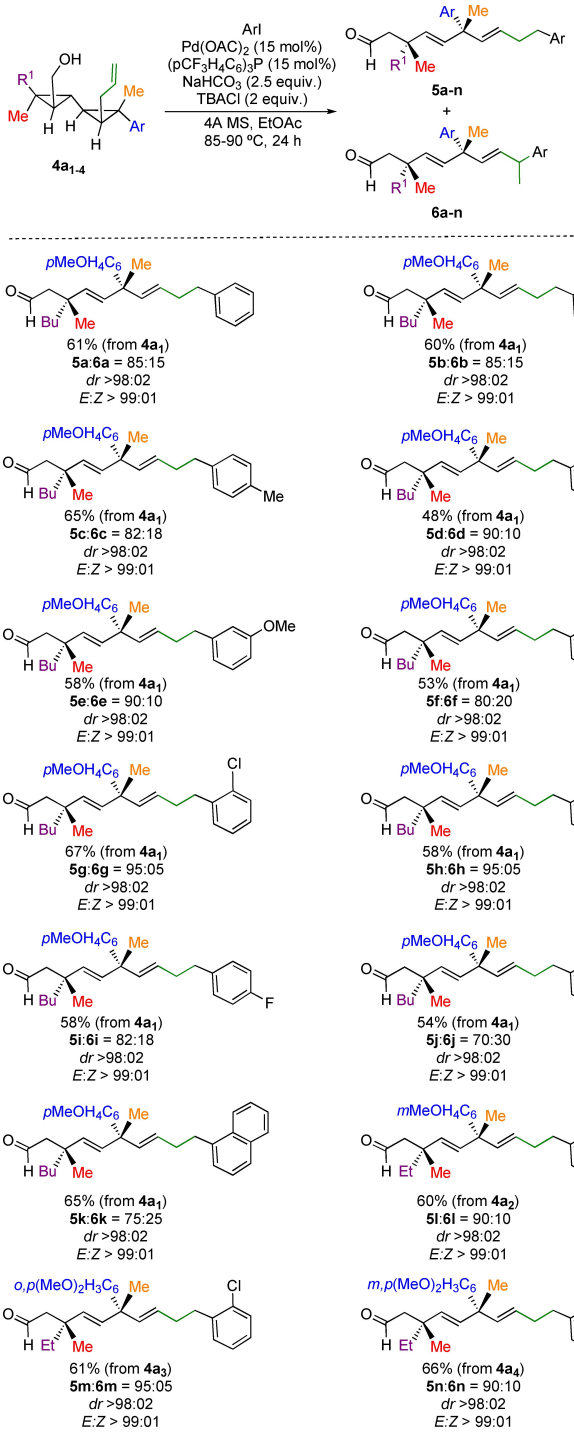
Scheme 2. One-pot preparation of ω-alkenyl-[1,1]-bicyclopropyl methanol derivative **4a,b$_{1-5}$**.

tion of diazoester promoting a [2+1] cycloaddition with an alkyne.[11] Although our initial *syn*-chelated copper-catalyzed carbomagnesiation reaction of **6** in Et_2O provided the expected carbometallated product **7a** in excellent diastereomeric ratio,[10a–c,12] all our attempts to react it with a second and non sp^2-substituted cyclopropenyl ring (i.e., **8**) failed (Scheme 2). It rapidly appeared that the high internal torsional strain due to all eclipsed bonds in **7a** was drastically reducing its reactivity towards external electrophiles.[13] However, the *anti*-directed carbocupration of cyclopropenyl ester **6**, successfully performed in THF at low temperature,[12] provided cyclopropyl copper intermediate **7b** as a single diastereomer and in good yield (as determined by NMR analysis of hydrolyzed aliquots, Scheme 2). As the carbon–metal bond in **7b** is less sterically hindered than in **7a**, the addition of a second cyclopropene **8** led to an equimolar mixture of the two regioisomers of [1,1]-bicyclopropyl copper species **9a** and **9b**. The formation of these two regioisomers result from the non-regioselective addition reaction of **7b** to either the C_1–C_2 or C_2–C_1 carbons of **8**.

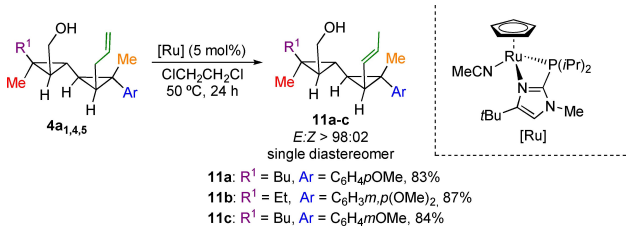
However, in all cases, a single *syn*-addition of **7** to the same face of the Me-substituent was detected (again as determined by analysis of the hydrolyzed products).[13] After trapping with allyl bromide, **10a** and **10b** were obtained in 25% yield from the starting cyclopropenyl ester **6**, as a single diastereomer in both cases. A simple reduction of the ester with DIBAL-H provides the two regioisomers **4a** and **4b**, easily separable by column chromatography on silica gel, as single diastereomer in each case (Scheme 2).[14] Although this strategy provides the two regioisomers **4a** and **4b** in moderate yields, the efficiency of this single-pot operation coupled with the excellent diastereoselectivity of the process and the easy purification of the required final isomer **4a** revealed to be very attractive for our study. The particular design of the proposed substituted alkenyl-[1,1]-bicyclopropyl methanol **4a** was based on our recent experimental and theoretical finding on the required close proximity between the alcohol and the double bond, necessary for the subsequent reaction to proceed.[15] For the isomer **4b**, this proximity is not existing anymore and should therefore not be reactive under our experimental conditions.

Having in hand a rapid access to **4a$_{1-5}$**, we turned our attention to the Pd-catalyzed Heck reactions[16] that have been previously reported to trigger an efficient migration of organometallic species over the hydrocarbon chain[17] with selective ring-opening of one cyclopropyl ring.[6–8] When the sequence was performed on our model substrate **4$_{a1}$**, under slightly modified Larock experimental conditions,[8,16c] we were pleased to observe the formation of the expected addition product **5a** in good yield as unique diastereomer accompanied by its Heck regioisomer **6a** as minor product.[18] The ratio for the two regioisomers of the Heck addition products (**5** versus **6**) depends mainly on the nature of the Ar–I engaged in the addition reaction, strictly following literature precedent.[18] It is however, important to note that both isomers undergo the β-hydride elimination and re-addition to trigger the chain-walking and highly selective double-ring-opening of the 1,1-biscyclopropyl ring towards the terminus position to lead to **5a** and **6a** (only **5a** are represented in Scheme 3). It should also be noticed that the presence of the methoxy groups on the aryl moiety of **4a$_{1-5}$** are only for the ease of purification by column chromatography but are not mandatory for the reaction to proceed. No other positional alkene isomers could be detected suggesting that not only the final product was at no risk of further olefin isomerization but also that the chain-walking process was exclusively triggered by the initial Heck arylation. To our delight, this transformation was compatible with the presence of functional groups on the aryl moiety of Ar–I such as halides (**5g–5i** and **5l–n**), electron-donating group (**5b,c** and **5f**) and electron-withdrawing group (**5j**). The substitution pattern on the quaternary stereocenter (R^1 and R^2) are also easily modified through our previously described flexible approach for the synthesis of such ω-alkenyl-[1,1]-bicyclopropyl. As expected from the respective position of the alcohol moiety and the terminus alkene in crowded system,[15] the isomers **4b$_{1-5}$** could not undergo the alcohol directed Pd-catalyzed addition and remain untouched under this experimental condition. This approach provides an interesting approach to the synthesis of pure (*E*,*E*)-skipped dienyl motif possessing two distant (1,4)-quaternary stereocenters and an aldehyde functionality as a single diastereomer. The stereochemistry was proposed based on X-ray analysis and theoretical calculation of reaction mechanism from previous reports.[8,15]

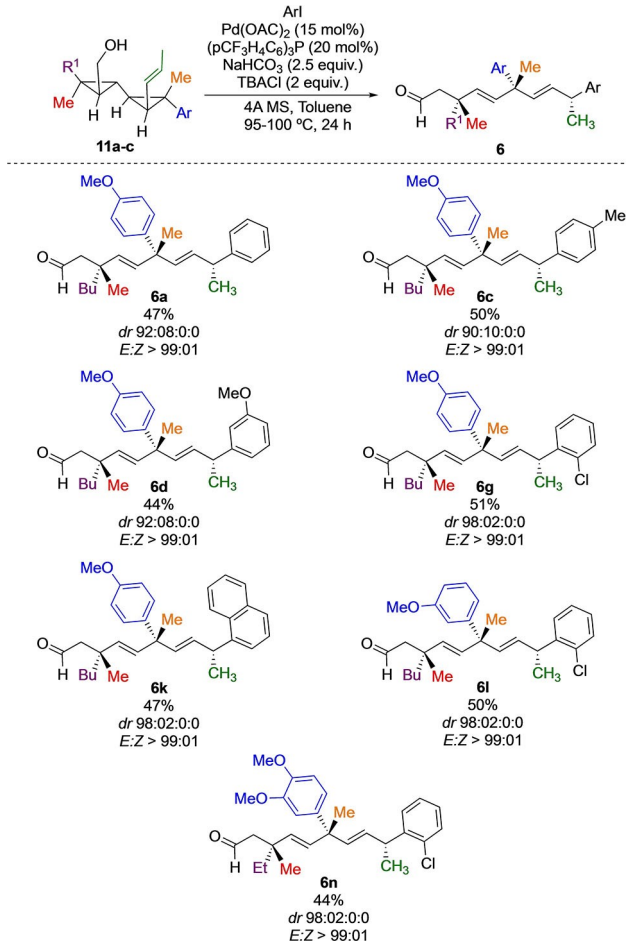
To further increase the complexity of the formed acyclic products, we also envisaged to investigate the Pd-catalyzed addition to ArI to internal alkenyl-[1,1]-bicyclopropyl methanol derivatives **11a-c**, easily accessible from **4a$_{1,4,5}$**, by the



Scheme 3. Selective remote functionalization and double ring-opening.



Scheme 4. Ru-catalyzed isomerization of ω-alkenyl- into (*E*)-propenyl-[1,1]-bicyclopropyl methanol derivatives **11a–c**.



Scheme 5. Pd-catalyzed Heck coupling of ArI with (*E*)-alkenyl-[1,1]-bicyclopropyl methanol.

well-developed Ru-catalyzed isomerization reactions (Scheme 4).[19] A single *E*-geometrical isomer was obtained in all cases.

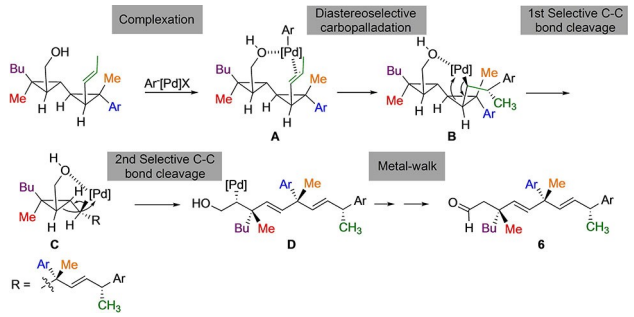
We then investigated the reactivity of **11a–c** in the Heck-type arylation reactions[16c] and aryl iodides could be coupled to **11a–c** to provide aldehydes **6** with excellent selectivities (Scheme 5). Indeed, applying these catalytic conditions to our model substrate (*E*)-**11a** with PhI, the corresponding skipped diene **6a**, possessing three distant stereocenters including two quaternary carbon stereocenters was obtained in a moderate 47 % yield as a single (*E,E*)-isomer (>99:01) and excellent diastereomeric ratio (*dr* 92:08:0:0). The same trend was found for the addition of various substituted aryl iodides and in all cases, the diastereomeric ratios as well as the stereochemistry of the two double bonds were excellent (**6**, Scheme 5). Here again, the nature of the substituents present on the aryl moiety could be varied and, in all cases, very high diastereoslectivities were observed.

Based on our previous studies on the diastereoselective Heck-addition,[6,15] we proposed that the aryl palladium complex[20] first interact with the alcohol and the alkene (formation of **A**, Scheme 6). From the two possible diastereotopic faces of the propenyl chain that could complex the palladium, only the one resulting from the *s-trans* conformer[15] should have a favorable interaction as it generates less steric hindrance with the remaining molecular backbone. After a diastereoselective aryl-addition, the first stereogenic center in **B** is created and the configurationally stable palladium species undergoes its first selective carbon-carbon bond cleavage to provide **C**. A subsequent second selective ring-opening occurs to provide **D** and, after a sequence of β-elimination and re-insertion of palladium hydride, the skipped diene **6** is finally obtained with three, including two distant quaternary, stereogenic centers within an acyclic system.

In conclusion, the diastereoselective double carbometallation reaction of cyclopropenes provides, in a single-pot operation, two ω-ene-[1,1]-bicyclopropyl ester derivatives **10**. Although this transformation provides the two regioisomers, the simplicity, ease and efficiency of the preparation counterbalance the lack of regioselectivity and provide the desired starting materials, each one as a unique diastereomer. The regioisomer **4a**, possessing the alcohol and the double bond in a close proximity then undergoes the Pd-catalyzed addition of aryl iodide to provide **5** with excellent diastereoselectivity for the creation of the two distant quaternary carbon stereocenters. The simple Ru-catalyzed isomerization of the remote double bond gives the *E*-propenyl-[1,1]-bicyclopropyl methanol. Under the same experimental conditions, the reaction now leads to the formation of **6** with an additional distant stereocenters. This simple strategy allows the formation of skipped dienes possessing several distant and congested stereocenters with exquisite selectivities.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation program under Grant Agreement No. 786976 and from the Israel Science Foundation administrated by the Israel Academy of Sciences and Humanities (Grant No. 487/21).



Scheme 6. Mechanistic hypothesis for the selective preparation of skipped diene **6**.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Bicyclopropyl Methanol · Carbometallalation · Cyclopropenes · Heck Addition · Quaternary Carbon Stereocenters

[1] E. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weiheim, **2009**.
[2] D. Pierrot, I. Marek, *Angew. Chem. Int. Ed.* **2020**, *59*, 36–49; *Angew. Chem.* **2020**, *132*, 36–49.
[3] For recent reports, see: a) W.-B. Liu, C. M. Reeves, S. C. Virgil, B. M. Stolz, *J. Am. Chem. Soc.* **2013**, *135*, 10626–10629; b) W.-B. Liu, C. M. Reeves, B. M. Stolz, *J. Am. Chem. Soc.* **2013**, *135*, 17298–17301; c) P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2010**, *132*, 10686–10688; d) M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 7092–7100; e) J. Liu, Z. Han, X. Wang, F. Meng, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2017**, *56*, 5050–5054; *Angew. Chem.* **2017**, *129*, 5132–5136; f) S. Krautwald, D. Sarlah, M. A. Schafroth, E. M. Carreira, *Science* **2013**, *340*, 1065–1068; g) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317; h) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; *Angew. Chem.* **2005**, *117*, 107–110; i) Kaldre, I. Klose, N. Maulide, *Science* **2018**, *361*, 664–667; j) D. Grassi, A. Alexakis, *Chem. Sci.* **2014**, *5*, 3803–3807; k) M. Cormier, A. de la Torre, I. Marek, *Angew. Chem. Int. Ed.* **2018**, *57*, 13237–13241; *Angew. Chem.* **2018**, *130*, 13421–13425; l) R. Suresh, I. Massad, I. Marek, *Chem. Sci.* **2021**, *12*, 9328–9332; m) I. Massad, I. Marek, *Angew. Chem. Int. Ed.* **2021**, *60*, 18509–18513; *Angew. Chem.* **2021**, *133*, 18657–18661; n) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. P. Das, *J. Am. Chem. Soc.* **2014**, *136*, 2682–2694.
[4] a) C. G. Watson, A. Balanta, T. G. Elford, S. Essafi, J. N. Harvey, V. K. Aggarwal, *J. Am. Chem. Soc.* **2014**, *136*, 17370–17373; b) Y.-C. Qin, C. E. Stivala, A. Zakarian, *Angew. Chem. Int. Ed.* **2007**, *46*, 7466–7469; *Angew. Chem.* **2007**, *119*, 7610–7613; c) D. Pierrot, I. Marek, *Angew. Chem. Int. Ed.* **2020**, *59*, 20434–20438; *Angew. Chem.* **2020**, *132*, 20614–20618.
[5] Y. Cohen, A. Cohen, I. Marek, *Chem. Rev.* **2021**, *121*, 140–161.
[6] J. Bruffaerts, D. Pierrot, I. Marek, *Nat. Chem.* **2018**, *10*, 1164–1170.
[7] A. Cohen, J. Chagneau, I. Marek, *ACS Catal.* **2020**, *10*, 7154–7161.
[8] S. Singh, J. Bruffaerts, A. Vasseur, I. Marek, *Nat. Commun.* **2017**, *8*, 14200.
[9] J. Bruffaerts, A. Vasseur, S. Singh, A. Masarwa, D. Didier, L. Oskar, L. Perrin, O. Eisenstein, I. Marek, *J. Org. Chem.* **2018**, *83*, 3497–3515.

[10] a) Y. Cohen, I. Marek, *Angew. Chem. Int. Ed.* **2021**, *60*, 26368–26372; *Angew. Chem.* **2021**, *133*, 26572–26576; b) Y. Cohen, A. Augustin, L. Levy, P. G. Jones, D. Werz, I. Marek, *Angew. Chem. Int. Ed.* **2021**, *60*, 11804–11808; *Angew. Chem.* **2021**, *133*, 11910–11914; c) Y. Cohen, I. Marek, *Org. Lett.* **2019**, *21*, 9162–9165; d) H. Sommer, I. Marek, *Chem. Sci.* **2018**, *9*, 6503–6508; e) L. Dian, I. Marek, *Angew. Chem. Int. Ed.* **2018**, *57*, 3682–3686; *Angew. Chem.* **2018**, *130*, 3744–3748; f) M. Simaan, I. Marek, *Angew. Chem. Int. Ed.* **2018**, *57*, 1543–1546; *Angew. Chem.* **2018**, *130*, 1559–1562; g) L. Dian, D. Müller, I. Marek, *Angew. Chem. Int. Ed.* **2017**, *56*, 6783–6787; *Angew. Chem.* **2017**, *129*, 6887–6891; h) D. Müller, I. Marek, *J. Am. Chem. Soc.* **2015**, *137*, 15414–15417.

[11] Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawryluk, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8916–8918.

[12] S. R. Roy, D. Didier, A. Kleiner, I. Marek, *Chem. Sci.* **2016**, *7*, 5989–5994.

[13] L. Dian, I. Marek, *Chem. Rev.* **2018**, *118*, 8415–8434.

[14] For previous reports for the preparation of less substituted 1,1-biscyclopropyl methanol derivatives on dienols using Simmons–Smith reactions, see: a) A. G. M. Barrett, W. W. Doubleday, G. J. Tustin, *Tetrahedron* **1996**, *52*, 15325–15338; b) W. S. McDonald, C. A. Verbicky, C. K. Zercher, *J. Org. Chem.* **1997**, *62*, 1215–1222; c) A. B. Charette, H. Lebel, *J. Am. Chem. Soc.* **1996**, *118*, 10327–10328; d) A. G. M. Barrett, K. Kasdorf, *J. Am. Chem. Soc.* **1996**, *118*, 11030–11037.

[15] A. Cohen, A. Kaushansky, I. Marek, *JACS Au* **2022**, *2*, 687–696.

[16] a) J. B. Melpolder, R. F. Heck, *J. Org. Chem.* **1976**, *41*, 265–272; b) A. J. Chalk, S. A. Magennis, *J. Org. Chem.* **1976**, *41*, 273–278; c) R. C. Larock, W.-Y. Leung, S. Stoltz-Dunn, *Tetrahedron Lett.* **1989**, *30*, 6629–6632; d) T. S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, *508*, 340–344; e) T. S. Mei, E. W. Werner, A. J. Burckle, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 6830–6833; f) Z. M. Chen, M. J. Hilton, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 11461–11464; g) L. Xu, M. J. Hilton, X. Zhang, P. O. Norrby, Y. D. Wu, M. S. Sigman, O. Wiest, *J. Am. Chem. Soc.* **2014**, *136*, 1960–1967; h) H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 3462–3465; i) L. Mantilli, D. Gerard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, *48*, 5143–5147; *Angew. Chem.* **2009**, *121*, 5245–5249; j) L. Mantilli, D. Gerard, S. Torche, C. Besnard, C. Mazet, *Chem. Eur. J.* **2010**, *16*, 12736–12745; k) H. Li, C. Mazet, *Acc. Chem. Res.* **2016**, *49*, 1232–1241; l) L. Lin, C. Romano, C. Mazet, *J. Am. Chem. Soc.* **2016**, *138*, 10344–10350; m) E. Larionov, L. Lin, L. Guenee, C. Mazet, *J. Am. Chem. Soc.* **2014**, *136*, 16882–16894; n) T. Kochi, S. Kanno, F. Kakiuchi, *Tetrahedron Lett.* **2019**, *60*, 150938; o) T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi, *J. Am. Chem. Soc.* **2012**, *134*, 16544–16547; p) T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi, T. Kochi, *J. Am. Chem. Soc.* **2015**, *137*, 16163–16171; q) S. Aspin, A. S. Goutierre, P. Larini, R. Jazzar, O. Baudoin, *Angew. Chem. Int. Ed.* **2012**, *51*, 10808–10811; *Angew. Chem.* **2012**, *124*, 10966–10969; r) S. Dupuy, K.-F. Zhang, A.-S. Goutierre, O. Baudoin, *Angew. Chem. Int. Ed.* **2016**, *55*, 14793–14797; *Angew. Chem.* **2016**, *128*, 15013–15017.

[17] For reviews on alkene isomerizations, see: a) E. Larionov, H. Li, C. Mazet, *Chem. Commun.* **2014**, *50*, 9816–9826; b) J. Bruffaerts, D. Pierrot, I. Marek, *Org. Biomol. Chem.* **2016**, *14*, 10325–10330; c) J. J. Molloy, T. Morack, R. Gilmour, *Angew. Chem. Int. Ed.* **2019**, *58*, 13654–13664; *Angew. Chem.* **2019**, *131*, 13789–13800; d) I. Massad, I. Marek, *ACS Catal.* **2020**, *10*, 5793–5804; e) D. Janssen-Müller, B. Sahoo, S. Z. Sun, R. Martin, *Isr. J. Chem.* **2020**, *60*, 195–206; f) D. Fiorito, S. Scaringi, C. Mazet, *Chem. Soc. Rev.* **2021**, *50*, 1391–1406.

[18] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[19] a) D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 9592–9593; b) J. Tao, F. Sun, F. T. Fang, *J. Organomet. Chem.* **2012**, *698*, 1–6; c) C. R. Larsen, D. B. Grotjahn, *J. Am. Chem. Soc.* **2012**, *134*, 10357–10360; d) G. Erdogan, D. B. Grotjahn, *Org. Lett.* **2014**, *16*, 2818–2821; e) C. R. Larsen, E. R. Paulson, G. Erdogan, D. B. Grotjahn, *Synlett* **2015**, *26*, 2462–2466; f) C. R. Larsen, G. Erdogan, D. B. Grotjahn, *J. Am. Chem. Soc.* **2014**, *136*, 1226–1229; g) E. R. Paulson, C. E. Moore, A. L. Rheingold, D. P. Pullman, R. W. Sindewald, A. L. Cooksy, D. B. Grotjahn, *ACS Catal.* **2019**, *9*, 7217–7231.

[20] a) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321; b) M. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559–1563.

Manuscript received: March 10, 2022
Accepted manuscript online: May 6, 2022
Version of record online: May 20, 2022