OL Organic Letters

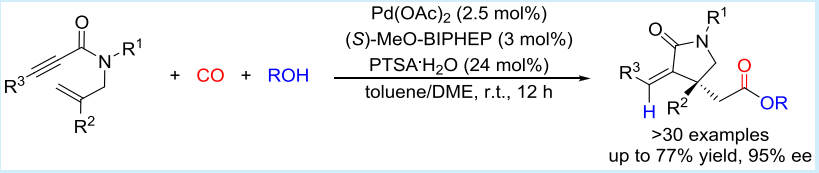
pubs.acs.org/OrgLett Letter

Enantioselective Hydroesterificative Cyclization of 1,6-Enynes to Chiral γ-Lactams Bearing a Quaternary Carbon Stereocenter

Xinyi Ren,[#] Lin Tang,[#] Chaoren Shen, Huimin Li, Peng Wang, and Kaiwu Dong*

Cite This: *Org. Lett.* 2021, 23, 3561−3566 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A palladium-catalyzed asymmetric hydroesterification-cyclization of 1,6-enynes with CO and alcohol was developed to efficiently prepare a variety of enantioenriched γ-lactams bearing a chiral quaternary carbon center and a carboxylic ester group. The approach featured good to high chemo-, region-, and enantioselectivities, high atom economy, and mild reaction conditions as well as broad substrate scope. The correlation between the multiple selectivities of such process and the *N*-substitutes of the amide linker in the 1,6-enyne substrate has been depicted by the crystallographic evidence and control experiments.

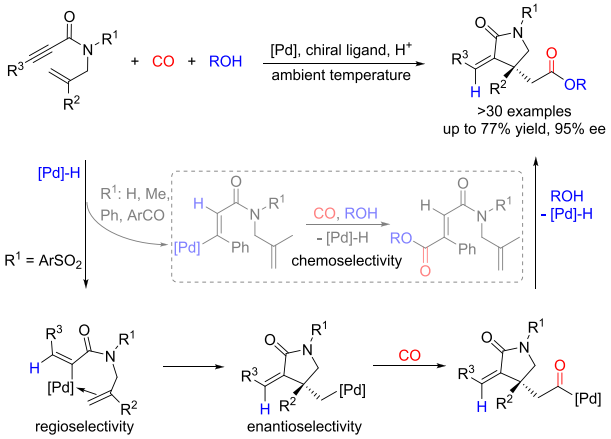
Chiral γ-lactams play a significant role in a variety of bioactive compounds and are also regarded as a serviceable synthesis precursor of *N*-heterocyclic molecules due to the versatile transformation of the amide functional group.[1] Thus, a variety of catalytic asymmetric methods has been established toward preparing optically active γ-lactams.[2] The intrinsic effect of all-carbon quaternary stereocenter on biological characteristics, *i.e.*, activity, metabolism, solubility, and hydrophobicity, endows its construction method with long-lasting research interest.[3] Owing to the congested circumstances, catalytic enantioselective creation of such a quaternary carbon center *via* a forming carbon−carbon bond is an imperative but quite challenging task.[4] In this context, despite significant progress in the enantioselective synthesis of chiral γ-lactams, only a few protocols could construct such a skeleton bearing an all-carbon quaternary stereocenter.[5]

Transition-metal-catalyzed stereoselective cycloisomerization,[6] reductive cyclization,[7] and hydrofunctionalizative cyclization[8−10] of 1,6-enynes provide an efficient and convenient access to five-membered (hetero)cycles. Especially, merging the hydrofunctionalization of unsaturated bond with the cyclization reaction manifests high bond-forming efficiency, rapid construction of complex molecules, and/or high atomic economy. Apart from the established asymmetric hydroboration-,[8] hydrosilylation-,[9] and hydrovinylation-cyclization,[11] to our knowledge, neither the nonasymmetric nor enantioselective hydrocarbonylation-cyclization process of dienes/enynes has yet to be exploited.[12] Palladium-catalyzed hydroesterification reaction constitutes one of the ideal routes to prepare carboxylic acid derivatives from readily available feedstocks of unsaturated hydrocarbons, CO, and alcohols.[13] Compared with the well-established industrial application of nonasymmetric alkoxycarbonylation, the development of corresponding asymmetric variant is rather sluggish, probably due to the difficulty of simultaneously controlling the chemo-, regio-, and enantioselectivities under a nonbeneficial reaction temperature and high CO pressure.[14] Following our interest in catalytic asymmetric carbonylation[15] and cyclization[16] reactions, we envisioned integrating the challenging but rewarding alkoxycarbonylation with enyne cyclization reaction would offer a novel entry to chiral heterocyclic compounds containing both a carboxylic ester group and a quaternary carbon center with high efficiency of carbon−carbon/heteroatom bond formation.

Herein, we described the first palladium-catalyzed asymmetric hydroesterificative cyclization of 1,6-enynes (Scheme 1). The type of amide-tethered 1,6-enyne substrate, containing an internal alkyne and a terminal gem-disubstituted alkene, was investigated recently for the palladium-catalyzed nonasymmetric hydrohalogenation-cyclization to δ-lactams by Pobladador-Bahamonde and Lautens[17] as well as the cobalt-catalyzed enantioselective hydroboration-cyclization to chiral γ-lactams from the group of Ge.[8a] Generally, these hydrofunctionalizative cyclization processes start with the formation of metal hydride followed by the alkyne group addition and subsequent intramolecular insertion of the alkene unit into the formed metal−alkenyl intermediates to generate a metal−alkyl complex. In the previous studies, such species were trapped

Received: March 22, 2021
Published: April 28, 2021

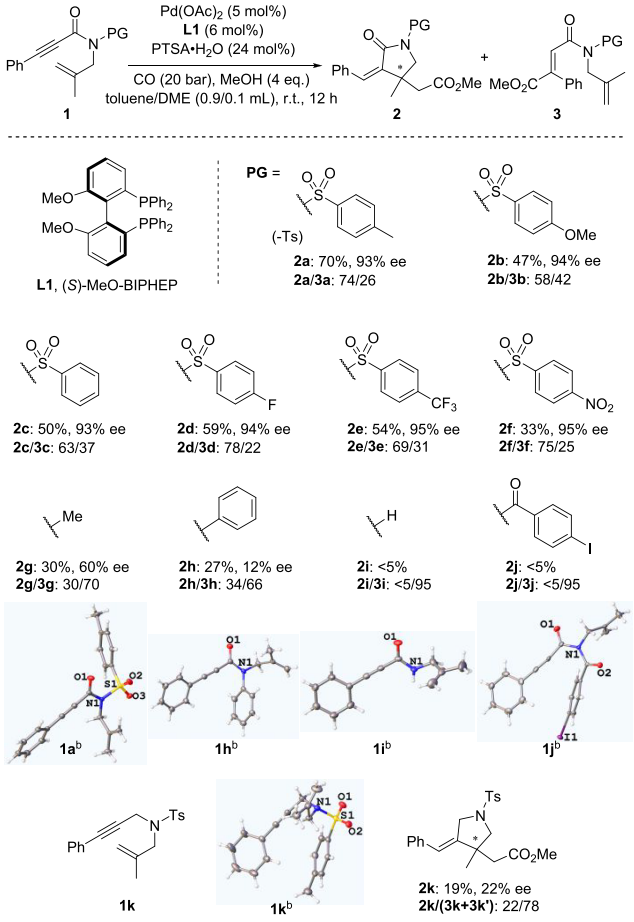
Scheme 1. Asymmetric Hydroesterification-Cyclization of Amide-Tethered 1,6-Enynes



by the reactive H-X (X = halide or -Bpin) substrate and converted into the corresponding lactams along with the active catalyst regeneration. In our protocol, CO was introduced to insert the palladium−alkyl complex, and the alcohol nucleophile was utilized to alcoholize the resulting palladium−acyl species (Scheme 1). A series of chiral carboxylic esters containing a γ-lactam skeleton and a quaternary carbon stereocenter were delivered. This approach proceeded under ambient reaction temperature and exhibited high bond construction efficiency and good functional group compatibility. By changing the *N*-substitutes of amide linker in the 1,6-enynes substrate to adjust the stable spatially conformation around the active metal center, the chemo-, regio-, and enantioselectivities of this unprecedented process were controlled.

At the beginning of our studies, the palladium-catalyzed asymmetric hydroesterificative cyclization of *p*-toluenesulfonate (Ts-) protected 1,6-enynes **1a** with CO and MeOH was chosen as the model reaction. After the optimization of the reaction conditions, the combination of $Pd(OAc)_2$, (*S*)-MeO-BIPHEP, and $TsOH{\cdot}H_2O$ was used as the catalyst system, and this tandem process was conducted with 4 equiv of alcohol under 20 bar pressure of CO in a mixed solvent of toluene/DCE (9/1) at room temperature (Scheme 2). The desired chiral γ-lactam **2a** was isolated in excellent ee value and good yield, along with the presence of uncyclized alkyne carbonylation compound **3a** (**2a**/**3a** = 74/36). Besides **3a**, no other uncyclized isomer was detected. On the basis of the reaction pathway (Scheme 1), this result indicated the irreversible regioselective hydropalladation step of the alkyne unit in **1a** with the active palladium-hydride catalyst determined the ratio of **2a**/**3a**. The subsequent cyclization step via adding the Pd^{II}−$C(sp^2)$ bond of Pd^{II}−alkenyl intermediate onto the C=C bond of the alkene moiety is crucial to both chemoselectivity and enatioselectivity. In principle, such an insertion step could be adjusted by the relative spatial position between Pd^{II}−alkenyl and alkene moieties, which probably could be affected by the *N*-substitutes of the amide linker in the substrate. Therefore, a series of substitutes on the *N*-atom as well as other type of the linker were investigated. Both electron-donating and electron-withdrawing substituents on the phenyl ring of the sulphonyl group in the enyne exhibited an unnoticeable effect on the enantioselectivity but considerable influence on the distribution of the cyclization/uncyclization

Scheme 2. Effect of the *N*-Substituent of the Substrate[a]



[a](a) Reactions were run on 0.1 mmol scale. Yield and ratio of **2a**/**3a** were determined by GC-FID using *n*-decane as an internal standard. Ee values were determined by HPLC analysis. Isolated yield. (b) ORTEP diagrams with thermal ellipsoids at the 50% probability level.

products (**2a**−**2f**). Replacing the sulphonyl group in the substrate by methyl (**2g**), phenyl (**2h**), hydrogen (**2i**), or aroyl (**2j**) group resulted in significantly low yield or trace amounts of wanted γ-lactams. When the tether was changed from the amide group to the corresponding protected amine unit (**1k**), the yield of cyclized product dropped significantly. These results suggested both the sulphonyl and carbonyl groups are essential to this carbonylation-cyclization reaction.

Because the configuration flipping of the amide linker between *Z* and *E* forms via C−N bond rotation in the enyne substrates is rather sluggish at such low reaction temperature,[17] the spatial conformation of these reactants might affect the ratio of **2**/**3** and the reaction stereoselectivity. To validate such a relationship, single crystals of the substrates (**1a**, **1h**, and **1i**−**1k**) were cultivated and suitable for the X-ray diffraction characterization (Scheme 2). Seemingly, the close distance between the alkyne and the alkene moieties in the 1,6-enynes was beneficial to the chemoselectivity toward cyclized products.

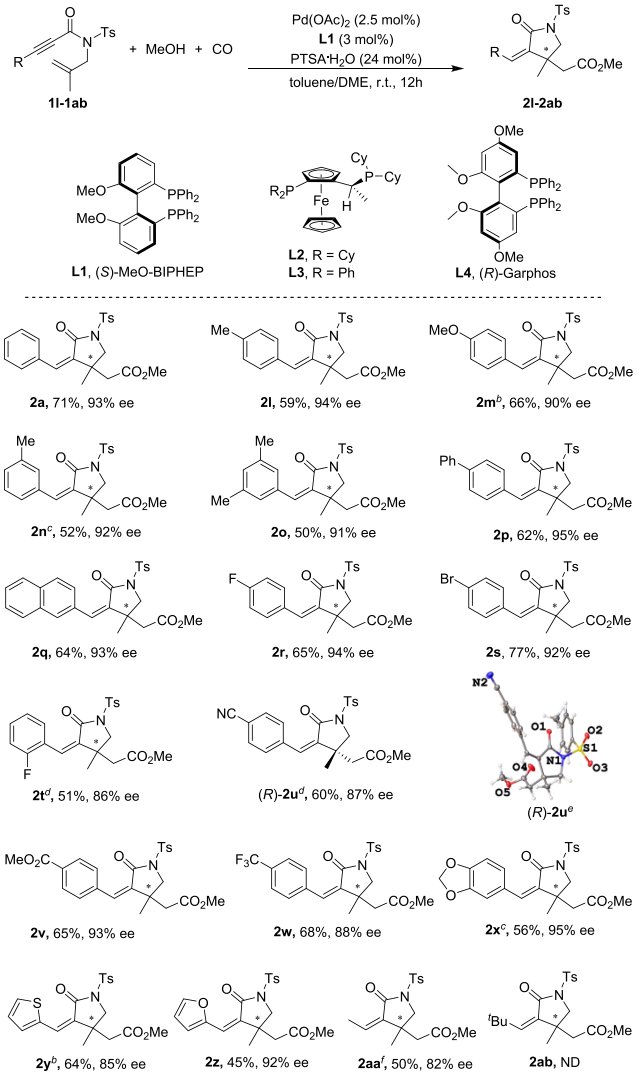
After exploring the effect of the *N*-substitute of the enyne substrate on the multiple selectivities for the tandem methoxycarbonylation-cyclization, we therefore began the evaluation of reaction conditions. The standard reaction was carried out with **1a**, CO (20 bar), and MeOH (4.0 equiv) using 2.5 mol % $Pd(OAc)_2$, 3 mol % **L1**, and 24 mol % PTSA·

https://doi.org/10.1021/acs.orglett.1c00952
Org. Lett. 2021, 23, 3561−3566

H_2O as the catalyst at room temperature (for details see Supporting Information (SI), Table S1). With the optimized reaction conditions in hand, the substrate scope and functional group compatibility for this catalytic asymmetric hydroesterfication-cyclization of 1,6-enynes were studied. First, the substituents on the alkyne moiety of **1** were varied and the desired chiral γ- lactams (**2l-2aa**) were afforded in reasonable to good yields with high enantioselectivity using the suitable chiral bidentate phosphine ligand and $Pd(OAc)_2$ as the catalyst system (Table 1). The aryl group attached to the triple bond of the substrate bearing both electron-rich (**2l**−**2o**) and electron-deficient substituents (**2r**−**2w**) at the *para*-, *ortho*-, or *meta*-position was suitable for this conversion, giving slightly lower yields with the same level of ee value. A variety of functional groups, such as methoxy (**2m**), halide (**2r**−**2t**), nitrile (**2u**), ester (**2v**), trifluoromethyl (**2w**), and piperonyl (**2x**), were well-tolerated with up to 95% ee without significantly compromising the yield under slightly modificated reaction conditions. Besides aryl and 2-naphthyl (**2q**) units, heteroaromatic rings, including 2-thienyl and 2-furyl groups (**2y**, **2z**), were also compatible and high ee value with reasonable to moderate yields was obtained. In addition, the enyne substrate with aliphatic methyl substitute at the terminus of the alkyne (**2aa**) was also smoothly transformed into the wanted γ-lactam in 50% yield with 82% ee using chiral phosphine ligand **L3** instead of **L1**. When the enyne (**1ab**) bearing tertiary butyl substituent at the terminus of the alkyne was used as the substrate, no substrate conversion was obtained.

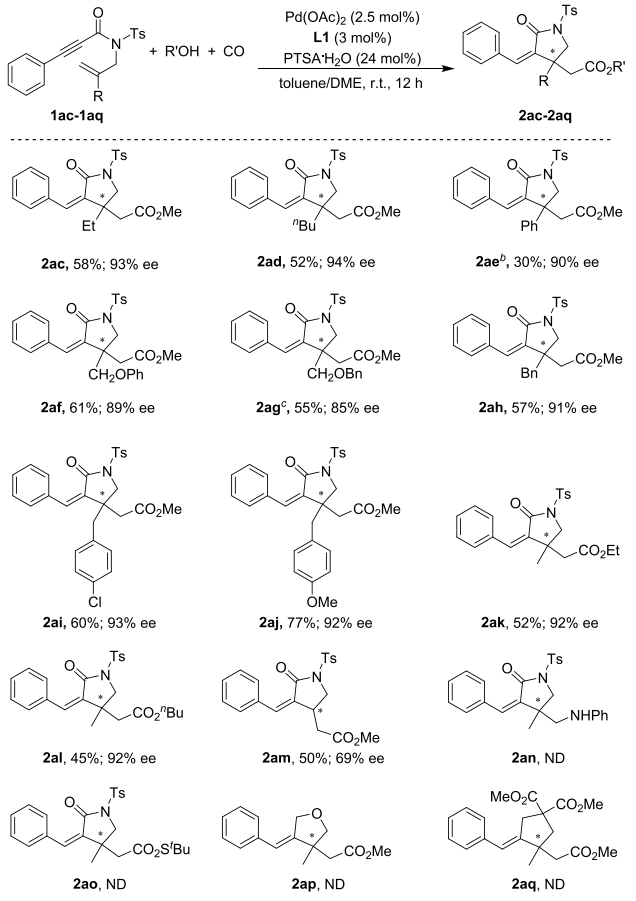
We next turned our attention to investigating the influence of the substituted alkene moiety of the enyne on this tandem cyclized alkoxycarbonylation (Table 2). Replacing the methyl group by ethyl, *n*-butyl, or ether-containing aliphatics was able to deliver the corresponding lactams **2ac**−**2ad** or **2af**−**2ag** in moderate yields with high ee value. Besides normal aliphatic one, phenyl-, and benzyl-substituted substrates were also compatible to furnish the products **2ae** and **2ah**−**2aj** with excellent enantioselectivity and reasonable to good yields. Both electron-acceptor (**2ai**) and electron-donor (**2aj**) groups on

Table 1. Scope of 1,6-Enynes with Various Substituted Alkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$/**L1**/PTSA•H_2O (2.5/3/24 mol %), CO (20 bar), MeOH (0.8 mmol, 4 equiv), toluene/DME (1.8/0.2 mL), rt, 12 h. [b]$Pd(OAc)_2$ (5 mol %), **L2** (6 mol %). [c]$Pd(OAc)_2$ (5 mol %), **L1** (6 mol %). [d]**L4** instead of **L1**. [e]ORTEP diagram with thermal ellipsoids at the 50% probability level. [f]$Pd(OAc)_2$ (5 mol %), **L3** (6 mol %), and reaction temperature was 10 °C.

Table 2. Scope of 1,6-Enynes with Different Substituted Alkenes[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$/**L1**/PTSA•H_2O (2.5/3/24 mol %), CO (20 bar), R′OH (0.8 mmol, 4 equiv), toluene/DME (1.8/0.2 mL), rt, 12 h. [b]**L4** instead of **L1**. [c]$Pd(OAc)_2$ (5 mol %), **L2** (6 mol %).

https://doi.org/10.1021/acs.orglett.1c00952
Org. Lett. 2021, 23, 3561−3566

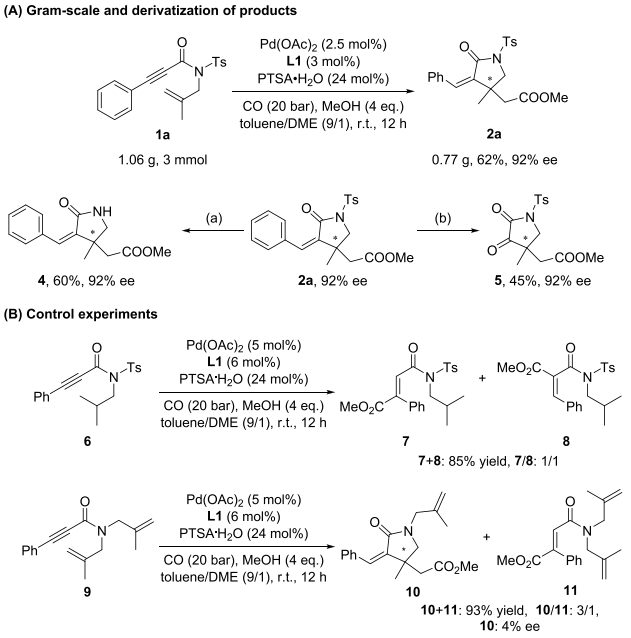
the benzyl ring tethered to the alkene exhibited no effect on this reaction. Inspired by these results, the nucleophile sources for such transformation were examined, and the alcohol EtOH and ^{n}BuOH were also amenable to generate target products **2ak** and **2al** with 92% ee and slightly diminished yield. The substrate **1am** (R = H) without methyl substituent on the alkene was also investigated in the enantioselective methoxycarbonylative cyclization, which gave the desired product **2am** in 50% isolated yield with 69% ee value. Other types of nucleophiles, such as amine and thiol, were demonstrated to be not suitable in this hydrocarbonylation-cyclization reaction (**2an** and **2ao**). Substrates (**1ap** and **1aq**) including O- and C-tethered 1,6-enynes failed to undergo such asymmetric hydroesterificative cyclization reaction.

After exploring the substrate scope of the hydroesterification-cyclization of the enynes, gram-scale synthesis was carried out, and the γ-lactam **2a** was obtained in good yield and excellent enantioselectivity (Scheme 3A). The protecting group -Ts in **2a** was easily removed by SmI_2 to give the corresponding chiral γ-lactam **4** in good yield and 92% ee. The chiral 2,3-pyrrolidinedione **5** could be readily obtained by oxidation of **2a** without diminishing enantiomeric excess, which could be further converted regioselectively to the β-amino acid derived *N*-carboxyanhydride according the reported reference.[18]

To probe the mechanism and disclose the role of the double bond in the enyne substrate on the reaction stereoselectivity for the palladium-catalyzed asymmetric hydroesterification-cyclization, control experiments using alkyne **6** and dienyne **9**, bearing isobutyl or two isobutenyl groups, were carried out under identical reaction conditions (Scheme 3B). Replacing the isobutenyl group of **1a** by an isobutyl group led to the carbonylation products of **7** and **8** with the ratio of 1:1 in high yield. The decreased regioselectivity with **6** as the substrate may be caused by the loss of the coordination of the alkene moiety in the enyne substrate to the palladium catalyst.[8a] With dienyne **9** as the substrate, cyclization/uncyclization products **10**/**11** with a ratio of 3/1 were afforded in high yield, wherein very low ee value of the lactam **10** was observed. These results suggested the alkene group of the enyne substrate plays a function to affect the site selectivity in the initial hydropalladation step, and the -Ts group is essential to the enantioselectivity.

In conclusion, the first palladium-catalyzed enantioselective hydroesterification-cyclization of amide-tethered 1,6-enynes was developed. Various chiral γ-lactams bearing all-carbon quaternary stereocenters with high ee value were synthesized efficiently under milder conditions. Changing the substituent on the amide tether of the enyne substrate could alter the relative spatial position between the alkyne and the alkene moieties, which was demonstrated to be critical to adjust the multiple selectivities of this reaction process.

Scheme 3. Derivatization and Control Experiments[a]



[a]Reaction conditions: (a) **2a** (0.1 mmol), SmI_2 (1.0 mL, 0.1 M in THF), THF (4 mL), rt, 10 min; (b) **2a** (0.1 mmol), $RuCl_3{\cdot}xH_2O$ (2 mol %), $NaIO_4$ (3 equiv), $CH_2Cl_2/CH_3CN/H_2O$ (0.5/0.5/1.0 mL), rt, 1 h. The ratio of **7**/**8** was determined by GC-FID. The ratio of **10**/**11** was determined by ^{1}H NMR.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00952.

Experimental details, X-ray data, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 2009853, 2010126, 2061495−2061498, and 2061500 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 Author

Kaiwu Dong − *Chang-Kung Chuang Institute, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China;* orcid.org/0000-0001-6250-2629; Email: kwdong@chem.ecnu.edu.cn

Authors

Xinyi Ren − *Chang-Kung Chuang Institute, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China*

Lin Tang − *Chang-Kung Chuang Institute, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China*

Chaoren Shen − *Chang-Kung Chuang Institute, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China;* orcid.org/0000-0002-2849-7990

Huimin Li − *Chang-Kung Chuang Institute, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes,*

https://doi.org/10.1021/acs.orglett.1c00952
Org. Lett. 2021, 23, 3561−3566

School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China

Peng Wang − *Chang-Kung Chuang Institute, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China;* orcid.org/0000-0003-1217-4801

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00952

Author Contributions

[#]X. Ren and L. Tang contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

National Natural Science Foundation of China and ECNU are gratefully acknowledged for their financial support.

■ REFERENCES

(1) For selected reviews, see: (a) Ye, L.-W.; Shu, C.; Gagosz, F. Recent Progress towards Transition Metal-Catalyzed Synthesis of γ-lactams. *Org. Biomol. Chem.* **2014**, *12*, 1833−1845. (b) Caruano, J.; Muccioli, G. G.; Robiette, R. Biologically Active γ-lactams: Synthesis and Natural Sources. *Org. Biomol. Chem.* **2016**, *14*, 10134−10156. (c) Rivas, F.; Ling, T. Advances toward the Synthesis of Functionalized γ-Lactams. *Org. Prep. Proced. Int.* **2016**, *48*, 254−295.

(2) (a) Rhee, J. U.; Krische, M. J. Highly Enantioselective Reductive Cyclization of Acetylenic Aldehydes via Rhodium Catalyzed Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2006**, *128*, 10674−10675. (b) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. Asymmetric Synthesis of β-Substituted γ-Lactams via Rhodium/Diene-Catalyzed 1,4-Additions: Application to the Synthesis of (*R*)-Baclofen and (*R*)-Rolipram. *Org. Lett.* **2011**, *13*, 788−791. (c) Kanbayashi, N.; Takenaka, K.; Okamura, T.-a.; 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*, 4897−4901. (d) Lang, Q.; Gu, G.; Cheng, Y.; Yin, Q.; Zhang, X. Highly Enantioselective Synthesis of Chiral γ-Lactams by Rh-Catalyzed Asymmetric Hydrogenation. *ACS Catal.* **2018**, *8*, 4824−4828. (e) Park, Y.; Chang, S. Asymmetric Formation of γ-lactams via C-H Amidation Enabled by Chiral Hydrogen-bond-donor Catalysts. *Nat. Catal.* **2019**, *2*, 219−227. (f) Wu, X.; Qu, J.; Chen, Y. Quinim: A New Ligand Scaffold Enables Nickel-Catalyzed Enantioselective Synthesis of α-Alkylated γ-Lactam. *J. Am. Chem. Soc.* **2020**, *142*, 15654−15660. (g) Panger, J.; Denmark, S. Enantioselective Synthesis of γ-Lactams by Lewis Base Catalyzed Sulfenoamidation of Alkenes. *Org. Lett.* **2020**, *22*, 2501−2505.

(3) (a) Christoffers, J.; Baro, A., Eds. *Quaternary Stereocenters—Challenges and Solutions for Organic Synthesis*; Wiley-VCH, 2005. (b) Ling, T.; Rivas, F. All-Carbon Quaternary Centers in Natural Products and Medicinal Chemistry: Recent Advances. *Tetrahedron* **2016**, *72*, 6729−6777. (c) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48*, 740−751.

(4) For selected reviews, see: (a) Eppe, G.; Didier, D.; Marek, I. Stereocontrolled Formation of Several Carbon-Carbon Bonds in Acyclic Systems. *Chem. Rev.* **2015**, *115*, 9175−9206. (b) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. All-Carbon Quaternary Stereogenic Centers in Acyclic Systems through the Creation of Several C-C Bonds per Chemical Step. *J. Am. Chem. Soc.* **2014**, *136*, 2682−2694. (c) Feng, J.; Holmes, M.; Krische, M. J. Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis. *Chem. Rev.* **2017**, *117*, 12564−12580. (d) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* **2016**, *116*, 7330−7396. (e) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres. *Nature* **2014**, *516*, 181−191.

(5) (a) Seki, T.; Tanaka, S.; Kitamura, M. Enantioselective Synthesis of Pyrrolidine-, Piperidine-, and Azepane-Type N-Heterocycles with α-Alkenyl Substitution: The CpRu-Catalyzed Dehydrative Intramolecular N-Allylation Approach. *Org. Lett.* **2012**, *14*, 608−611. (b) Song, T.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 603−607. (c) 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 γ-Lactams with Aryl Chlorides and Bromides. *Angew. Chem., Int. Ed.* **2019**, *58*, 4297−4301.

(6) (a) Deng, Xu.; Shi, L.-Y.; Lan, J.; Guan, Y.-Q.; Zhang, X.; Lv, H.; Chung, L.; Zhang, X. Enantioselective Rhodium-Catalyzed Cycloisomerization of 1,6-Allenynes to access 5/6-Fused Bicycle[4.3.0]-nonadienes. *Nat. Commun.* **2019**, *10*, 949. (b) Nishimura, T.; Maeda, Y.; Hayashi, T. Chiral Diene-Phosphine Tridentate Ligands for Rhodium-Catalyzed Asymmetric Cycloisomerization of 1,6-Enynes. *Org. Lett.* **2011**, *13*, 3674−3677. (c) Masutomi, K.; Noguchi, K.; Tanaka, K. Enantioselective Cycloisomerization of 1,6-Enynes to Bicyclo[3.1.0]hexanes Catalyzed by Rhodium and Benzoic Acid. *J. Am. Chem. Soc.* **2014**, *136*, 7627−7630. (d) Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. Rhodium-Catalyzed Asymmetric Enyne Cycloisomerization of Terminal Alkynes and Formal Total Synthesis of (−)-Platensimycin. *Angew. Chem., Int. Ed.* **2009**, *48*, 6293−6295. (e) Trost, B. M.; Ryan, M. C.; Rao, M.; Markovic, T. Z. Construction of Enantioenriched [3.1.0] Bicycles via a Ruthenium-Catalyzed Asymmetric Redox Bicycloisomerization Reaction. *J. Am. Chem. Soc.* **2014**, *136*, 17422−17425. (f) Dieckmann, M.; Jang, Y.-S.; Cramer, N. Chiral Cyclopentadienyl Iridium(III) Complexes Promote Enantioselective Cycloisomerizations Giving Fused Cyclopropanes. *Angew. Chem., Int. Ed.* **2015**, *54*, 12149−12152. (g) Liang, R.-X.; Song, L.-J.; Lu, J.-B.; Xu, W.-Y.; Ding, C.; Jia, Y.-X. Palladium-Catalyzed Enantioselective Heteroarenyne Cycloisomerization Reaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 7412−7417.

(7) (a) Park, J. H.; Kim, S. M.; Chung, Y. K. Rh-Catalyzed Reductive Cyclization of Enynes using Ethanol as a Source of Hydrogen. *Chem. - Eur. J.* **2011**, *17*, 10852−10856. (b) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. Enantioselective Reductive Cyclization of 1,6-Enynes via Rhodium-Catalyzed Asymmetric Hydrogenation: C-C Bond Formation Precedes Hydrogen Activation. *J. Am. Chem. Soc.* **2005**, *127*, 6174−6175.

(8) (a) Wang, C.; Ge, S. Versatile Cobalt-Catalyzed Enantioselective Entry to BorylFunctionalized All-Carbon Quaternary Stereogenic Centers. *J. Am. Chem. Soc.* **2018**, *140*, 10687−10690. (b) Yu, S.; Wu, C.; Ge, S. Cobalt-Catalyzed Asymmetric Hydroboration/Cyclization of 1,6-Enynes with Pinacolborane. *J. Am. Chem. Soc.* **2017**, *139*, 6526−6529.

(9) (a) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. Enantioselective Cyclization/Hydrosilylation of 1,6-Enynes Catalyzed by a Cationic Rhodium Bis(phosphine) Complex. *Org. Lett.* **2003**, *5*, 157−159. (b) Fan, B.-M.; Xie, J.-H.; Li, S.; Wang, L.-X.; Zhou, Q.-L. Highly Enantioselective Hydrosilylation/Cyclization of 1,6-Enynes Catalyzed by Rhodium(I) Complexes of Spiro Diphosphines. *Angew. Chem., Int. Ed.* **2007**, *46*, 1275−1277.

(10) (a) Whyte, A.; Torelli, A.; Mirabi, B.; Prieto, L.; Rodríguez, J. F.; Lautens, M. Cobalt-Catalyzed Enantioselective Hydroarylation of 1,6-Enynes. *J. Am. Chem. Soc.* **2020**, *142*, 9510−9517. (b) Whyte, A.; Bajohr, J.; Torelli, A.; Lautens, M. Enantioselective Cobalt-Catalyzed Intermolecular Hydroacylation of 1,6-Enynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 16409−16413.

(11) (a) Li, Ke.; Li, M.-L.; Zhang, Q.; Zhu, S.-F.; Zhou, Q.-L. Highly Enantioselective Nickel-Catalyzed Intramolecular Hydroalkenylation of N- and O-Tethered 1,6-Dienes to Form Six-Membered Heterocycles. *J. Am. Chem. Soc.* **2018**, *140*, 7458−7461. (b) Pagar, V. V.;

RajanBabu, T. V. Tandem Catalysis for Asymmetric Coupling of Ethylene and Enynes to Functionalized Cyclobutanes. *Science* **2018**, *361*, 68−72.

(12) For selected examples for asymmetric heck/carbonylation, see: (a) Yuan, Z.; Zeng, Y.; Feng, Z.; Guan, Z.; Lin, A.; Yao, H. Constructing Chiral Bicyclo[3.2.1]octanes via Palladium-Catalyzed Asymmetric Tandem Heck/Carbonylation Desymmetrization of Cyclopentenes. *Nat. Commun.* **2020**, *11*, 2544. (b) Chen, M.; Wang, X.; Yang, P.; Kou, X.; Ren, Z.-H.; Guan, Z.-H. Palladium-Catalyzed Enantioselective Heck Carbonylation with a Monodentate Phosphoramidite Ligand: Asymmetric Synthesis of (+)-Physostigmine, (+)-Physovenine, and (+)-Folicanthine. *Angew. Chem., Int. Ed.* **2020**, *59*, 12199−12205. (c) Carmona, R. C.; Köster, O. D.; Correia, C. R. D. Chiral N,N Ligands Enabling Palladium-Catalyzed Enantioselective Intramolecular Heck-Matsuda Carbonylation Reactions by Sequential Migratory and CO Insertions. *Angew. Chem., Int. Ed.* **2018**, *57*, 12067−12070. (d) Cheng, C.; Wan, B.; Zhou, B.; Gu, Y.; Zhang, Y. Enantioselective Synthesis of Quaternary 3,4-dihydroisoquinolinones via Heck Carbonylation Reactions: Development and Application to the Synthesis of Minalrestat analogues. *Chem. Sci.* **2019**, *10*, 9853−9858. (e) Hu, H.; Teng, F.; Liu, J.; Hu, W.; Luo, S.; Zhu, Q. Enantioselective Synthesis of 2-Oxindole Spirofused Lactones and Lactams by Heck/Carbonylative Cylization Sequences: Method Development and Applications. *Angew. Chem., Int. Ed.* **2019**, *58*, 9225−9229.

(13) (a) Kollär, L. *Modern Carbonylation Methods*; Wiley-VCH: Weinheim, 2008. (b) Peng, J.-B.; Geng, H.-Q.; Wu, X.-F. The Chemistry of CO: Carbonylation. *Chem.* **2019**, *5*, 526−552. (c) Kiss, G. Palladium-Catalyzed Reppe Carbonylation. *Chem. Rev.* **2001**, *101*, 3435−3456. (d) Yang, J.; Liu, J.; Neumann, H.; Franke, R.; Jackstell, R.; Beller, M. Direct Synthesis of Adipic Acid Esters via Palladium-Catalyzed Carbonylation of 1,3-dienes. *Science* **2019**, *366*, 1514−1517. (e) Brennführer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Alkenes and Alkynes. *ChemCatChem* **2009**, *1*, 28−41.

(14) (a) Godard, C.; Munoz, B. K.; Ruiz, A.; Claver, C. Pd-Catalysed Asymmetric Mono- and Bis-alkoxycarbonylation of Vinylarenes. *Dalton Trans* **2008**, 853−860. (b) Alper, H.; Hamel, N. Asymmetric Synthesis of Acids by the Palladium-Catalyzed Hydrocarboxylation of Olefins in the Presence of (*R*)-(−)- or (*S*)-(+)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate. *J. Am. Chem. Soc.* **1990**, *112*, 2803−2804. (c) Konrad, T. M.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. Highly Enantioselective Hydroxycarbonylation and Alkoxycarbonylation of Alkenes using Dipalladium Complexes as Precatalysts. *Angew. Chem., Int. Ed.* **2010**, *49*, 9197−9200. (d) Wang, X.; Wang, B.; Yin, X.; Yu, W.; Liao, Y.; Ye, J.; Wang, M.; Hu, L.; Liao, J. Palladium-Catalyzed Enantioselective Thiocarbonylation of Styrenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 12264−12270. (e) 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.

(15) Xu, Z.; Shen, C.; Zhang, H.; Wang, P.; Dong, K. Constructing chiral aza-quaternary carbon centers by enantioselective carbonylative Heck reaction of *o*-iodoanilines with allenes. *Org. Chem. Front.***2021**, *8*1163.

(16) Xu, Z.; Tang, Y.; Shen, C.; Zhang, H.; Gan, Y.; Ji, X.; Tian, X.; Dong, K. Nickel-Catalyzed Regio- and Diastereoselective Hydroarylative and Hydroalkenylative Cyclization of 1,6-dienes. *Chem. Commun.* **2020**, *56*, 7741−7744.

(17) Petrone, D. A.; Franzoni, I.; Ye, J.; Rodríguez, J. F.; Poblador-Bahamonde, A. I.; Lautens, M. Palladium-Catalyzed Hydrohalogenation of 1,6-Enynes: Hydrogen Halide Salts and Alkyl Halides as Convenient HX Surrogates. *J. Am. Chem. Soc.* **2017**, *139*, 3546−3557.

(18) Badiola, E.; Olaizola, I.; Vazquez, A.; Vera, S.; Mielgo, A.; Palomo, C. $\beta^{2,2}$-Amino Acid *N*-Carboxyanhydrides Relying on Sequential Enantioselective C(4)-Functionalization of Pyrrolidin-2,3-diones and Regioselective Baeyer-Villiger Oxidation. *Chem. - Eur. J.* **2017**, *23*, 8185−8195.

https://doi.org/10.1021/acs.orglett.1c00952
Org. Lett. 2021, 23, 3561−3566