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Letter

Copper-Catalyzed Diastereo- and Enantioselective Decarboxylative [3 + 2] Cyclization of Alkyne-Substituted Cyclic Carbamates with Azlactones: Access to γ-Butyrolactams Bearing Two Vicinal Tetrasubstituted Carbon Stereocenters

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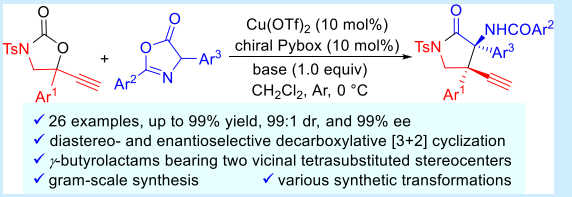
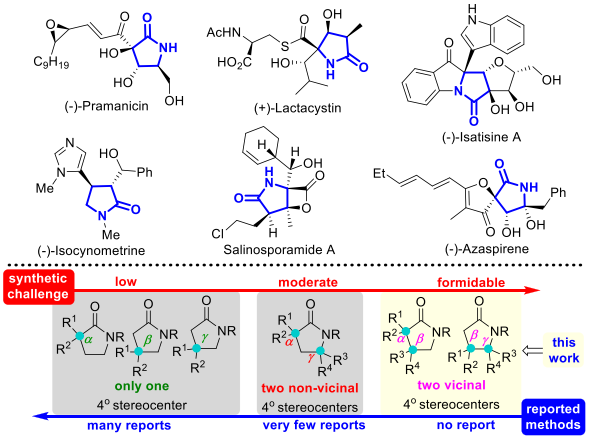
ABSTRACT: A copper-catalyzed diastereo- and enantioselective decarboxylative [3 + 2] cyclization reaction of alkyne-substituted cyclic carbamates with azlactones has been established. A range of optically pure γ-butyrolactams bearing two vicinal tetrasubstituted carbon stereocenters were obtained in high yields with good to excellent stereoselectivities (up to 99% yield, 99:1 dr, and 99% ee). This is the first example of asymmetric synthesis γ-butyrolactams containing sterically congested vicinal tetrasubstituted stereocenters via a decarboxylative cyclization pathway.



γ-Butyrolactam structures often constitute the vital structure motifs of a great number of natural products and pharmaceutically active molecules with a wide range of promising biological properties.[1] Among them, the chiral γ-butyrolactams bearing two or three vicinal carbon stereocenters at the 2-pyrrolidinone ring are particularly abundant in the biologically active molecules, as exemplified in Scheme 1.[2] Therefore, considerable efforts have been devoted to exploiting various strategies for the construction of diverse functionalized chiral γ-butyrolactam scaffolds containing vicinal stereocenters.[3] Despite the existence of a lot of elegant precedents, a careful survey of the literature revealed that, compared to the widely studied γ-butyrolactams with a single tetrasubstituted carbon stereocenter and rare research on the γ-butyrolactams with two nonvicinal tetrasubstituted carbon stereocenters,[3d] there is no report on the synthesis of γ-butyrolactams with two vicinal tetrasubstituted carbon stereocenters in a catalytic asymmetric manner so far (Scheme 1, bottom). Theoretically, it remains a formidable challenge to create two vicinal tetrasubstituted carbon stereocenters in one reaction step due to the high steric congestion among the six substituents located at the two vicinal tetrasubstituted carbon atoms.[4] Nonetheless, in consideration of the growing demand for the structural diversity of privileged three-dimensional heterocycles in the field of drug discovery process, the development of novel, practical strategy for the construction of chiral γ-butyrolactams containing vicinal tetrasubstituted carbon stereocenters is a rather fascinating research goal.

In the past decade, the copper-catalyzed asymmetric propargylic substitution reaction via a copper−allenylidene intermediate has emerged as a powerful approach for the construction of chiral molecules bearing a tetrasubstituted

Scheme 1. Representative Biologically Active Compounds Containing a Chiral γ-Butyrolactam Motif and the Profile of the Reported Methods for the Synthesis of γ-Butyrolactams Bearing Tetrasubstituted Carbon Stereocenters



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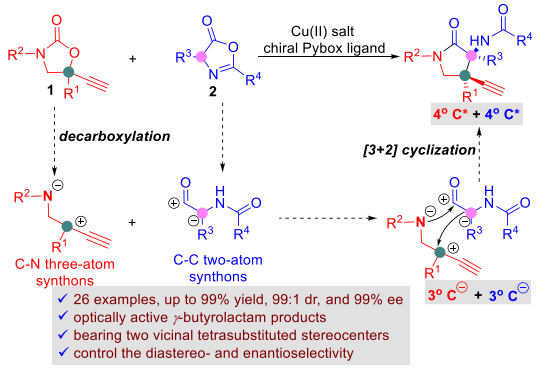
carbon stereocenter.[5] In this research area, diverse ethynyl-substituted cyclic carbamates have been designed and applied in copper-catalyzed decarboxylative cyclization reactions for the synthesis of chiral nitrogen-containing heterocycles.[6−9] Although these elegant advances have been achieved, only one report on the application of alkyne-substituted cyclic carbamates **1** for the enantioselective synthesis of optically active γ-butyrolactams with two vicinal tertiary and quaternary stereocenters was documented.[7] Meanwhile, inspired by these earlier successes,[6−9] we conceived that the cyclic carbamates **1** could serve as C−N three-atom synthons involving a tertiary carbocation and a nitrogen anion for the possible [3 + *n*] cyclization reaction in the presence of copper catalyst (Scheme 2). On the other hand, azlactones were employed as versatile

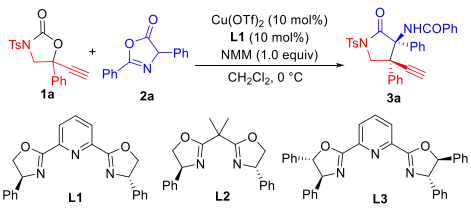
Scheme 2. Strategy for the Construction of Optically Active γ-Butyrolactams Bearing Two Vicinal Tetrasubstituted Carbon Stereocenters



two-carbon synthons for a series of [*n* + 2] cyclization reactions by using the nucleophilicity of the α-tertiary carbon atom and the electrophilicity of the carbonyl group.[10] Along this line, from the asymmetric synthesis perspective, we speculated that the reaction between alkyne-substituted cyclic carbamates **1** and azlactones should occur under the catalysis of a copper catalyst, thus undergoing an intermolecular [3 + 2] cyclization reaction to form chiral γ-butyrolactams bearing two vicinal tetrasubstituted carbon stereocenters (Scheme 2). As a continuation of our research interest in the transition-metal-catalyzed decarboxylative reaction,[11] recently, we have developed a diastereo- and enantioselective decarboxylative [3 + 2] cyclization of cyclic carbamates **1** and azlactones **2** with chiral Cu(II)/Pybox complex as the catalyst, which allows us to generate a series of optically active γ-butyrolactams in high yields with good to excellent stereoselectivities (up to 99% yield, up to 99:1 dr, and 99% ee) (Scheme 2). Notably, this represents the first successful example on the catalytic asymmetric synthesis of γ-butyrolactams bearing highly congested vicinal tetrasubstituted stereocenters. Herein we wish to report our studies on this subject.

Our optimization studies began with a model reaction of cyclic carbamate **1a** and azlactone **2a**. After systematic optimization of various parameters, a set of promising reaction conditions comprising a chiral complex from $Cu(OTf)_2$ and Pybox ligand **L1** as catalyst and *N*-methylmorpholine (NMM) as base at 0 °C in CH_2Cl_2 were recognized, which furnished the cycloadduct **3a** in 99% yield with 94:6 dr and 97% ee (Table 1, entry 1). As shown in Table 1, upon replacing the ligand **L1** with **L2** or **L3** for the reaction, it was found that the two chiral ligands were less effective than **L1** in the

Table 1. Optimization of Reaction Conditions[a]



entry	variation from the standard conditions	t (h)	yield (%)[b]	dr[c]	ee (%)[c]
1	none	2	99	94:6	97
2	**L2** instead of **L1**	2	99	66:34	18
3	**L3** instead of **L1**	2	90	73:27	48
4	toluene instead of CH_2Cl_2	14	99	87:13	86
5	CH_3CN instead of CH_2Cl_2	20	80	84:16	62
6	MeOH instead of CH_2Cl_2	4	99	78:22	69
7	THF instead of CH_2Cl_2	4	90	73:27	69
8	DABCO instead of NMM	2	90	92:8	88
9	Et_3N instead of NMM	2	90	91:9	90
10	−20 °C instead of 0 °C	10	96	85:15	84

[a]The reactions were carried out with **1a** (0.10 mmol), **2a** (0.20 mmol), $Cu(OTf)_2$ (10 mol%), **L** (10 mol%) and base (1.0 equiv) in solvent (1.0 mL) at 0 °C for the specified time. [b]Isolated yields. [c]The dr and ee values were determined by chiral HPLC analysis. DABCO = 1,4-diaza[2.2.2]bicyclooctane. NMM = *N*-methylmorpholine.

stereoselectivity (entries 2 and 3). The solvent was also crucial for the transformation as the results of cyclization in solvents including toluene, CH_3CN, MeOH, and THF were inferior to that in CH_2Cl_2 (entries 4−7). Changing the base to DABCO or Et_3N, the reaction could proceed completely in 2 h and generate **3a** in 90% yield, but with 92:8 dr, 88% ee and 91:9 dr, 90% ee, respectively (entries 8 and 9), which were inferior to the results with NMM as base. Ultimately, we sought to further improve the diastereo- and enantioselectivity by decreasing the temperature to −20 °C, instead leading to an adverse effect on the stereoselectivity (entry 10).

With the optimized reaction conditions in hand, we investigated the scope of the asymmetric decarboxylative [3 + 2] cyclization reaction, first by evaluating the influence from the aromatic substitution pattern of cyclic carbamates **1**. As shown in Scheme 3, the Ar group of cyclic carbamates bearing an electron-donating substituent (^{t}Bu−, MeO−, or Me−) was tolerated well in the reaction, delivering the corresponding γ-butyrolactams **3b−d** in 92−99% yields with high diastereo- and enantioselectivities. In addition, different electron-withdrawing substituents (F−, Cl−, and Br−) incorporated into the phenyl group, regardless of their substituted position, were also allowed in the cyclization reaction with **2a**, smoothly affording products **3e−h** in good to quantitative yields with high to excellent diastereoselectivities and 93−97% ee. Moreover, as for a disubstituted phenyl group embedded in cyclic carbamates, it was found that 3,4-dichloro-substituted substrate could furnish the corresponding product **3i** in excellent results, whereas the 2,6-disubstitutedcarbamate could give **3j** in obviously decreased results (45% yield, 59:41 dr, and 70% ee for the diastereomers, respectively), perhaps due to the inherent steric hindrance from the substitution position. In comparison with **3j**, product **3k**, bearing the same two substituents but in different substitution positions, was obtained in 97% yield with 99:1 dr and 89% ee. The 2-naphthyl-substituted cyclic carbamate also worked well

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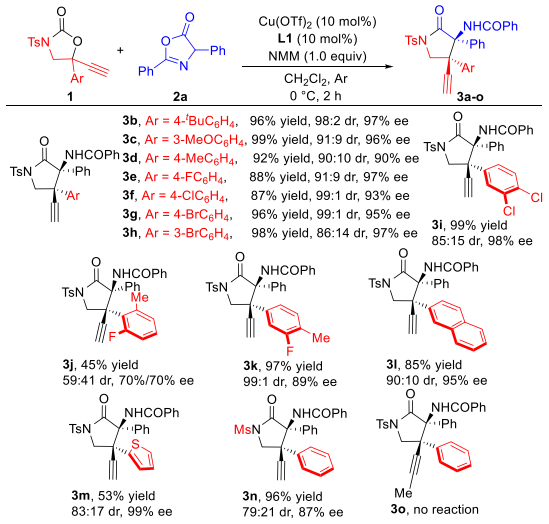
Scheme 3. Substrate Scope of Alkyne-Substituted Cyclic Carbamates 1[a]



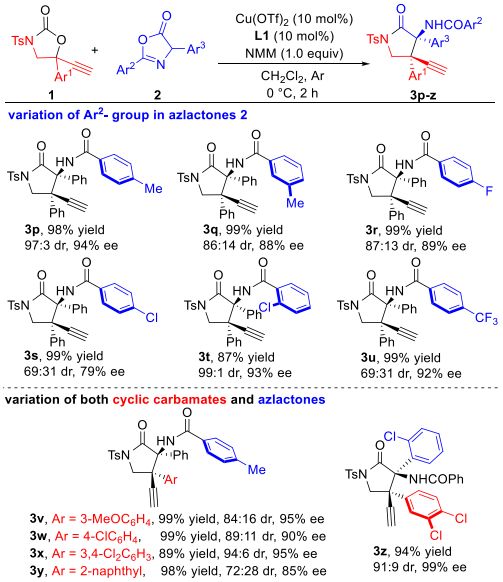
[a]Reaction conditions: the reactions were carried out with **1** (0.10 mmol), **2a** (0.20 mmol), $Cu(OTf)_2$ (10 mol%), **L1** (10 mol%), and NMM (1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C for 2 h under argon atmosphere. The yields refer to the isolated yields of **3** as a mixture of diastereomers. The dr and ee values were determined by chiral HPLC analysis.

under the standard conditions to give **3l** in 85% yield with 90:10 dr and 95% ee. A heteroaromatic substrate was also found to be feasible in the reaction, providing **3m** in moderate yield with 99% ee. Moreover, *N*-Ms-substituted substrate was well tolerated and produced **3n** in acceptable results. Unfortunately, nonterminal alkyne-substituted cyclic carbonate was found to be infeasible in the catalytic system (as shown by product **3o**), which indicated the terminal alkyne group was crucial for the reaction.

The scope of azlactones **2** was examined in the reaction with cyclic carbamates. As shown in Scheme 4, the azlactones bearing an electron-donating or electron-withdrawing substituent at the aryl moiety (Ar^2) were well tolerated, providing the expected γ-butyrolactams **3p**–**u** in 87–99% yields with 69:31 to 99:1 dr and 79–94% ee. *p*-Methylphenyl group (Ar^2)-substituted azlactone could smoothly react with diverse cyclic carbamates bearing a MeO– or Cl– substituent, even bearing two chlorine substituents on the benzene ring, **3v**–**x**, with excellent results. Likewise, the naphthyl group substituted cyclic carbamate could give the corresponding product **3y** in 98% yield with 72:28 dr and 85% ee. Ultimately, product **3z** containing three chlorine atom at the Ar^1 of cyclic carbamate and Ar^3 of azlactone could be smoothly prepared in 98% yield with 91:9 dr and 99% ee. However, alkyl-substituted azlatones (Ar^3 = ethyl, 2-phenylethyl) are not adapted to the catalytic system to deliver the expected product.

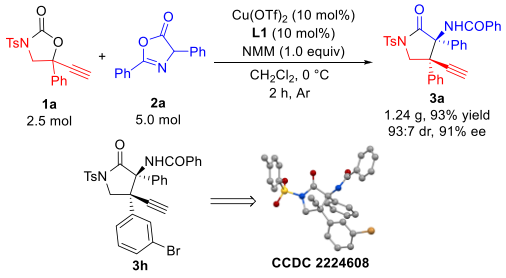
In order to demonstrate the scalability of the developed asymmetric decarboxylative [3 + 2] cyclization reaction, a gram-scale experiment of **1a** and **2a** was conducted under the standard conditions. As shown in Scheme 5, the reaction proceeded well and afforded the γ-butyrolactam **3a** in 93% yield (1.24 g) with 93:7 dr and 91% ee.[12] Fortunately, we obtained the single-crystal structure of product **3h**. The relative and absolute configuration of **3h** was unambiguously determined by single-crystal X-ray diffraction analysis to be

Scheme 4. Substrate Scope of Azlactones 2[a]



[a]Reaction conditions: the reactions were carried out with **1** (0.10 mmol), **2** (0.20 mmol), $Cu(OTf)_2$ (10 mol%), **L1** (10 mol%) and NMM (1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C for 2 h under argon atmosphere. The yields refer to the isolated yields of **3** as a mixture of diastereomers. The dr and ee values were determined by chiral HPLC analysis.

Scheme 5. Gram-Scale Reaction and the X-Ray ORTEP Structure of 3h



the (*C3R,C4S*)-configuration. Assuming a common reaction pathway, the configurations of the other γ-butyrolactams were tentatively assigned by analogy.

To validate the synthetic utility of this methodology, some derivatization reactions starting from γ-butyrolactam **3a** were performed.[12] As shown in Scheme 6, a Sonagashira coupling of **3a** with iodobenzene smoothly occurred in DMF at room temperature, giving product **4** in 95% yield with 97:3 dr and 95% ee. In the presence of $AgSbF_6$ and $Au(PPh_3)Cl$, an intramolecular oxycyclization of **3a** proceeded well in CH_2Cl_2, leading to the formation of bicyclic product **5** in 86% yield with 95:5 dr and 91% ee. The alkyne group of **3a** could be reduced to an ethyl group via Pd-catalyzed hydrogenation in methanol, resulting in compound **6** in 94% yield with excellent stereoselectivity. Copper thiophene-2-carboxylate could catalyze an azide–alkyne click reaction of **3a** with (azidomethyl)-benzene under mild conditions, generating product **7** in 95% yield with > 99:1 dr and 92% ee. These transformations fully reflect the practicability and reliability for accessing structurally diverse optically pure γ-butyrolactam compounds from the developed decarboxylative [3 + 2] cyclization reaction.

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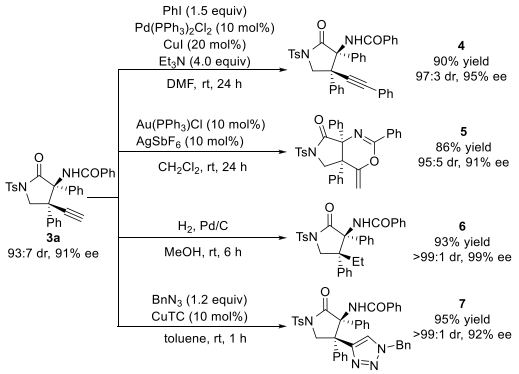
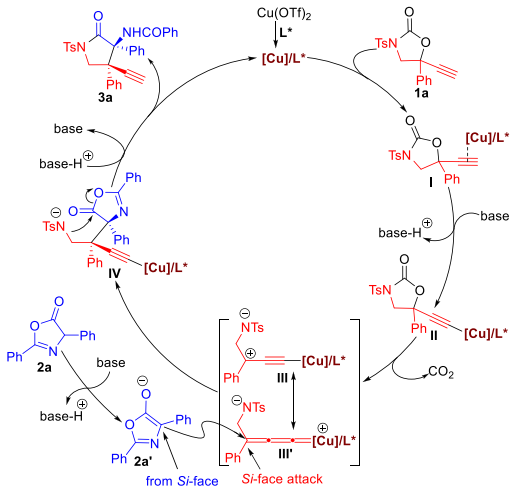
Scheme 6. Synthetic Transformations of 3a



Based on our experimental results and previous literature,[6−9] a possible catalytic cycle was proposed in Scheme 7 to

Scheme 7. Proposed Catalytic Cycle



elucidate the pathway of the decarboxylative [3 + 2] cyclization reaction. A chiral copper complex [Cu]/L*, in situ generated from $Cu(OTf)_2$ and ligand **L1**, coordinates to the alkyne moiety of cyclic carbamate **1a** to give a π-complex **I**, which is deprotonated with base to form a copper acetylide species **II**. And then, a decarboxylative ring opening of **II** results in the formation of a copper−acetylide zwitterionic intermediate **III** and its copper−allenylidene zwitterionic resonance structure **III′**. Subsequently, the α-position of the enolate intermediate **2a′** generated from **2a** would stereoselectively attack (from its *Si*-face) to the Cγ-position of intermediate **III′** via the *Si*-face, leading to the generation of an addition intermediate **IV**. Maarseveen's model[6a,7a,13] was employed to elucidate the stereoselectivity in our proposed transition state (see the Supporting Information). Ultimately, an intramolecular aminolysis followed by a protonation of the copper−acetylide intermediate **IV** gives rise to the cycloaddition product **3a** and regenerates the active catalyst entering into the next catalytic cycle.

In conclusion, an efficient copper-catalyzed asymmetric decarboxylative [3 + 2] cyclization of alkyne-substituted cyclic carbamates with azlactones has been established. A range of optically active γ-butyrolactams bearing two vicinal tetrasubstituted carbon stereocenters were obtained in high yields with good to excellent diastereo- and enantioselectivities (up to 99% yield, 99:1 dr, and 99% ee). This represents the first successful example on the asymmetric synthesis γ-butyrolactams containing highly congested vicinal tetrasubstituted stereocenters. The developed protocol was amenable to gram scale preparation, and the synthetic utility of this method was also elucidated by versatile transformations of the product. Further research on transition-metal-catalyzed asymmetric decarboxylation reaction will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00075.

Experimental details, full analysis data (melting point, NMR data, and HRMS) for new compounds; copies of NMR spectra (PDF)

Accession Codes

CCDC 2224608 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.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. Synthesis of γ-lactams and γ-lactones via intramolecular Pd-catalyzed allylic alkylations. *Acc. Chem. Res.* **2014**, *47*, 3439. (b) Caruano, J.; Muccioli, G. G.; Robiette, R. Biologically active γ-lactams: synthesis and natural sources. *Org. Biomol. Chem.* **2016**, *14*, 10134. (c) Jusseau, X.; Chabaud, L.; Guillou, C. Synthesis of γ-butenolides and α,β-unsaturated γ-butyrolactams by addition of vinylogous nucleophiles to Michael acceptors. *Tetrahedron* **2014**, *70*, 2595.

(2) (a) Schwartz, R. E.; Helms, G. L.; Bolessa, E. A.; Wilson, K. E.; Giacobbe, R. A.; Tkacz, J. S.; Bills, G. F.; Liesch, J. M.; Zink, D. L.; Curotto, J. E.; Pramanik, B.; Onishi, J. C. Pramanicin, a novel antimicrobial agent from a fungal fermentation. *Tetrahedron* **1994**, *50*, 1675. (b) Asami, Y.; Kakeya, H.; Komi, Y.; Kojima, S.; Nishikawa, K.; Beebe, K.; Neckers, L.; Osada, H. Azaspirene, a fungal product, inhibits angiogenesis by blocking Raf-1 activation. *Cancer Sci* **2008**, *99*, 1853. (c) Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. Inhibition of Proteasome Activities and Subunit-Specific Amino-Terminal Threonine Modification by Lactacystin. *Science* **1995**, *268*, 726. (d) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. Salinosporamide A: A Highly Cytotoxic Proteasome Inhibitor from a Novel Microbial Source, a Marine Bacterium of the New Genus *Salinospora*. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (e) Tchissambou, L.; Benechie, M.; Khuong-Huu, F. Alcaloides imidazoliques—VI: Alcaloides du *cynometra lujae* isolement, structures, synthese. *Tetrahedron* **1982**, *38*, 2687. (f) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. Isatisine A, a Novel Alkaloid with an Unprecedented Skeleton from Leaves of *Isatis indigotica*. *Org. Lett.* **2007**, *9*, 4127.

(3) For a review, see: (a) Ye, L.-W.; Shu, C.; Gagosz, F. Recent progress towards transition metal-catalyzed synthesis of γ-lactams. *Org. Biomol. Chem.* **2014**, *12*, 1833. (b) Zhao, X.; DiRocco, D. A.; Rovis, T. N-Heterocyclic Carbene and Brønsted Acid Cooperative Catalysis: Asymmetric Synthesis of *trans*-γ-Lactams. *J. Am. Chem. Soc.* **2011**, *133*, 12466. (c) Kanbayashi, N.; Takenaka, K.; Okamura, T.; Onitsuka, K. Asymmetric Auto-Tandem Catalysis with a Planar-Chiral Ruthenium Complex: Sequential Allylic Amidation and Atom-Transfer Radical Cyclization. *Angew. Chem., Int. Ed.* **2013**, *52*, 4897. (d) Hatano, M.; Nishimura, T. Hydroxoiridium/Chiral Diene Complexes as Effective Catalysts for Asymmetric Annulation of **α**-Oxo- and Iminocarboxamides with 1,3-Dienes. *Angew. Chem., Int. Ed.* **2015**, *54*, 10949. (e) Ni, C.; Chen, J.; Zhang, Y.; Hou, Y.; Wang, D.; Tong, X.; Zhu, S.-F.; Zhou, Q.-L. Phosphine-Catalyzed Asymmetric (3 + 2) Annulations of δ-Acetoxy Allenoates with β-Carbonyl Amides: Enantioselective Synthesis of Spirocyclic β-Keto γ-Lactams. *Org. Lett.* **2017**, *19*, 3668. (f) Ashida, K.; Hoshimoto, Y.; Tohnai, N.; Scott, D. E.; Ohashi, M.; Imaizumi, H.; Tsuchiya, Y.; Ogoshi, S. Enantioselective Synthesis of Polycyclic γ-Lactams with Multiple Chiral Carbon Centers via Ni(0)-Catalyzed Asymmetric Carbonylative Cycloadditions without Stirring. *J. Am. Chem. Soc.* **2020**, *142*, 1594. (g) Wu, L.-S.; Ding, Y.; Han, Y.-Q.; Shi, B.-F. Asymmetric Synthesis of γ-Lactams Containing α,β-Contiguous Stereocenters via Pd(II)-Catalyzed Cascade Methylene C(sp^3)−H Alkenylation/Aza-Wacker Cyclization. *Org. Lett.* **2021**, *23*, 2048. (h) Panger, J. L.; Denmark, S. E. Enantioselective Synthesis of γ-Lactams by Lewis Base Catalyzed Sulfenoamidation of Alkenes. *Org. Lett.* **2020**, *22*, 2501. (i) Qian, H.; Sun, S.; Zhao, W.; Sun, J. An efficient [3 + 2] annulation for the asymmetric synthesis of densely-functionalized pyrrolidinones and γ-butenolides. *Chem. Commun.* **2020**, *56*, 11295. (j) Pedroni, J.; Cramer, N. Chiral **γ**-Lactams by Enantioselective Palladium(0)-Catalyzed Cyclopropane Functionalizations. *Angew. Chem., Int. Ed.* **2015**, *54*, 11826.

(4) (a) Yus, M.; González-Gómez; Foubelo, F. Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, 5595. (b) Leonori, D.; Aggarwal, V. K. Lithiation−Borylation Methodology and Its Application in Synthesis. *Acc. Chem. Res.* **2014**, *47*, 3174. (c) Zhou, F.; Zhu, L.; Pan, B.-W.; Shi, Y.; Liu, Y.-L.; Zhou, J. Catalytic Enantioselective Construction of Vicinal Quaternary Carbon Stereocenters. *Chem. Sci.* **2020**, *11*, 9341.

(5) For selected reviews, see: (a) Nishibayashi, Y. Transition-Metal-Catalyzed Enantioselective Propargylic Substitution Reactions of Propargylic Alcohol Derivatives with Nucleophiles. *Synthesis* **2012**, 489. (b) Zhang, D.-Y.; Hu, X.-P. Recent advances in copper-catalyzed propargylic substitution. *Tetrahedron Lett.* **2015**, *56*, 283. (c) Hu, X.-H.; Liu, Z.-T.; Shao, L.; Hu, X.-P. Recent Advances in Catalytic Stereocontrolled Cycloaddition with Terminal Propargylic Compounds. *Synthesis* **2015**, *47*, 913. (d) Li, T.-R.; Wang, Y.-N.; Xiao, W.-J.; Lu, L.-Q. Transition-metal-catalyzed cyclization reactions using vinyl and ethynyl benzoxazinones as dipole precursors. *Tetrahedron Lett.* **2018**, *59*, 1521. (e) Roh, S. W.; Choi, K.; Lee, C. Transition Metal Vinylidene- and Allenylidene-Mediated Catalysis in Organic Synthesis. *Chem. Rev.* **2019**, *119*, 4293. (f) Zhang, J.; Chen, Y.; Wang, Q.; Shen, J.; Liu, Y.; Deng, W. Transition Metal-Catalyzed Asymmetric Cyclizations Involving Allyl or Propargyl Heteroatom-Dipole Precursors. *Chin. J. Org. Chem.* **2022**, *42*, 3051.

(6) For selected examples on copper-catalyzed decarboxylative cyclization of ethynyl benzoxazinanones, see: (a) Wang, Q.; Li, T.-R.; Lu, L.-Q.; Li, M.-M.; Zhang, K.; Xiao, W.-J. Catalytic Asymmetric [4 + 1] Annulation of Sulfur Ylides with Copper−Allenylidene Intermediates. *J. Am. Chem. Soc.* **2016**, *138*, 8360. Song, J.; Zhang, Z.-J.; Gong, L.-Z. Asymmetric [4 + 2] Annulation of C1 Ammonium Enolates with Copper-Allenylidenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 5212. (c) Shao, W.; You, S.-L. Highly Diastereo- and Enantioselective Synthesis of Tetrahydro-*5H*-Indolo[2,3-*b*]quinolines through Copper-Catalyzed Propargylic Dearomatization of Indoles. *Chem. Eur. J.* **2017**, *23*, 12489. (d) Ji, D.; Wang, C.; Sun, J. Asymmetric [4 + 2]-Cycloaddition of Copper−Allenylidenes with Hexahydro-1,3,5-triazines: Access to Chiral Tetrahydroquinazolines. *Org. Lett.* **2018**, *20*, 3710. (e) Lu, S.; Ong, J.-Y.; Poh, S. B.; Tsang, T.; Zhao, Y. Transition-Metal-Free Decarboxylative Propargylic Substitution/Cyclization with either Azolium Enolates or Acyl Anions. *Angew. Chem., Int. Ed.* **2018**, *57*, 5714. (f) Zhang, Y.-C.; Zhang, Z.-J.; Fan, L.-F.; Song, J. Enantioselective Decarboxylative Propargylation/Hydroamination Enabled by Organo/Metal Cooperative Catalysis. *Org. Lett.* **2018**, *20*, 2792. (g) Wang, Y.; Zhu, L.; Wang, M.; Xiong, J.; Chen, N.; Feng, X.; Xu, Z.; Jiang, X. Catalytic Asymmetric [4 + 3] Annulation of *C,N*-Cyclic Azomethine Imines with Copper Allenylidenes. *Org. Lett.* **2018**, *20*, 6506. (h) Chen, H.; Lu, X.; Xia, X.; Zhu, Q.; Song, Y.; Chen, J.; Cao, W.; Wu, X. Asymmetric Catalytic [4 + 2] Cycloaddition via Cu−Allenylidene Intermediate: Stereoselective Synthesis of Tetrahydroquinolines Fused with a γ-Lactone Moiety. *Org. Lett.* **2018**, *20*, 1760. (i) Zhang, Z.-J.; Zhang, L.; Geng, R.-L.; Song, J.; Chen, X.-H.; Gong, L.-Z. N-Heterocyclic Carbene/Copper Cooperative Catalysis for the Asymmetric Synthesis of Spirooxindoles. *Angew. Chem., Int. Ed.* **2019**, *58*, 12190. (j) Simlandy,

A. K.; Ghosh, B.; Mukherjee, S. Enantioselective [4 + 2]-Annulation of Azlactones with Copper-Allenylidenes under Cooperative Catalysis: Synthesis of α-Quaternary α-Acylaminoamides. *Org. Lett.* **2019**, *21*, 3361. (k) Yang, X.-P.; Lv, H.-P.; Yang, H.-D.; Wang, B.-L.; Wang, X.-W. Box-copper catalyzed cascade asymmetric amidation for chiral *exo*-methylene aminoindoline derivatives. *Org. Biomol. Chem.* **2021**, *19*, 9373.

(7) For the copper-catalyzed decarboxylative cyclization of tertiary propargylic carbamates, see: (a) Xu, Y.-W.; Hu, X.-P. Diastereo- and Enantioselective Copper-Catalyzed Decarboxylative Ring-Opening [3 + 2] Annulation of Tertiary Propargylic Carbamates through Regioselective α-Attack of γ-Butenolides. *Org. Lett.* **2019**, *21*, 8091. Just with the carbamate as a single case in: (b) Zhang, Y.-C.; Zhang, B.-W.; Geng, R.-L.; Song, J. Enantioselective [3 + 2] Cycloaddition Reaction of Ethynylethylene Carbonates with Malononitrile Enabled by Organo/Metal Cooperative Catalysis. *Org. Lett.* **2018**, *20*, 7907.

(8) For the copper-catalyzed decarboxylative cyclization of ethynyl indoloxazolidones, see: (a) Zhang, J.; Ni, T.; Yang, W.-L.; Deng, W.-P. Catalytic Asymmetric [3 + 2] Annulation via Indolyl Copper−Allenylidene Intermediates: Diastereo- and Enantioselective Assembly of Pyrrolo[1,2-a]indoles. *Org. Lett.* **2020**, *22*, 4547. (b) Shen, J.-H.; Tian, F.; Yang, W.-L.; Deng, W.-P. Synergistic Copper and Chiral Lewis Base Catalysis for the Asymmetric Synthesis of Pyrrolo[1,2-*a*]indoles. *Chin. J. Chem.* **2021**, *39*, 3292. (c) Zhang, J.; Gao, Y.-S.; Gu, B.-M.; Yang, W.-L.; Tian, B.-X.; Deng, W.-P. Cooperative N-heterocyclic Carbene and Iridium Catalysis Enables Stereoselective and Regiodivergent [3 + 2] and [3 + 3] Annulation Reactions. *ACS Catal* **2021**, *11*, 3810.

(9) For the copper-catalyzed decarboxylative cyclization of ethynyl methylene cyclic carbamates, see: Shen, L.; Lin, Z.; Guo, B.; Zi, W. Synthesis of cycloheptanoids through catalytic enantioselective (4 + 3)-cycloadditions of 2-aminoallyl cations with dienol silyl ethers. *Nat. Synth.* **2022**, *1*, 883.

(10) For reviews on the azlactone chemistry, see: (a) Fisk, J. S.; Mosey, R. A.; Tepe, J. The diverse chemistry of oxazol-5-(4*H*)-ones. *J. Chem. Soc. Rev.* **2007**, *36*, 1432. (b) Hewlett, N. M.; Hupp, C. D.; Tepe, J. J. Reactivity of Oxazol-5-(4*H*)-ones and Their Application toward Natural Product Synthesis. *Synthesis* **2009**, *2009*, 2825. (c) Alba, A. N. R.; Rios, R. Oxazolones in organocatalysis, new tricks for an old reagent. *Chem. Asian. J.* **2011**, *6*, 720. (d) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. Azlactone Reaction Developments. *Chem. Eur. J.* **2016**, *22*, 10294.

(11) (a) Lu, W.-Y.; Wang, Y.; You, Y.; Wang, Z.-H.; Zhao, J.-Q.; Zhou, M.-Q.; Yuan, W.-C. Copper-Catalyzed Decarboxylative [3 + 2] Annulation of Ethynylethylene Carbonates with Azlactones: Access to γ-Butyrolactones Bearing Two Vicinal Quaternary Carbon Centers. *J. Org. Chem.* **2021**, *86*, 1779. (b) Lu, W.-Y.; You, Y.; Li, T.-T.; Wang, Z.-H.; Zhao, J.-Q.; Yuan, W.-C. CuI-Catalyzed Decarboxylative Thiolation of Propargylic Cyclic Carbonates/Carbamates to Access Allenyl Thioethers. *J. Org. Chem.* **2021**, *86*, 6711. (c) Li, T.-T.; Lu, W.-Y.; Shen, L.-W.; Wang, Z.-H.; Zhao, J.-Q.; You, Y.; Yuan, W.-C. CuI-catalyzed decarboxylative highly regioselective phosphonylation of terminal alkyne-substituted cyclic carbonates/carbamates to access 4-phosphonyl 2,3-allenols/2,3-allenamines. *Tetrahedron* **2022**, *104*, 132606. (d) Li, T.-T.; You, Y.; Sun, T.-J.; Zhang, Y.-P.; Zhao, J.-Q.; Wang, Z.-H.; Yuan, W.-C. Copper-Catalyzed Decarboxylative Cascade Cyclization of Propargylic Cyclic Carbonates/Carbamates with Pyridinium 1,4-Zwitterionic Thiolates to Fused Polyheterocyclic Structures. *Org. Lett.* **2022**, *24*, 5120. (e) You, Y.; Li, T.-T.; Sun, T.-J.; Zhang, Y.-P.; Wang, Z.-H.; Zhao, J.-Q.; Yuan, W.-C. Enantioselective Construction of Vicinal Quaternary-Tetrasubstituted Carbon Stereocenters by Copper-Catalyzed Decarboxylative Propargylic Substitution. *Org. Lett.* **2022**, *24*, 7671.

(12) For details of the procedure, see the Supporting Information.

(13) Nakajima, K.; Shibata, M.; Nishibayashi, Y. Copper-Catalyzed Enantioselective Propargylic Etherification of Propargylic Esters with Alcohols. *J. Am. Chem. Soc.* **2015**, *137*, 2472.

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