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JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Cite This: J. Am. Chem. Soc. 2019, 141, 13788−13794

pubs.acs.org/JACS

Copper Hydride Catalyzed Enantioselective Synthesis of Axially Chiral 1,3-Disubstituted Allenes

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Supporting Information

ABSTRACT: The general enantioselective synthesis of axially chiral disubstituted allenes from prochiral starting materials remains a long-standing challenge in organic synthesis. Here, we report an efficient enantio- and chemoselective copper hydride catalyzed semireduction of conjugated enynes to furnish 1,3-disubstituted allenes using water as the proton source. This protocol is sufficiently mild to accommodate an assortment of functional groups including keto, ester, amino, halo, and hydroxyl groups. Additionally, applications of this method for the selective synthesis of monodeuterated allenes and chiral 2,5-dihydropyrroles are described.

Allenes form a distinctive class of compounds capable of exhibiting axial chirality. They are represented in over 2,900 natural metabolites and synthetic compounds, and have been studied with regard to biological activity for over 40 years.[1] The introduction of allenes into steroids, prostaglandins, carbacyclins, and unnatural amino acids and nucleosides has been shown to increase the metabolic stability, bioavailability, and potency of these bioactive compounds.[2] Additionally, these cumulated dienes have found use in molecular materials and as synthetic intermediates in complex chemical syntheses as substrates due to their substituent-loading capability and enhanced reactivity under mild reaction conditions. Their tranformation often takes advantage of axial-to-central chirality transfer to generate one or more new stereogenic centers.[3] Finally, chiral allenes have also been explored in asymmetric autocatalysis and as ligands for the development of enantioselective transformations.[4−6]

While the utility of chiral allenes has been widely explored, the selective synthesis of these valuable materials still remains a challenge in organic synthesis.[3a,7] Traditional approaches to access enantioenriched allenes most commonly start from chiral, enantioenriched precursors wherein the allene product is generated through nucleophilic displacement, rearrangement, or elimination with central-to-axial chirality transfer (Figure 1) or through resolution of racemic allenes. More recently, several methods have employed achiral or racemic starting materials in catalytic asymmetric versions of these reactions to access the desired product using catalysts bearing chiral ligands. However, the majority of these reports target the synthesis of tri- or tetrasubstituted allenes.[8]

The direct catalytic conversion of prochiral 1,3-enynes to enantioenriched allenes has become a practical synthetic strategy in recent years, owing to the accessibility of these

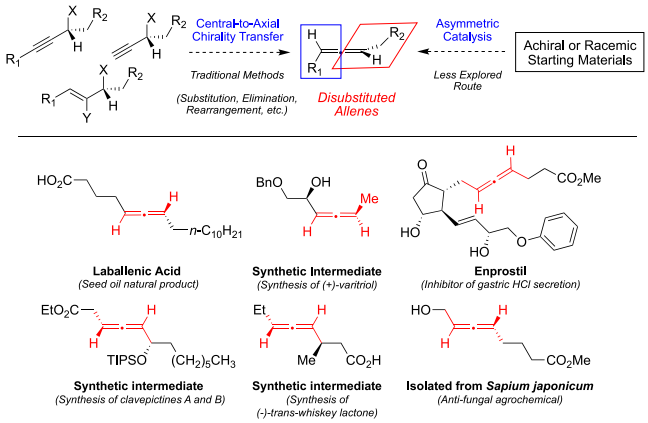


Figure 1. Synthetic strategies for the construction of enantioenriched allenes and representative examples of valuable 1,3-disubstituted allenes.

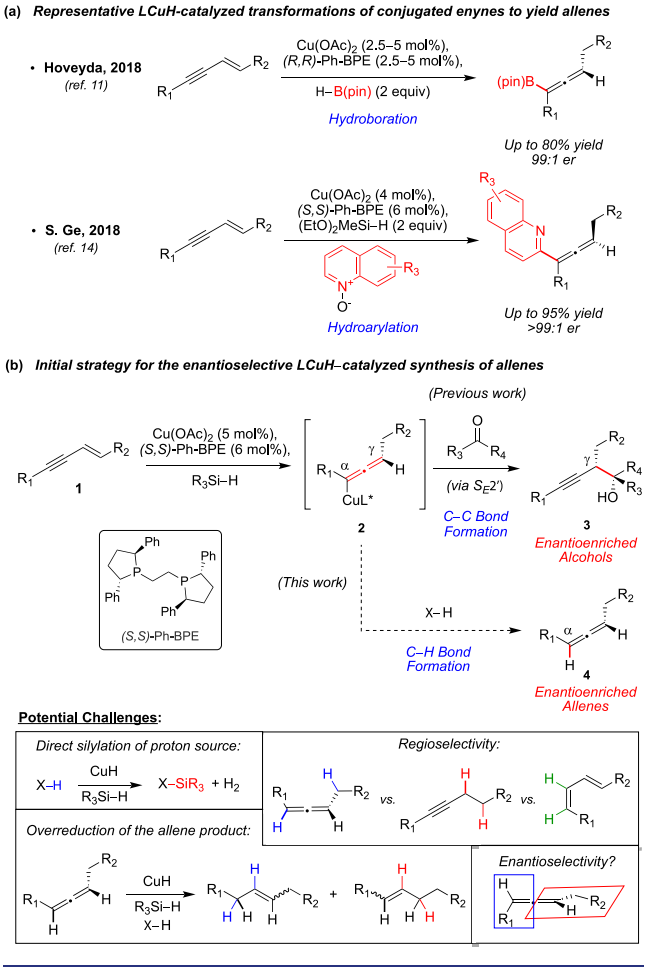
substrates.[9] Early reports by Hayashi describe the direct catalytic and enantioselective conversion of 1,3-enynes to boryl, silyl, or aryl allenes via palladium or rhodium catalysis.[8a−d] Since then, methods detailing the stereoselective transformations of enynes, including reports by Loh, Feng, Tang, Sun, and Malcolmson, have provided novel routes to enantioenriched allenes containing esters, lactones, or amines.[8g,l,n,p,10]

The LCuH-catalyzed hydrofunctionalization of 1,3-enynes to access enantioenriched allenes was first reported by the Hoveyda group wherein trisubstituted allenyl boronate derivatives are generated in high yield and enantioselectivity (Scheme 1a).[11] Shortly thereafter, the Ge and Engle groups independently disclosed their own reports of enyne hydroboration, followed by Ge's report of the catalytic asymmetric hydroarylation of enynes to provide access to quinoline-substituted allenes.[12−14]

Despite these recent advances, fewer reports describe the catalytic synthesis of enantioenriched 1,3-disubstituted allenes from prochiral or racemic precursors.[10,15−21] While these methods have offered elegant and innovative routes to this class of allenes, the vast majority of them provide access to a limited scope of products including allenyl esters,[16,18] alcohols,[19] and amines.[10,16,20] This modest scope is perhaps due to difficulty in controlling the stereochemical outcome of a three-carbon axis of chirality possessing two hydrogen

Received: July 18, 2019
Published: August 17, 2019

Scheme 1. Precedent for the Proposed Asymmetric LCuH-Catalyzed Semi-reduction of 1,3-Enynes



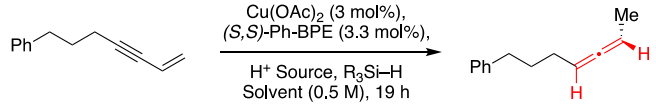
substituents without an additional functional group handle. Consequently, there persists an unmet need for a general strategy to access a broad range of 1,3-disubstituted axially chiral allenes.

In the course of our ongoing studies on the hydroalkylation of 1,3-enynes with imines, we serendipitously discovered an alternative strategy for the synthesis of 1,3-disubstituted allenes (Scheme 1b). Analogous to our previous report on the hydroalkylation of conjugated enynes with ketones,[22] enantioenriched allenyl copper intermediates **2** are generated via hydrocupration of an achiral 1,3-enyne starting material (**1**). However, trapping of the allenyl copper species **2** directly with a proton, instead of a ketone (which favors the alternative S_E2' reaction pathway to yield γ-adduct **3**), would provide access to axially chiral 1,3-disubstituted allenes (**4**). Potential challenges in developing this reaction include avoiding the unproductive silylation of the protonating reagent,[23] controlling the regioselectivity[24] and enantioselectivity of the process, and preventing further reduction of the allene product in the presence of the copper hydride catalyst. To date, the semireduction of 1,3-enynes to enantioenriched disubstituted allenes has only been demonstrated with the stoichiometric use of chiral metal reducing agents.[25] Herein, we report the asymmetric catalytic semireduction of 1,3-enynes to furnish axially chiral allenes enabled by CuH-catalysis.

We began our studies utilizing 1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane [(*S*,*S*)-Ph-BPE] in combination with $Cu(OAc)_2$ and dimethoxy(methyl)silane (DMMS) to generate a chiral LCuH complex previously shown to engage 1,3-enyne **1a** (Table 1).[22] At room temperature with *t*-BuOH as the proton source, the complete consumption of **1a** occurred yielding a complex mixture consisting primarily of products from the unselective hydrogenation of the desired product, allene **4a** (entry 1). Decreasing the reaction temperature to −10 °C slowed the over-reduction and provided **4a** in 34% yield and 60:40 enantiomeric ratio (er) (entry 2). A subsequent screen of several ethereal solvents indicated that both chemo- and enantioselectivity were enhanced by replacing THF with 1,2-dimethoxyethane (DME) (entries 3−5).

The use of a sterically less hindered proton source, *i*-PrOH, provided improved conversion and enantiomeric ratio of product **4a**. Moreover, we found that by decreasing the quantity of *i*-PrOH to 1.1 equiv minimized the amount of

Table 1. Reaction Optimization[a]



1a 4a

entry	*T* (°C)	solvent	proton source	silane	% conv	% yield[b]	er[c]
1	23	THF	*t*-BuOH (1.5 equiv)	DMMS	100	0	–
2	−10	THF	*t*-BuOH (1.5 equiv)	DMMS	100	34	60:40
3	−10	MTBE[d]	*t*-BuOH (1.5 equiv)	DMMS	64	36	87:13
4	−10	1,4-Dioxane	*t*-BuOH (1.5 equiv)	DMMS	67	26	92:8
5	−10	DME	*t*-BuOH (1.5 equiv)	DMMS	50	36	96:4
6	−10	DME	*i*-PrOH (1.5 equiv)	DMMS	100	68	99:1
7	−10	DME	*i*-PrOH (1.1 equiv)	DMMS	100	90	99:1
8	−10	DME	H_2O (0.55 equiv)	DMMS	100	90	>99:1
9[e]	−10	DME	H_2O (0.52 equiv)	TMCTS	100	90[f]	>99:1

[a]Conditions: Reactions were carried out under a N_2 atmosphere. 0.2 mmol enyne (1 equiv), copper(II) acetate (3 mol %), (*S*,*S*)-Ph-BPE (3.3 mol %), silane (4 equiv) in solvent (0.4 mL). [b]Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using mesitylene as an internal standard. [c]Enantiomeric ratio was determined by GC analysis, and the absolute configuration of **4a** was determined by analogy to desilylated **4f** (see the Supporting Information for more details). [d]MTBE = methyl *tert*-butyl ether. [e]Reaction was run with 1 mol % copper(II) acetate and 1.1 mol % (*S*,*S*)-Ph-BPE over 16.5 h instead. [f]Reported as an average of two isolated yields.

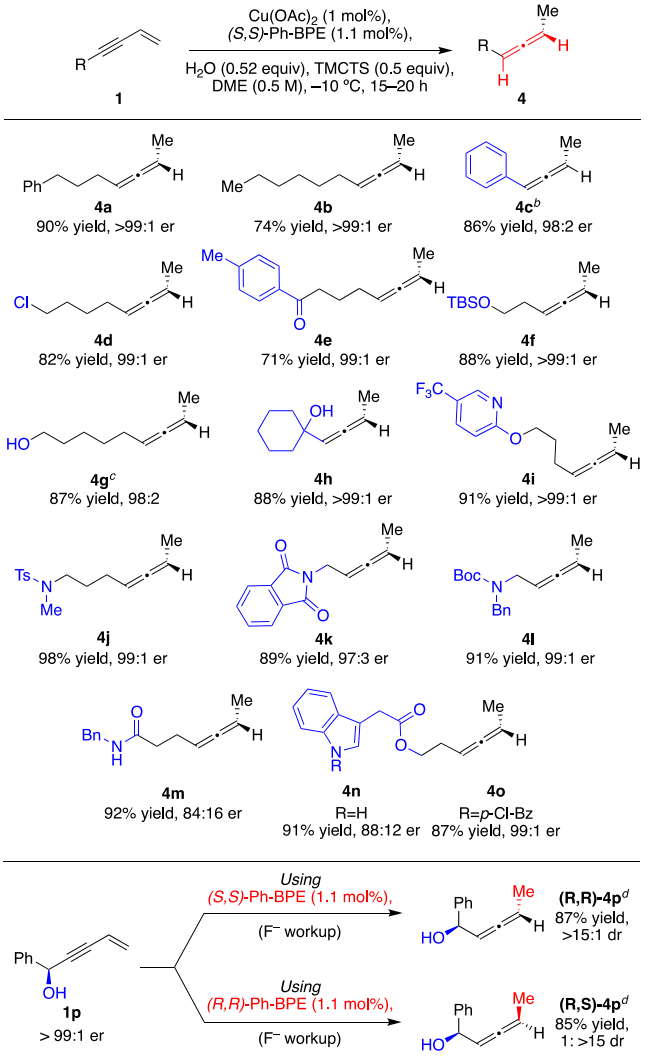
DOI: 10.1021/jacs.9b07582
J. Am. Chem. Soc. 2019, 141, 13788−13794

overreduction that was observed (entries 6–7). As the use of a less hindered proton source proved beneficial for both yield and er, we next examined the use of H_2O (0.55 equiv) which resulted in the efficient delivery of both protons in the enyne semireduction (entry 8). Further, we found that substituting DMMS with 0.5 equiv of 2,4,6,8-tetramethylcyclotetrasiloxane (TMCTS) and decreasing the catalyst loading to 1 mol % provided improved reaction conditions for the enantioselective semireduction of 1,3-enyne **1a** affording the desired product (*R*)-**4a** in 90% isolated yield and >99:1 er (entry 9).

Next, we surveyed the generality of the LCuH-catalyzed asymmetric semireduction of an assortment of terminal 1,3-enynes (Table 2).[26] Unfunctionalized substrates are efficiently converted to the corresponding allenes in good yield and exceptional er (**4a–c**). Enynes bearing a variety of functional groups are tolerated under the reaction conditions including potentially reducible groups such as alkyl chlorides (**4d**) and ketones (**4e**) as well as ethers (**4f**, **4i**), amines (**4j**, **4l**), and various heterocycles (**4i**, **4k**, **4n**, **4o**). Substrates containing unprotected alcohols are not only tolerated, but the unhindered primary alcohol of enyne **1g**, itself, serves as a proton source in the reduction, permitting the use of only 0.25 equiv of H_2O additive to furnish allene **4g**. The reactivity and selectivity of the sterically more encumbered enyne **1h**, bearing an unprotected propargylic alcohol, were unaffected, providing allenyl alcohol **4h** with 88% yield and >99:1 er. While substrates containing free N–H bonds react with a high yield, the allene products are produced with a diminished er (**4m**, **n**). In the case of **1n** it was demonstrated that the use of the protected variant, **1o**, provided significantly improved results (**4o**). Finally, this protocol exhibits excellent catalyst control in the semireduction of chiral enyne **1p** to furnish either diastereomer of allene **4p** depending on the enantiomer of ligand used.

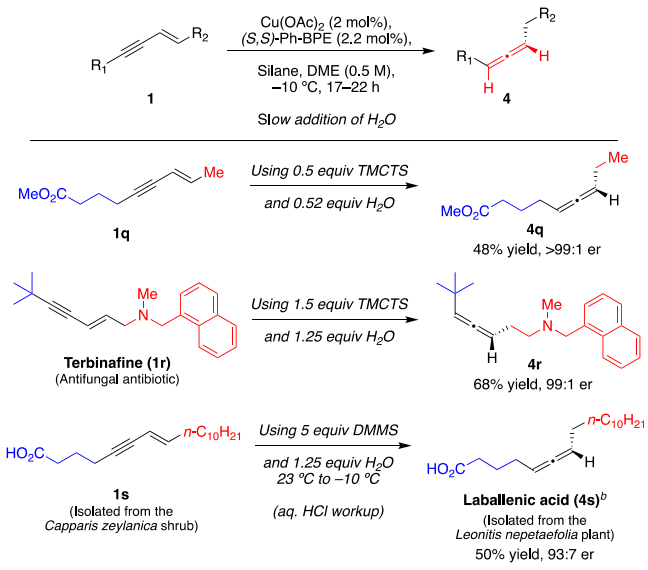
Our initial efforts to effect the asymmetric semireduction of internal 1,3-enyne substrates proved considerably more challenging. This difficulty was presumably due, in part, to an increased energetic barrier to hydrocupration, resulting in low conversion (possibly owing to unproductive silylation of the proton source) as well as, in some cases, competitive overreduction of the initially formed allene products.[27] To ameliorate these issues, we found that the utilization of a protocol with the slow addition of water was essential (Table 3). The reaction of ester-containing enyne **1q** occurred in moderate yield, largely due to competitive overreduction of the desired product, **4q**. The antifungal antibiotic Terbinafine (**1r**) was cleanly transformed to **4r** in 68% yield and 99:1 er, although it necessitated an increase in H_2O and TMCTS loading.[28] The direct conversion of fatty acid natural product **1s** to laballenic acid (**4s**), a seed oil natural product isolated

Table 2. Substrate Scope of the LCuH-Catalyzed Asymmetric Semi-reduction of 1,3-Enynes to Allenes[a]



[a]Reactions were carried out under a N_2 atmosphere at −10 °C. Isolated yields and enantiomeric ratios are reported as an average of two independent runs. [b]Yield was determined by ^1H NMR spectroscopy using mesitylene as an internal standard due to the volatility of the product. [c]With 0.25 equiv of H_2O instead. [d]Yield and diastereomeric ratio reported for a single run.

Table 3. Select Examples of the LCuH-Catalyzed Asymmetric Semi-reduction of Internal Enynes to Allenes[a]



[a]Reactions were carried out under a N_2 atmosphere at −10 °C, and H_2O was added over a 16 h time period. Isolated yields and enantiomeric ratios are reported as an average of two independent runs. [b]Reaction required a 1 h prestir at room temperature prior to addition of water at −10 °C.

DOI: 10.1021/jacs.9b07582
J. Am. Chem. Soc. 2019, 141, 13788–13794

from the *Leonitis nepetaefolia* plant, could also be accomplished.[29−32] The *in situ* protection of carboxylic acid **1s** with DMMS (to furnish the corresponding silyl ester) at room temperature was carried out, followed by slow addition of water at −10 °C to deliver laballenic acid in 50% yield and 93:7 er.

Based on previous mechanistic studies and DFT calculations,[11,22] we propose the following mechanism detailed in Figure 2. After generation of the chiral LCuH complex **I**,

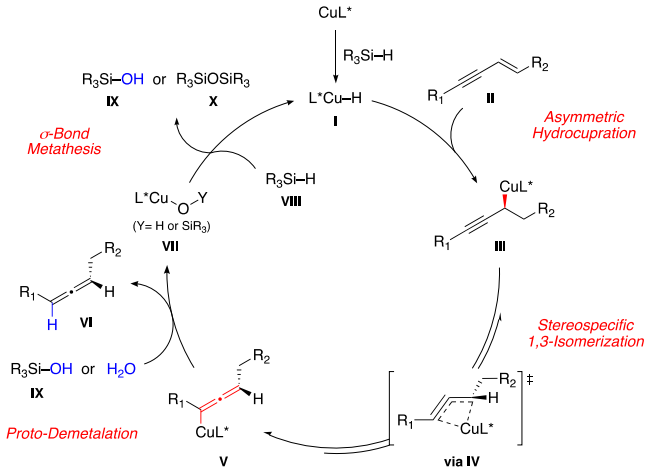
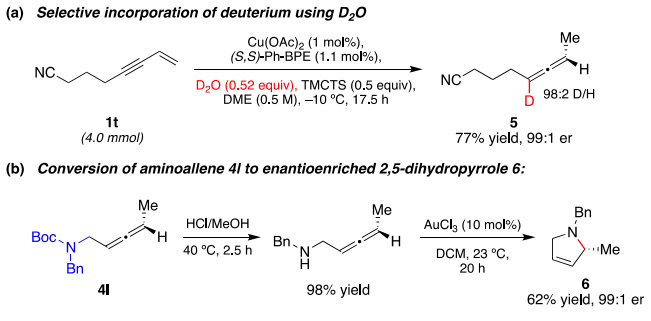


Figure 2. Proposed catalytic cycle for the LCuH-catalyzed conversion of 1,3-enynes to allenes.

enantioselective hydrocupration of enyne **II** affords a chiral propargylic copper species (**III**). This undergoes a stereospecific 1,3-isomerization to yield allenyl copper intermediate **V**. Next intermediate **V** is protonated to furnish the final product, allene **VI**. σ-Bond metathesis between **VII** and silane (**VIII**) results in the formation of silanol **IX** and regeneration of **I**. As less than a full equivalent of water is utilized in this process, we propose that silanol **IX** can also facilitate protodemetalation, producing siloxane **X**.

Two examples demonstrating further applications of this methodology are depicted in Scheme 2. The incorporation of

Scheme 2. Applications of the LCuH-Catalyzed Asymmetric Reduction for Deuterium Incorporation and Heterocycle Synthesis



deuterium into molecular scaffolds is pervasive not only in the pharmaceutical industry, due to the enhanced metabolic stability and safety imparted by corresponding deutero-analogs, but also in mechanistic studies and protein crystallography.[33] Substitution of H_2O for D_2O selectively delivers enantioenriched monodeuterated products, as exhibited in the conversion of enyne **1t** to allene **5** with 98:2 D/H incorporation (Scheme 2a). This protocol represents a new strategy for the deuterium labeling of allenes, employing an affordable, easy to handle, and abundant deuterium source.

Additionally, enantioenriched allenyl alcohols and amines are known to serve as valuable synthetic intermediates toward the production of chiral heterocycles including dihydrofurans and dihydropyrroles.[3h,34,35] Taking advantage of the highly selective nature of gold-catalyzed cycloisomerization chemistry, α-aminoallene **4l** furnished 2,5-dihydropyrrole **6** with complete axial-to-point chirality transfer (Scheme 2b).[36,37]

In summary, we have developed a LCuH-catalyzed asymmetric semireduction of 1,3-enynes to supply highly enantioenriched 1,3-disubstituted allenes in up to 98% yield and >99:1 er. This chemistry benefits from the functional group tolerance afforded by the mild reducing nature of LCuH catalysts and employs only a 1−2 mol % catalyst loading. Moreover, the utilization of substoichiometric quantities of H_2O as the proton source and TMCTS as the hydride source provides an efficient protocol for the hydrogenation of terminal 1,3-enynes. The reduction of internal conjugated enynes is enabled via slow addition of water and has been demonstrated through the late-stage derivatization of antibiotic Terbinafine and the synthesis of the seed oil natural product, laballenic acid. Furthermore, this protocol provides an efficient synthetic route for the construction of deutero-allenes as well as azaheterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07582.

General procedural information and characterization data (PDF)

NMR spectra (PDF)

SFC, GC, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Research reported in this publication was supported by the Arnold and Mabel Beckman Foundation (L.B.-R.) and the National Institutes of Health (R35-GM122483). The authors would like to thank Nippon Chemical Industrial Co., Ltd., Solvias AG, and Takasago International Corporation for donations of ligands used in this project. We thank Dr. M. Kumar for his assistance with HRMS analysis and R. Liu, Dr. A. Thomas, and Dr. S. McCann for their counsel in the preparation of this manuscript. We are grateful to E. Tsai, Drs. S. Guo, and Y. Yang for supplying some of the starting materials used in this project and the National Institutes of Health for a supplemental grant for the purchase of supercritical fluid chromatography (SFC) equipment (GM058160-17S1). The content is solely the responsibility

DOI: 10.1021/jacs.9b07582
J. Am. Chem. Soc. 2019, 141, 13788−13794

of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

(1) For selected reviews on allenes, see: (a) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley−VCH: 2004. (b) Hoffmann−Röder, A.; Krause, N. Synthesis and Properties of Allenic Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196−1216. (c) Dembitsky, V. M.; Maoka, T. Allenic and cumulenic lipids. *Prog. Lipid Res.* **2007**, *46*, 328−375. (d) Kim, H.; Williams, L. Recent developments in allene-based synthetic methods. *Curr. Opin. Drug Discovery Devel.* **2008**, *11*, 870−894.

(2) For selected referenes on bioactive allenes, see: (a) Krause, N.; Hoffmann-Röder, A. Allenic Natural Products and Pharmaceuticals. In *Modern Allene Chemistry*; Wiley-VCH: 2004. (b) Ban, H. S.; Onagi, S.; Uno, M.; Nabeyama, W.; Nakamura, H. Allene as an Alternative Functional Group for Drug Design: Effect of C−C Multiple Bonds Conjugated with Quinazolines on the Inhibition of EGFR Tyrosine Kinase. *ChemMedChem* **2008**, *3*, 1094−1103. (c) Ching, C. K.; Lam, S. K. A comparison of two prostaglandin analogues (enprostil vs misoprostol) in the treatment of acute duodenal ulcer disease. *J. Gastroenterol.* **1995**, *30*, 607−614.

(3) For selected reviews and references on the synthetic utility of allenes, see: (a) Hoffmann-Röder, A.; Krause, N. Enantioselective Synthesis of and with Allenes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933−2935. (b) Brummond, K. M.; Chen, H. Allenes in Natural Product Synthesis. In *Modern Allene Chemistry*; Wiley-VCH: 2004. (c) Hashmi, A. S. K. New and Selective Transition Metal Catalyzed Reactions of Allenes. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590−3593. (d) Rivera-Fuentes, P.; Diederich, F. Allenes in Molecular Materials. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818−2828. (e) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112. (f) Ma, S. Electrophilic Addition and Cyclization Reactions of Allenes. *Acc. Chem. Res.* **2009**, *42*, 1679−1688. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C. Exploiting [2 + 2] cycloaddition chemistry: achievements with allenes. *Chem. Soc. Rev.* **2010**, *39*, 783−816. (h) Krause, N.; Winter, C. Gold−Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles. *Chem. Rev.* **2011**, *111*, 1994−2009. (i) Adams, C. S.; Weatherly, C. D.; Burke, E. G.; Schomaker, J. M. The conversion of allenes to strained three-membered heterocycles. *Chem. Soc. Rev.* **2014**, *43*, 3136−3163. (j) Alonso, J. M.; Quirós, M. T.; Muñoz, M. P. Chirality transfer in metal−catalyzed intermolecular addition reactions involving allenes. *Org. Chem. Front.* **2016**, *3*, 1186−1204. (k) Sutherland, D. R.; Kinsman, L.; Angiolini, S. M.; Rosair, G. M.; Lee, A.-L. Gold(I)−Catalysed Hydroarylation of 1,3-Disubstituted Allenes with Efficient Axial-to-Point Chirality Transfer. *Chem. - Eur. J.* **2018**, *24*, 7002−7009.

(4) Sato, I.; Matsueda, Y.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Soai, K. Highly Enantioselective Asymmetric Autocatalysis of Pyrimidin-5-yl Alkanol Induced by Chiral 1,3-Disubstituted Hydrocarbon Allenes. *Helv. Chim. Acta* **2002**, *85*, 3383−3387.

(5) Cai, F.; Pu, X.; Qi, X.; Lynch, V.; Radha, A.; Ready, J. M. Chiral Allene-Containing Phosphines in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2011**, *133*, 18066−18069.

(6) Vanitcha, A.; Damelincourt, C.; Gontard, G.; Vanthuyne, N.; Mouriès-Mansuy, V.; Fensterbank, L. Bis-phosphine allene ligand: coordination chemistry and preliminary applications in catalysis. *Chem. Commun.* **2016**, *52*, 6785−6788.

(7) For selected reviews on the asymmetric synthesis of allenes, see: (a) Krause, N.; Hoffmann-Röder, A. Synthesis of allenes with organometallic reagents. *Tetrahedron* **2004**, *60*, 11671−11694. (b) Brummond, K. M.; DeForrest, J. E. Synthesizing Allenes Today (1982−2006). *Synthesis* **2007**, *2007*, 795−818. (c) Yu, S.; Ma, S. How easy are the syntheses of allenes? *Chem. Commun.* **2011**, *47*, 5384−5418. (d) Ye, J.; Ma, S. Conquering three−carbon axial chirality of allenes. *Org. Chem. Front.* **2014**, *1*, 1210−1224. (e) Shirakawa, S.; Liu, S.; Kaneko, S. Organocatalyzed Asymmetric Synthesis of Axially, Planar, and Helical Chiral Compounds. *Chem. - Asian J.* **2016**, *11*, 330−341. (f) Chu, W.−D.; Zhang, Y.; Wang, J. Recent advances in catalytic asymmetric synthesis of allenes. *Catal. Sci. Technol.* **2017**, *7*, 4570−4579.

(8) For references concerning the catalytic asymmetric synthesis of chiral tri- or tetrasubstituted allenes, see: (a) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. Axially chiral allenylboranes: catalytic asymmetric synthesis by palladium-catalysed hydroboration of but-1-en-3-ynes and their reaction with an aldehyde. *J. Chem. Soc., Chem. Commun.* **1993**, 1468−1469. (b) Han, J. W.; Tokunaga, N.; Hayashi, T. Palladium-Catalyzed Asymmetric Hydrosilylation of 4-Substituted 1-Buten-3-ynes. Catalytic Asymmetric Synthesis of Axially Chiral Allenylsilanes. *J. Am. Chem. Soc.* **2001**, *123*, 12915−12916. (c) Hayashi, T.; Tokunaga, N.; Inoue, K. Rhodium-Catalyzed Asymmetric 1,6-Addition of Aryltitanates to Enynones Giving Axially Chiral Allenes. *Org. Lett.* **2004**, *6*, 305−307. (d) Ogasawara, M.; Ito, A.; Yoshida, K.; Hayashi, T. Synthesis of 2,5-Bis(binaphthyl)phospholes and Phosphametallocene Derivatives and Their Application in Palladium-Catalyzed Asymmetric Hydrosilylation. *Organometallics* **2006**, *25*, 2715−2718. (e) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. Iron Porphyrin-Catalyzed Olefination of Ketenes with Diazoacetate for the Enantioselective Synthesis of Allenes. *J. Am. Chem. Soc.* **2007**, *129*, 1494−1495. (f) Nemoto, T.; Kanematsu, M.; Tamura, S.; Hamada, Y. Palladium-Catalyzed Asymmetric Allylic Alkylation of 2,3-Allenyl Acetates Using a Chiral Diaminophosphine Oxide. *Adv. Synth. Catal.* **2009**, *351*, 1773−1778. (g) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. Enantioselective Bromolactonization of Conjugated (Z)-Enynes. *J. Am. Chem. Soc.* **2010**, *132*, 3664−3665. (h) Li, H.; Müller, D.; Guénée, L.; Alexakis, A. Copper-Catalyzed Enantioselective Synthesis of Axially Chiral Allenes. *Org. Lett.* **2012**, *14*, 5880−5883. (i) Inokuma, T.; Furukawa, M.; Suzuki, Y.; Kimachi, T.; Kobayashi, Y.; Takemoto, Y. Organocatalyzed Isomerization of α-Substituted Alkynoates into Trisubstituted Allenoates by Dynamic Kinetic Resolution. *ChemCatChem* **2012**, *4*, 983−985. (j) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. Phase-transfer-catalysed asymmetric synthesis of tetrasubstituted allenes. *Nat. Chem.* **2013**, *5*, 240. (k) Wang, Y.; Zhang, W.; Ma, S. A Room-Temperature Catalytic Asymmetric Synthesis of Allenes with ECNU-Phos. *J. Am. Chem. Soc.* **2013**, *135*, 11517−11520. (l) Qian, H.; Yu, X.; Zhang, J.; Sun, J. Organocatalytic Enantioselective Synthesis of 2,3-Allenoates by Intermolecular Addition of Nitroalkanes to Activated Enynes. *J. Am. Chem. Soc.* **2013**, *135*, 18020−18023. (m) Tap, A.; Blond, A.; Wakchaure, V. N.; List, B. Chiral Allenes via Alkynylogous Mukaiyama Aldol Reaction. *Angew. Chem., Int. Ed.* **2016**, *55*, 8962−8965. (n) Wang, M.; Liu, Z.-L.; Zhang, X.; Tian, P.-P.; Xu, Y.-H.; Loh, T.-P. Synthesis of Highly Substituted Racemic and Enantioenriched Allenylsilanes via Copper-Catalyzed Hydrosilylation of (Z)-2-Alken-4-ynoates with Silylboronate. *J. Am. Chem. Soc.* **2015**, *137*, 14830−14833. (o) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. Direct Synthesis of Chiral Allenoates from the Asymmetric C−H Insertion of α-Diazoesters into Terminal Alkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512−9516. (p) Yao, Q.; Liao, Y.; Lin, L.; Lin, X.; Ji, J.; Liu, X.; Feng, X. Efficient Synthesis of Chiral Trisubstituted 1,2-Allenyl Ketones by Catalytic Asymmetric Conjugate Addition of Malonic Esters to Enynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 1859−1863. (q) Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. Enantioselective Synthesis of Trisubstituted Allenes via Cu(I)-Catalyzed Coupling of Diazoalkanes with Terminal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 14558−14561. (r) Poulsen, P. H.; Li, Y.; Lauridsen, V. H.; Jørgensen, D. K. B.; Palazzo, T. A.; Meazza, M.; Jørgensen, K. A. Organocatalytic Formation of Chiral Trisubstituted Allenes and Chiral Furan Derivatives. *Angew. Chem., Int. Ed.* **2018**, *57*, 10661−10665. (s) Zhang, Y.; Yu, B.; Gao, B.; Zhang, T.; Huang, H. Triple-Bond Insertion Triggers Highly Regioselective 1,4-Aminomethylamination of 1,3-Enynes with Aminals Enabled by Pd-Catalyzed C−N Bond Activation. *Org. Lett.* **2019**, *21*, 535−539.

DOI: 10.1021/jacs.9b07582
J. Am. Chem. Soc. 2019, 141, 13788−13794

(9) For selected reviews on the synthesis of 1,3-enynes, see: (a) Zhou, Y.; Zhang, Y.; Wang, J. Recent advances in transition–metal–catalyzed synthesis of conjugated enynes. *Org. Biomol. Chem.* **2016**, *14*, 6638–6650. (b) Trost, B. M.; Masters, J. T. Transition metal–catalyzed couplings of alkynes to 1,3–enynes: modern methods and synthetic applications. *Chem. Soc. Rev.* **2016**, *45*, 2212–2238.
(10) Adamson, N. J.; Jeddi, H.; Malcolmson, S. J. Preparation of Chiral Allenes through Pd–Catalyzed Intermolecular Hydroamination of Conjugated Enynes: Enantioselective Synthesis Enabled by Catalyst Design. *J. Am. Chem. Soc.* **2019**, *141*, 8574–8583.
(11) Huang, Y.; del Pozo, J.; Torker, S.; Hoveyda, A. H. Enantioselective Synthesis of Trisubstituted Allenyl–B(pin) Compounds by Phosphine–Cu–Catalyzed 1,3–Enyne Hydroboration. Insights Regarding Stereochemical Integrity of Cu–Allenyl Intermediates. *J. Am. Chem. Soc.* **2018**, *140*, 2643–2655.
(12) Sang, H. L.; Yu, S.; Ge, S. Copper–catalyzed asymmetric hydroboration of 1,3–enynes with pinacolborane to access chiral allenylboronates. *Org. Chem. Front.* **2018**, *5*, 1284–1287.
(13) Gao, D.–W.; Xiao, Y.; Liu, M.; Liu, Z.; Karunananda, M. K.; Chen, J. S.; Engle, K. M. Catalytic, Enantioselective Synthesis of Allenyl Boronates. *ACS Catal.* **2018**, *8*, 3650–3654.
(14) Yu, S.; Sang, H. L.; Zhang, S.–Q.; Hong, X.; Ge, S. Catalytic asymmetric synthesis of chiral trisubstituted heteroaromatic allenes from 1,3–enynes. *Commun. Chem.* **2018**, *1*, 64.
(15) Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. Catalytic Synthesis of Allenes via Isomerization of Alkynes under Phase-Transfer Catalyzed Conditions. *Synlett* **2000**, *2000*, 493–494.
(16) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. Dynamic Kinetic Asymmetric Allylic Alkylations of Allenes. *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187.
(17) Wei, X.-F.; Wakaki, T.; Itoh, T.; Li, H.-L.; Yoshimura, T.; Miyazaki, A.; Oisaki, K.; Hatanaka, M.; Shimizu, Y.; Kanai, M. Catalytic Regio- and Enantioselective Proton Migration from Skipped Enynes to Allenes. *Chem.* **2019**, *5*, 585–599.
(18) For examples of catalytic asymmetric allenyl ester or ketone synthesis, see: (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. Palladium–Catalyzed Asymmetric Synthesis of Axially Chiral Allenes: A Synergistic Effect of Dibenzalacetone on High Enantioselectivity. *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090. (b) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.–I. Palladium–Catalyzed Asymmetric Alkylation of 2,3-Alkadienyl Phosphates. Synthesis of Optically Active 2-(2,3-Alkadienyl)malonates. *Chem. Lett.* **2002**, *31*, 140–141. (c) Ogasawara, M.; Nagano, T.; Hayashi, T. A New Route to Methyl (R,E)-(−)-Tetradeca-2,4,5-trienoate (Pheromone of Acanthoscelides obtectus) Utilizing a Palladium–Catalyzed Asymmetric Allene Formation Reaction. *J. Org. Chem.* **2005**, *70*, 5764–5767. (d) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. Enantioselective Synthesis of Chiral Allenoates by Guanidine–Catalyzed Isomerization of 3-Alkynoates. *J. Am. Chem. Soc.* **2009**, *131*, 7212–7213. (e) Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. Bifunctional Hydrogen–Bond Donors That Bear a Quinazoline or Benzothiadiazine Skeleton for Asymmetric Organocatalysis. *Chem. - Eur. J.* **2011**, *17*, 10470–10477. (f) Crouch, I. T.; Neff, R. K.; Frantz, D. E. Pd–Catalyzed Asymmetric β–Hydride Elimination en Route to Chiral Allenes. *J. Am. Chem. Soc.* **2013**, *135*, 4970–4973. (g) Line, N.; Witherspoon, B.; Hancock, E.; Brown, K. Synthesis of *ent*-[3]-Ladderanol: Development and Application of Intramolecular Chirality Transfer [2 + 2] Cycloadditions of Allenic Ketones and Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 14392–14395. (h) Song, S.; Zhou, J.; Fu, C.; Ma, S. Catalytic enantioselective construction of axial chirality in 1,3–disubstituted allenes. *Nat. Commun.* **2019**, *10*, 507.
(19) For examples of catalytic asymmetric allenyl alcohol synthesis, see: (a) Ye, J.; Li, S.; Chen, B.; Fan, W.; Kuang, J.; Liu, J.; Liu, Y.; Miao, B.; Wan, B.; Wang, Y.; Xie, X.; Yu, Q.; Yuan, W.; Ma, S. Catalytic Asymmetric Synthesis of Optically Active Allenes from Terminal Alkynes. *Org. Lett.* **2012**, *14*, 1346–1349. (b) Jiang, Y.; Diagne, A. B.; Thomson, R. J.; Schaus, S. E. Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions. *J. Am. Chem. Soc.* **2017**, *139*, 1998–2005.
(20) For examples of catalytic asymmetric allenyl amine synthesis, see: (a) Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.-I.; Naota, T. Palladium–Catalyzed Asymmetric Amination and Imidation of 2,3-Allenyl Phosphates. *Org. Lett.* **2005**, *7*, 5837–5839. (b) Imada, Y.; Nishida, M.; Naota, T. Sequential asymmetric homoallenylation of primary amines with a palladium catalyst. *Tetrahedron Lett.* **2008**, *49*, 4915–4917. (c) Boutier, A.; Kammerer–Pentier, C.; Krause, N.; Prestat, G.; Poli, G. Pd–Catalyzed Asymmetric Synthesis of N–Allenyl Amides and Their Au–Catalyzed Cycloisomerizative Hydroalkylation: A New Route Toward Enantioenriched Pyrrolidones. *Chem. - Eur. J.* **2012**, *18*, 3840–3844. (d) Wan, B.; Ma, S. Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines. *Angew. Chem., Int. Ed.* **2013**, *52*, 441–445. (e) Wu, Z.; Berhal, F.; Zhao, M.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V. Palladium–Catalyzed Efficient Enantioselective Synthesis of Chiral Allenes: Steric and Electronic Effects of Ligands. *ACS Catal.* **2014**, *4*, 44–48. (f) Poh, J.–S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. V. Rapid Asymmetric Synthesis of Disubstituted Allenes by Coupling of Flow–Generated Diazo Compounds and Propargylated Amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 1864–1868.
(21) These products are also accessible via protodeboration of the allenyl-Bpin products from refs 11–13 using $Cu(OAc)_2$ (5 mol%), dppe (5 mol%), and methanol (2 equiv), as described in the Supporting Information of ref 11.
(22) Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. Copper–catalyzed asymmetric addition of olefin–derived nucleophiles to ketones. *Science* **2016**, *353*, 144.
(23) For selected references on copper-catalyzed alcohol silylation with hydrosilanes, see: (a) Schubert, U.; Lorenz, C. Conversion of Hydrosilanes to Silanols and Silyl Esters Catalyzed by $[Ph_3PCuH]_6$. *Inorg. Chem.* **1997**, *36*, 1258–1259. (b) Ito, H. W.; Watanabe, A.; Sawamura, M. Versatile Dehydrogenative Alcohol Silylation Catalyzed by Cu(I)–Phosphine Complex. *Org. Lett.* **2005**, *7*, 1869–1871. (c) Jeon, M.; Han, J.; Park, J. Catalytic Synthesis of Silanols from Hydrosilanes and Applications. *ACS Catal.* **2012**, *2*, 1539–1549.
(24) For an example of the selective reduction of a 1,3-enyne to a 1,3-diene, see: Whittaker, A. M.; Lalic, G. Monophasic Catalytic System for the Selective Semireduction of Alkynes. *Org. Lett.* **2013**, *15*, 1112–1115.
(25) For examples of chiral aluminum hydride reagents used for the semireduction of 1,3-enynes, see: (a) Evans, R. J. D.; Landor, S. R.; Regan, J. P. The asymmetric synthesis and absolute configuration of allenic alcohols. *Chem. Commun.* **1965**, 397–398. (b) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R. The asymmetric reduction of alkenynols with the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuration complex and the determination of the absolute configuration of naturally occurring allenes. *Chem. Commun.* **1966**, *0*, 585–586. (c) Cowie, J. S.; Landor, P. D.; Landor, S. R.; Punja, N. Allenes. Part XXII. The synthesis and absolute configuration of laballenic and lamenallenic acids. *J. Chem. Soc., Perkin Trans. 1* **1972**, *1*, 2197–2201. (d) Evans, R. J. D.; Landor, S. R.; Regan, J. P. Asymmetric syntheses. Part VII. Asymmetric reduction of ketones and alk–2–en–4–yn–1–ols with a lithium bismenthyloxyaluminium hydride complex; determination of the absolute configurations of allenic alcohols. *J. Chem. Soc., Perkin Trans. 1* **1974**, 552–556. (e) Landor, S. R.; Miller, B. J.; Regan, J. P.; Tatchell, A. R. Asymmetric syntheses. Part VIII. Asymmetric synthesis of β–allenic alcohols with the lithium aluminium hydride–3–O–benzyl–1,2–O–cyclohexylidene–α–D–glucofuranose complex; determination of the absolute configuration of marasin (nona–3,4–diene–6,8–diyn–1–ol) and 9–methylmarasin (deca–3,4–diene–6,8–diyn–1–ol). *J. Chem. Soc., Perkin Trans. 1* **1974**, 557–561.
(26) For examples of substrates which gave poor reactivity or selectivity, see the Supporting Information.
(27) Using the standard reaction conditions detailed in Table 2 with a 5 mol% catalyst loading, substrate **1q** gave only 51% conversion with

DOI: 10.1021/jacs.9b07582
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a 24% ^{1}H NMR yield of **4q** and a 20% combined ^{1}H NMR yield of over-reduction products. Additionally, using the same conditions with a 2 mol% catalyst loading, substrate **1r** gave only 33% conversion with a 33% ^{1}H NMR yield of **4r**.

(28) McClellan, K. J.; Wiseman, L. R.; Markham, A. Terbinafine. An update of its use in superficial mycoses. *Drugs* **1999**, *58*, 179−202.

(29) Tlili, N.; Elfalleh, W.; Saadaoui, E.; Khaldi, A.; Triki, S.; Nasri, N. The caper (Capparis L.): Ethnopharmacology, phytochemical and pharmacological properties. *Fitoterapia* **2011**, *82*, 93−101.

(30) Bagby, M. O.; Smith, C. R.; Wolff, I. A. Laballenic Acid. A New Allenic Acid from Leonotis nepetaefolia Seed Oil. *J. Org. Chem.* **1965**, *30*, 4227−4229.

(31) Tang, X.; Huang, X.; Cao, T.; Han, Y.; Jiang, X.; Lin, W.; Tang, Y.; Zhang, J.; Yu, Q.; Fu, C.; Ma, S. $CuBr_2$−catalyzed enantioselective routes to highly functionalized and naturally occurring allenes. *Org. Chem. Front.* **2015**, *2*, 688−691.

(32) Yu, Q.; Ma, S. An Enantioselective Synthesis of (R)−5,6−Octadecadienoic Acid. *Eur. J. Org. Chem.* **2015**, *2015*, 1596−1601.

(33) Gant, T. G. Using Deuterium in Drug Discovery: Leaving the Label in the Drug. *J. Med. Chem.* **2014**, *57*, 3595−3611.

(34) Ma, S. Transition Metal−Catalyzed/Mediated Reaction of Allenes with a Nucleophilic Functionality Connected to the α−Carbon Atom. *Acc. Chem. Res.* **2003**, *36*, 701−712.

(35) Alcaide, B.; Almendros, P. Novel Cyclization Reactions of Aminoallenes. *Adv. Synth. Catal.* **2011**, *353*, 2561−2576.

(36) Morita, N.; Krause, N. Gold Catalysis in Organic Synthesis: Efficient Cycloisomerization of α-Aminoallenes to 3-Pyrrolines. *Org. Lett.* **2004**, *6*, 4121−4123.

(37) Morita, N.; Krause, N. Gold-Catalyzed Cycloisomerization of α-Aminoallenes to 3-Pyrrolines− Optimization and Mechanistic Studies. *Eur. J. Org. Chem.* **2006**, *2006*, 4634−4641.

DOI: 10.1021/jacs.9b07582
J. Am. Chem. Soc. 2019, 141, 13788−13794