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Communication

Total Synthesis of Penicibilaenes via C−C Activation-Enabled Skeleton Deconstruction and Desaturation Relay-Mediated C−H Functionalization

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Cite This: J. Am. Chem. Soc. 2021, 143, 8272−8277
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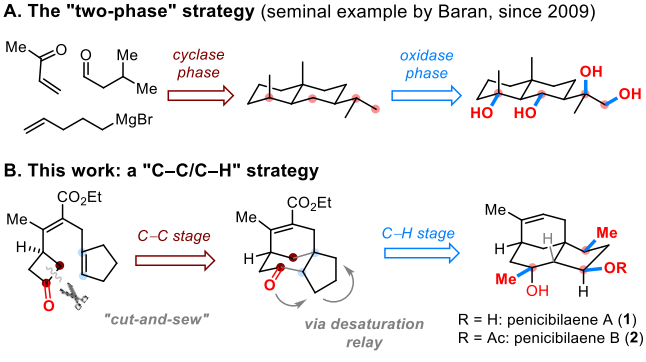
ABSTRACT: Herein, we describe the first total synthesis of sesquiterpene penicibilaenes A and B through a "C−C/C−H" approach. In the "C−C" stage, the Rh-catalyzed "cut-and-sew" transformation between trisubstituted alkene and cyclobutanone has been employed to construct the unique tricyclo[6.3.1.0^{1,5}]dodecane skeleton and the all-carbon quaternary center. Critical linker and Lewis acid effects have been identified for the C−C activation process. In the "C−H" stage, a desaturation relay-based strategy involving consecutive ketone α,β-dehydrogenation and β-functionalization has been adopted to introduce the 1,3,5-triad stereocenters to the core. The synthesis of penicibilaenes A and B has been completed in 13 and 14 steps, respectively, in the longest linear sequence.

Terpenes and their derivatives have been a rich source of therapeutic agents, agrochemicals, and fragrances.[1] In addition, they often exhibit intriguing and complex chemical structures, such as bridged/fused rings and diverse substitutions. As such, terpenes have been highly attractive target molecules in the synthetic community.[2] Inspired by the biosynthesis of terpenes, a "two-phase" strategy has been advanced by Baran and co-workers, leading to a number of elegant total syntheses since 2009.[3] This strategy involves a cyclase phase to first build the carbon backbone from a linear or less complex precursor, followed by an oxidase phase to install oxygen functionalities at proper positions (Scheme 1A).[3] Notably, in the cyclase phase, polyene cyclization and various cycloadditions, such as Diels−Alder reaction and Robinson annulation, are commonly employed for synthesizing multiring systems.[3] On the other hand, the transition-metal-catalyzed C−C activation[4] of cyclic ketones followed by insertion of an unsaturated 2π-unit, namely, a "cut-and-sew" process,[5] has been found useful for constructing various bridged and fused rings. In addition, the resulting carbonyl moiety could provide a convenient handle for site-selective C−H functionalization.[6] Thus, terpene synthesis could also be envisioned to go through a closely related but complementary strategy, which utilizes C−C activation to construct the core skeleton[7] and then ketone-directed or -mediated C−H functionalization to introduce the substituents (Scheme 1B). Comparing to the "two-phase" strategy, one subtle difference with this "C−C/C−H" approach is that not all carbons in the terpene core need to be introduced in the "C−C" stage, as some carbon substituents can be installed in the later "C−H" stage. Herein, we describe a proof-of-concept of utilizing this "C−C/C−H" strategy in a concise total synthesis of penicibilaenes A (**1**) and B (**2**).

Scheme 1. Approaches for Terpene Synthesis



Isolated from the marine fungus *Penicillium bilaiae* MA-267 by Wang and co-workers in 2014, sesquiterpene penicibilaenes A (**1**) and B (**2**) display selective and potent activity against the plant pathogenic fungus *Colletotrichum gloeosporioides*, which is responsible for anthracnose in many fruits and vegetables.[8] In particular, penicibilaene B even shows better efficacy than broad-spectrum antibiotic zeocin. To the best of our knowledge, total synthesis of penicibilaenes has not been reported. These sesquiterpenes possess interesting chemical structures, including a tricyclo[6.3.1.0^{1,5}]dodecane skeleton constituted by [3.3.1]-bridged and [4.3.0]-fused junctions, as well as five adjacent stereocenters with one being all-carbon quaternary. Of note, the substitutions on the tricyclic skeleton exhibit a 1,3,5-triad pattern. While a number of efficient and

Received: April 26, 2021
Published: May 26, 2021

https://doi.org/10.1021/jacs.1c04335
J. Am. Chem. Soc. 2021, 143, 8272−8277

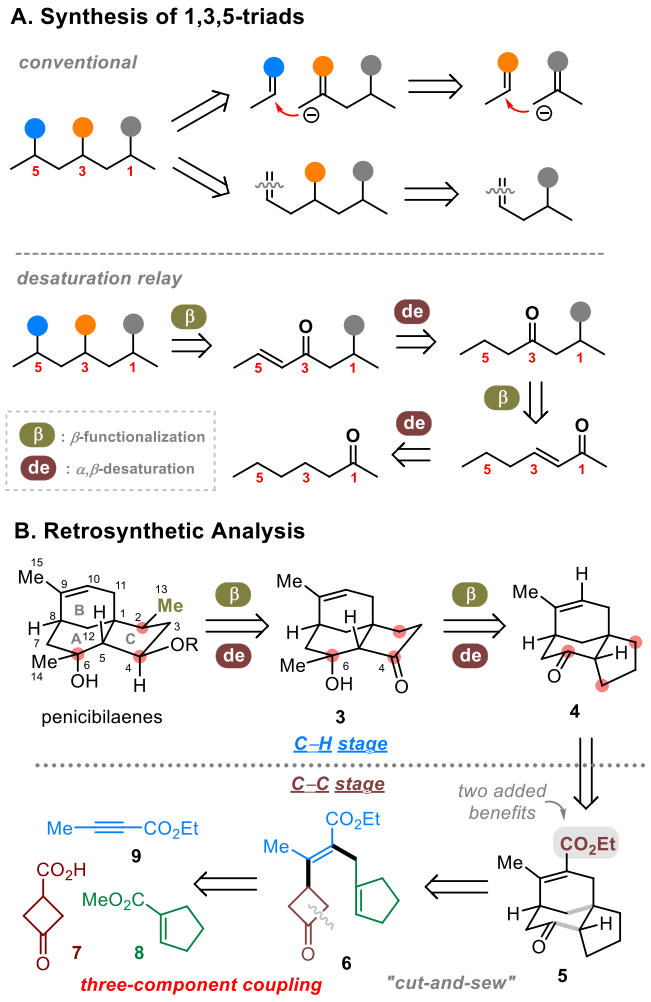
stereoselective approaches are known to form 1,3,5-triad stereocenters, e.g., aldol-type condensations and allylation followed by oxidative cleavage, they would require disconnecting the carbon skeletons of the target compounds (Scheme 2A). We questioned whether such 1,3,5 "skipped" functional groups can be installed through an alternative "desaturation relay" process,[9] in which a single carbonyl moiety can be used as the initiation group (at the C1 position) to install a hydroxy moiety at the C3 position through α,β-desaturation and conjugate addition.[10] Upon converting the C1 carbonyl to the desired moiety, the C3-OH can be oxidized to a ketone, which could enable another β-functionalization at the C5 position through the carbonyl desaturation and conjugate addition.

From the retrosynthetic viewpoint (Scheme 2B), the C13 methyl group in penicibilaenes A (**1**) and B (**2**) could be introduced in the late stage via the desaturation-based β-functionalization from intermediate **3**. It can be further envisaged that the C4 oxygen functional group can also be installed via a similar desaturation-based β-functionalization sequence from ketone **4**, and the C6 tertiary alcohol stereocenter can be introduced through an axial-selective carbonyl addition reaction (*vide infra*). The core tricyclic skeleton in **5** is then expected to be constructed by the "cut-and-sew" reaction through C−C activation of cyclobutanone **6**. Finally, the precursor (**6**) for the "cut-and-sew" is proposed to be rapidly prepared via a Cu-mediated three-component coupling, ultimately from three commercially available chemicals: cyclobutanone **7**, enoate **8**, and ynoate **9**. It is noteworthy that an ester moiety is strategically introduced in the tricycle intermediate **5** because it can (i) greatly simplify substrate preparation and (ii) play a pivotal role in the "cut-and-sew" reaction (*vide infra*).

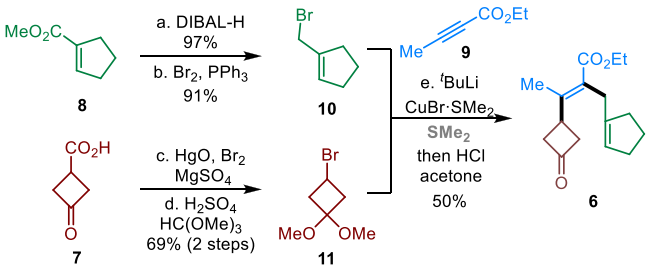
The synthesis began with the preparation of the "cut-and-sew" precursor, cyclobutanone **6** (Scheme 3). Reduction of ester **8** by DIBAL-H,[11] followed by bromination, delivered allylbromide **10** in good yield.[12] Meanwhile, Hunsdiecker reaction with carboxylic acid **7**[13] and subsequent protection of the ketone moiety gave cyclobutyl bromide **11**. With these two bromides in hand, cyclobutanone **6** was efficiently prepared in one step by a copper-mediated three-component coupling[14] using commercially available ynoate **9** as the linchpin. The reaction started with generation of the cyclobutyl lithium through treatment of bromide **11** with ^{t}BuLi, followed by transmetalation to a copper(I) salt. The generated cuprate then underwent *cis*-addition into the electrophilic alkynyl group in a regioselective manner, and the resulting vinyl cuprate intermediate was quenched by reactive allyl bromide **10**. Upon *in situ* ketal hydrolysis, cyclobutanone **6** was isolated in good overall yield, despite the complexity of the cascade sequence. The copper(I) salt had a significant influence on the efficiency of the three-component coupling (for details, see Supporting Information): CuBr·SMe$_2$ proved to be optimal, and additional dimethyl sulfide ligand was also beneficial.

The stage was then set for the key "cut-and-sew" step to construct the tricyclo[6.3.1.0^{1,5}]dodecane skeleton. Compared to benzocyclobutenones,[5a,15] intramolecular [4 + 2] cycloaddition with saturated cyclobutanones are generally more challenging due to (i) competing decarbonylation to form cyclopropanes[16] and (ii) lack of rigid scaffolds to promote cyclization. Clearly, the linkers between cyclobutanones and olefins play a critical role in the "cut-and-sew" reaction, as they can provide favorable conformations for the desired cyclization. To date, only three kinds of linkers including benzo-, amide-, and malonate-based ones (**Lk1**−**3**) have succeeded in this type of annulation reactions (Figure 1).[5b] A strong Thorpe−Ingold effect appears to be important for bridged-ring formation. In the context of penicibilaene synthesis, a number of carbon-based linkers were attempted in the proposed "cut-and-sew" reaction. Using the native trisubstituted alkene as the linker (**Lk4**), the olefin moiety proved to be labile and tended to isomerize under the reaction conditions. "Masked" alkenes, such as epoxide (**Lk5**), tertiary alcohol (**Lk6**), and ether (**Lk7**), were also prepared;[17] however, they proved to be either unstable or inactive for cyclization. Finally, the ester-substituted alkenyl linker (**Lk8**) was found to be ideal. The

Scheme 2. Our Strategy to Synthesize Penicibilaenes



Scheme 3. Synthesis of the "Cut-and-Sew" Precursor



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J. Am. Chem. Soc. 2021, 143, 8272−8277

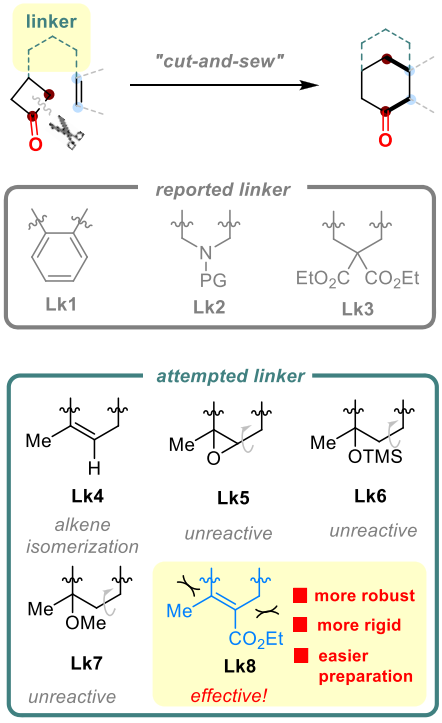
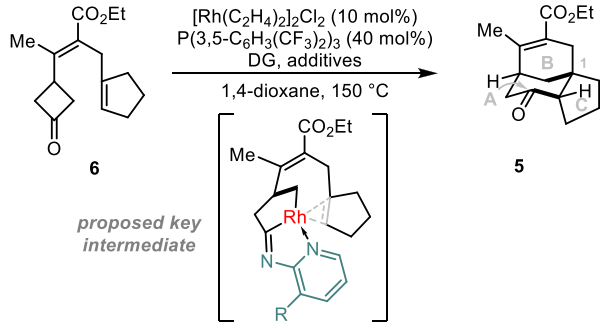


Figure 1. Linker effect in the "cut-and-sew" reaction.

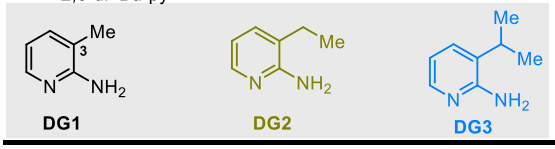
conjugation and the electron-withdrawing feature of the ester moiety inhibited double-bond migration. The enhanced rigidity of the tetrasubstituted alkene and the buttressing effect between the methyl and the ester groups are expected to be factors that benefit the cyclization. More importantly, with the ester moiety, synthesis of the "cut-and-sew" precursor became much simpler (*vide supra*, the three-component coupling).

Besides the linker, another challenge of the proposed "cut-and-sew" reaction was the use of a trisubstituted alkene as the coupling partner. The carboacylation between saturated cyclobutanones and trisubstituted alkenes has been rare due to the steric hindrance.[18] Hence, a more efficient catalytic system was needed to realize this transformation. It was not surprising that, under the prior optimal conditions (entry 1, Table 1),[19] the reaction with substrate **6** gave no desired product. Interestingly, by adding zinc chloride as a Lewis acid,[5a] the desired "cut-and-sew" product **5** was obtained in 12% yield (entry 2, Table 1), although the exact role of the Lewis acid remains unclear at this stage. In addition, zinc triflate was found to be more effective than zinc chloride likely due to enhanced Lewis acidity (entry 3, Table 1). Notably, the use of 2-aminopyridines as a temporary directing group (DG)[4a,20] was critical to avoid competing decarbonylation by forming the corresponding imine intermediate.[4a] Reducing the loading of the temporary DG and prolonging the reaction time further improved the yield (entries 4 and 5, Table 1). Moreover, the effect of the DG substituent was subsequently examined. By increasing the size of the 3-substituent on the DG, the yield was enhanced accordingly. It is possible that, like the linker effect (*vide supra*), the larger sterics on the DG can provide a more conformationally rigid intermediate that would be beneficial for the cyclization. However, further increasing the bulkiness on the DG, such as using 2-amino-3-trimethylsilylpyridine, only gave a trace amount of the product. Finally, after changing the solvent from 1,4-dioxane to toluene

Table 1. Selected Optimization of the "Cut-and-Sew" Step[a]



Entry	Additives	Directing Group	Time	Yield[b]
1	--	**DG-1** (100 mol%)	12 h	trace
2	$ZnCl_2$	**DG-1** (100 mol%)	12 h	12%
3	$Zn(OTf)_2$	**DG-1** (100 mol%)	12 h	20%
4	$Zn(OTf)_2$	**DG-1** (20 mol%)	12 h	23%
5	$Zn(OTf)_2$	**DG-1** (20 mol%)	48 h	34%
6	$Zn(OTf)_2$	**DG-2** (20 mol%)	48 h	35%
7	$Zn(OTf)_2$	**DG-3** (20 mol%)	48 h	**47%**
8	$Zn(OTf)_2$	**DG-3** (20 mol%)	48 h	**48%**[c]
9	$Zn(OTf)_2$ 2,6-di-^{t}Bu-py	**DG-3** (20 mol%)	48 h	42%[c,d,e]



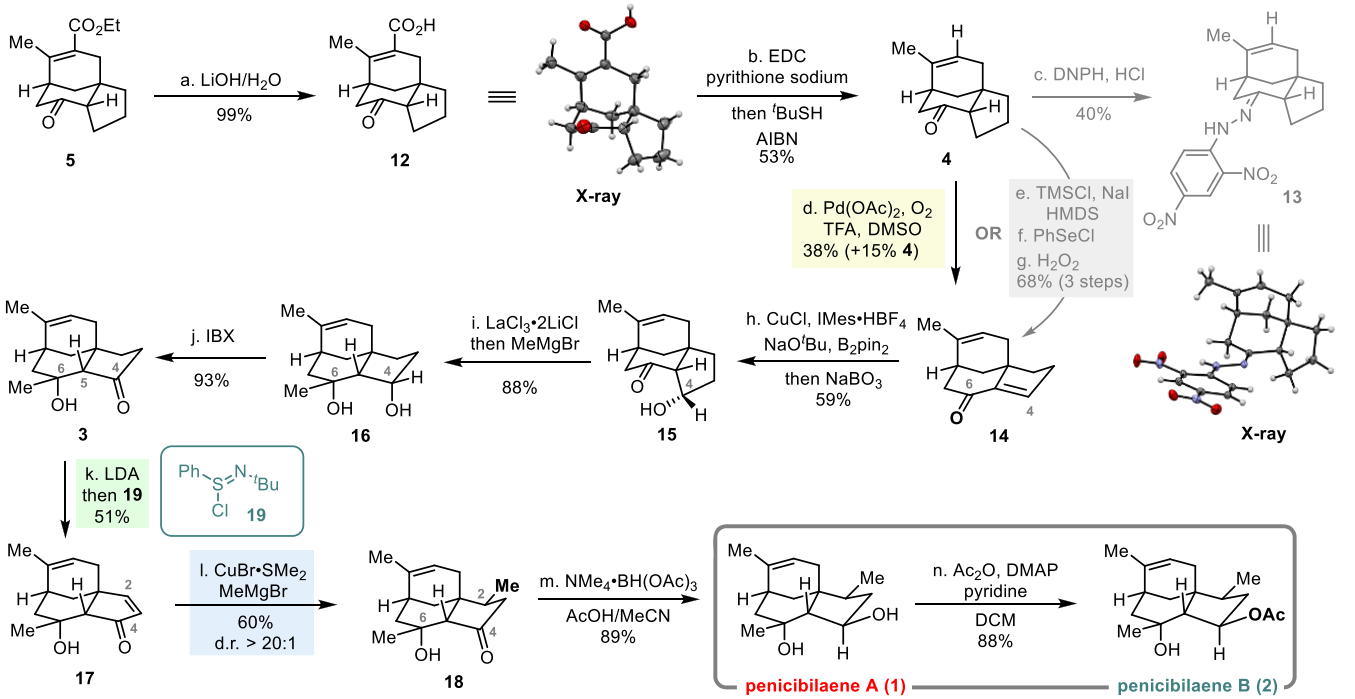
[a]Unless otherwise mentioned, the reaction was run on a 0.05 mmol scale. [b]Determined by GC using 1-methylnaphthalene as the internal standard. [c]Toluene was used as the solvent. [d]Isolated yield. [e]The reaction was run on a gram scale.

and buffering the reaction with a bulky pyridine base, a consistent yield can be obtained on a gram scale (entries 8 and 9, Table 1). Through this "cut-and-sew" transformation, the A/B rings and the all-carbon C1 quaternary center were simultaneously constructed. Note that, besides the cyclopentenyl moiety, mono- and 1,1-disubstituted alkenes can also be efficiently coupled to form bridged bicycles, which implies some generality of this method (for details, see the Supporting Information).

The ester moiety in ketone **5** can be conveniently removed by a sequence of hydrolysis and Barton decarboxylation (Scheme 4). X-ray structures of the carboxylic acid (**12**) and the hydrazone derivative of the decarboxylation product (**13**) were obtained to allow unambiguous characterization. With a scalable route to access the tricyclic compound (**4**), the stage was now set for introducing the required functional groups to the core skeleton. Initial attempts of various ketone- and alcohol-directed β-C−H functionalizations, including Sanford C−H acetoxylation (proceeded with poor conversion),[21] Schonecker−Baran C−H oxidation (occurred at the undesired C5 position),[22] and Hartwig C−H silylation (occurred at the undesired C14 position),[23] were not fruitful, likely due to the relatively rigid scaffold that lacks favorable conformation to access the desired C4 methylene. Ultimately, α,β-desaturation under the Stahl conditions,[24] followed by conjugate borylation[25] and oxidation, installed a hydroxy group at the C4 position in moderate yield. Alternatively, a three-step

https://doi.org/10.1021/jacs.1c04335
J. Am. Chem. Soc. 2021, 143, 8272−8277

Scheme 4. Completing the Synthesis of Penicibilaenes A and B



step d

Conditions	Yield
IBX, toluene/DMSO, 75 °C	trace
$Pd(DMSO)_2TFA_2$, O_2, HOAc, 80 °C	trace
$Pd(TFA)_2$, $Pd(OAc)_2$, O_2, DMSO, 80 °C	7% (45% SM)
$Pd(OAc)_2$, TFA, O_2, DMSO, 80 °C	32% (30% SM)
$Pd(OAc)_2$, TFA, O_2, DMSO, 60 °C	38% (15% SM)

step k

Conditions	Yield
$Pd(COD)(TFA)_2$, BQ, PhCl	trace
CuTC, DTBP, PhH	trace
IBX, MPO, DMSO	trace
$Pd(TFA)_2$, O_2, DMSO	trace
LDA, then **19**, THF	51%

step l

Conditions	Yield
$CuBr•SMe_2$, MeLi, Et_2O	trace
CuI, MeLi, Et_2O	trace
$Cu(OTf)_2$, $AlMe_3$, toluene	trace
$Ni(acac)_2$, $AlMe_3$, THF	52% (d.r. = 1.6:1)
$CuBr•SMe_2$, MeMgBr, THF	60% (d.r. > 20:1)

protocol involving regioselective enolization, selenylation, and selenoxide-mediated *syn*-elimination can afford a 68% yield of enone **14**. The C4-alcohol provided a convenient handle to allow a stereoselective methyl addition of the C6-ketone through chelation control. Treatment of ketone **15** with $LaCl_3$ and MeMgBr[26] delivered 1,3-diol **16** as a single diastereomer in 88% yield, which was further oxidized by IBX[27] to produce ketone **3**. At this stage, a new carbonyl moiety was introduced at the C4 position, with stereochemistry at the C5 and C6 positions correctly set.

To complete the synthesis, another β-functionalization—installing a methyl group at the C2 position—was required. Due to the presence of a labile C6 tertiary alcohol, various ketone desaturation conditions were found unsuccessful to introduce the cyclopentenone moiety. Eventually, the use of Mukaiyama's one-pot desaturation method[28] with *N-tert*-butyl phenylsulfinimidoyl chloride (**19**) as the reagent delivered the desired enone product (**17**) in 51% yield without the need to protect the C6 alcohol. The unique half-cage structure of enone **17** allowed a copper-mediated conjugate addition[29] selectively at the convex face to furnish the methyl group as a single diastereomer. The choice of the methyl nucleophile appears to be important; the nickel-mediated conjugate addition[30] also gave the desired product, albeit in low diastereoselectivity. In the end game, an alcohol-directed *syn*-reduction of ketone **18** by NMe_4·$BH(OAc)_3$[31] delivered penicibilaene A (**1**) in 88% yield. Penicibiaene B (**2**) was further prepared from penicibilaene A in good yield via a chemoselective acylation of the secondary alcohol.

In summary, we have described the first total synthesis of penicibilaenes A (**1**) and B (**2**) in 13 and 14 steps, respectively, in the longest linear sequence from commercially available starting materials. The synthesis features a deconstructive formation of the tricyclic skeleton via C−C activation of cyclobutanones and the use of carbonyl desaturation relay to replace β-C−H bonds with the desired functional groups. Such a "C−C/C−H" approach may inspire alternative bond-disconnecting strategies for natural product syntheses. In addition, the discovery of a new linker system and a Lewis acid effect in the Rh-catalyzed "cut-and-sew" reaction between cyclobutanones and bulky alkenes could have broader implications on preparing other all-carbon bridged/fused rings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04335.

Experimental procedures, spectral data (PDF)

Accession Codes

CCDC 2078710 and 2078965 contain 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

https://doi.org/10.1021/jacs.1c04335
J. Am. Chem. Soc. 2021, 143, 8272−8277

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

NIGMS (2R01GM109054) and University of Chicago are acknowledged for research support. We thank Mr. Shusuke Ochi and Dr. Xin Liu from University of Chicago for X-ray crystallography. Umicore AG & Co. KG is acknowledged for a generous donation of Rh salts. Mr. Benjamin L Ratchford from University of Chicago is thanked for proofreading the Supporting Information.

REFERENCES

(1) Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*; Wiley-VCH: Weinheim, 2006.

(2) (a) Cherney, E. C.; Baran, P. S. Terpenoid-Alkaloids: Their Biosynthetic Twist of Fate and Total Synthesis. *Isr. J. Chem.* **2011**, *51*, 391−405. (b) Justicia, J.; de Cienfuegos, L. A.; Campana, A. G.; Miguel, D.; Jakoby, V.; Gansauer, A.; Cuerva, J. M. Bioinspired Terpene Synthesis: a Radical Approach. *Chem. Soc. Rev.* **2011**, *40*, 3525−3537. (c) Urabe, D.; Asaba, T.; Inoue, M. Convergent Strategies in Total Syntheses of Complex Terpenoids. *Chem. Rev.* **2015**, *115*, 9207−9231. (d) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **2017**, *117*, 11753−11795.

(3) For selected examples and reviews, see: (a) Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C-H Oxidations. *Nature* **2009**, *459*, 824−828. (b) Ishihara, Y.; Baran, P. S. Two-Phase Terpene Total Synthesis: Historical Perspective and Application to the Taxol® Problem. *Synlett* **2010**, *2010*, 1733−1745. (c) Foo, K.; Usui, I.; Gotz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. Scalable, Enantioselective Synthesis of Germacrenes and Related Sesquiterpenes Inspired by Terpene Cyclase Phase Logic. *Angew. Chem., Int. Ed.* **2012**, *51*, 11491−11495. (d) Jorgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. 14-Step Synthesis of (+)-Ingenol from (+)-3-Carene. *Science* **2013**, *341*, 878−882. (e) Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. Two-Phase Synthesis of (−)-Taxuyunnanine D. *J. Am. Chem. Soc.* **2014**, *136*, 4909−4912. (f) Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. Two-Phase Synthesis of Taxol. *J. Am. Chem. Soc.* **2020**, *142*, 10526−10533.

(4) (a) Jun, C. H. Transition Metal-Catalyzed Carbon-Carbon Bond Activation. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (b) Dong, G., Ed. *C-C Bond Activation*; Springer-Verlag: Berlin, 2014; Vol. *346*. (c) Souillart, L.; Cramer, N. Catalytic C-C Bond Activations via Oxidative Addition to Transition Metals. *Chem. Rev.* **2015**, *115*, 9410−9464. (d) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C-C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404−9432. (e) Deng, L.; Dong, G. Carbon-Carbon Bond Activation of Ketones. *Trends Chem.* **2020**, *2*, 183−198. (f) Murakami, M.; Ishida, N. Cleavage of Carbon-Carbon σ-Bonds of Four-Membered Rings. *Chem. Rev.* **2021**, *121*, 264−299.

(5) (a) Xu, T.; Dong, G. Rhodium-Catalyzed Regioselective Carboacylation of Olefins: A C-C Bond Activation Approach for Accessing Fused-Ring Systems. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567−7571. (b) Chen, P. H.; Billett, B. A.; Tsukamoto, T.; Dong, G. Cut and Sew" Transformations via Transition-Metal-Catalyzed Carbon-Carbon Bond Activation. *ACS Catal.* **2017**, *7*, 1340−1360.

(6) For reviews on site-selectivte C−H functionalization and site-selectivity, see: (a) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition Metal-Catalyzed Ketone-Directed or Mediated C-H Functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786. (b) Hartwig, J. F. Catalyst-Controlled Site-Selective Bond Activation. *Acc. Chem. Res.* **2017**, *50*, 549−555. (c) Huang, Z.; Dong, G. Site-Selectivity Control in Organic Reactions: A Quest To Differentiate Reactivity among the Same Kind of Functional Groups. *Acc. Chem. Res.* **2017**, *50*, 465−471.

(7) (a) Murakami, M.; Ishida, N. Potential of Metal-Catalyzed C-C Single Bond Cleavage for Organic Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 13759−13769. (b) Wang, B.; Perea, M. A.; Sarpong, R. Transition Metal-Mediated C-C Single Bond Cleavage: Making the Cut in Total Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 18898−18919.

(8) Meng, L. H.; Li, X. M.; Liu, Y.; Wang, B. G. Penicibilaenes A and B, Sesquiterpenes with a Tricyclo[6.3.1.$0^{1,5}$]dodecane Skeleton from the Marine Isolate of *Penicillium bilaiae* MA-267. *Org. Lett.* **2014**, *16*, 6052−6055.

(9) For a recent review on desaturation-mediated β C−H functionalization, see: Wang, C.; Dong, G. Catalytic β-Functionalization of Carbonyl Compounds Enabled by α,β-Desaturation. *ACS Catal.* **2020**, *10*, 6058−6070.

(10) Chen, Y.; Huang, D.; Zhao, Y.; Newhouse, T. R. Allyl-Palladium-Catalyzed Ketone Dehydrogenation Enables Telescoping with Enone α,β-Vicinal Difunctionalization. *Angew. Chem., Int. Ed.* **2017**, *56*, 8258−8262.

(11) Kapat, A.; Nyfeler, E.; Giuffredi, G. T.; Renaud, P. Intramolecular Schmidt Reaction Involving Primary Azidoalcohols under Nonacidic Conditions: Synthesis of Indolizidine (−)-167B. *J. Am. Chem. Soc.* **2009**, *131*, 17746−17747.

(12) Kim, D. D.; Lee, S. J.; Beak, P. Asymmetric Lithiation-Substitution Sequences of Substituted Allylamines. *J. Org. Chem.* **2005**, *70*, 5376−5386.

(13) Li, X.; Danishefsky, S. J. Cyclobutenone as a Highly Reactive Dienophile: Expanding Upon Diels-Alder Paradigms. *J. Am. Chem. Soc.* **2010**, *132*, 11004−11005.

(14) Zhu, N.; Hall, D. G. Effect of Additives on the Sterochemical Integrity and Reactivity of α-Alkoxycarbonyl Alkenylcopper Intermediates. Optimal Conditions for the Synthesis of Isomerically Pure Tetrasubstituted Alkenes. *J. Org. Chem.* **2003**, *68*, 6066−6069.

(15) (a) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. Highly Enantioselective Rh-Catalyzed Carboacylation of Olefins: Efficient Syntheses of Chiral Poly-Fused Rings. *J. Am. Chem. Soc.* **2012**, *134*, 20005−20008. (b) Xu, T.; Dong, G. Coupling of Sterically Hindered Trisubstituted Olefins and Benzocyclobutenones by C-C Activation: Total Synthesis and Structural Revision of Cycloinumakiol. *Angew. Chem., Int. Ed.* **2014**, *53*, 10733−10736. (c) Deng, L.; Chen, M.; Dong, G. Concise Synthesis of (−)-Cycloclavine and (−)-5-*epi*-Cycloclavine via Asymmetric C-C Activation. *J. Am. Chem. Soc.* **2018**, *140*, 9652−9658. (d) Qiu, B.; Li, X. T.; Zhang, J. Y.; Zhan, J. L.; Huang, S. P.; Xu, T. Catalytic Enantioselective Synthesis of 3,4-Polyfused Oxindoles with Quaternary All-Carbon Stereocenters: A Rh-Catalyzed C-C Activation Approach. *Org. Lett.* **2018**, *20*, 7689−7693. (e) Zhang, Y.; Shen, S.; Fang, H.; Xu, T. Total Synthesis of Galanthamine and Lycoramine Featuring an Early-Stage C-C and a Late-Stage Dehydrogenation via C-H Activation. *Org. Lett.* **2020**, *22*, 1244−1248.

(16) For a seminal work on the cyclobutanone/olefin coupling, see: Murakami, M.; Itahashi, T.; Ito, Y. Catalyzed Intramolecular Olefin Insertion into a Carbon-Carbon Single Bond. *J. Am. Chem. Soc.* **2002**, *124*, 13976−13977.
(17) These substrates were prepared via a different and longer synthetic route from substrate **6**.
(18) To our knowledge, the only example was shown by Cramer with a benzene-like substrate: Souillart, L.; Parker, E.; Cramer, N. Highly Enantioselective Rhodium(I)-Catalyzed Activation of Enantiotopic Cyclobutanone C-C Bonds. *Angew. Chem., Int. Ed.* **2014**, *53*, 3001−3005.
(19) Ko, H. M.; Dong, G. Cooperative Activation of Cyclobutanones and Olefins Leads to Bridged Ring Systems by a Catalytic [4 + 2] Coupling. *Nat. Chem.* **2014**, *6*, 739−744.
(20) Xia, Y.; Dong, G. Temporary or Removable Directing Groups Enable Activation of Unstrained C-C Bonds. *Nat. Rev. Chem.* **2020**, *4*, 600−614.
(21) Desai, L. V.; Hull, K. L.; Sanford, M. S. Palladium-Catalyzed Oxygenation of Unactivated sp^3 C-H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543.
(22) (a) Schonecker, B.; Zheldakova, T.; Liu, Y.; Kotteritzsch, M.; Gunther, W.; Gorls, H. Biomimetic Hydroxylation of Nonactivated CH_2 Groups with Copper Complexes and Molecular Oxygen. *Angew. Chem., Int. Ed.* **2003**, *42*, 3240−3244. (b) See, Y. Y.; Herrmann, A. T.; Aihara, Y.; Baran, P. S. Scalable C-H Oxidation with Copper: Synthesis of Polyoxypregnanes. *J. Am. Chem. Soc.* **2015**, *137*, 13776−13779.
(23) Li, B.; Driess, M.; Hartwig, J. F. Iridium-Catalyzed Regioselective Silylation of Secondary Alkyl C-H Bonds for the Synthesis of 1,3-Diols. *J. Am. Chem. Soc.* **2014**, *136*, 6586−6589.
(24) (a) Diao, T.; Stahl, S. S. Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 14566−14569. (b) Pan, G. F.; Zhu, X. Q.; Guo, R. L.; Gao, Y. R.; Wang, Y. Q. Synthesis of Enones and Enals via Dehydrogenation of Saturated Ketones and Aldehydes. *Adv. Synth. Catal.* **2018**, *360*, 4774−4783.
(25) Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. Efficient C-B Bond Formation Promoted by N-Heterocyclic Carbenes: Synthesis of Tertiary and Quaternary B-Substituted Carbons through Metal-Free Catalytic Boron Conjugate Additions to Cyclic and Acyclic α,β-Unsaturated Carbonyls. *J. Am. Chem. Soc.* **2009**, *131*, 7253−7255.
(26) (a) Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide Salts ($LnCl_3$·2LiCl) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2006**, *45*, 497−500. (b) Breitler, S.; Carreira, E. M. Total Synthesis of (+)-Crotogoudin. *Angew. Chem., Int. Ed.* **2013**, *52*, 11168−11171.
(27) For a recent example, see: Boyko, Y. D.; Huck, C. J.; Ning, S.; Shved, A. S.; Yang, C.; Chu, T.; Tonogai, E. J.; Hergenrother, P. J.; Sarlah, D. Synthetic Studies on Selective, Proapoptotic Isomalabaricane Triterpenoids Aided by Computational Techniques. *J. Am. Chem. Soc.* **2021**, *143*, 2138−2155.
(28) Mukaiyama, T.; Matsuo, J.; Kitagawa, H. A New and One-Pot Synthesis of α,β-Unsaturated Ketones by Dehydrogenation of Various Ketones with *N-tert*-butyl Phenylsulfinimidoyl Chloride. *Chem. Lett.* **2000**, *29*, 1250−1251.
(29) Cao, M. Y.; Ma, B. J.; Lao, Z. Q.; Wang, H.; Wang, J.; Liu, J.; Xing, K.; Huang, Y. H.; Gan, K. J.; Gao, W.; Wang, H.; Hong, X.; Lu, H. H. Optically Active Flavaglines-Inspired Molecules by a Palladium-Catalyzed Decarboxylative Dearomative Asymmetric Allylic Alkylation. *J. Am. Chem. Soc.* **2020**, *142*, 12039−12045.
(30) Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. Asymmetric Total Synthesis of (+)-Waihoensene. *J. Am. Chem. Soc.* **2020**, *142*, 6511−6515.
(31) Evans, D. A.; Chapman, K. T.; Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

https://doi.org/10.1021/jacs.1c04335
J. Am. Chem. Soc. 2021, 143, 8272−8277