JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

# Use of Strain-Release for the Diastereoselective Construction of Quaternary Carbon Centers

Tobias Pinkert, Mowpriya Das, Malte L. Schrader, and Frank Glorius*

Cite This: J. Am. Chem. Soc. 2021, 143, 7648−7654
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Herein, we describe the formation of quaternary carbon centers with excellent diastereoselectivity via a strain-release protocol. An organometallic species is generated by Cp*Rh(III)-catalyzed C−H activation, which is then coupled with strained bicyclobutanes (BCBs) and a prochiral carbon electrophile in a three-component reaction. This work illustrates a rare example of BCBs in transition metal catalysis and demonstrates their broad potential to access novel reaction pathways. The method developed exhibits ample functional group tolerance, and the products can be further transformed into valuable $\alpha$-quaternary $\beta$-lactones. Preliminary mechanistic investigations suggest a twofold C−C bond cleavage sequence involving $\sigma$-bond insertion and an ensuing $\beta$-carbon elimination event.

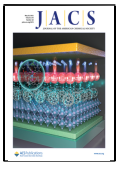


During the past decades strain-release driven transformations have gathered significant attention in synthetic organic chemistry,[1,2] materials science,[3] and bioconjugation.[4] Accordingly, molecules that bear a bridging bond between opposite carbon or nitrogen atoms such as [1.1.1]propellane, bicyclo[1.1.0]butanes (BCBs), or 1-azabicyclo[1.1.0]butanes have emerged as a privileged class of compounds.[5] Owing to their relative destabilization, arising from bond length and bond angle distortions, torsional strain, and nonbonded as well as transannular steric interactions,[6] these "spring-loaded"[7] compounds display $\pi$-bond-type behavior towards nucleophiles, electrophiles, and radicals.[5] Such versatile reactivity is especially desirable in the field of medicinal chemistry where they are commonly used to install the bicyclo[1.1.1]pentane, cyclobutane, and azetidine moieties, motifs which serve as bioisosteres in the development and modification of pharmaceuticals.[8]

Since Baran's fundamental work on C−N bond formation by a strain-release approach,[9] chemists' interest in utilizing the unique properties of these molecules has been renewed.[10,11] In 2019, the group of Aggarwal expanded the toolbox of BCB chemistry by carbopalladation of the central C−C $\sigma$-bond of BCB boronate complexes triggered by a 1,2-metalate rearrangement (Figure 1a). Subsequent cross-coupling gave access to valuable difunctionalized cyclobutyl boronates.[12] To overcome the inherent electrophilic reactivity of electron-deficient BCBs, Gryko and co-workers reported a formal polarity-reversal approach. Co(I)-catalysis allowed the generation of nucleophilic radicals upon light-induced homolysis of the intermediate Co(III)−alkyl species. These radicals could be coupled with electrophiles to afford disubstituted cyclobutanes (Figure 1b).[13] Besides these inspiring examples, transition metal catalyzed transformations involving BCBs remain scarce.[14] Wipf and co-workers hinted at the various mechanistic pathways of reactions of BCBs that might be enabled by the application of transition metal catalysis. They showed that nitrogen-tethered BCBs could undergo a Rh(I)-catalyzed cycloisomerization-cyclopropanation sequence that resulted in the formation of pyrrolidines and azepines (Figure 1c).[15] The development of novel metal catalyzed methodologies and exploration of further reaction pathways of BCBs is therefore highly desirable.[5g,15c] In order to expand the library of known reactivity, we envisioned the reaction of an organometallic species with a BCB and identified C−H activation as a suitable strategy, since it enables the mild generation of these intermediates from ubiquitous C−H bonds that are known to engage a multitude of different coupling partners (Figure 1d).[16] In this context, especially multicomponent reactions have recently[17] revealed their potential in generating complex molecular structures in a single step, which represents an attractive feature for organic synthesis.[18]

We began our studies to develop such a transition metal catalyzed, three-component protocol by reacting oxime ether **1a** together with benzyl BCB ester **2a** and ethyl glyoxylate **3** as an additional electrophile in the presence of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ as the catalyst and CsOAc as a base in TFE. We were intrigued when we observed the *anti*-product **4aa** in 60% yield with excellent *E*-selectivity and diastereoselectivity that was formed upon twofold C−C bond cleavage of the BCB moiety and subsequent addition to aldehyde **3** (Table 1, entry 1). This class of compounds containing an $\alpha$-carbonyl quaternary center was recently utilized as a key intermediate in the synthesis of novel pantothenamide analogues displaying promising antiplasmodial activity.[19] We continued to optimize the reaction conditions, and a solvent screen revealed TFE to be essential

Received: April 1, 2021
Published: May 11, 2021







https://doi.org/10.1021/jacs.1c03492
J. Am. Chem. Soc. 2021, 143, 7648−7654

for the reaction outcome, with other solvents leading to low yields or no reactivity (entries 2–4). Variation of the temperature did not improve the yield (entries 5–7). We examined different bases, including $Na_2CO_3$, KOAc, NaOAc, and $K_3PO_4$, which all resulted in diminished yields (entries 8–11). To our delight, the use of 2.0 equiv of BCB ester **2a** delivered the desired product in 82% yield with perfect diastereoselectivity and *E*-selectivity (entry 12). Subsequent control experiments showed that the rhodium catalyst was essential for the reaction, and an absence of base led to a decreased yield (entries 13 and 14).

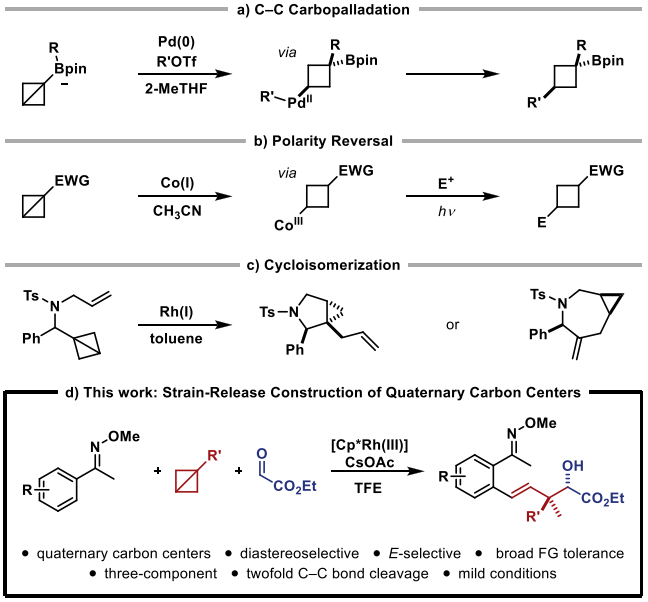
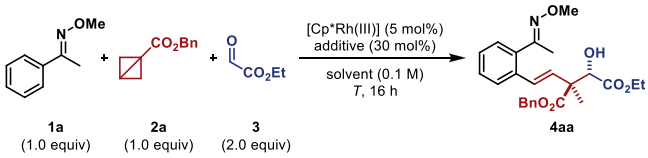



**Figure 1.** Transition metal catalyzed reactions of BCBs. (a) C–C $\sigma$-bond carbopalladation. (b) Photochemical polarity reversal via Co(I)-catalysis. (c) Rh(I)-catalyzed cycloisomerization. (d) This work: diastereoselective formation of quaternary carbon centers by twofold C–C bond cleavage. FG = functional group. TFE = 2,2,2-trifluoroethanol.

With the optimized conditions in hand, we set out to explore the substrate scope of the strain-release reaction and started with the exploration of the arene scope (Table 2). Halides were well tolerated and delivered the corresponding products in good yields and with excellent diastereo- and *E*-selectivities (**4ba–4da**, **4wa**). Triflate and ester substituents underwent the reaction smoothly and the products were isolated in moderate to good yields (**4ea–4ga**). Substrates bearing electron-donating functionalities, such as methoxy, phenol, and Boc-protected amino groups (**4ha–4ja**), could also be employed and furnished the products in moderate to very good yields. In addition, sterically demanding alkyl and aryl substituents were tolerated as well (**4ka**, **4la**). We continued to investigate naphthalene (**4ma**) and thiophene (**4na**) derivatives and were pleased to obtain the respective products in moderate to good yields with perfect diastereoselectivity, *E*-selectivity, and site selectivity in favor of the more accessible or more reactive position, respectively. A wide range of electron-deficient functional groups, including cyano, nitro, trifluoromethyl, trifluoromethoxy as well as sulfonyl, sulfamoyl, and a challenging sulfenyl moiety were well tolerated and afforded the desired products in moderate to very good yields with excellent selectivities (**4oa–4ua**). In the case of the thioether

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | solvent | additive | *T* | dr | yield |
|---|---|---|---|---|---|
| 1 | TFE | CsOAc | 60 °C | >20:1 | 60% |
| 2 | DCE | CsOAc | 60 °C | – | traces |
| 3 | 1,4-dioxane | CsOAc | 60 °C | – | – |
| 4 | HFIP | CsOAc | 60 °C | >20:1 | 8% |
| 5 | TFE | CsOAc | rt | >20:1 | 9% |
| 6 | TFE | CsOAc | 40 °C | >20:1 | 40% |
| 7 | TFE | CsOAc | 80 °C | >20:1 | 47% |
| 8 | TFE | $Na_2CO_3$ | 60 °C | >20:1 | 28% |
| 9 | TFE | KOAc | 60 °C | >20:1 | 55% |
| 10 | TFE | NaOAc | 60 °C | >20:1 | 49% |
| 11 | TFE | $K_3PO_4$ | 60 °C | >20:1 | 30% |
| 12[b] | TFE | CsOAc | 60 °C | >20:1 | 82% |
| 13[c] | TFE | CsOAc | 60 °C | – | – |
| 14 | TFE | – | 60 °C | >20:1 | 52% |

[a]Reactions were performed on a 0.10 mmol scale with $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ as the catalyst. Yields and diastereomeric ratios (dr) were determined by LC-UV using 1-fluoronaphthalene as the internal standard. The *E*-isomer was observed exclusively in all cases. [b]2.0 equiv of **2a**. [c]No catalyst. HFIP = hexafluoroisopropanol. rt = room temperature.

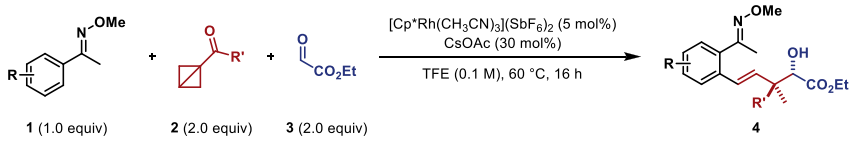
**4ua**, the diminished yield was attributed to the strong coordinating properties of the sulfur atom. Notably, *meta*-substituted oxime ethers could be successfully applied and reacted with perfect site selectivity (**4va**, **4wa**). Similar reactivity was observed for disubstituted substrates that provided the products in moderate to good yields with outstanding selectivities (**4xa**, **4ya**). We were delighted that even an *ortho*-substituted oxime ether was suitable in the developed strain-release reaction despite the high steric congestion (**4za**). In addition to the broad functional group tolerance, several BCB esters could be applied. Ethyl and isobutyl esters gave the corresponding products (**4ab**, **4ac**) and gratifyingly, a Weinreb amide was also reactive in this protocol (**4ad**). In terms of the aldehyde scope, we examined alkyl as well as aryl aldehydes. However, only trace amounts of product were observed in these cases (see the Supporting Information for further details). The relative configuration of the stereocenters was unambiguously assigned by X-ray crystallographic analysis of a derivative of sulfone **4sa** that was obtained after esterification and subsequent debenzylation (see the Supporting Information for further details).

In addition, to further illustrate the synthetic value of this protocol we sought to convert the products into valuable $\beta$-lactones.[20] Indeed, compound **4aa** was successfully debenzylated and hydrogenated under reducing conditions using Pd/C as the catalyst (Figure 2). The resulting carboxylic acid **5** was then transformed into the corresponding $\alpha$-quaternary $\beta$-lactone **6** (PyBOP, $NEt_3$) in good yield and without the observation of isomerization. NOE experiments confirmed the stereochemistry indicated.

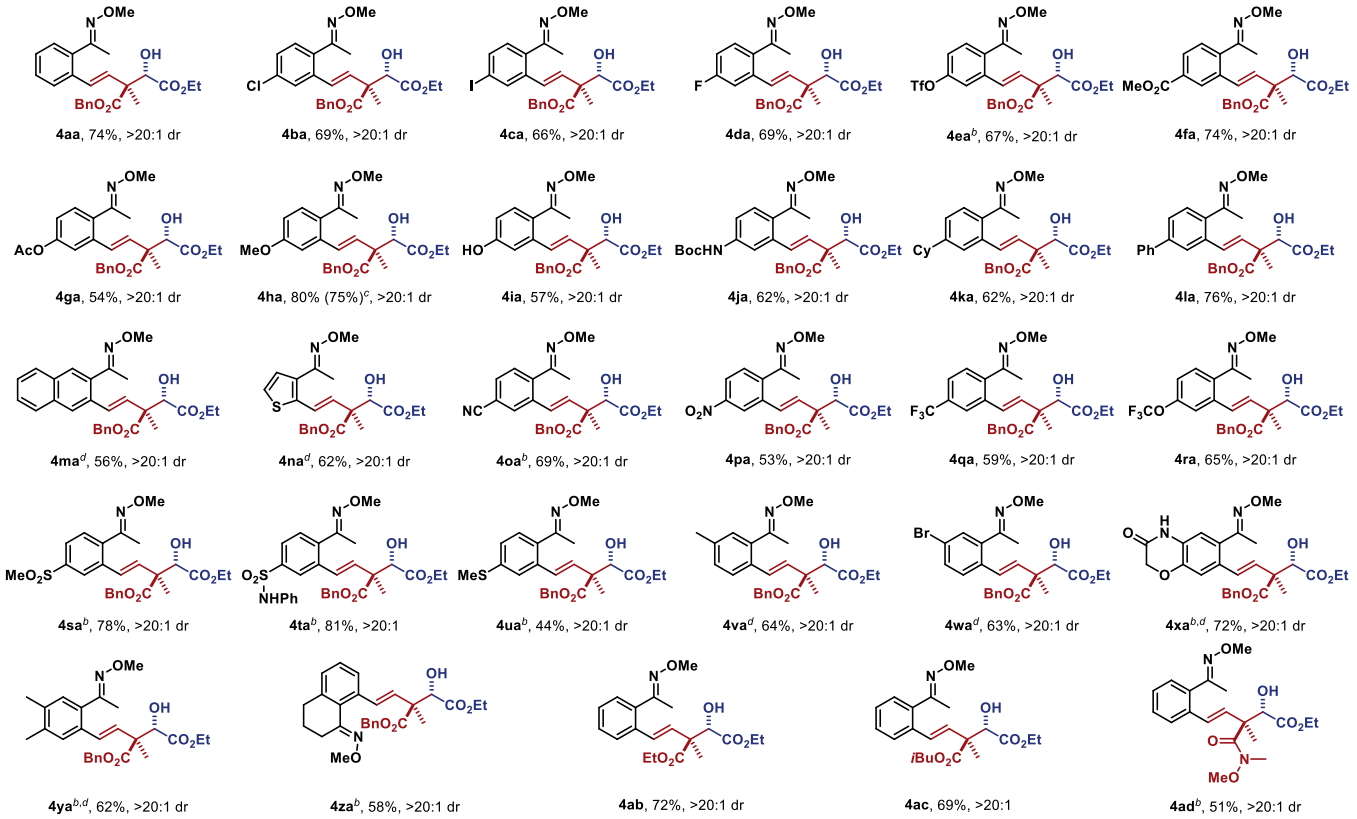
Furthermore, the respective epimer could be accessed complementarily under Mitsunobu conditions (see the Supporting Information for further details).


https://doi.org/10.1021/jacs.1c03492
J. Am. Chem. Soc. 2021, 143, 7648–7654

**Table 2. Scope of the Strain-Release Construction of Quaternary Carbon Centers**[a]




Substrate Scope




[a]Standard reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2** (0.40 mmol, 2.0 equiv), **3** (0.40 mmol, 2.0 equiv), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (5 mol %), CsOAc (30 mol %), TFE (0.10 M), 60 °C, 16 h. Diastereomeric ratios and site selectivities were determined by LC-UV of the crude reaction mixture. All products were obtained exclusively as the *E*-isomer. See the Supporting Information for full experimental details. [b]$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (10 mol %) was used. [c]Performed on 1.00 mmol scale. [d]>20:1 site selectivity. Tf = trifluoromethylsulfonyl. Cy = cyclohexyl.

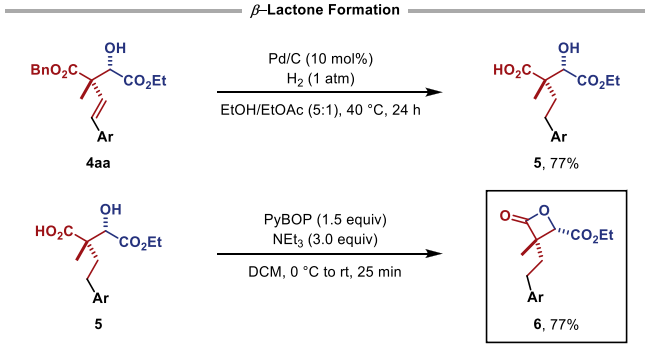



**Figure 2.** Synthesis of an $\alpha$-quaternary $\beta$-lactone. Ar = 2-(C(Me)=NOMe)-$C_6H_4$.

In order to get insight into the underlying reaction mechanism a preliminary series of mechanistic experiments was conducted (Figure 3). First, the kinetic isotope effect was determined by two parallel experiments. A KIE value of 1.2 indicates that the C−H activation might not be involved in the rate-determining step (Figure 3a).[21] Moreover, two-component experiments were performed under the optimized reaction conditions (Figure 3b). In the absence of aldehyde **3**, olefinated product **7** was obtained in 19% yield. In contrast, omission of BCB ester **2a** led to selective addition of the organometallic species generated to aldehyde **3** yielding alcohol **8**. These results suggest that a stepwise mechanism of an initial rearrangement-olefination and subsequent aldol-type addition might be operative. Nevertheless, when olefin **7** and aldehyde **3** were exposed to the standard conditions, the desired product **4aa** was obtained in low yield and with a decreased dr of 7:1 (Figure 3c). A stepwise mechanism is therefore unlikely to proceed. In addition, we conducted an isomerization experiment of BCB ester **2a** under the conditions developed to examine whether a rhodium catalyzed diene isomerization might be part of the catalytic cycle.[14a] However, no isomers were detected and **2a** was recovered in 83% yield (see the Supporting Information for further details). Based on these experiments and literature known mechanistic characteristics of Cp*Rh(III)-catalyzed C−H activation,[22] we propose the following catalytic cycle (Figure 3d): The catalytically



https://doi.org/10.1021/jacs.1c03492
J. Am. Chem. Soc. 2021, 143, 7648−7654

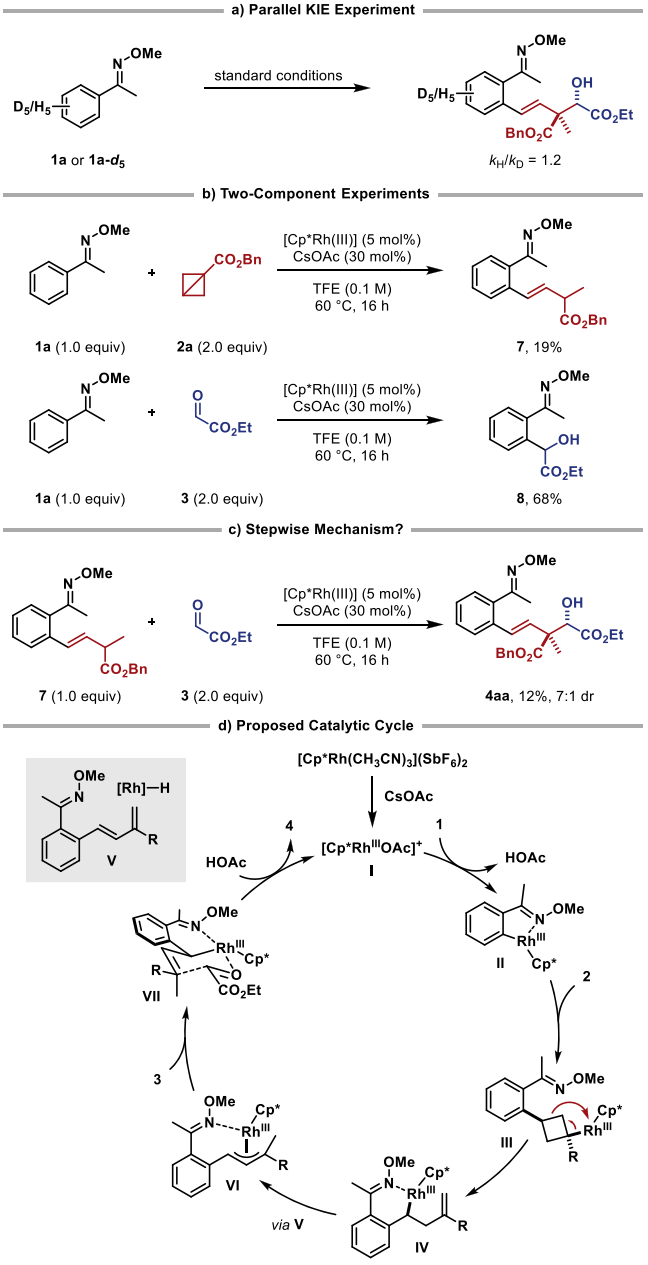



**Figure 3.** Mechanistic investigations and proposed catalytic cycle. [Cp*Rh(III)] = $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$.

active species **I** is generated from the catalyst precursor $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ and CsOAc by ligand exchange. Oxime ether **1** coordinates to the metal center, and rhodacycle **II** is formed by C−H activation. BCB ester **2** associates to the metal center and inserts into the Rh−C bond to give Rh−cyclobutyl species **III**. This intermediate undergoes $\beta$-carbon elimination to generate **IV**, that is transformed into $\pi$-allyl species **VI** via a *syn*-$\beta$-hydride elimination-reinsertion sequence through diene **V**. This species isomerizes to the corresponding $\sigma$-allyl intermediate before adding to aldehyde **3** via chairlike transition state **VII**,[17g] which leads to the observed stereochemistry. Finally, protodemetalation delivers product **4** and closes the catalytic cycle to regenerate the active species **I**.

In conclusion, we have developed a highly diastereoselective and *E*-selective three-component protocol for the construction of quaternary carbon centers via strain-release from BCB esters by twofold C−C bond cleavage. The reaction proceeds under mild conditions and tolerates a wide range of common functional groups. The products could be further transformed into valuable $\alpha$-quaternary $\beta$-lactones. The high diastereoselectivity was rationalized by mechanistic investigations that suggest a catalytic cycle proceeding through a key C−C $\sigma$-bond insertion, followed by a $\beta$-carbon elimination and a subsequent allylation via a six-membered transition state. This method exhibits a rare example of transition metal catalysis in the field of BCB chemistry and showcases the diversity of reactivity pathways accessible to these strained compounds. Ultimately, we believe that this work will inspire researchers to further explore the potential of these fascinating molecules in transition metal catalysis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03492.

Experimental and details (PDF)

### Accession Codes

CCDC 2070494 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Author

**Frank Glorius** − *Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany;* orcid.org/0000-0002-0648-956X; Email: glorius@uni-muenster.de

### Authors

**Tobias Pinkert** − *Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany*

**Mowpriya Das** − *Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany*

**Malte L. Schrader** − *Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, 48149 Münster, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c03492


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Roman Kleinmans, Dr. Frederik Sandfort, Dr. J. Luca Schwarz, Dr. Andreas Lerchen, Toryn Dalton, Tobias Wagener (all WWU), Mariusz Milewski, and Prof. Karol Grela (both University of Warsaw) for helpful discussions; Dr. Klaus Bergander for NMR analysis; and Dr. Constantin G. Daniliuc and Birgit Wibbeling for X-ray crystallographic analysis. Financial support from the Deutsche Forschungsgemeinschaft (Leibniz Award, SFB 858) is gratefully acknowledged.

## ■ REFERENCES

(1) For selected reviews, see: (a) Liebman, J. F.; Greenberg, A. A survey of strained organic molecules. *Chem. Rev.* **1976**, *76*, 311−365.

(b) de Meijere, A.; Kozhushkov, S. I.; Schill, H. Three-Membered-Ring-Based Molecular Architectures. *Chem. Rev.* **2006**, *106*, 4926−4996. (c) Shi, M.; Shao, L.-X.; Lu, J.-M.; Wei, Y.; Mizuno, K.; Maeda, H. Chemistry of Vinylidenecyclopropanes. *Chem. Rev.* **2010**, *110*, 5883−5913. (d) Souillart, L.; Cramer, N. Catalytic C−C Bond Activations via Oxidative Addition to Transition Metals. *Chem. Rev.* **2015**, *115*, 9410−9464.

(2) For selected examples, see: (a) Huffman, M. A.; Liebeskind, L. S. Rhodium(I)-Catalyzed intramolecular carbocyclic ring fusion: a new approach to medium-sized-ring ketones. *J. Am. Chem. Soc.* **1993**, *115*, 4895−4896. (b) Nishimura, T.; Ohe, K.; Uemura, S. Palladium(II)-Catalyzed Oxidative Ring Cleavage of *tert*-Cyclobutanols under Oxygen Atmosphere. *J. Am. Chem. Soc.* **1999**, *121*, 2645−2646. (c) Converso, A.; Burow, K.; Marzinzik, A.; Sharpless, K. B.; Finn, M. G. 2,6-Dichloro-9-thiabicyclo[3.3.1]nonane: A Privileged, Bivalent Scaffold for the Display of Nucleophilic Components. *J. Org. Chem.* **2001**, *66*, 4386−4392. (d) Young, I. S.; Kerr, M. A. A Homo [3 + 2] Dipolar Cycloaddition: The Reaction of Nitrones with Cyclopropanes. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023−3026. (e) Wipf, P.; Stephenson, C. R. J.; Okumura, K. Transition-Metal-Mediated Cascade Reactions: *C,C*-Dicyclopropylmethylamines by Way of Double C,C-$\sigma$-Bond Insertion into Bicyclobutanes. *J. Am. Chem. Soc.* **2003**, *125*, 14694−14695. (f) Wipf, P.; Walczak, M. A. A. Pericyclic Cascade Reactions of (Bicyclo[1.1.0]butylmethyl)amines. *Angew. Chem., Int. Ed.* **2006**, *45*, 4172−4175. For selected examples in total synthesis, see: (g) Wender, P. A.; Howbert, J. J. Synthetic Studies on Arene-Olefin Cycloadditions: Total Synthesis of (±)-$\alpha$-Cedrene. *J. Am. Chem. Soc.* **1981**, *103*, 688−690. (h) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. Strain-Release Rearrangement of *N*-Vinyl-2-Arylaziridines. Total Synthesis of the Anti-Leukemia Alkaloid (−)-Deoxyharringtonine. *J. Am. Chem. Soc.* **2006**, *128*, 10370−10371. (i) Panish, R. A.; Chintala, S. R.; Fox, J. M. A Mixed-Ligand Chiral Rhodium(II) Catalyst Enables the Enantioselective Total Synthesis of Piperarborenine B. *Angew. Chem., Int. Ed.* **2016**, *55*, 4983−4987.

(3) For selected reviews, see: (a) Hall, H. K., Jr.; Padias, A. B. Bicyclobutanes and Cyclobutenes: Unusual Carbocyclic Monomers. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 625−635. (b) Dilmaç, A. M.; Spuling, E.; de Meijere, A.; Bräse, S. Propellanes − From a Chemical Curiosity to "Explosive" Materials and Natural Products. *Angew. Chem., Int. Ed.* **2017**, *56*, 5684−5718.

(4) For selected examples, see: (a) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. A Strain-Promoted [3 + 2] Azide-Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems. *J. Am. Chem. Soc.* **2004**, *126*, 15046−15047. (b) Zhang, P.; Zhuang, R.; Wang, X.; Liu, H.; Li, J.; Su, X.; Chen, X.; Zhang, X. Highly Efficient and Stable Strain-Release Radioiodination for Thiol Chemoselective Bioconjugation. *Bioconjugate Chem.* **2018**, *29*, 467−472. (c) Tokunaga, K.; Sato, M.; Kuwata, K.; Miura, C.; Fuchida, H.; Matsunaga, N.; Koyanagi, S.; Ohdo, S.; Shindo, N.; Ojida, A. Bicyclobutane Carboxylic Amide as a Cysteine-Directed Strained Electrophile for Selective Targeting of Proteins. *J. Am. Chem. Soc.* **2020**, *142*, 18522−18531.

(5) For selected reviews, see: (a) Hoz, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; pp 1121−1191. (b) Wiberg, K. B.; Waddell, S. T. Reactions of [1.1.1]propellane. *J. Am. Chem. Soc.* **1990**, *112*, 2194−2216. (c) Bartnik, R.; Marchand, A. P. Synthesis and Chemistry of Substituted 1-Azabicyclo[1.1.0]butanes. *Synlett* **1997**, *1997*, 1029−1039. (d) Levin, M. D.; Kaszynski, P.; Michl, J. Bicyclo[1.1.1]-pentanes, [*n*]Staffanes, [1.1.1]Propellanes, and Tricyclo[2.1.0.0$^{2,5}$]-pentanes. *Chem. Rev.* **2000**, *100*, 169−234. (e) Kanazawa, J.; Uchiyama, M. Recent Advances in the Synthetic Chemistry of Bicyclo[1.1.1]pentane. *Synlett* **2019**, *30*, 1−11. (f) Fawcett, A. Recent advances in the chemistry of bicyclo- and 1-azabicyclo[1.1.0]butanes. *Pure Appl. Chem.* **2020**, *92*, 751−765. (g) Turkowska, J.; Durka, J.; Gryko, D. Strain release − an old tool for new transformations. *Chem. Commun.* **2020**, *56*, 5718−5734. (h) Andresini, M.; Degennaro, L.; Luisi, R. The renaissance of strained 1-azabicyclo[1.1.0]butanes as useful reagents for the synthesis of functionalized azetidines. *Org. Biomol. Chem.* **2020**, *18*, 5798−5810.

(6) Wiberg, K. B. The Concept of Strain in Organic Chemistry. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312−322.

(7) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139*, 3209−3226.

(8) (a) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug Discovery* **2018**, *17*, 709−727. (b) Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. Put a ring on it: application of small aliphatic rings in medicinal chemistry. *RSC Med. Chem.* **2021**, *12*, 448−471.

(9) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-release amination. *Science* **2016**, *351*, 241−246.

(10) For recent selected synthetic applications of [1.1.1]propellane, see: (a) Kanazawa, J.; Maeda, K.; Uchiyama, M. Radical Multicomponent Carboamination of [1.1.1]Propellane. *J. Am. Chem. Soc.* **2017**, *139*, 17791−17794. (b) Makarov, I. S.; Brocklehurst, C. E.; Karaghiosoff, K.; Koch, G.; Knochel, P. Synthesis of Bicyclo[1.1.1]-pentane Bioisosteres of Internal Alkynes and *para*-Disubstituted Benzenes from [1.1.1]Propellane. *Angew. Chem., Int. Ed.* **2017**, *56*, 12774−12777. (c) Caputo, D. F. G.; Arroniz, C.; Dürr, A. B.; Mousseau, J. J.; Stepan, A. F.; Mansfield, S. J.; Anderson, E. A. Synthesis and applications of highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes. *Chem. Sci.* **2018**, *9*, 5295−5300. (d) Shelp, R. A.; Walsh, P. J. Synthesis of BCP Benzylamines From 2-Azaallyl Anions and [1.1.1]Propellane. *Angew. Chem., Int. Ed.* **2018**, *57*, 15857−15861. (e) Yu, S.; Noble, A.; Bedford, R. B.; Aggarwal, V. K. Methylenespiro[2.3]hexanes via Nickel-Catalyzed Cyclopropanations with [1.1.1]Propellane. *J. Am. Chem. Soc.* **2019**, *141*, 20325−20334. (f) Yu, S.; Jing, C.; Noble, A.; Aggarwal, V. K. 1,3-Difunctionalizations of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes. *Angew. Chem., Int. Ed.* **2020**, *59*, 3917−3921. (g) Kim, J. H.; Ruffoni, A.; Al-Faiyz, Y. S. S.; Sheikh, N. S.; Leonori, D. Divergent Strain-Release Amino-Functionalization of [1.1.1]Propellane with Electrophilic Nitrogen-Radicals. *Angew. Chem., Int. Ed.* **2020**, *59*, 8225−8231. (h) Zhang, X.; Smith, R. T.; Le, C.; McCarver, S. J.; Shireman, B. T.; Carruthers, N. I.; MacMillan, D. W. C. Copper-mediated synthesis of drug-like bicyclopentanes. *Nature* **2020**, *580*, 220−226. (i) Wong, M. L. J.; Sterling, A. J.; Mousseau, J. J.; Duarte, F.; Anderson, E. A. Direct catalytic asymmetric synthesis of $\alpha$-chiral bicyclo[1.1.1]pentanes. *Nat. Commun.* **2021**, *12*.

(11) For recent selected examples involving 1-azabicyclo[1.1.0] butanes, see: (a) Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. Strain-Release-Driven Homologation of Boronic Esters: Application to the Modular Synthesis of Azetidines. *J. Am. Chem. Soc.* **2019**, *141*, 4573−4578. (b) Gianatassio, R.; Kadish, D. Direct Alkylation of 1-Azabicyclo[1.1.0]butanes. *Org. Lett.* **2019**, *21*, 2060−2063. (c) Musci, P.; von Keutz, T.; Belaj, F.; Degennaro, L.; Cantillo, D.; Kappe, O.; Luisi, R. Flow Technology for Telescoped Generation, Lithiation and Electrophilic ($C_3$) Functionalization of Highly Strained 1-Azabicy-clo[1.1.0]butanes. *Angew. Chem., Int. Ed.* **2021**, *60*, 6395−6399. (d) Gregson, C. H. U.; Noble, A.; Aggarwal, V. K. Divergent, Strain-Release Reactions of Azabicyclo[1.1.0]butyl Carbinols: Semipinacol or Spiroepoxy Azetidine Formation. *Angew. Chem., Int. Ed.* **2021**, *60*, 7360−7365.

(12) Fawcett, A.; Biberger, T.; Aggarwal, V. K. Carbopalladation of C−C $\sigma$-bonds enabled by strained boronate complexes. *Nat. Chem.* **2019**, *11*, 117−122.



https://doi.org/10.1021/jacs.1c03492
J. Am. Chem. Soc. 2021, 143, 7648−7654

(13) Ociepa, M.; Wierzba, A. J.; Turkowska, J.; Gryko, D. Polarity-Reversal Strategy for the Functionalization of Electrophilic Strained Molecules via Light-Driven Cobalt Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 5355−5361.
(14) (a) Bishop, K. C., III Transition metal catalyzed rearrangements of small ring organic molecules. *Chem. Rev.* **1976**, *76*, 461−486. For other recent synthetic applications of BCBs, see: (b) Panish, R.; Chintala, S. R.; Boruta, D. T.; Fang, Y.; Taylor, M. T.; Fox, J. M. Enantioselective Synthesis of Cyclobutanes via Sequential Rh-catalyzed Bicyclobutanation/Cu-catalyzed Homoconjugate Addition. *J. Am. Chem. Soc.* **2013**, *135*, 9283−9286. (c) Milligan, J. A.; Busacca, C. A.; Senanayake, C. H.; Wipf, P. Hydrophosphination of Bicyclo[1.1.0]butane-1-carbonitriles. *Org. Lett.* **2016**, *18*, 4300−4303. (d) Wu, X.; Hao, W.; Ye, K.-Y.; Jiang, B.; Pombar, G.; Song, Z.; Lin, S. Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors. *J. Am. Chem. Soc.* **2018**, *140*, 14836−14843. (e) Silvi, M.; Aggarwal, V. K. Radical Addition to Strained $\sigma$-Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters. *J. Am. Chem. Soc.* **2019**, *141*, 9511−9515. (f) Ma, X.; Sloman, D. L.; Han, Y.; Bennett, D. J. A Selective Synthesis of 2,2-Difluorobicyclo[1.1.1]pentane Analogues: "BCP-$F_2$. *Org. Lett.* **2019**, *21*, 7199−7203. (g) Bychek, R. M.; Hutskalova, V.; Bas, Y. P.; Zaporozhets, O. A.; Zozulya, S.; Levterov, V. V.; Mykhailiuk, P. K. Difluoro-Substituted Bicyclo[1.1.1]pentanes for Medicinal Chemistry: Design, Synthesis, and Characterization. *J. Org. Chem.* **2019**, *84*, 15106−15117. (h) Pratt, C. J.; Aycock, R. A.; King, M. D.; Jui, N. T. Radical $\alpha$-C−H Cyclobutylation of Aniline Derivatives. *Synlett* **2020**, *31*, 51−54. (i) Ernouf, G.; Chirkin, E.; Rhyman, L.; Ramasami, P.; Cintrat, J.-C. Photochemical Strain-Release-Driven Cyclobutylation of C($sp^3$)-Centered Radicals. *Angew. Chem., Int. Ed.* **2020**, *59*, 2618−2622. (j) Schwartz, B. D.; Zhang, M. Y.; Attard, R. H.; Gardiner, M. G.; Malins, L. R. Structurally Diverse Acyl Bicyclobutanes: Valuable Strained Electrophiles. *Chem. - Eur. J.* **2020**, *26*, 2808−2812. (k) Bennett, S. H.; Fawcett, A.; Denton, E. H.; Biberger, T.; Fasano, V.; Winter, N.; Aggarwal, V. K. Difunctionalization of C−C $\sigma$-Bonds Enabled by the Reaction of Bicyclo[1.1.0]butyl Boronate Complexes with Electrophiles: Reaction Development, Scope, and Stereochemical Origins. *J. Am. Chem. Soc.* **2020**, *142*, 16766−16775. (l) Guo, L.; Noble, A.; Aggarwal, V. K. $\alpha$-Selective Ring-Opening Reactions of Bicyclo[1.1.0]butyl Boronic Ester with Nucleophiles. *Angew. Chem., Int. Ed.* **2021**, *60*, 212−216. (m) Yu, X.; Lübbesmeyer, M.; Studer, A. Oligosilanes as Silyl Radical Precursors through Oxidative Si−Si Bond Cleavage Using Redox Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 675−679.
(15) (a) Walczak, M. A. A.; Wipf, P. Rhodium(I)-Catalyzed Cycloisomerizations of Bicyclobutanes. *J. Am. Chem. Soc.* **2008**, *130*, 6924−6925. For further examples of transition metal catalyzed cycloisomerizations of BCBs, see: (b) Walczak, M. A. A. *Synthesis and Reactions of Bicyclo[1.1.0]butanes*; Ph.D. Thesis, University of Pittsburgh, Pittsburgh, PA, 2010. (c) Walczak, M. A. A.; Krainz, T.; Wipf, P. Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes. *Acc. Chem. Res.* **2015**, *48*, 1149−1158.
(16) For selected reviews, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C−H Activation/C−C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation. *Chem. Rev.* **2010**, *110*, 624−655. (c) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C−H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (e) Yang, L.; Huang, H. Transition-Metal-Catalyzed Direct Addition of Unactivated C−H Bonds to Polar Unsaturated Bonds. *Chem. Rev.* **2015**, *115*, 3468−3517. (f) Wang, F.; Yu, S.; Li, X. Transition metal-catalysed couplings between arenes and strained or reactive rings: combination of C−H activation and ring scission. *Chem. Soc. Rev.* **2016**, *45*, 6462−6477. (g) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C−H Bond Addition to Carbonyls, Imines, and Related Polarized $\pi$ Bonds. *Chem. Rev.* **2017**, *117*, 9163−9227. (h) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C−H Activation. *Chem. Rev.* **2019**, *119*, 2192−2452.
(17) For selected three-component reactions in the field of C−H activation, see: (a) Boerth, J. A.; Ellman, J. A. Rh(III)-catalyzed diastereoselective C−H bond addition/cyclization cascade of enone tethered aldehydes. *Chem. Sci.* **2016**, *7*, 1474−1479. (b) Boerth, J. A.; Hummel, J. R.; Ellman, J. A. Highly Stereoselective Cobalt(III)-Catalyzed Three-Component C−H Bond Addition Cascade. *Angew. Chem., Int. Ed.* **2016**, *55*, 12650−12654. (c) Boerth, J. A.; Ellman, J. A. A Convergent Synthesis of Functionalized Alkenyl Halides through Cobalt(III)-Catalyzed Three-Component C−H Bond Addition. *Angew. Chem., Int. Ed.* **2017**, *56*, 9976−9980. (d) Zhang, S.-S.; Xia, J.; Wu, J.-Q.; Liu, X.-G.; Zhou, C.-J.; Lin, E.; Li, Q.; Huang, S.-L.; Wang, H. Three-Component Catalytic Carboxygenation of Activated Alkenes Enabled by Bimetallic Rh(III)/Cu(II) Catalysis. *Org. Lett.* **2017**, *19*, 5868−5871. (e) Boerth, J. A.; Maity, S.; Williams, S. K.; Mercado, B. Q.; Ellman, J. A. Selective and synergistic cobalt(III)-catalysed three-component C−H bond addition to dienes and aldehydes. *Nat. Catal.* **2018**, *1*, 673−679. (f) Tang, M.; Li, Y.; Han, S.; Liu, L.; Ackermann, L.; Li, J. Rhodium(III)-Catalyzed C−H Alkylation/Nucleophilic Addition Domino Reaction. *Eur. J. Org. Chem.* **2019**, *2019*, 660−664. (g) Li, R.; Ju, C.-W.; Zhao, D. Rhodium(III) vs. cobalt(III): a mechanistically distinct three-component C−H bond addition cascade using a Cp*$Rh^{III}$ catalyst. *Chem. Commun.* **2019**, *55*, 695−698. (h) Dongbang, S.; Shen, Z.; Ellman, J. A. Synthesis of Homoallylic Alcohols with Acyclic Quaternary Centers through $Co^{III}$-Catalyzed Three-Component C−H Bond Addition to Internally Substituted Dienes and Carbonyls. *Angew. Chem., Int. Ed.* **2019**, *58*, 12590−12594. (i) Pinkert, T.; Wegner, T.; Mondal, S.; Glorius, F. Intermolecular 1,4-Carboamination of Conjugated Dienes Enabled by Cp*$Rh^{III}$-Catalyzed C−H Activation. *Angew. Chem., Int. Ed.* **2019**, *58*, 15041−15045. (j) Wang, X.-G.; Li, Y.; Liu, H.-C.; Zhang, B.-S.; Gou, X.-Y.; Wang, Q.; Ma, J.-W.; Liang, Y.-M. Three-Component Ruthenium-Catalyzed Direct *Meta*-Selective C−H Activation of Arenes: A New Approach to the Alkylarylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 13914−13922. (k) Maity, S.; Potter, T. J.; Ellman, J. A. $\alpha$-Branched amines by catalytic 1,1-addition of C−H bonds and aminating agents to terminal alkenes. *Nat. Catal.* **2019**, *2*, 756−762. (l) Dongbang, S.; Ellman, J. A. Synthesis of Nitrile Bearing Acyclic Quaternary Centers through Co(III)-Catalyzed Sequential C−H Bond Addition to Dienes and *N*-Cyanosuccinimide. *Angew. Chem., Int. Ed.* **2021**, *60*, 2135−2139. (m) Brandes, D. S.; Sirvent, A.; Mercado, B. Q.; Ellman, J. A. Three-Component 1,2-Carboamidation of Bridged Bicyclic Alkenes via $Rh^{III}$-Catalyzed Addition of C−H Bonds and Amidating Reagents. *Org. Lett.* **2021**, *23*, 2836−2840.
(18) (a) de Graaff, C.; Ruijter, E.; Orru, R. V. A. Recent developments in asymmetric multicomponent reactions. *Chem. Soc. Rev.* **2012**, *41*, 3969−4009. (b) Cho, H. Y.; Morken, J. P. Catalytic bismetallative multicomponent coupling reactions: scope, applications, and mechanisms. *Chem. Soc. Rev.* **2014**, *43*, 4368−4380.
(19) Hoegl, A.; Darabi, H.; Tran, E.; Awuah, E.; Kerdo, E. S. C.; Habib, E.; Saliba, K. J.; Auclair, K. Stereochemical modification of geminal dialkyl substituents on pantothenamides alters antimicrobial activity. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3274−3277.
(20) Robinson, S. L.; Christenson, J. K.; Wackett, L. P. Biosynthesis and chemical diversity of $\beta$-lactone natural products. *Nat. Prod. Rep.* **2019**, *36*, 458−475.
(21) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C−H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.
(22) For selected reviews, see: (a) Kuhl, N.; Schröder, N.; Glorius, F. Formal $S_N$-Type Reactions in Rhodium(III)-Catalyzed C−H Bond Activation. *Adv. Synth. Catal.* **2014**, *356*, 1443−1460. (b) Song, G.; Li, X. Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes. *Acc. Chem. Res.* **2015**, *48*,


https://doi.org/10.1021/jacs.1c03492
J. Am. Chem. Soc. 2021, 143, 7648−7654

1007−1020. (c) Kazerouni, A. M.; McKoy, Q. A.; Blakey, S. B. Recent advances in oxidative allylic C−H functionalization via group IX-metal catalysis. *Chem. Commun.* **2020**, *56*, 13287−13300. See also ref 16e−g.



https://doi.org/10.1021/jacs.1c03492
*J. Am. Chem. Soc.* 2021, 143, 7648−7654