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An enyne cycloisomerization/[5+1] reaction sequence to synthesize tetrahydroisoquinolinones from enyne-enes and CO†

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An enyne cycloisomerization/[5+1] reaction sequence was developed to synthesize tetrahydroisoquinolinones from linear enyne-enes and CO. The first step is a gold(I)-catalyzed enyne cycloisomerization, generating six-membered-ring-fused vinylcyclopropanes. The second step is a rhodium(I)-catalyzed [5+1] reaction of vinylcyclopropanes with CO. This two-step reaction could also be carried out in one-pot without isolating the cycloisomerization product generated from the first step of this sequence.

Perhydroisoquinoline ring systems, including tetrahydroisoquinolines, tetrahydroisoquinolinones, hexahydroisoquinolines, and other partially reduced forms, reside at the core of numerous bioactive natural products and synthetic pharmaceutical compounds.[1] Fig. 1 shows some natural products with reduced forms of isoquinoline skeletons such as reserpine, manzamine A, and morphine.[2] The significant bioactive properties and complex structures of these natural products have been stimulating organic chemists to develop new routes to construct these privileged skeletons.

Our group recently developed a cationic Rh(I)-catalyzed [5+1] cycloaddition between vinylcyclopropanes (VCPs) and CO to synthesize monocyclic β,γ- or α,β-cyclohexenones (Scheme 1a).[3a,b,4] This reaction was used in the asymmetric synthesis of (−)-mesembrine.[3b] We also found that this [5+1] reaction could access bicyclic skeletons when the VCP was fused with other rings (Scheme 1b).[3a] Inspired by the recent development of cycloisomerization of nitrogen-tethered 1,6-enynes catalyzed by Au,[5] Pt,[6] Rh,[7] Ir,[8] and Mn[9] to obtain bicyclo[4.1.0]heptenes,[10] we envisioned that we could use easily prepared linear enyne-enes to give six-membered ring fused VCPs. Then we could subject the generated VCPs to the Rh(I)-catalyzed [5+1] reactions to synthesize tetrahydroisoquinolinones (Scheme 1c). A two-step reaction could also be carried out in one-pot to increase the efficiency of the synthesis, if two catalysts both performed their independent roles and did not interfere with each other.[11] The present enyne cycloisomerization/[5+1] reaction sequence could be

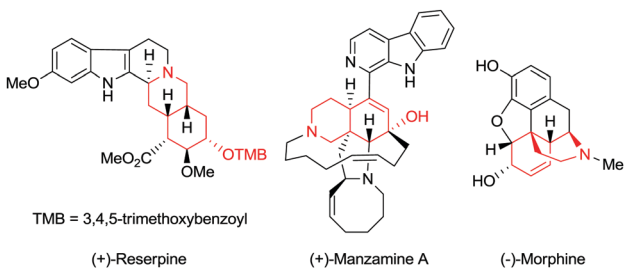
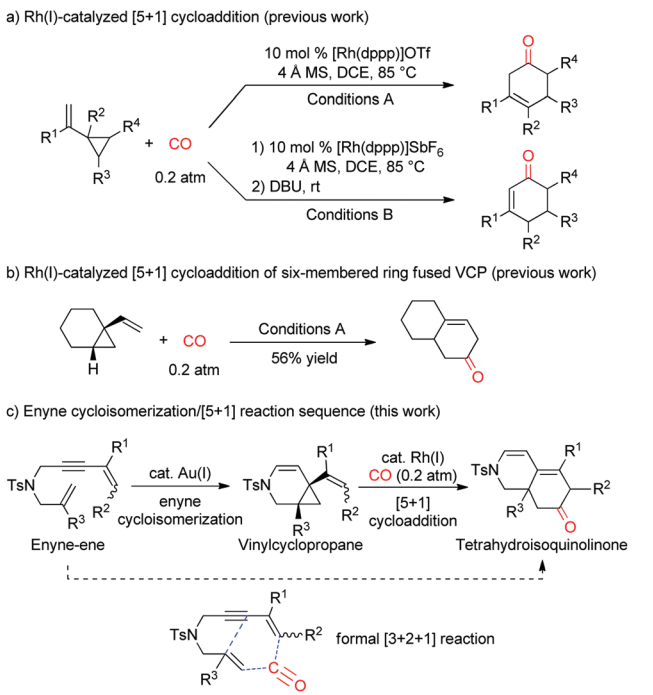


Fig. 1 Natural products with perhydroisoquinoline rings.



Scheme 1 Previous work and this work.

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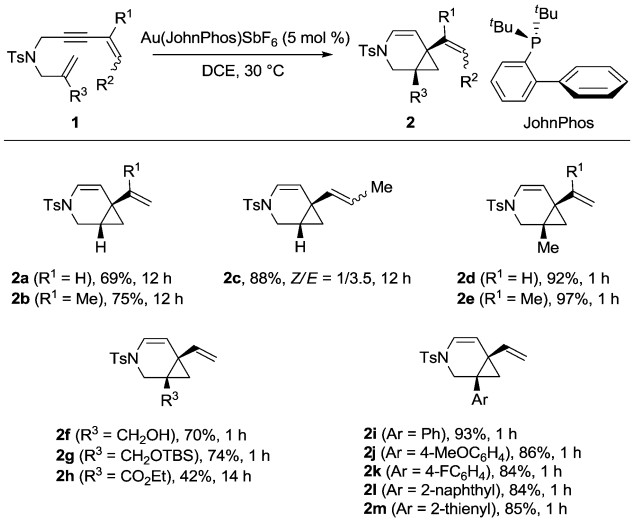
envisioned as a formal [3+2+1] reaction of linear enyne-enes with CO to give tetrahydroisoquinolinones.[12]

We had several concerns at the outset of this work. One was whether the first cycloisomerization could have a broad scope and could give the desired VCPs in high yields, which is critical for making the present synthetic strategy practical. Even though many useful cycloisomerizations of 1,6-enynes to cyclopropanated products have been developed, the cycloisomerization of enyne-enes with various substituents to the VCPs has not been well investigated. For example, Echavarren's group reported the Au(I)-catalyzed cycloisomerization of nitrogen-tethered linear 1,6-enynes. However, the chemoselectivity was not good and a low yield was found in their work. Moreover, the scope and the tolerance of functional groups had not been fully explored by them.[5a,b] The second challenge was related to the generality of the [5+1] cycloaddition. We did not investigate previously whether the [5+1] cycloaddition could be used to build 6/6-ring systems with a quaternary center at the bridgehead carbon or in the β-substituted VCPs, respectively. Considering the importance of the tetrahydroisoquinolinone skeleton and the difficulty in the synthesis of all-carbon quaternary centers,[13] realization of the present enyne cycloisomerization/[5+1] reaction would be very significant.

To carry out the enyne cycloisomerization/[5+1] reaction, we first tested the cycloisomerization of enyne-enes by screening various gold catalysts. Our extensive optimization (see Table S1 in the ESI†) of the reaction conditions suggested that using Au(JohnPhos)SbF_6 (Echavarren's catalyst, which can be prepared *in situ* or is commercially available, see Table S1 in the ESI†), the cycloisomerization of nitrogen-tethered 1,6-enyne-ene **1a** in DCE gave the desired bicyclo[4.1.0]heptene derivative **2a**. It should be noted that the protecting group in nitrogen-tethered linear 1,6-enynes is crucial for them to undergo enyne cycloisomerization. We found that Boc, Bn and *o*-Ns protected 1,6-enynes failed to give any desired product.[14] Then we tested a series of enyne-ene substrates under the optimized reaction conditions to study the reaction scope. We found that the present cycloisomerization could tolerate methyl substituents on the inner or outer positions of the ene and enyne moieties of the substrates (**2b–e**, Table 1). Since cycloisomerization of substrates with an alkyl or aryl substituent at the inner position of the ene moiety could give VCPs with additional quaternary centers, which could then be applied to synthesize tetrahydroisoquinolinones with a quaternary center by the [5+1] cycloaddition, we synthesized the substrates with various substituents at the enes' inner position and investigated their reactions. To our delight, we found that almost all cycloisomerization reactions from substrates with R^3 = alkyl, aryl groups gave VCPs in high yields (**2f–m**, Table 1). In particular, the present cycloisomerization could tolerate R^3 substituents such as ester, silyloxy and hydroxyl groups (**2f–h**, Table 1). It should be pointed out here that the cycloisomerization of electron-withdrawing substituent **2h** just had a modest reaction yield. The aromatic R^3 substituents could be either electron-donating or electron-withdrawing groups and good yields could also be achieved in these cases (**2i–k**, Table 1).

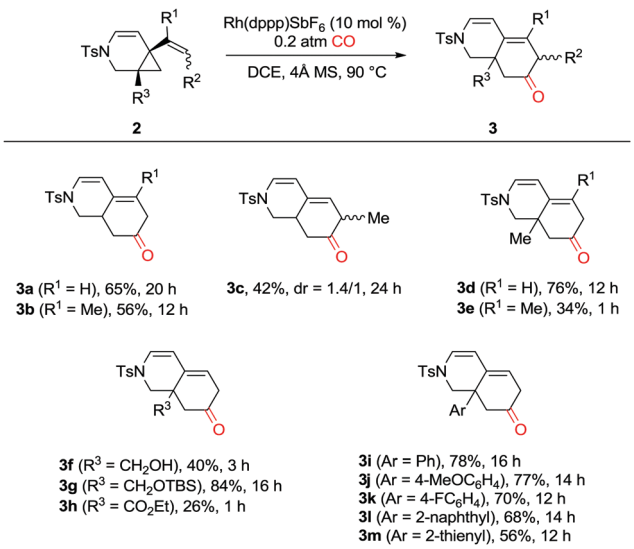
With the six-membered ring fused VCPs in hand, the substrate scope (Table 2, 0.2 atm CO here means that a balloon pressured mixed gas of CO and N_2 with a CO/N_2 ratio of 1/4 was applied) of the

Table 1 Au(I)-catalyzed enyne cycloisomerization[a,b]



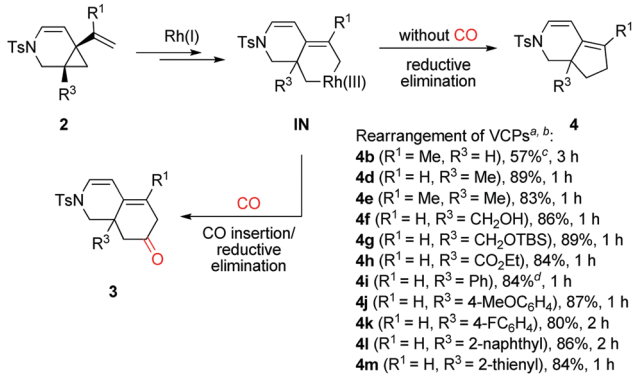
[a] Reaction conditions: 0.1 mmol **1**, 5 mol% Au(JohnPhos)SbF_6, DCE (0.05 M), 30 °C. [b] Average yield of two runs.

Table 2 Rh(I)-catalyzed [5+1] cycloaddition[a,b,c]



[a] Reaction conditions: 0.1 mmol **2**, 10 mol% Rh(dppp)SbF_6, DCE (0.05 M), 0.08 g 4 Å MS, 0.2 atm CO, 90 °C. [b] All substrates (except **2a**, **2c**, **2g**, **2i**) also gave VCP rearrangement products (structures are given in Scheme 2): **4b** (29%), **4d** (12%), **4e** (65%), **4f** (36%), **4h** (62%), **4j** (11%), **4k** (24%), **4l** (28%), **4m** (30%). [c] Average yield of two runs.

Rh(I)-catalyzed [5+1] cycloaddition was then evaluated using the optimized reaction conditions (see Table S3 in the ESI†). Compound **2a** without a substituent on both the alkene moiety and the cyclopropane ring gave the [5+1] product in 65% yield. Substrate α-methyl VCP **2b** was a good reactant for the [5+1] reaction, although its reaction yield to give **3b** was only 56%. The lower yield here was due to the competing VCP isomerisation of **2b** to give **4b** (the proposed mechanism and structure are given in Scheme 2). We found that almost all substrates (except **2a**, **2c**, **2g**, **2i**) had such a competing VCP rearrangement reaction and this decreased the yield

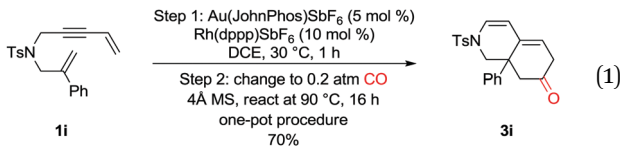


Scheme 2 Rh(I)-catalyzed [5+1] cycloaddition and rearrangement of VCPs. [a]Reaction conditions: 0.1 mmol **2**, 10 mol% Rh(dppp)SbF_6, DCE (0.05 M), 0.08 g 4 Å MS, under N_2, 90 °C. [b]Average yield of two runs. [c]20 mol% Rh(dppp)SbF_6. [d]One-pot procedure from **1i** can give **4i** in 76% yield.

of the desired [5+1] reaction (see notes of Table 2 for the yields of these side reactions; changing CO pressure did not give improved results, see the ESI†). Our previous investigations indicated that β-substituted VCPs were not suitable substrates for the Rh(I)-catalyzed [5+1] cycloaddition.[3] However, to our delight, β-methyl VCP **2c** succeeded in affording **3c** in 42% yield and a 1.4/1 diastereoisomeric ratio. We were happy to note that the [5+1] cycloaddition of **2d** took place smoothly, giving rise to tetrahydroisoquinolinone **3d** with a bridgehead quaternary center. We then synthesized a series of tetrahydroisoquinolinones with a bridgehead quaternary center, finding that all these [5+1] reactions occurred smoothly with modest to good yields (**3e–m**, Table 2). Ester, silyloxy, hydroxyl, aromatic and heteroaromatic groups can all be tolerated in the [5+1] cycloaddition.

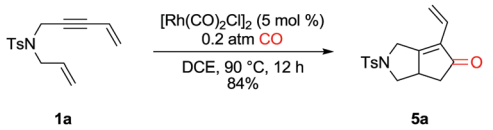
Considering that the 6/5 ring system is an important skeleton in natural products and pharmaceutical compounds, we also investigated the scope of the VCP rearrangement of **2** (Scheme 2). In the absence of the CO atmosphere, VCPs were converted under similar conditions (see Table S5 in the ESI†) to cycloisomerization product cyclopentenes in good yields. However, substrates **2a** and **2c** gave only complex mixtures.

The enyne cycloisomerization/[5+1] reaction sequence could also be carried out in one-pot to realize the formal [3+2+1] reaction: adding both Au and Rh catalysts together to **1i** in DCE, allowing the cycloisomerization to take place at 30 °C for 1 h; then changing the nitrogen atmosphere to a 0.2 atm CO atmosphere and increasing the reaction temperature to 90 °C for an additional 16 h, the final product **3i** was obtained in 70% yield, just 3% lower than the two-step procedure (eqn (1)). We also tried to carry out the one-pot reaction by adding an Rh catalyst after the completion of cycloisomerization and found that this procedure can give **3i** in 75% yield (see Part VII in the ESI†).



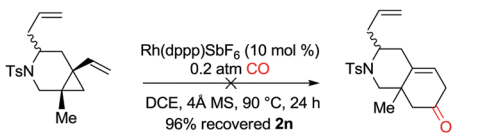
(1)

Considering that Rh could catalyze both cycloisomerization[7] and [5+1] cycloaddition, we tested this hypothesized Rh-catalyzed tandem reaction of **1a** to synthesize tetrahydroisoquinolinone *via* a one-step procedure. But we only obtained the Pauson–Khand cycloaddition product **5a** in 84% yield (eqn (2)).[15] When we used cationic Rh catalysts, we obtained some unidentified decomposed products.

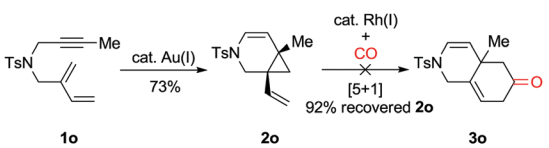


(2)

After achieving the enyne cycloisomerization/[5+1] reaction sequence to synthesize tetrahydroisoquinolinones, we wondered whether the inner double bond of the bicyclo[4.1.0]heptenes initially generated in the cycloisomerization was critical to the success of the ensuing Rh(I)-catalyzed [5+1] cycloaddition. To answer this question, a control experiment was conducted, showing that the reaction of allylated substrate **2n** could not afford the [5+1] cycloaddition product **3n** under the standard reaction conditions (eqn (3), 96% of **2n** was recovered). This result clearly indicated that the double bond within the six-membered ring of **2** is essential to facilitate the ring opening of cyclopropane *via* coordination to a metal species when the [5+1] reaction was used to build the bridgehead quaternary center (this is not required compared to the [5+1] reaction in Scheme 1b).[12,16,17] Also, this was the reason why β-substituted VCP **2c** could undergo [5+1] cycloaddition in this system. Based on this observation, **2o** synthesized from conjugated diene-yne failed to afford the desired [5+1] cycloaddition product **3o** (eqn (4)).

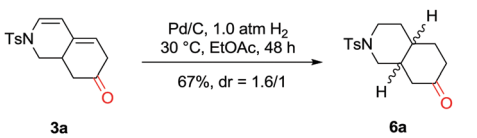


(3)

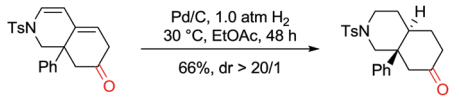


(4)

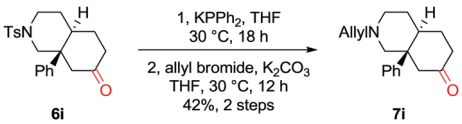
To demonstrate the synthetic utility of this method, we have performed several transformations of the formed products. The double bonds of **3a** can be easily reduced by Pd/C to give perhydroisoquinoline **6a** in 67% yield and a 1.6/1 diastereoisomeric ratio (eqn (5)). **3i** with a bridgehead all-carbon quaternary center can also afford *trans*-perhydroisoquinoline **6i** in 66% yield (eqn (6)). To access other N-substituted cycloadducts, we have tried several methods to remove this protecting group for further functionalization. The traditional methods such as Na/naphthalene and Mg/MeOH failed to give any desired product, but we found that $KPPh_2$ was efficient in fulfilling the deprotection (eqn (7)).



(5)



(6)



(7)

In conclusion, we have developed an efficient enyne cycloisomerization/[5+1] reaction sequence to obtain tetrahydroisoquinolinones from easily prepared enyne-enes and CO. The reaction sequence included a cycloisomerization of enyne-ene to generate six-membered ring fused VCP and a Rh(I)-catalyzed [5+1] cycloaddition of VCP and CO. The two-step reaction sequence could also be carried out in one-pot, even though the yield was slightly decreased in the latter case. The fact that the present enyne cycloisomerization/[5+1] reaction sequence could build tetrahydroisoquinolinones with a bridgehead all-carbon quaternary center is of significant importance. We found that the enyne-ene substrates can also be used to synthesize a 6/5 skeleton by enyne cycloisomerization/VCP rearrangement (Scheme 2). Developing the asymmetric version of the enyne cycloisomerization/[5+1] reaction sequence,[5d,f–h,l,m,6c–g,7c,f,g,8a,d,e] enyne cycloisomerization/VCP rearrangement, and their application in synthesis can be envisioned.

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