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Letter

Palladium(II)-Catalyzed Reductive Cyclization of N-Tosyl-Tethered 1,7-Enynes: Enantioselective Synthesis of 1,2,3,4-Tetrahydroquinolines

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Supporting Information

ABSTRACT: A novel Pd(II)-catalyzed reductive asymmetric cyclization of *N*-tosyl-tethered 1,7-enynes using ethanol as a hydrogen source is reported. This reaction provides facile ways for the synthesis of two types of 1,2,3,4-tetrahydroquinolines possessing a chiral quaternary carbon center in high yields with excellent enantioselectivities. The obtained products can also be converted to other chiral functionalized tetrahydroquinolines efficiently. The procedure involves a palladium-catalyzed intramolecular hydropalladation/1,4-addition or β -heteroatom elimination cascade process.

ransition-metal-catalyzed carbon-carbon bond formation reactions are the most useful synthetic strategy in organic chemistry.¹ In recent decades, transition-metal-catalyzed reductive coupling using alcohols as a hydrogen resource between various unsaturated compounds such as alkene, alkyne, and allene with the carbonyl group has been efficiently developed in Krische's group.²⁻⁴ Krische mainly used iridium, ruthenium, or rhodium as the catalyst, and he realized the asymmetric intermolecular coupling successfully. We have been developing many palladium(II)-catalyzed intramolecular couplings of alkyne-tethered ketones or aldehydes initiated by nucleopalladation or transmatelation and quenched by addition to the carbonyl group via a redox-neutral approach for years.^{5,6} Recently, we reported the reductive coupling of alkyne-tethered ketones initiated by hydropalladation of alkynes using ethanol as a clean and cheap hydrogen source. In 2018, a palladium(II)-catalyzed reductive cyclization of cyclohexadienone-containing 1,6-enynes was also successfully realized in our group, which represents the first palladiumcatalyzed enyne cyclization using ethanol as the hydrogen source in the literature (Scheme 1, eq 1).⁸ In this cyclization, the 1,4-addition of the carbon-palladium bond to the unsaturatred alkene was used as the quenching step. However, in all of our works initiated by hydropallation of alkynes, the asymmetric versions were not successful, although we tried many chiral ligands and catalytic systems.

1,2,3,4-Tetrahydroquinoline skeletons are privileged scaffolds present in many biologically active natural products and pharmacologically relevant therapeutic agents,⁹ and therefore, the development of enantioselective approaches to these cyclic skeletons is of major significance.¹⁰ Among which, the most used method is Lewis acid or organocatalyzed cyclization of



Scheme 1. Our Previous Work and Present Work



arylamine derivatives. In contrast, there are fewer examples to produce these chiral heterocycles catalyzed by transition metals.¹¹ As a continuation of our efforts on the reductive cyclization of alkyne-tethered ketones and 1,6-enynes, we began our research by exploring the asymmetric reaction of *N*tosyl-tethered 1,7-enynes initiated by hydropalladation to synthesize 1,2,3,4-tetrahydroquinolines possessing a chiral quaternary carbon center (Scheme 1, eq 2). In the procedure, two types of 1,2,3,4-tetrahydroquinolines were provided depending on the functional group (FG) on the terminal alkenes. When the FG is an electron-withdrawing group (EWG), the reaction employs 1,4-addition as the quenching step to give products bearing a mono-exocyclic double bond. On the other hand, when a leaving group is located on the

Received: July 12, 2019 Published: September 26, 2019 alkene (FG = CH_2OCO_2Et), products containing two exocyclic double bonds would be obtained by using β heteroatom elimination as the quenching step.

At the outset of our investigation, we selected substrate **1a** for the optimization of the conditions for this palladium(II)-catalyzed reductive cyclization reaction. As depicted in Table 1,



^{*a*}Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), $Pd(CH_3CN)_4(BF_4)_2$ (5 mol %) and ligand (5 mol %) were dissolved in solvent/EtOH (0.2 mL/1 mL), and then the solution was stirred overnight. ^{*b*1}H NMR yields were based on 1,3,5-trimethoxybenzene internal standard. ^{*c*}Ee value was detected by HPLC. ^{*d*}1.2 mL of EtOH was added. ^{*e*}1.2 mL of CH₃CN was added. ^{*f*}5 mol % of Pd(OAc)₂ was added. ^{*g*}2.5 mol % of Pd₂(dba)₃ was added.

 $Pd(CH_3CN)_4(BF_4)_2$ and various commercially available chiral diphosphine ligands were used to screen the reaction. When the reaction was run in DMF/EtOH (1/5) in the presence of ligand L1 (5 mol %) at 60 °C, no cyclization product was detected (entry 1). To our delight, when ligand L2 was used in place of L1, the desired tetrahydroquinoline 2a was generated in high yield with moderate enantioselectivity (entry 2). Then, BINAP (L3) and some modified-BINAP complexes (L4–L8) were evaluated, and all of them can give good results (entries 3-8). Among which, SEGPHOS (L4) provided the highest yield and ee value (85% yield, 95% ee) (entry 4). Me-DuPhos L9 was unfavorable for the cyclization (entry 9). Cosolvent screening showed that the influence of them is not obvious (entries 10-14), and CH₃CN can increase the yield and enantioselectivity slightly (90% yield, 96% ee). (entry 14). When EtOH was used as the sole solvent, the yield was decreased slightly (entry 15). The reaction did not occur in the absence of EtOH, which indicates that EtOH is indispensable for the reductive cyclization and it offers a hydrogen source in the procedure (entry 16). Other alcohols bearing an α hydrogen such as MeOH and *i*-PrOH were also investigated. No reaction was observed to occur in the solvent of MeOH (entry 17). Conversely, i-PrOH gave the same yield and ee value as EtOH (entry 18). The influence of the temperature on the reaction was also investigated. It was found that a lower temperature (40 °C) only gave a trace amount of the product (entry 19). In contrast, when the temperature was increased to 80 °C, a maintained enantioselectivity was obtained with a slightly decreased yield (entry 20). Finally, Pd catalysts such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ were tested and both were not suitable for this reaction (entries 21 and 22).

Having established the optimized reaction conditions, we next evaluated the substrate scope of this reaction (Scheme 2).

Scheme 2. Reductive Cyclization of Substrates 1^{a-c}



^{*a*}Reaction conditions: **1** (0.1 mmol, 1.0 equiv), $Pd(CH_3CN)_4(BF_4)_2$ (5 mol %), and ligand (5 mol %) were dissolved in $CH_3CN/EtOH$ (0.2 mL/1 mL); the mixture was stirred at 60 °C until consumption of **1** as monitored by TLC. ^{*b*}Isolated yield. ^{*c*}Ee value was detected by HPLC. ^{*d*}The reaction was conducted at 80 °C. ^{*c*}7.5 mol % of $Pd(CH_3CN)_4(BF_4)_2$ and (*R*)-SEGPHOS were used.

First, the substrates substituted with different groups (\mathbb{R}^1) on the benzene ring were tested, and the results show that the reaction exhibits high functional group tolerance. Electrondonating groups such as the methyl or methoxyl group provided **2b**-**2d** in good yields with excellent ee values. Halogens such as F and Cl were tolerated in this reaction (**2e**, **2f**). When bromide and trifluoromethyl were located on the benzene ring, the corresponding products **2g** and **2h** were obtained in excellent ee value, albeit slightly more catalyst and ligand should be added at a higher temperature. The phenyl group also gave a good result (**2i**). Then, substrates bearing other bulky substituents on alkynes (\mathbb{R}^4) were investigated. DMPS (dimethylphenylsilyl) provided a similar result as TMS (**2j**). TBS (*tert*-butyldimethylsilyl) and a tertiary butyl group offered good enantioselectivities, albeit in a lower yield than TMS (trimethylsilyl) (**2k** and **2l**). Similar to our previous work,^{7,8} when the phenyl or methyl group was used to replace TMS, the reaction was complicated or no reaction occurred.

To further show the generality of this protocol, we also investigated different electron-withdrawing groups on the terminal alkene (\mathbb{R}^3) under the optimal conditions and the desired products were obtained in good yields and enantioselectivities. Compared to the ester group, substrates bearing a cyano, carbonyl, and amide group worked well to deliver products **2m**-**2o** with similar ee values and lower yields. To our surprise, when the substituent on the other side of the alkene (\mathbb{R}^2) was changed from methyl to ethyl, both the yield and ee value of the product **2p** decreased. We then wanted to test the reactivity of O- or C-tethered alkynes; however, the starting material cannot be obtained at present.

Next, the substrates containing a carbonate as a leaving group were tested under similar reaction conditions. As summarized in Scheme 3, the reaction exhibits high functional group tolerance. Substrates with a methyl, methoxyl, halide, or trifluoromethyl group on the benzene ring proceeded well to give products 4b-4h with excellent enantioselectivities, albeit in moderate yields. When the bulky group was changed from TMS to TBS or a tertiary butyl group, both the yield and ee value decreased (4i and 4j).



^{*a*}Reaction conditions: **3** (0.1 mmol, 1.0 equiv), $Pd(CH_3CN)_4(BF4)_2$ (5 mol %), and ligand (5 mol %) were dissolved in CH₃CN/EtOH (0.2 mL/1 mL); the mixture was stirred at 80 °C until consumption of **3** as monitored by TLC. ^{*b*}Isolated yield. ^{*c*}Ee value was detected by HPLC. ^{*d*}7.5 mol % of Pd(CH₃CN)₄(BF₄)₂ and (*R*)-SEGPHOS were added to the reaction.

The synthetic utility of the reaction was then performed by using 2a as the starting material (Scheme 4). When 2a was





"Reaction conditions: (a) TBAF, THF, 70 °C; (b) NIS (4.0 equiv), CH₃CN, rt; (c) DIBAL-H, THF, -20 °C; (d) TBSCl, TEA, DCM, rt; (e) NIS (2.0 equiv), CH₃CN, rt; (f) Ethynyltrimethylsilane, Pd(PPh₃)₂Cl₂, CuI, TEA, rt.

reacted with tetrabutylammonium fluoride (TBAF), the desilated product **5a** bearing a terminal alkene was obtained in good yield with excellent ee value. Surprisingly, when compound **2a** was reacted with *N*-iodosuccinimide (NIS), an unexpected product **8a** with three chiral centers was efficiently obtained. The absolute configuration of **8a** was unambiguously determined by single-crystal X-ray diffraction analysis (CCDC 1919857). Compound **2a** can also be converted into product **6a** successfully via sequential reduction, etherification, and iodination. Furthermore, Sonogashira coupling of **6a** with trimethylsilylacetylene delivered the alkyne modified compound **7a**.

Finally, we turned our attention to address the mechanism by performing the reaction of 1a in *d*-ethanol. Product d-2a with the deuterium on the α -position to the ester group was obtained in the presence of CH₃CH₂OD (50% yield, 95% ee, Scheme 5, eq 3). On the other hand, the use of CH₃CD₂OH afforded d-2a', having a deuterium at the vinyl position (46% yield, 94% ee, Scheme 5, eq 4).

On the basis of the above result of the deuterium labeling studies, a proposed reaction pathway is illustrated in Scheme 6. First, Pd ethoxide complex A is formed from the reaction of the palladium catalyst and ethanol, which subsequently gives the key intermediate Pd hydride complex B via β -H





Scheme 6. Proposed Catalytic Cycle



elimination. Then, intermediate C is generated via insertion of the carbon-carbon triple bond in substrate 1a or 3a into a hydrogen-palladium bond in intermediate B. Next, the carbon-palladium bond adds to the intramolecular alkene to produce intermediate D. If the functional group (FG) is an electron-withdrawing group, protonolysis of D yields product 2a and regenerates the palladium(II) catalyst. The deuteriumlabeling experiments showed that the hydrogen in the exocyclic double bond is from the α -H in ethanol and OH furnishes the hydrogen in the protonolysis step. On the other hand, if the functional group is a carbonate, product 4a is obtained from intermediate D using β -heteroatom elimination as the quenching step.

In summary, we have developed a Pd(II)-catalyzed asymmetric cyclization of N-tosyl-tethered 1,7-enynes using ethanol as a hydrogen source. The initiation step of the cyclization is hydropalladation of alkynes, and the quenching step is 1,4-addition to the intramolecular conjugate alkenes or β -heteroatom elimination. This transformation provides facile ways for the synthesis of two types of chiral 1,2,3,4tetrahydroquinolines in high yields with excellent enantioselectivities. The obtained products can also be converted to other chiral functionalized tetrahydroquinolines efficiently using known synthetic methods. Further studies to better understand the mechanism as well as to apply the method for the synthesis of natural product and drug are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b02412.

Experimental procedures, characterization data, NMR spectra, and HPLC data for all new compounds (PDF)

Accession Codes

CCDC 1919857 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 Cam-

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Notes

The authors declare no competing financial interest.

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