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

Nickel-Catalyzed Enantioconvergent and Diastereoselective Allenylation of Alkyl Electrophiles: Simultaneous Control of Central and Axial Chirality

Asik Hossain, Robert L. Anderson, Claudia S. Zhang, Peng-Jui Chen, and Gregory C. Fu*

Cite This: J. Am. Chem. Soc. 2024, 146, 7173−7177
Read Online

ABSTRACT: In recent years, remarkable progress has been described in the development of methods that simultaneously control vicinal stereochemistry, wherein both stereochemical elements are central chirality; in contrast, methods that control central and axial chirality are comparatively rare. Herein we report that a chiral nickel catalyst achieves the enantioconvergent and diastereoselective coupling of racemic secondary alkyl electrophiles with prochiral 1,3-enynes (in the presence of a hydrosilane) to generate chiral tetrasubstituted allenes that bear an adjacent stereogenic center. A carbon−carbon and a carbon−hydrogen bond are formed in this process, which provides good stereoselectivity and is compatible with an array of functional groups.

Because the construction of carbon−carbon bonds and the control of stereochemistry are two central challenges in modern organic synthesis,[1,2] the development of methods, particularly catalytic processes, that simultaneously achieve both objectives is an important goal.[3] Metal-catalyzed coupling reactions of alkyl electrophiles with carbon (pro)nucleophiles are a powerful tool for carbon−carbon bond formation, and numerous enantioselective variants have been described that control a single stereochemical element at the new carbon−carbon bond (e.g., central or axial chirality).[4,5] Controlling *two* stereochemical elements further elevates the challenge and the potential of such couplings, and initial progress has recently been described in addressing this objective, specifically, controlling *two stereogenic centers* (Figure 1A).[6−9] In contrast, to our knowledge the challenge of controlling two *different* stereochemical elements (e.g., central and axial chirality) has not yet been achieved (Figure 1B).[10−12]

Figure 1C provides an outline of part of a pathway through which this type of catalytic asymmetric coupling might proceed. Thus, a chiral transition-metal hydride undergoes a site-selective, regioselective, and stereoselective β-migratory insertion into the prochiral double bond of a 1,3-enyne to form a secondary propargylmetal complex (**A**). A stereospecific 1,3-migration of this intermediate generates an allenylmetal complex (**B**), wherein central chirality has been transformed into axial chirality. Intermediate **B** then couples with the racemic alkyl halide via an organic radical to furnish the desired allene, which includes a stereogenic axis and center.

Herein, we describe the development of a method that achieves the coupling of an alkyl electrophile to generate a carbon−carbon bond with control of both central and axial chirality (Figure 1B), specifically, a nickel-catalyzed reaction of racemic alkyl halides with prochiral 1,3-enynes to afford enantioenriched allenes (Figure 1D).[13]

RESULTS AND DISCUSSION

Chiral allenes are of substantial interest, as they are found in natural products and have utility in wide-ranging fields such as asymmetric catalysis,[14] medicinal chemistry,[15,16] and materials science;[17] consequently, considerable attention has been focused on the development of methods for their synthesis.[18−22] We envisioned a new approach to the synthesis of enantioenriched allenes, through a metal-catalyzed coupling of an alkyl halide with a 1,3-enyne in the presence of a hydride reagent (Figure 1C).[23]

Upon surveying an array of parameters, we determined that $NiBr_2$·glyme and chiral pyridine−oxazoline ligand **L*** can catalyze the coupling of racemic alkyl electrophiles with 1,3-enynes in the presence of a hydrosilane to generate the desired allene not only in good yield but also with good stereoselectivity (Figure 2); it is noteworthy that, to control central chirality in this process, the catalyst must efficiently differentiate between two sp^3-hybridized carbon substituents of the electrophile (alkyl vs CF_3). Compounds that bear a trifluoromethyl substituent are of significant interest in areas such as materials chemistry, agrochemistry, and particularly the pharmaceutical industry, since the trifluoromethyl group is an increasingly common functional group in marketed drugs.[24−26]

This new nickel-catalyzed asymmetric allenylation is not highly sensitive to moisture or to air (Figure 2, entry 1: under otherwise identical conditions, in the presence of 1.0 equiv of water or 1.0 mL of air: ≥60% yield, 92% ee, and ≥90:10 dr; see Section VI of the Supporting Information), and it proceeds with

Received: January 13, 2024
Revised: February 14, 2024
Accepted: February 21, 2024
Published: March 6, 2024

https://doi.org/10.1021/jacs.4c00593
J. Am. Chem. Soc. 2024, 146, 7173−7177

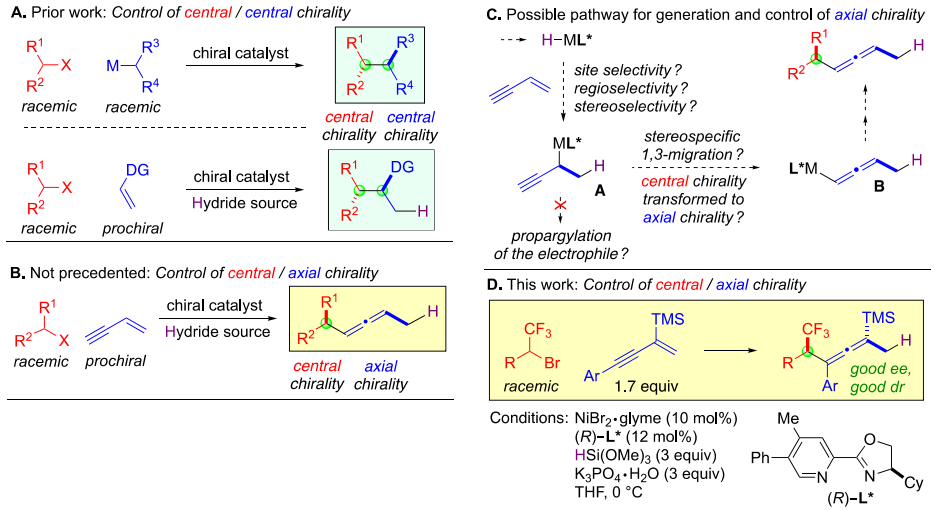

Figure 1. Metal-catalyzed couplings of racemic alkyl electrophiles with carbon (pro)nucleophiles: Simultaneous control of two stereochemical elements at the new carbon−carbon bond. (A) Prior work: Control of central/central chirality. (B) Not precedented: Control of central/axial chirality. (C) Outline of a possible pathway for generation and control of axial chirality. (D) This work: Control of central/axial chirality. DG = directing group, X = halide.

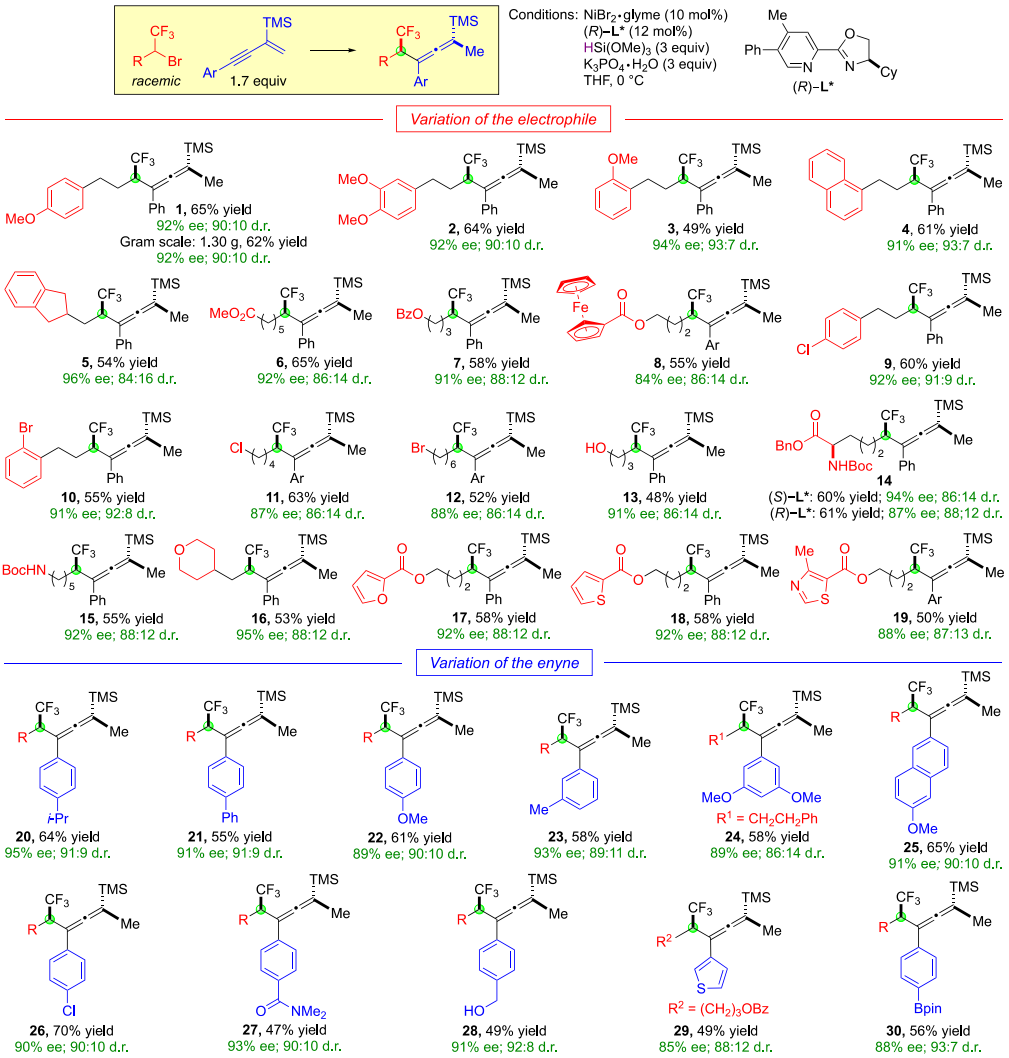

Figure 2. Asymmetric allenylations of racemic alkyl electrophiles: Scope. Reactions were conducted on a 0.8 mmol scale, unless otherwise noted. All data are the average of two experiments. All yields are of purified products. Ar = *p*-anisyl. R = CH_2CH_2(*p*-anisyl), unless otherwise noted.

https://doi.org/10.1021/jacs.4c00593
J. Am. Chem. Soc. 2024, 146, 7173−7177

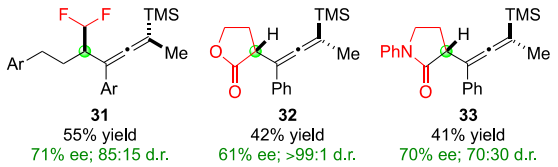

Figure 3. Asymmetric allenylations of racemic alkyl electrophiles: New families of electrophiles (preliminary results under the standard coupling conditions (Figure 2) without further optimization). Reactions were conducted on a 0.8 mmol scale. All data are the average of two experiments. All yields are of purified products. Ar = *p*-anisyl.

similar efficiency when conducted on a gram, rather than a 0.8 mmol, scale (entry 1). A variety of trifluoromethyl-substituted alkyl bromides serve as suitable coupling partners (entries 1−19), and the method is tolerant of an array of functional groups: in addition to an ether and ester (entries 1−3 and 6−8), it is compatible with potentially problematic functionalities such as an aryl chloride and bromide, primary alkyl chloride and bromide, hydroxyl, secondary carbamate, and a variety of heterocycles (tetrahydropyran, furan, thiophene, and thiazole) (entries 9−19; also, a secondary alkyl bromide,[27] quinoline, indole, and epoxide: see the Supporting Information). The stereoselectivity is relatively consistent, with ee's typically >90% and d.r.'s generally ≥86:14 (entries 1−19).

With respect to the 1,3-enyne coupling partner, an array of asymmetric allenylations proceed with good stereoselectivity (Figure 2, entries 20−30), including when the aromatic substituent is/bears an aryl chloride, tertiary amide, hydroxyl, thiophene, or boronate ester (entries 26−30).[28] While the coupling displays good functional-group tolerance, it is less tolerant of steric hindrance; for example, an α-branched electrophile and a 1,3-enyne that bears an ortho-substituted aromatic group are not suitable reaction partners under the present conditions (see Section V of the Supporting Information).

In preliminary studies, we have obtained promising lead results when applying this method directly to other families of electrophiles, indicating the potential breadth for this strategy for catalytic asymmetric allenylation (Figure 3). Not only an electrophile that is modestly different (CF_2H in place of CF_3) but also those that are entirely distinct (an α-bromolactone and an α-bromolactam) couple with encouraging stereoselectivity.

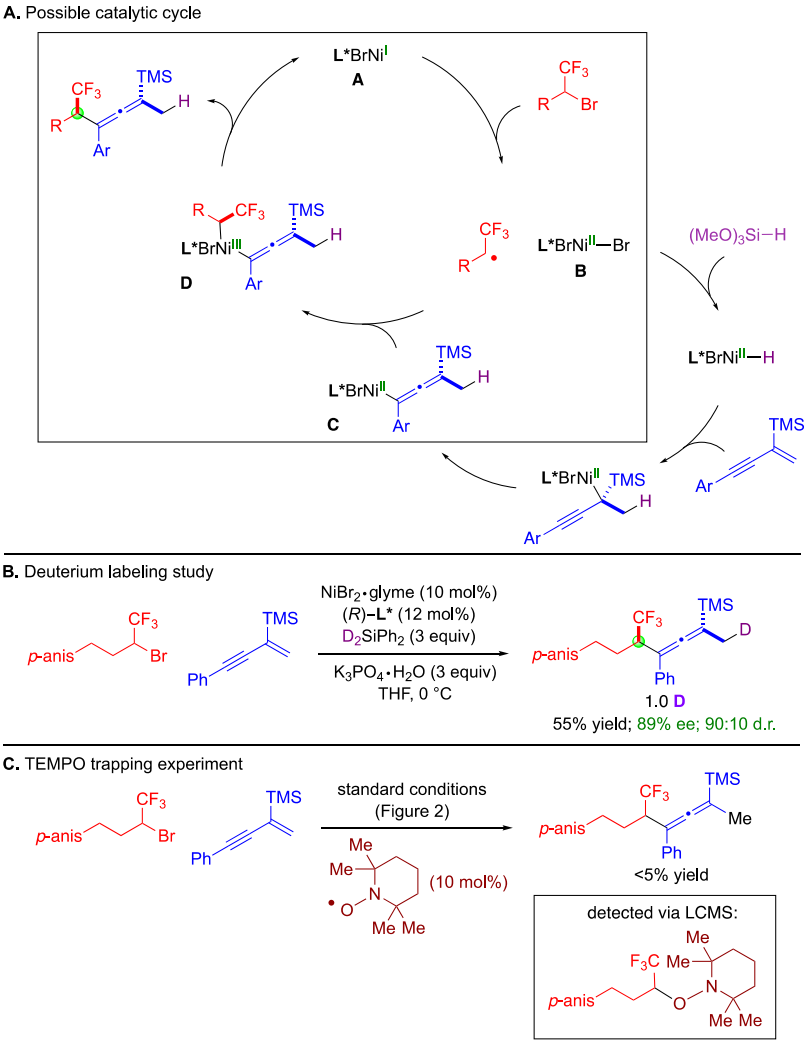

Figure 4. Asymmetric allenylations of racemic alkyl electrophiles: Mechanistic studies. (A) Possible catalytic cycle. Not every intermediate is illustrated, and for the sake of simplicity the elementary steps are depicted as irreversible. (B) Deuterium labeling study. (C) TEMPO trapping experiment.

https://doi.org/10.1021/jacs.4c00593
J. Am. Chem. Soc. 2024, 146, 7173−7177

With regard to mechanism, we hypothesize that these asymmetric allenylations may be proceeding in analogy to a pathway that we recently suggested for nickel-catalyzed enantioconvergent couplings of racemic alkyl halides with terminal olefins in the presence of a hydrosilane (Figure 4A).[29,30] We carried out preliminary mechanistic studies to gain insight into our new process. To examine the reversibility of oxidative addition/olefin binding/β-migratory insertion, we employed a deuterated silane in the asymmetric allenylation (commercially available D_2SiPh_2; H_2SiPh_2 provides comparable results to $HSi(OMe)_3$ under our standard coupling conditions); our observation that 1.0 deuterium is incorporated into the allene product suggests that oxidative addition/olefin binding/β-migratory insertion are not highly reversible (Figure 4B). Furthermore, when an asymmetric allenylation is conducted in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), a radical trap, coupling is inhibited and a TEMPO adduct of the electrophile is observed (Figure 4C), consistent with the generation of an organic radical from the alkyl bromide under the reaction conditions.[31]

CONCLUSIONS

We developed a nickel-catalyzed enantioconvergent and diastereoselective cross-coupling between racemic alkyl halides and prochiral 1,3-enynes to form chiral tetrasubstituted allenes. Whereas tremendous advances have been reported in achieving stereoselective coupling reactions of alkyl electrophiles, to the best of our knowledge this is the first such process wherein elements of central and axial chirality are controlled in the new carbon−carbon bond. Further efforts are underway to exploit earth-abundant metals in the catalytic asymmetric synthesis of motifs of interest in medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c00593.

Experimental details: general information, preparation of coupling partners, preparation of **L***, procedure for enantioconvergent and diastereoselective cross-coupling, effect of reaction parameters, studies of functional-group compatibility, assignment of absolute configuration, mechanistic studies, NMR spectra, SFC data, and references (PDF)

Accession Codes

CCDC 2311642 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

Gregory C. Fu − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0002-0927-680X; Email: gcfu@caltech.edu

Authors

Asik Hossain − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0001-8731-7083

Robert L. Anderson − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Claudia S. Zhang − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Peng-Jui Chen − *Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0002-3594-0081

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c00593

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R35-GM145315), the German Research Foundation (Deutsche Forschungsgemeinschaft (DFG); postdoctoral fellowship grant HO 6688/1-1 to A.H.), the Beckman Institute (support for the Center for Catalysis and Chemical Synthesis and for the X-ray Crystallography Facility), and the Dow Next-Generation Educator Fund (grant to Caltech). We thank Dr. Lygia Silva De Moraes, Dr. Mona Shahgholi, Dr. Michael K. Takase, Dr. David G. VanderVelde, Dr. Scott C. Virgil, Hyungdo Cho, Dr. Alexander Q. Cusumano, Xiaoyu Tong, Zhuoyan Wang, Dr. Feng Zhong, and Dr. Giuseppe Zuccarello for assistance and discussions.

REFERENCES

(1) Marek, I., Ed. Carbon−Carbon Bond Formation. In *Comprehensive Organic Synthesis*, Vol. 3; Elsevier, 2014.

(2) Carreira, E. M.; Yamamoto, H., Eds. *Comprehensive Chirality*; Elsevier, 2012.

(3) For a classic example, see: Mahrwald, R., Ed. *Modern Methods in Stereoselective Aldol Reactions*; Wiley-VCH, 2014.

(4) For leading references, see: Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to S_N1 and S_N2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692−700.

(5) Yus, M.; Nájera, C.; Foubelo, F.; Sansano, J. M. Metal-Catalyzed Enantioconvergent Transformations. *Chem. Rev.* **2023**, *123*, 11817−11893.

(6) For examples, see: Mu, X.; Shibata, Y.; Makida, Y.; Fu, G. C. Control of Vicinal Stereocenters through Nickel-Catalyzed Alkyl-Alkyl Cross-Coupling. *Angew. Chem., Int. Ed.* **2017**, *56*, 5821−5824.

(7) Huo, H.; Gorseline, B. J.; Fu, G. C. Catalyst-controlled doubly enantioconvergent coupling of racemic alkyl nucleophiles and electrophiles. *Science* **2020**, *367*, 559−564.

(8) Bera, S.; Fan, C.; Hu, X. Enantio- and diastereoselective construction of vicinal C(sp^3) centres via nickel-catalysed hydroalkylation of alkenes. *Nat. Catal.* **2022**, *5*, 1180−1187.

(9) Chen, J.; Wu, L.; Zhao, Y.; Zhu, S. Enantio- and Diastereoselective NiH-Catalyzed Hydroalkylation of Enamides or Enecarbamates with Racemic α-Bromoamides. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202311094.

(10) For related studies, see: He, C.-Y.; Tan, Y.-X.; Wang, X.; Ding, R.; Wang, Y.-F.; Wang, F.; Gao, D.; Tian, P.; Lin, G.-Q. Copper(I)-catalyzed diastereo- and enantio-selective construction of optically pure exocyclic allenes. *Nat. Commun.* **2020**, *11*, 4293.

(11) Zhang, F.-H.; Guo, X.; Zeng, X.; Wang, Z. Asymmetric 1,4-functionalization of 1,3-enynes via dual photoredox and chromium catalysis. *Nat. Commun.* **2022**, *13*, 5036.
(12) Dai, J.; Duan, X.; Zhou, J.; Fu, C.; Ma, S. Catalytic Enantioselective Simultaneous Control of Axial Chirality and Central Chirality in Allenes. *Chin. J. Chem.* **2018**, *36*, 387−391.
(13) For access to related structures through stoichiometric couplings of enantiopure nucleophiles with enantiopure electrophiles, see: Skotnitzki, J.; Kremsmair, A.; Keefer, D.; Schüppel, F.; Le Cacher de Bonneville, B.; de Vivie-Riedle, R.; Knochel, P. Regio- and diastereoselective reactions of chiral secondary alkylcopper reagents with propargylic phosphates: preparation of chiral allenes. *Chem. Sci.* **2020**, *11*, 5328−5332.
(14) For example, see: Pu, X.; Qi, X.; Ready, J. M. Allenes in Asymmetric Catalysis: Asymmetric Ring Opening of *meso*-Epoxides Catalyzed by Allene-Containing Phosphine Oxides. *J. Am. Chem. Soc.* **2009**, *131*, 10364−10365.
(15) For examples, see: 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.
(16) Souli, C.; Avlonitis, N.; Calogeropoulou, T.; Tsotinis, A.; Maksay, G.; Bíró, T.; Politi, A.; Mavromoustakos, T.; Makriyannis, A.; Reis, H.; Papadopoulos, M. Novel 17β-Substituted Conformationally Constrained Neurosteroids that Modulate $GABA_A$ receptors. *J. Med. Chem.* **2005**, *48*, 5203−5214.
(17) For leading references, see: Rivera-Fuentes, P.; Diederich, F. Allenes in molecular materials. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818−2828.
(18) For leading references, see: Zhao, J.; Xu, Y. *Axially Chiral Compounds: Asymmetric Synthesis and Applications*; Tan, B., Ed.; Wiley-VCH, 2021; Chapter 6.
(19) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112.
(20) Xiao, W.; Wu, J. Recent advances in the metal-catalyzed asymmetric synthesis of chiral allenes. *Org. Chem. Front.* **2022**, *9*, 5053−5073.
(21) Nguyen, T. T. Organocatalytic synthesis of axially chiral tetrasubstituted allenes. *Org. Biomol. Chem.* **2023**, *21*, 252−272.
(22) Hoffmann-Röder, A.; Krause, N. Synthesis and properties of allenic natural products and pharmaceuticals. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196−1216.
(23) Fu, L.; Greßies, S.; Chen, P.; Liu, G. Recent Advances and Perspectives in Transition Metal-Catalyzed 1,4-Functionalizations of Unactivated 1,3-Enynes for the Synthesis of Allenes. *Chin. J. Chem.* **2020**, *38*, 91−100.
(24) For leading references, see: Lishchynskyi, A.; Novak, P.; Grushin, V. V. *Trifluoromethylation. Science of Synthesis, C-1 Building Blocks in Organic Synthesis* **2014**, *2*, 367−408.
(25) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. *Chem. Rev.* **2015**, *115*, 826−870.
(26) Mandal, D.; Maji, S.; Pal, T.; Sinha, S. K.; Maiti, D. Recent advances in transition metal-mediated trifluoromethylation reactions. *Chem. Commun.* **2022**, *58*, 10442−10468.
(27) DFT calculations indicate that the replacement of a CH_3 group with a CF_3 group leads to the weakening of a geminal C−Br bond by ∼3 kcal/mol.
(28) Obtaining a 70% yield of coupling product with good stereoselectivity (entry 26 of Figure 2) when the racemic electrophile is the limiting reagent indicates that both enantiomers of the electrophile are being converted into the product; that is, this is an enantioconvergent reaction of the electrophile, not a simple kinetic resolution. At partial conversion, the unreacted electrophile is racemic.
(29) Wang, Z.; Yin, H.; Fu, G. C. Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins. *Nature* **2018**, *563*, 379−383.
(30) Schley, N. D.; Fu, G. C. Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation. *J. Am. Chem. Soc.* **2014**, *136*, 16588−16593.
(31) Montanari, F.; Quicio, S. 2,2,6,6-Tetramethyl-1-piperidinyloxy. In *E-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley, 2016.

https://doi.org/10.1021/jacs.4c00593
J. Am. Chem. Soc. 2024, 146, 7173−7177