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

Enantioselective Copper-Catalyzed Borylative Amidation of Allenes

Seunghwan Byun, Abdikani Omar Farah, Henry R. Wise, Andrew Katchmar, Paul H.-Y. Cheong,* and Karl A. Scheidt*

Cite This: https://doi.org/10.1021/jacs.2c10507
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An approach for the copper-catalyzed synthesis of enantioenriched amides bearing an α-stereogenic center is disclosed. This method involves the addition of an allyl copper species to an isocyanate and allows access to α-substituted chiral amides in high yields and high-to-excellent enantioselectivities. The utility of α-vinyl β-boryl amides in synthesis is highlighted by the diversification of products to afford highly useful scaffolds. DFT calculations reveal that the catalyst preferentially coordinates to the oxygen of the isocyanate. Enantiocontrol arises from the steric repulsion between the boryl group and the stereodirecting phenyl of the chiral ligand.

Enantiopure amides containing α-stereogenic centers constitute an essential class of bioactive structural motifs (Figure 1A).[1] Current research efforts have focused on the development of catalytic approaches for the synthesis of amides in an asymmetric fashion. Enantiomerically enriched amide scaffolds containing an α-stereogenic center can be accessed by a variety of methods, including the α-functionalization of amides,[2] C−H insertion of carbenoids,[3] and hydrogenation/hydroboration of α,β-unsaturated amides.[4] Yet, the efficient asymmetric synthesis of chiral amides remains challenging.

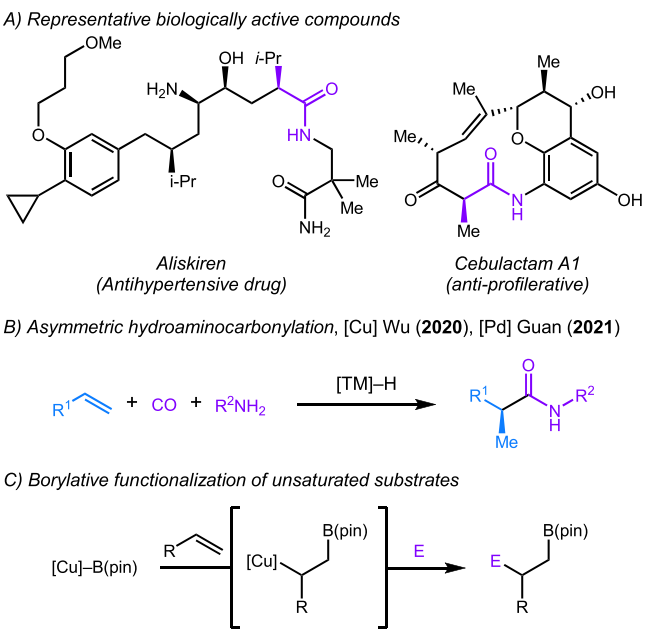


Figure 1. (A) Representative biologically active compounds containing α-substituted chiral amides. (B) Asymmetric hydroaminocarbonylation. (C) Copper-catalyzed borylative reaction. (D) Our strategy to build α-aliphatic substituted chiral amides via a process that features a six-membered transition state.

As an alternative approach, aminocarbonylation has attracted significant attention, enabling the direct transformation of simple alkenes, amines, and carbon monoxide (as well as CO surrogates) to valuable amides via transition metal catalysis.[5] While carboxylic acid and ester derivatives containing an α-stereogenic center may be accessed by asymmetric hydroxycarbonylation and alkoxylcarbonylation,[5] the enantioselective aminocarbonylation of alkenes for the synthesis of α-substituted chiral amides remains relatively underdeveloped. Recent efforts have led to the development of copper- and palladium-catalyzed aminocarbonylation strategies to furnish α-substituted amides in an asymmetric manner (Figure 1B).[6] Palladium-catalyzed methods for the enantioselective synthesis of chiral amides from aliphatic alkenes suffer from limited substrate scopes, low enantioselectivities, and moderate regioselectivities.[6b] As such, the direct synthesis of α-substituted chiral amides from aliphatic unsaturated substrates requires further development.

Since their discovery, copper-catalyzed borylative reactions represent an efficient strategy for preparing multifunctional building blocks from unsaturated substrates and electrophiles.[7] Although the Cu−B intermediate species can react with both

Received: October 5, 2022
Published: December 6, 2022

the unsaturated substrate and the electrophile, the majority of approaches developed to date proceed through the migratory insertion of unsaturated substrates to the Cu−B species, followed by the interception of the Cu−C species by an electrophile (Figure 1C). In this regard, asymmetric approaches to access chiral amides featuring an α-stereogenic center have been demonstrated using aryl alkenes as the unsaturated substrate.[8]

Due to the prevalence of aliphatic groups at the α-position of amide motifs in biologically active molecules, we sought to develop an asymmetric method to directly access α-aliphatic substituted amides. The asymmetric addition of an allyl copper species to electrophiles has emerged as an attractive strategy to construct versatile alkenyl boronates.[9,10] To the best of our knowledge, an enantioselective approach for the synthesis of α-aliphatic substituted amides remains unreported. Herein, we disclose a highly enantioselective copper-catalyzed borylative amidation of aryl and alkyl allenes using alkyl isocyanates to access α-vinyl β-boryl amides containing an α-stereogenic center in high yield and enantioselectivity (Figure 1D).

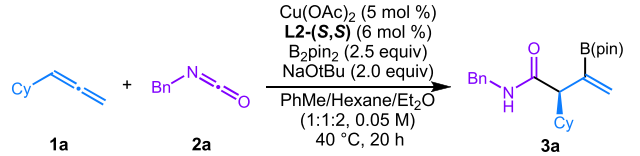
We began our investigation of this copper borylative amidation process using cyclohexyl allene **1a** and benzyl isocyanate **2a** (Table 1). Notably, aliphatic isocyanates are typically less reactive electrophiles compared to aryl isocyanate counterparts.[1c] In 2018, we reported the asymmetric synthesis of α-alkyl amidoboronates[11] using planar chiral *N*-heterocyclic carbene (NHC)−Cu complexes.[12] When our chiral NHC−Cu complexes were used, the addition of the NHC−Cu−B(pin) species to imines afforded α-alkyl amidoboronates. Based on this initial result, we hypothesized that this Cu−B(pin) species could be intercepted by the unsaturated substrate **1a** and subsequently reacted with isocyanate **2a** to produce the desired product **3a**. A preliminary screen investigated the use of our planar chiral mono- and bidentate NHC salts/copper complexes, but these were unsuccessful in providing the desired product **3a** (entry 2, Table 1; see Table S1).

To our delight, we found that $Cu(OAc)_2$ and **L2-(*S*,*S*)** delivered the branched product **3a** in 78% yield and 92:8 enantiomeric ratio (e.r.) at 40 °C (entry 1, Table 1). The use of other bisphosphines provided no improvement in yields and enantioselectivities (entries 3−6). A significant drop in yield was observed using other alkoxide bases (entries 8−11). However, the use of Et_2O as a cosolvent improved the yield and maintained the enantioselectivity (entries 12−15).

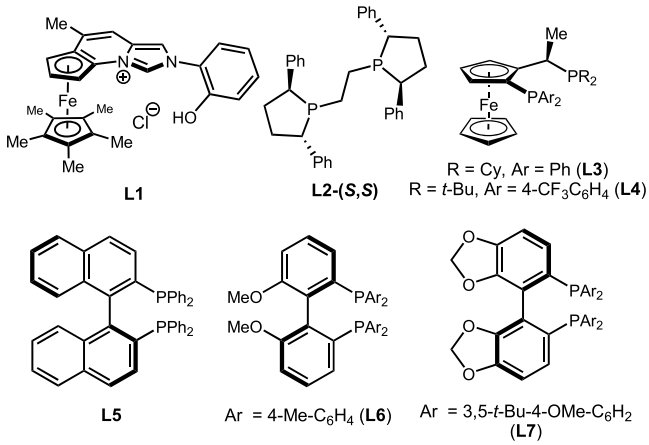
The asymmetric borylative amidation of aryl and alkyl substituted allenes **1** with cyclohexyl isocyanate **2a** was explored under the optimal conditions (Table 2). A broad range of α-vinyl β-boryl aliphatic amides containing an α-stereogenic center were produced with excellent levels of enantiopurity. The reaction of aryl allenes featuring electron-donating and -withdrawing groups at the *para*-(**3c**,**d**), *meta*-(**3e**,**f**), and *ortho*-positions (**3g**−**i**) were found to be suitable, and products were isolated in good-to-high yields and exceptional enantiomeric ratio.

A dioxolane and 1-naphthyl group were tolerated as well, furnishing the enantioenriched **3j**,**k**. Products featuring sterically large aryl groups (**3g**−**i**,**k**) were accessed with excellent enantiomeric ratios. It should be noted that the reaction was compatible with allenes featuring simple aliphatic groups (**3l**,**m**), silyl ethers (**3n**), esters (**3o**), chlorides (**3p**), and phenyls, (**3q**) and the products were isolated with high-to-excellent yield and high er. The absolute configuration of the major enantiomer (*S* for **3b**) was determined by X-ray crystallographic analysis.[13]

Table 1. Optimization of Reaction Conditions for the Cu-Catalyzed Borylative Amidation of Allenes[a]



entry	variation of standard condition	yield (%)[b]	*e.r.* (%)[c]
1	none	78[d]	92:8
2	**L1** instead of **L2-(*S*,*S*)**	–	*nd*
3	**L3** instead of **L2-(*S*,*S*)**	77	79:21
4	**L4** instead of **L2-(*S*,*S*)**	52	92:8
5	**L5** instead of **L2-(*S*,*S*)**	66	91:9
6	**L6** instead of **L2-(*S*,*S*)**	42	90:10
7	**L7** instead of **L2-(*S*,*S*)**	–	*nd*
8	KOtBu instead of NaOtBu	–	*nd*
9	LiOtBu instead of NaOtBu	17	92:8
10	NaOMe instead of NaOtBu	–	*nd*
11	NaOtAm instead of NaOtBu	50	92:8
12	PhMe instead of PhMe/Hexane/Et_2O	42	92:8
13	THF instead of PhMe/Hexane/Et_2O	34	89:11
14	Et_2O instead of PhMe/Hexane/Et_2O	73	86:14
15	Hexane instead of PhMe/Hexane/Et_2O	45	92:8



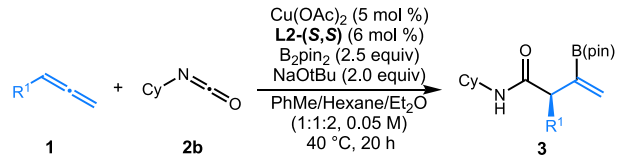
[a]Reactions performed with **1a** (0.2 mmol), **2a** (0.6 mmol), $B_2(pin)_2$ (0.5 mmol), base (0.4 mmol), $Cu(OAc)_2$ (5 mol %), Ligand (6 mol %), toluene/hexane/Et_2O (1:1:2, 0.05 M). Absolute configuration of **3a** determined based on X-ray crystallographic analysis of **3b**.[13] [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c]E.r. determined by chiral-phase SFC analysis. [d]Yield of isolated product.

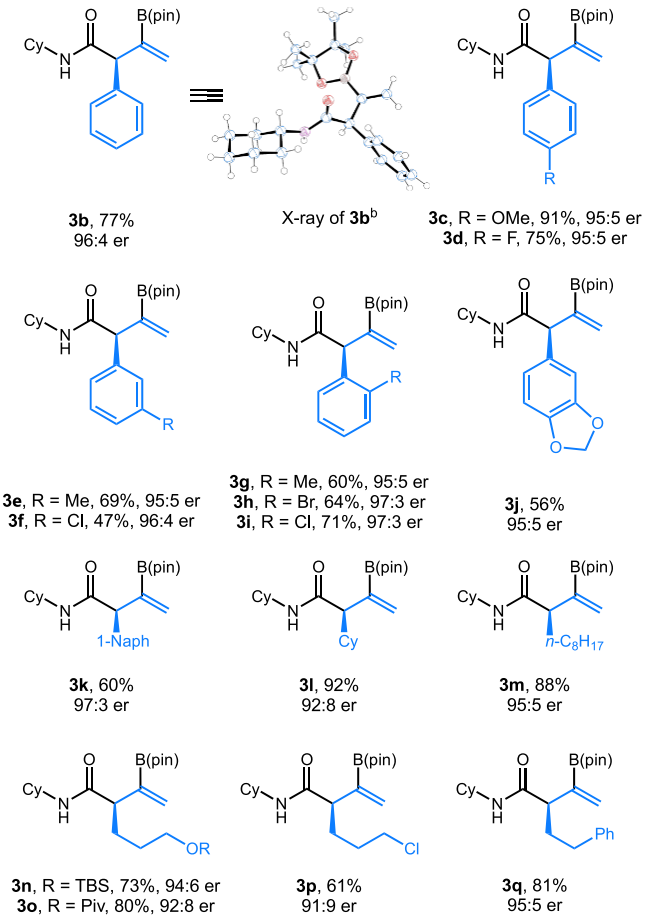
We next explored the scope with regard to isocyanates **2** in the asymmetric borylative amidation (Table 3). While simple alkyl isocyanates afforded the corresponding products (**3r**−**3t**), an isocyanate bearing a 4-methoxy gave the product **3u** in high yield but with diminished enantiomeric ratio. Highly enantiopure aliphatic secondary amides proceeded efficiently with isocyanates featuring silyl ether and an allyl isocyanate to yield products **3v** and **3w**, respectively. Furthermore, an isocyanate containing a stereogenic center was efficiently transformed to the amide products (**3x**,**y**) when either chiral ligands (**L2-*S*,*S***, and **L2-*R*,*R***) were employed, indicating that the enantiocontrol is ultimately governed by the chiral catalysts.

We further investigated the possibility of other types of allenes. An attempt to access a quaternary stereogenic center using a 1,1-disubstituted allene was successful, providing **4a** in

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

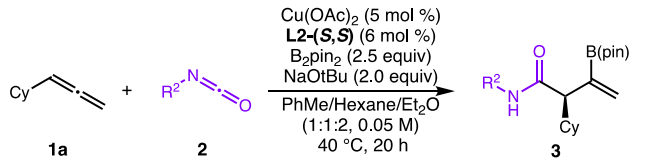
Table 2. Evaluation of Allene Substrate Scope[a]

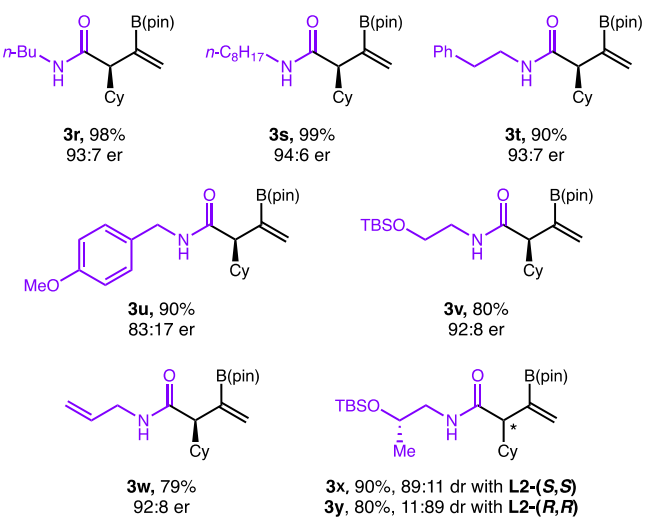




[a]Reactions performed at a 0.2 mmol scale. See the Supporting Information for details. Yields reported for isolated product. E.r. determined by chiral-phase SFC analysis. [b]Reference 13.

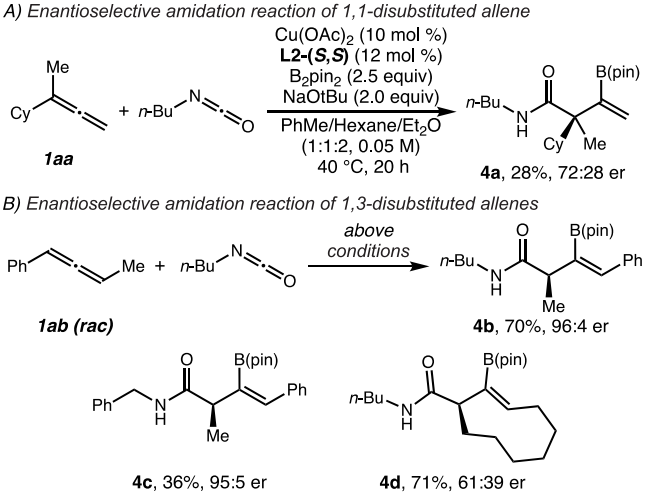
Table 3. Evaluation of the Isocyanate Scope[a]





[a]Reactions performed at a 0.2 mmol scale. See the Supporting Information for details. Yields reported for isolated product. E.r. determined by chiral-phase SFC analysis.

Scheme 1. Extension of Substrate Scope



28% yield and 72:28 er (Scheme 1A). However, when employing racemic 1,3-disubstituted allene **1ab**, product **4b** was obtained in high yield, excellent regio- and stereoselectivity (>20:1 E), and excellent enantioselectivity. The reaction of **1ab** with benzyl isocyanate afforded **4c** in 36% yield and 95:5 er, whereas product **4d** was obtained from racemic cyclic allene in somewhat diminished enantioselectivity. The reaction of racemic 1,3-disubstituted allenes using copper catalysts to provide enantioenriched products is still underdeveloped,[14−16] and the mechanistic rationale behind these enantioconvergent transformations is currently under investigation (Scheme 1B).[17]

A plausible catalytic cycle for the borylative amidation of allenes can be proposed based on previous as well as our own computational studies (Figure 2).[18,19] Initially, catalytically active bisphosphine ligated-copper alkoxide **A** is generated *in situ* via the reaction of $Cu(OAc)_2$, **L2**, and NaO*t*Bu.[20] Subsequent transmetalation with $B_2(pin)_2$ affords copper-B(pin) species **B** (*step 1*). Intermediate **B** reacts regio- and chemoselectively with allene **1** to furnish allyl copper intermediate **C** (*step 2*). **C** undergoes γ-addition (*step 3*) rather than α-addition to the isocyanate via six-membered transition state **D** (*step 4*). Regeneration of copper alkoxide **A** provides the desired α-vinyl β-boryl aliphatic amide containing an α-substituted stereogenic center (**3**, *step 5*).

We engaged DFT (PBE[21]-D3BJ[22]/6-31G*[23]/SMD[24] (Et_2O) at 313 K) to elucidate the origins of enantioselectivity for the borylative amidation, specifically for the isocyanate addition (**D**, Figure 2). We explored the α- vs γ-addition processes and the impact of E/Z configuration of the allyl−Cu species as well as Cu−N vs −O coordination in the key enantiodetermining step.[18] The lowest energy transition

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

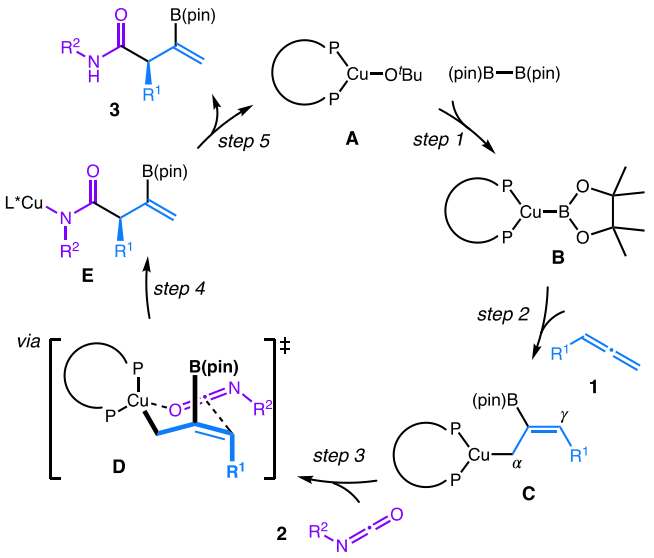


Figure 2. Proposed catalytic cycle.

structures are shown in Figure 3. α-Addition was found not to be a stationary point on the potential energy surface. The *Z* allyl transition structures were universally more stable than the A-1,2-strained *E* structures.[18] Surprisingly, transition structures bearing Cu−O coordination was energetically similar to the sterically congested Cu−N (**Major-Cu-O-(*S*)-TS** vs **Major-Cu-N-(*S*)-TS**, $\Delta G^{\ddagger}$ = 0.3 kcal/mol; Figure 3A). This was a sharp contrast to the minor transition structures, where, as expected, the congested Cu−N coordinated transition structure (**Minor-Cu-N-(*R*)-TS**) was significantly higher in energy than the Cu−O (**Minor-Cu-O-(*R*)-TS**) ($\Delta G^{\ddagger}$ = 2.2 vs 7.0 kcal/mol, respectively). The computed enantioselectivity of 2.2 kcal/mol for the minor product arising from **Minor-Cu-O-(*R*)-TS** agreed well with the experimental selectivity of 2.4 kcal/mol (96:4 e.r., **3b**, Table 2). To elucidate the origins of the observed enantioselectivity, we engaged in a quadrant steric map analysis (Figure 3C). The **Cu-L2-(*S,S*)** complex has clearly defined quadrants where approach of the substrate is blocked (Figure 3C, center). The **Major-TS-(*S*)**, which leads to the experimentally observed (*S*)-product, experiences minimal steric interaction with the catalyst system (*Right*,Figure 3C). In contrast, the boryl group of the **Minor-TS-(*R*)** directly experiences a destabilizing steric repulsion with the stereodirecting phenyl group. Specifically, this interaction is between the proximal boryl oxygen and the *ortho*-hydrogen of the stereodirecting phenyl group (**Minor-Cu-O-(*R*)-TS**, Figure 3B).

Subsequently, synthetic derivatizations were carried out to further demonstrate the utility of this asymmetric borylative

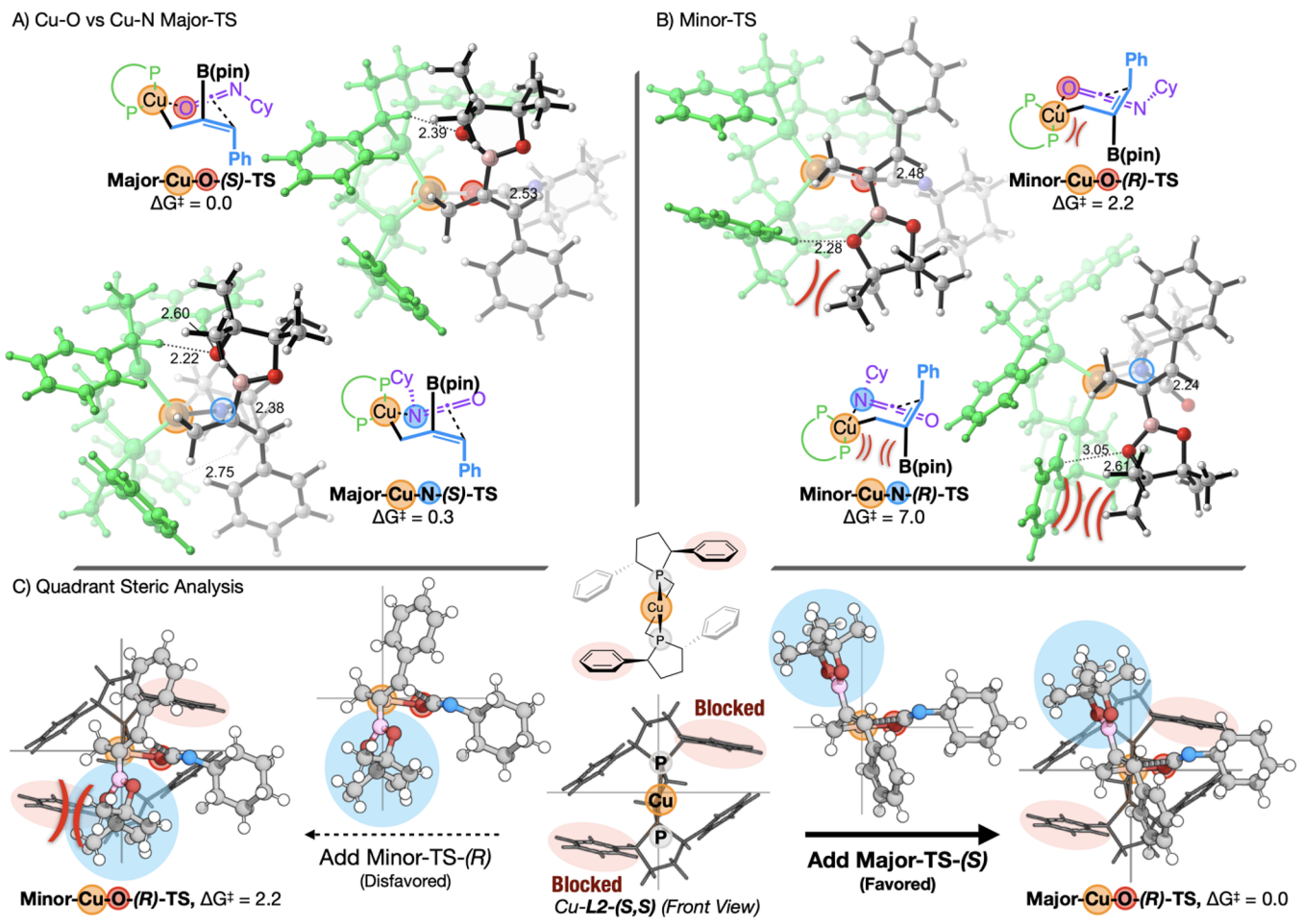
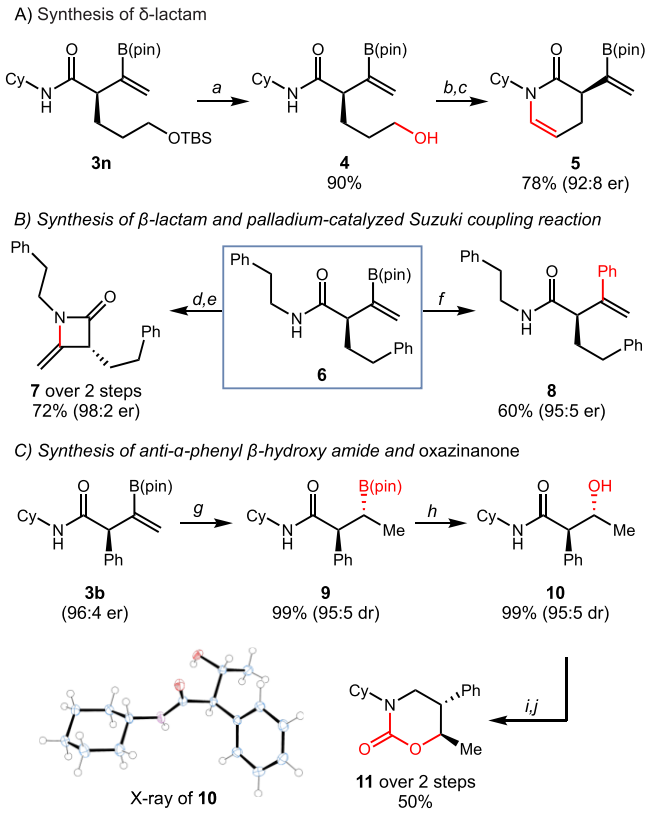


Figure 3. DFT computed transition structures (TS) for the enantioselective copper-catalyzed borylative amidation of allenes. (A) Major-Cu-O-TS vs major-Cu-N. (B) Minor-Cu-O-TS vs minor Cu-N. (C) Quadrant steric analysis showing the steric accessibility of Cu-**L2-(*S,S*)** (center), the lack of steric repulsion with the **Major-TS-(*S*)** (right), and the significant steric repulsion with the **Minor-TS-(*R*)** (left).

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

amidation in synthesis (Scheme 2). We envisioned that deprotection of **3n** would afford an alcohol that could be oxidized, and intramolecular condensation of the resulting aldehyde yielded the δ-lactam **5** in 70% total yield with a high er (92:8) (Scheme 2A).[25] We found that the treatment of the B(pin) group of **6** with $CuBr_2$ and subsequent cyclization via Cu-catalyzed Ullmann coupling delivered the corresponding β-lactam **7** in high yield in two steps without enantioerosion (98:2 e.r.) (Scheme 2B). Moreover, when alkenyl boronate **6** was subjected to a Suzuki coupling using Pd/dppf, the corresponding 1,1-disubstituted alkene **8** (60% yield, 95:5 e.r.) was easily accessed without competitive epimerization or isomerization[9b] (Scheme 2C). Finally, a rhodium-catalyzed hydrogenation of the alkenyl boronate of **3b** provided the synthetically important amide **9** with high diastereoselectivity (>95:5 d.r.). The *anti* α-phenyl-β-hydroxy amide **10** was obtained by subsequent stereoretentive oxidation of the B(pin) group of **9** in quantitative yield with excellent diastereoselectivity (>95:5 d.r.). This process provides a unique way to access typically difficult anti aldol type motifs. The *anti*-stereochemistry of the products **9** and **10** was determined by X-ray crystallographic analysis.[13] Reduction of an amide group and cyclization afforded the cyclic carbamate **11** in 50% overall yield.

Scheme 2. Synthetic Applications



[a]Conditions: (a) TBAF (2.0 equiv), THF, 60 °C, (b) DMP (1.0 equiv), CH_2Cl_2, (c) *p*-TsOH (1.0 equiv), CH_2Cl_2, (d) $CuBr_2$ (3 equiv), $MeOH/H_2O$, 100 °C, 12 h (1:1), (e) CuI (5 mol %), $Me_2NCH_2CO_2H$ (10 mol %), K_2CO_3 (2.0 equiv), THF (0.1 M), 90 °C, 20 h, (f) PhI (3.0 equiv), $PdCl_2$(dppf) (5 mol %), Cs_2CO_3 (2.0 equiv), CH_3CN, (g) H_2 (1 bar), $Rh(COD)_2BF_4$ (5 mol %), dppb (6 mol %), CH_2Cl_2. (h) H_2O_2, NaOH (3.0 M), THF, rt, 3 h.[13] (i) BH_3·THF, THF, 70 °C, 2 h. (j) CDI (1.0 equiv), Et_3N (3.0 equiv) CH_2Cl_2, 2 h.

In summary, we have developed an efficient copper-catalyzed enantioselective borylative amidation reaction using readily accessible allenes and simple isocyanates. The addition of the allyl copper species to isocyanates results in nearly exclusive regioselectivity. This protocol allows for the synthesis of α-vinyl β-boryl amides containing an α-stereogenic center with high-to-excellent enantioselectivity. The reaction proceeds efficiently with broad functional group tolerance and can access enantioenriched aryl and alkyl substituted α-stereogenic centers without isomerization or epimerization. The synthetic utility of alkenyl boronates was demonstrated by several transformations. DFT investigations revealed the mode of coordination and source of enantiocontrol in the transformation. Further developments of stereoselective borylative reactions based on these findings are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c10507.

Experimental details and characterization data, computational data, and crystallographic data (CCDC 2181752 (**3b**) and 2182017 (**10**)) (PDF)

Accession Codes

CCDC 2181752 and 2182017 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 Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Paul H.-Y. Cheong − *Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, United States;* orcid.org/0000-0001-6705-2962; Email: cheongh@oregonstate.edu

Karl A. Scheidt − *Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States;* orcid.org/0000-0003-4856-3569; Email: scheidt@northwestern.edu

Authors

Seunghwan Byun − *Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States*

Abdikani Omar Farah − *Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, United States*

Henry R. Wise − *Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, United States;* orcid.org/0000-0001-7811-6968

Andrew Katchmar − *Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c10507

Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

This work is dedicated to the memory of Professor David A. Evans (1941−2022), a supremely talented scientist and remarkable mentor. We thank the NSF (CHE-1665141, CHE-2154820) and Northwestern University for financial support of this work. A.K. thanks Northwestern for a summer undergraduate research grant. PHYC is the Bert and Emelyn Christensen professor of OSU, and gratefully acknowledges financial support from the Vicki & Patrick F. Stone family and the computing infrastructure in part provided by the NSF Phase-2 CCI, Center for Sustainable Materials Chemistry (NSF CHE-1102637). We thank Dr. Anna Bay for her comments and assistance with the preparation of this manuscript. We thank Charlotte Stern and Cullen Schull for X-ray crystallographic assistance as well as Dr. Ada Kwong and Dalton Kim for assistance with HRMS.

■ REFERENCES

(1) (a) Wang, X. Challenges and outlook for catalytic direct amidation reactions. *Nat. Catal.* **2019**, *2*, 98−102. (b) Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D. A green chemistry perspective on catalytic amide bond formation. *Nat. Catal.* **2019**, *2*, 10−17. (c) Serrano, E.; Martin, R. Forging Amides Through Metal-Catalyzed C-C Coupling with Isocyanates. *Eur. J. Org. Chem.* **2018**, *2018*, 3051−3064. (d) de Figueiredo, R. M.; Suppo, J. S.; Campagne, J. M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, *116*, 12029−12122. (e) Allen, C. L.; Williams, J. M. Metal-catalysed approaches to amide bond formation. *Chem. Soc. Rev.* **2011**, *40*, 3405−3415. (f) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev.* **2016**, *20*, 140−177. (g) Brown, D. G.; Bostrom, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443−4458.

(2) (a) Li, B.; Li, T.; Aliyu, M. A.; Li, Z. H.; Tang, W. Enantioselective Palladium-Catalyzed Cross-Coupling of alpha-Bromo Carboxamides and Aryl Boronic Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 11355−11359. (b) Jette, C. I.; Geibel, I.; Bachman, S.; Hayashi, M.; Sakurai, S.; Shimizu, H.; Morgan, J. B.; Stoltz, B. M. Palladium-Catalyzed Construction of Quaternary Stereocenters by Enantioselective Arylation of gamma-Lactams with Aryl Chlorides and Bromides. *Angew. Chem., Int. Ed.* **2019**, *58*, 4297−4301. (c) Starkov, P.; Moore, J. T.; Duquette, D. C.; Stoltz, B. M.; Marek, I. Enantioselective Construction of Acyclic Quaternary Carbon Stereocenters: Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully Substituted Amide Enolates. *J. Am. Chem. Soc.* **2017**, *139*, 9615−9620. (d) Feng, J.; Holmes, M.; Krische, M. J. Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis. *Chem. Rev.* **2017**, *117*, 12564−12580. (e) Cano, R.; Zakarian, A.; McGlacken, G. P. Direct Asymmetric Alkylation of Ketones: Still Unconquered. *Angew. Chem., Int. Ed.* **2017**, *56*, 9278−9290. (f) Hayashi, M.; Bachman, S.; Hashimoto, S.; Eichman, C. C.; Stoltz, B. M. Ni-Catalyzed Enantioselective C-Acylation of alpha-Substituted Lactams. *J. Am. Chem. Soc.* **2016**, *138*, 8997−9000. (g) Zhang, K.; Peng, Q.; Hou, X. L.; Wu, Y. D. Highly enantioselective palladium-catalyzed alkylation of acyclic amides. *Angew. Chem., Int. Ed.* **2008**, *47*, 1741−1744. (h) Smith, S. M.; Thacker, N. C.; Takacs, J. M. Efficient Amide-Directed Catalytic Asymmetric Hydroboration. *J. Am. Chem. Soc.* **2008**, *130*, 3734−3735.

(3) (a) Mandour, H. S. A.; Chanthamath, S.; Shibatomi, K.; Iwasa, S. Inter- and Intramolecular Cyclopropanations of Diazo Weinreb Amides Catalyzed by Ruthenium(II)-Amm-Pheox. *Adv. Synth. Catal.* **2017**, *359*, 1742−1746. (b) Shim, S. Y.; Kim, J. Y.; Nam, M.; Hwang, G.-S.; Ryu, D. H. Enantioselective Cyclopropanation with α-Alkyl-α-diazoesters Catalyzed by Chiral Oxazaborolidinium Ion: Total Synthesis of (+)-Hamavellone B. *Org. Lett.* **2016**, *18*, 160−163. (c) Shin, S. H.; Baek, E. H.; Hwang, G. S.; Ryu, D. H. Enantioselective Synthesis of syn-alpha-Aryl-beta-hydroxy Weinreb Amides: Catalytic Asymmetric Roskamp Reaction of alpha-Aryl Diazo Weinreb Amides. *Org. Lett.* **2015**, *17*, 4746−4749. (d) Qiu, H.; Li, M.; Jiang, L. Q.; Lv, F. P.; Zan, L.; Zhai, C. W.; Doyle, M. P.; Hu, W. H. Highly enantioselective trapping of zwitterionic intermediates by imines. *Nat. Chem.* **2012**, *4*, 733−738.

(4) (a) Gao, T. T.; Zhang, W. W.; Sun, X.; Lu, H. X.; Li, B. J. Stereodivergent Synthesis through Catalytic Asymmetric Reversed Hydroboration. *J. Am. Chem. Soc.* **2019**, *141*, 4670−4677. (b) Lu, W.-J.; Hou, X.-L. Highly Enantioselective Construction of the α-Chiral Center of AmidesviaIridium-Catalyzed Hydrogenation of α,β-Unsaturated Amides. *Adv. Synth. Catal.* **2009**, *351*, 1224−1228. (c) Thorpe, S. B.; Guo, X.; Santos, W. L. Regio- and stereoselective copper-catalyzed β-borylation of allenoates by a preactivated diboron. *Chem. Commun.* **2011**, *47*, 424−426. (d) Yuan, W.; Zhang, X.; Yu, Y.; Ma, S. Amide-Controlled Highly Selective Catalytic Borylcupration of Allenes. *Chem.—Eur. J.* **2013**, *19*, 7193−7202. (e) Hirano, K.; Yorimitsu, H.; Oshima, K. Nickel-Catalyzed β-Boration of α,β-Unsaturated Esters and Amides with Bis(pinacolato)diboron. *Org. Lett.* **2007**, *9*, 5031−5033.

(5) (a) Wu, X. F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. Transition-metal-catalyzed carbonylation reactions of olefins and alkynes: a personal account. *Acc. Chem. Res.* **2014**, *47*, 1041−1053. (b) Wu, X. F.; Neumann, H.; Beller, M. Synthesis of heterocycles via palladium-catalyzed carbonylations. *Chem. Rev.* **2013**, *113*, 1−35.

(6) (a) Feng, S.; Dong, Y.; Buchwald, S. L. Enantioselective Hydrocarbamoylation of Alkenes. *Angew. Chem., Int. Ed.* **2022**, *n/a*, No. e202206692. (b) Yao, Y. H.; Yang, H. Y.; Chen, M.; Wu, F.; Xu, X. X.; Guan, Z. H. Asymmetric Markovnikov Hydroaminocarbonylation of Alkenes Enabled by Palladium-Monodentate Phosphoramidite Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 85−91. (c) Yuan, Y.; Zhao, F.; Wu, X. F. Copper-catalyzed enantioselective carbonylation toward alpha-chiral secondary amides. *Chem. Sci.* **2021**, *12*, 12676−12681. (d) Wu, F.-P.; Holz, J.; Yuan, Y.; Wu, X.-F. Copper-Catalyzed Carbonylative Synthesis of β-Boryl Amides via Boroamidation of Alkenes. *CCS Chem.* **2021**, *3*, 2643−2654. (e) Yuan, Y.; Wu, F. P.; Schunemann, C.; Holz, J.; Kamer, P. C. J.; Wu, X. F. Copper-Catalyzed Carbonylative Hydroamidation of Styrenes to Branched Amides. *Angew. Chem., Int. Ed.* **2020**, *59*, 22441−22445.

(7) (a) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. Copper-Catalyzed Borylative Difunctionalization of π-Systems. *ACS Catal.* **2020**, *10*, 11578−11622. (b) Talbot, F. J. T.; Dherbassy, Q.; Manna, S.; Shi, C.; Zhang, S.; Howell, G. P.; Perry, G. J. P.; Procter, D. J. Copper-Catalyzed Borylative Couplings with C-N Electrophiles. *Angew. Chem., Int. Ed.* **2020**, *59*, 20278−20289. (c) Hoveyda, A. H.; Zhou, Y.; Shi, Y.; Brown, M. K.; Wu, H.; Torker, S. Sulfonate N-Heterocyclic Carbene-Copper Complexes: Uniquely Effective Catalysts for Enantioselective Synthesis of C-C, C-B, C-H, and C-Si Bonds. *Angew. Chem., Int. Ed.* **2020**, *59*, 21304−21359. (d) Hemming, D.; Fritzemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G. Copper-boryl mediated organic synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7477−7494.

(8) (a) Larin, E. M.; Torelli, A.; Loup, J.; Lautens, M. One-Pot, Three-Step Synthesis of Benzoxazinones via Use of the Bpin Group as a Masked Nucleophile. *Org. Lett.* **2021**, *23*, 2720−2725. (b) Torelli, A.; Whyte, A.; Polishchuk, I.; Bajohr, J.; Lautens, M. Stereoselective Construction of gamma-Lactams via Copper-Catalyzed Borylacylation. *Org. Lett.* **2020**, *22*, 7915−7919. (c) Su, Z.; Feng, Y.; Zou, R.; Qiu, X.; Wang, J.; Tao, C. Copper-catalyzed borylamidation of vinyl arenes with isocyanates. *Chem. Commun.* **2020**, *56*, 7483−7486. (d) Fiorito, D.; Liu, Y.; Besnard, C.; Mazet, C. Direct Access to Chiral Secondary Amides by Copper-Catalyzed Borylative Carboxamidation of Vinylarenes with Isocyanates. *J. Am. Chem. Soc.* **2020**, *142*, 623−632. (e) Whyte, A.; Torelli, A.; Mirabi, B.; Lautens, M. Enantioselective Copper-Catalyzed Borylative Cyclization with Cyclic Imides. *Org. Lett.* **2019**, *21*, 8373−8377. (f) Whyte, A.; Burton, K. I.; Zhang, J.; Lautens, M. Enantioselective Intramolecular Copper-

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Catalyzed Borylacylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 13927−13930.
(9) (a) Pozo, J. D.; Zhang, S.; Romiti, F.; Xu, S.; Conger, R. P.; Hoveyda, A. H. Streamlined Catalytic Enantioselective Synthesis of alpha-Substituted beta,gamma-Unsaturated Ketones and Either of the Corresponding Tertiary Homoallylic Alcohol Diastereomers. *J. Am. Chem. Soc.* **2020**, *142*, 18200−18212. (b) Li, Z. H.; Zhang, L.; Nishiura, M.; Luo, G.; Luo, Y.; Hou, Z. M. Enantioselective Cyanoborylation of Allenes by N-Heterocyclic Carbene-Copper Catalysts. *ACS Catal.* **2020**, *10*, 11685−11692. (c) Zhang, S.; del Pozo, J.; Romiti, F.; Mu, Y.; Torker, S.; Hoveyda, A. H. Delayed catalyst function enables direct enantioselective conversion of nitriles to NH2-amines. *Science* **2019**, *364*, 45−51. (d) Han, J.; Zhou, W.; Zhang, P. C.; Wang, H. M.; Zhang, R. H.; Wu, H. H.; Zhang, J. L. Design and Synthesis of WJ-Phos, and Application in Cu-Catalyzed Enantioselective Boroacylation of 1,1-Disubstituted Allenes. *ACS Catal.* **2019**, *9*, 6890−6895. (e) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. Catalytic diastereo- and enantioselective additions of versatile allyl groups to N−H ketimines. *Nat. Chem.* **2017**, *9*, 1269−1275. (f) Yeung, K.; Ruscoe, R. E.; Rae, J.; Pulis, A. P.; Procter, D. J. Enantioselective Generation of Adjacent Stereocenters in a Copper-Catalyzed Three-Component Coupling of Imines, Allenes, and Diboranes. *Angew. Chem., Int. Ed.* **2016**, *55*, 11912−11916. (g) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. Catalytic enantioselective 1,6-conjugate additions of propargyl and allyl groups. *Nature* **2016**, *537*, 387−393. (h) Meng, F.; McGrath, K. P.; Hoveyda, A. H. Multifunctional organoboron compounds for scalable natural product synthesis. *Nature* **2014**, *513*, 367−374. (i) Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. Cu-Catalyzed Chemoselective Preparation of 2-(Pinacolato)boron-Substituted Allylcopper Complexes and their In Situ Site-, Diastereo-, and Enantioselective Additions to Aldehydes and Ketones. *Angew. Chem., Int. Ed.* **2013**, *52*, 5046−5051.
(10) (a) Wilhelmsen, C. A.; Zhang, X.; Myhill, J. A.; Morken, J. P. Enantioselective Synthesis of Tertiary beta-Boryl Amides by Conjunctive Cross-Coupling of Alkenyl Boronates and Carbamoyl Chlorides. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202116784. (b) Davis, C. R.; Luvaga, I. K.; Ready, J. M. Enantioselective Allylation of Alkenyl Boronates Promotes a 1,2-Metalate Rearrangement with 1,3-Diastereocontrol. *J. Am. Chem. Soc.* **2021**, *143*, 4921−4927. (c) Nishikawa, T.; Ouchi, M. An Alkenyl Boronate as a Monomer for Radical Polymerizations: Boron as a Guide for Chain Growth and as a Replaceable Side Chain for Post-Polymerization Transformation. *Angew. Chem., Int. Ed.* **2019**, *58*, 12435−12439. (d) Gerleve, C.; Kischkewitz, M.; Studer, A. Synthesis of alpha-Chiral Ketones and Chiral Alkanes Using Radical Polar Crossover Reactions of Vinyl Boron Ate Complexes. *Angew. Chem., Int. Ed.* **2018**, *57*, 2441−2444. (e) Silvi, M.; Sandford, C.; Aggarwal, V. K. Merging Photoredox with 1,2-Metallate Rearrangements: The Photochemical Alkylation of Vinyl Boronate Complexes. *J. Am. Chem. Soc.* **2017**, *139*, 5736−5739. (f) Kischkewitz, M.; Okamoto, K.; Mück-Lichtenfeld, C.; Studer, A. Radical-polar crossover reactions of vinylboron ate complexes. *Science* **2017**, *355*, 936−938. (g) Edelstein, E. K.; Namirembe, S.; Morken, J. P. Enantioselective Conjunctive Cross-Coupling of Bis(alkenyl)borates: A General Synthesis of Chiral Allylboron Reagents. *J. Am. Chem. Soc.* **2017**, *139*, 5027−5030.
(11) Schwamb, C. B.; Fitzpatrick, K. P.; Brueckner, A. C.; Richardson, H. C.; Cheong, P. H.; Scheidt, K. A. Enantioselective Synthesis of alpha-Amidoboronates Catalyzed by Planar-Chiral NHC-Cu(I) Complexes. *J. Am. Chem. Soc.* **2018**, *140*, 10644−10648.
(12) Check, C. T.; Jang, K. P.; Schwamb, C. B.; Wong, A. S.; Wang, M. H.; Scheidt, K. A. Ferrocene-based planar chiral imidazopyridinium salts for catalysis. *Angew. Chem., Int. Ed.* **2015**, *54*, 4264−4268.
(13) CCDC 2181752 (**3b**), 2182017 (**10**).
(14) Huang, Y.; Torker, S.; Li, X.; Del Pozo, J.; Hoveyda, A. H. Racemic Vinylallenes in Catalytic Enantioselective Multicomponent Processes: Rapid Generation of Complexity through 1,6-Conjugate Additions. *Angew. Chem., Int. Ed.* **2019**, *58*, 2685−2691.
(15) Hilpert, L. J.; Sieger, S. V.; Haydl, A. M.; Breit, B. Palladium- and Rhodium-Catalyzed Dynamic Kinetic Resolution of Racemic Internal Allenes Towards Chiral Pyrazoles. *Angew. Chem., Int. Ed.* **2019**, *58*, 3378−3381.
(16) Chen, M.; Roush, W. R. Enantioconvergent Hydroboration of a Racemic Allene: Enantioselective Synthesis of (E)-δ-Stannyl-anti-homoallylic Alcohols via Aldehyde Crotylboration. *J. Am. Chem. Soc.* **2011**, *133*, 5744−5747.
(17) The Interconversion of allyl copper species was discussed in the literature: References 4d and 9i, and see also the following literature: (a) Ozawa, Y.; Iwamoto, H.; Ito, H. Copper(i)-catalysed regio- and diastereoselective intramolecular alkylboration of terminal allenes via allylcopper(i) isomerization. *Chem. Commun.* **2018**, *54*, 4991−4994. (b) Xiong, M.; Xie, X.; Liu, Y. Copper-Catalyzed Borylative Cyclization of in Situ Generated o-Allenylaryl Nitriles with Bis-(pinacolato)diboron. *Org. Lett.* **2017**, *19*, 3398−3401. (c) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. NHC−Cu-Catalyzed Protoboration of Monosubstituted Allenes. Ligand-Controlled Site Selectivity, Application to Synthesis and Mechanism. *Org. Lett.* **2013**, *15*, 1414−1417.
(18) For selected literatures: References 9b, c, and e and: (a) Zhao, C.-Y.; Zheng, H.; Ji, D.-W.; Min, X.-T.; Hu, Y.-C.; Chen, Q.-A. Copper-Catalyzed Asymmetric Carboboronation of Allenes to Access α-Quaternary Amino Esters with Adjacent Stereocenters. *Cell Rep. Phys. Sci.* **2020**, *1*, 100067.
(19) See the Supporting Information for details (page S86).
(20) The catalytic cycle begins with the reduction of the Cu(II) to produce the catalytically active Cu(I). For examples, see: (a) Han, J.; Zhou, W.; Zhang, P.-C.; Wang, H.; Zhang, R.; Wu, H.-H.; Zhang, J. Design and Synthesis of WJ-Phos, and Application in Cu-Catalyzed Enantioselective Boroacylation of 1,1-Disubstituted Allenes. *ACS Catal.* **2019**, *9*, 6890−6895. (b) Boreux, A.; Indukuri, K.; Gagosz, F.; Riant, O. Acyl Fluorides as Efficient Electrophiles for the Copper-Catalyzed Boroacylation of Allenes. *ACS Catal.* **2017**, *7*, 8200−8204. (c) Tani, Y.; Fujihara, T.; Terao, J.; Tsuji, Y. Copper-Catalyzed Regiodivergent Silacarboxylation of Allenes with Carbon Dioxide and a Silylborane. *J. Am. Chem. Soc.* **2014**, *136*, 17706−17709. (d) Guzman-Martinez, A.; Hoveyda, A. H. Enantioselective Synthesis of Allylboronates Bearing a Tertiary or Quaternary B-Substituted Stereogenic Carbon by NHC-Cu-Catalyzed Substitution Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 10634−10637.
(21) Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized Gradient Approximation Made Simple. *Phys. Rev. Lett.* **1996**, *77*, 3865−3868.
(22) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **2011**, *32*, 1456−1465.
(23) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian-Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972**, *56*, 2257−2261.
(24) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(25) (a) Miller, E. R.; Hovey, M. T.; Scheidt, K. A. A Concise, Enantioselective Approach for the Synthesis of Yohimbine Alkaloids. *J. Am. Chem. Soc.* **2020**, *142*, 2187−2192. (b) Kawanaka, Y.; Kobayashi, K.; Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.; Fujii, A.; Hirai, K.; Naka, M.; Komeno, M.; Odagaki, Y.; Nakai, H.; Toda, M. Design and Synthesis of Orally Bioavailable Inhibitors of Inducible Nitric Oxide Synthase. Identification of 2-Azabicyclo[4.1.0]heptan-3-imines. *Biorg. Med. Chem.* **2003**, *11*, 1723−1743.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on December 6, 2022 with production errors in Table 1 (missing graphic heading) and in

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

two author names (Paul H.-Y. Cheong and Karl A. Scheidt). The errors were corrected and the revised manuscript was reposted on December 7, 2022.

https://doi.org/10.1021/jacs.2c10507
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX