Cycloaddition

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Rhodium(I)-Catalyzed Bridged [5+2] Cycloaddition of *cis*-Allene-vinylcyclopropanes to Synthesize the Bicyclo[4.3.1]decane Skeleton

*Cheng-Hang Liu and Zhi-Xiang Yu**

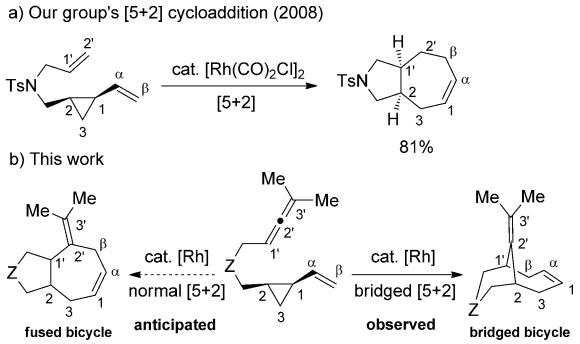
Dedicated to Professor Yun-Dong Wu on the occasion of his 60th birthday

Abstract: *Previously reported was that cis-ene-vinylcyclopropanes (cis-ene-VCPs) underwent Rh-catalyzed [5+2] reaction to give 5,7-fused bicyclic products, where vinylcyclopropane (VCP) acts as five-carbon synthon. Unfortunately, this reaction had very limited scope. Replacing the 2π component of cis-ene-VCPs to allene moiety, the corresponding cis-allene-VCPs did not undergo the expected normal [5+2] cycloaddition to give 5,7-fused bicyclic products. Instead, the challenging bicyclo-[4.3.1]decane skeleton was obtained via an unprecedented bridged [5+2] cycloaddition. DFT calculations were applied to understand why this bridged [5+2] reaction is favored over the anticipated but not realized normal [5+2] reaction.*

Seven-membered carbocycles are widely found in natural products of biological and pharmaceutical importance. However, methods which access seven-membered carbocycles are limited and this greatly hinders the synthesis of target functional molecules and their analogues, and additionally slows down the downstream study and investment of these molecules in chemical biology, medicine, and other related fields. Consequently, developing new methods to access seven-membered carbocycles, which can serve as a powerful tool to access functional molecules, has been the frontier of reaction development in the chemical community.[1]

One of the powerful methods for synthesis of seven-membered rings is the transition metal catalyzed [5+2] reaction[2] between vinylcyclopropanes (VCPs) and 2π-systems.[3,4] In 1995, Wender et al. first reported the intramolecular rhodium-catalyzed cycloaddition of VCPs with alkynes.[5a] Since then, the cycloadditions were further developed by Wender et al. and many other groups[5–7] and the π-systems were expanded to alkenes[8,9] and allenes.[10] In addition, the intermolecular cycloadditions of VCPs with π-systems[11–13] and other transition metal catalyzed [5+2] cycloadditions[14,15] have been reported. In 2015, Zhang replaced VCPs with vinyl aziridines and developed the hetero-[5+2] cycloaddition[16] to synthesize azepine derivatives.

Our group has strong interests in discovering and developing transition metal catalyzed cycloadditions, and applying these reactions in the synthesis of natural products.[17] In 2008, we reported the intramolecular [5+2] cycloaddition of *cis*-ene-vinylcyclopropanes (*cis*-ene-VCPs) to afford *cis*-fused bicyclic products (Scheme 1 a).[18,19] However, only three



Scheme 1. a) Previous [5+2] cycloaddition of *cis*-ene-VCP. b) This work: Unexpected bridged [5+2] cycloaddition of *cis*-allene-VCPs.

substrates for *cis*-ene-VCPs gave the desired [5+2] products and other substrates failed. Considering that allenes, with high reactivity,[12b] could also participate in the [5+2] cycloadditions as a 2π-component,[10,13] we wondered whether [5+2] reaction could occur with broad substrate scope using *cis*-allene-vinylcyclopropanes (*cis*-allene-VCPs) as substrates. To our surprise, we did not get the anticipated fused bicyclic product by the normal [5+2] cycloaddition. Instead, we observed an unexpected new type of [5+2] reaction (referred here as bridged [5+2] cycloaddition), which gave a bridged bicyclic product (Scheme 1 b).[20] Herein, we report our experimental results of this novel bridged [5+2] cycloaddition to synthesize the bicyclo[4.3.1]decane skeleton.[21] DFT calculations were also conducted to explain the experimentally observed regioselectivity.

We commenced our study with the NTs-tethered *cis*-allene-VCP **1a** (for structure see Table 1) as the standard substrate. After extensive optimization (see the Supporting Information), we found that treatment of **1a** with [Rh-$(CO)_2Cl]_2$ in 1,4-dioxane gave a new symmetrical bicyclo-[4.3.1]decane cycloadduct, **2a**, in 77% yield. Here, the inner double bond of the allene acts as the 2π component and participates in the [5+2] cycloaddition to give the bridged ring

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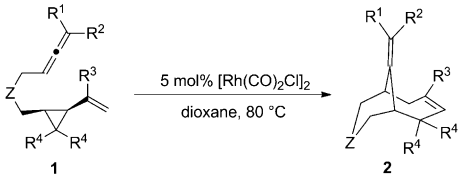
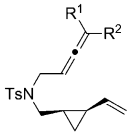
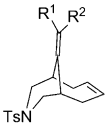
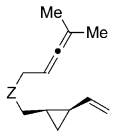
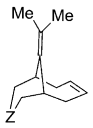
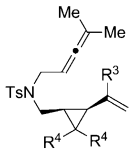
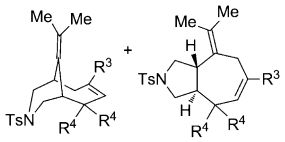
Table 1: Scope of the [5+2] cycloadditions of *cis*-allene-VCPs.



1 **2**

Entry	Substrate	Product[a]
		
1	**1a**, $R^1=R^2=$Me	**2a**, 4 h, 80%
2	**1b**, $R^1=R^2=$-$CH_2(CH_2)_4CH_2$-	**2b**, 4 h, 73%
3	**1c**, $R^1=R^2=$Et	**2c**, 4 h, 73%
4	**1d**, $R^1=$Me, $R^2=$Et	**2d**, 4 h, 80%
5	**1e**, $R^1=$Me, $R^2=$*i*-Pr	**2e**, 5 h, 78%
6	**1f**, $R^1=$Me, $R^2=$Ph	**2f**, 6 h, 62%
7	**1g**, $R^1=$H, $R^2=$*p*-C_6H_5Br	no reaction[b]
8	**1h**, $R^1=$H, $R^2=$*n*-Pr	no reaction[b]
9	**1i**, $R^1=R^2=$H	no reaction[b]
		
10	**1j**, Z=NNs	**2j**, 4 h, 78%
11	**1k**, Z=NBs	**2k**, 7 h, 76%
12	**1l**, Z=NSO_2Ph	**2l**, 3 h, 74%
13	**1m**, Z=NMs	**2m**, 3 h, 75%
14	**1n**, Z=$C(CO_2Me)_2$	no reaction[b]
15	**1o**, Z=O	complex mixture
		
16	**1p**, $R^3=$Ph, $R^4=$H	**2p** + **3p**, 3 h, 70%(1:7)[c,d]
17	**1q**, $R^3=$Me, $R^4=$H	**2q** + **3q**, 4 h, 76% (3:1)[c]
18	**1r**, $R^3=$H, $R^4=$Me	no reaction[b]

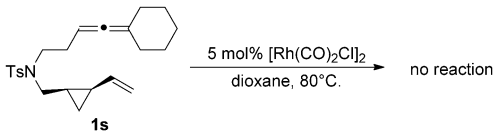
The reaction was performed on a 0.2 mmol scale and 4 mL 1,4-dioxane was used. [a] Yield given in an average of two runs. [b] Slowly decomposed at 100 °C. When cationic Rh catalyst was used, decomposition was also observed. [c] 10 mol% catalyst loading. [d] 100 °C. Bs = 4-bromobenzenesulfonyl, Ms = methanesulfonyl, Ns = 4-nitrobenzenesulfonyl.

skeleton, in an opposite manner compared to the previously reported normal [5+2] cycloadditions which gave fused 5/7 and 6/7 skeletons.[22]

After obtaining the optimal reaction conditions, we began to investigate the scope of the bridged [5+2] cycloaddition (Table 1). First, terminally disubstituted allenes were found to be excellent substrates (entries 1–6) and highly symmetrical bicyclo[4.3.1]decane cycloadducts (**2a–c**) were obtained when symmetrical allenes were used (entries 1–3). For the substrate **1f**, with a phenyl substituent, the desired reaction gave a slightly lower reaction yield after 6 hours. Substrates with terminally monosubstituted or nonsubstituted allenes proved to be unsuitable and these substrates decomposed slowly when the temperature was raised to 100 °C (entries 7–9). We reasoned that, in this case, the rhodium catalyst preferred to coordinate at the distal double bond of the allene[23] and many competing side reactions could happen.[24] This so called "terminal methyl effect" was also noticed in many reactions.[23b,25]

Next, we changed the NTs tether in the substrate to NNs, NBs, NMs, and NSO_2Ph and the desired products were delivered with good yields under the standard reaction conditions (Table 1, entries 10–13). The bicyclo[4.3.1]decane skeleton of the product was further confirmed by single-crystal X-ray crystallography analysis of **2k**.[26] Unfortunately, C-tethered substrates could not be converted into the desired bicyclo[4.3.1]decane cycloadduct and no reaction took place even after performing this reaction at 100 °C (entry 14). The O-tethered substrate **1o** was also not suitable for this transformation and the complex mixture was generated when treating **1o** under the standard reaction conditions (entry 15).

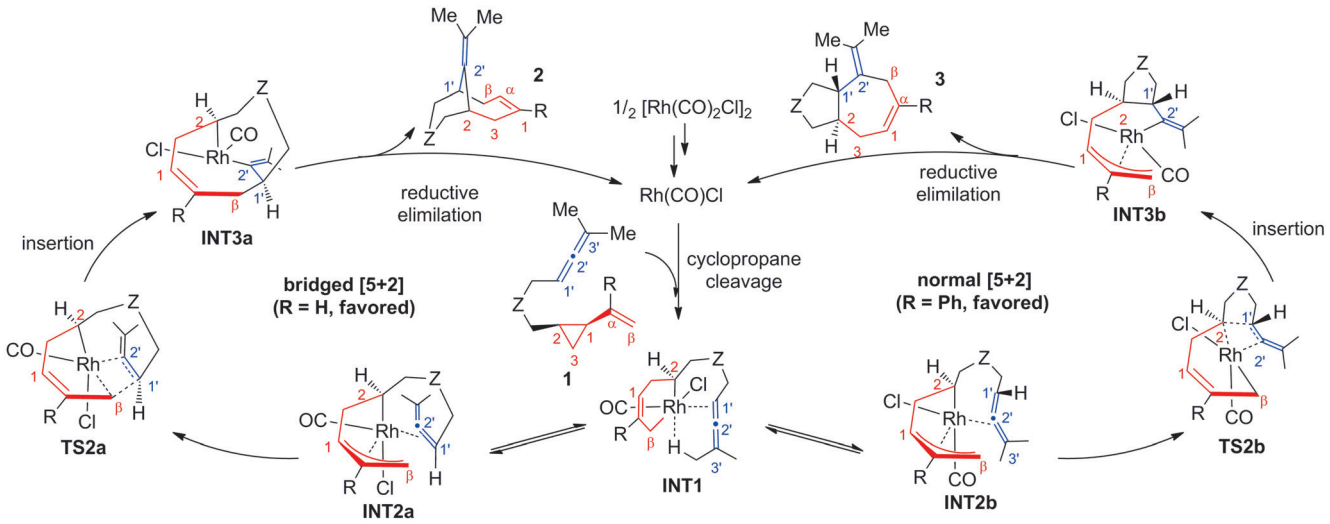
We also synthesized the substrates **1p–r** and examined how the variations on the VCP moiety of the substrates affected the reaction outcomes (entries 16–18). No reaction occurred when substrate **1r** with substitution at the cyclopropane moiety was used, which could be attributed to the steric hindrance of the substrate. Substrates **1p–q** with substitution in the alkene moiety showed low reactivities so the catalyst loading was increased to 10 mol% and the temperature was raised to 100 °C. A mixture of the bicyclo-[4.3.1]decane products **2p–q** and bicyclo[5.3.0]decane products **3p–q**, the originally expected normal [5+2] cycloadducts, can be isolated for substrates **1p–q**. For **1p**, with bulkier phenyl group, the product **3p** was the major product and the structure was confirmed by X-ray crystallography.[26] In stark contrast to previous work (Scheme 1), the *trans* bicyclo-[5.3.0]decane product was achieved here. Finally, we tested a longer tether, hoping to achieve the bicyclo[4.4.1]undecane product (Scheme 2). However no product could be observed and the starting material was recovered.



1s

Scheme 2. Rhodium-catalyzed cycloaddition reaction of **1s** with an elongated tether.

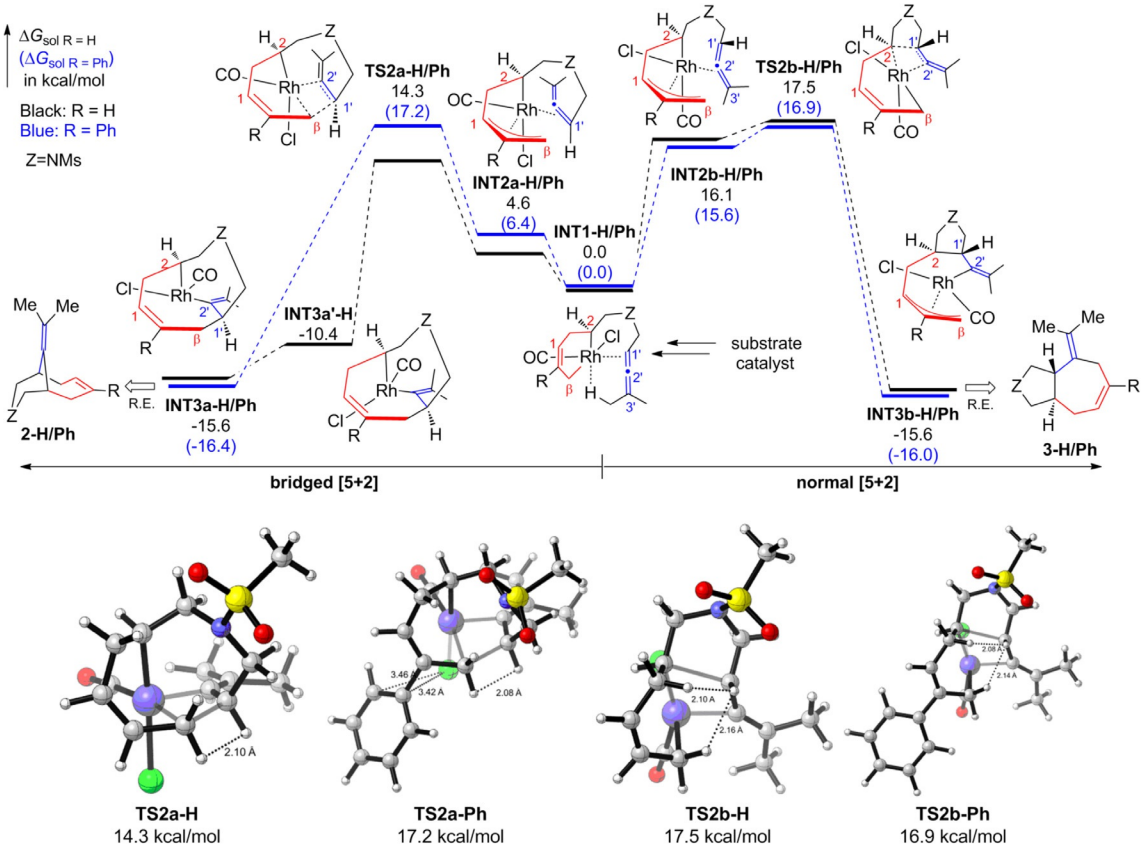
The proposed mechanism, together with preliminary support from DFT calculations, is given in Scheme 3. The catalytic cycle starts with the complexation of [Rh(CO)Cl] with the substrate, followed by cyclopropane ring cleavage at C1−C2 to give the intermediate **INT1**, which has the allene coordination and agostic interaction of methyl with the rhodium center. When R = H, the allene moiety will fold back and C1′ of allene will approach Cβ to form **INT2a**. After insertion of the inner double bond (via **TS2a** to form



Scheme 3. Proposed mechanisms of bridged and normal [5+2] cycloadditions.

INT3a),[27] reductive elimination occurs to form the C2–C2′ bond, thus furnishing the bridged bicyclic adduct **2**. However, when R = Ph, the normal [5+2] reaction pathway is favored. C1′ of the allene will approach C2 to form **INT2b**. Then *trans* insertion[27] of the inner double bond into Rh–C2 bond forms **INT3b** (via **TS2b**).[28] Finally, the fused bicyclic product **3** is formed by reductive elimination and the [Rh(CO)Cl] species is regenerated to furnish the catalytic cycle.

To understand how the substituents at the alkene moiety of the substrates affect the regioselectivity, we performed preliminary DFT calculations[29] using the M06-2X/6-311 + G(d,p)(SDD)//B3LYP/6-31G(d)(LANL2DZ) method (see



Scheme 4. M06-2X//B3LYP computed free-energy surfaces of the two competing pathways in 1,4-dioxane. For full energy surfaces, see the Supporting Information.

the Supporting Information). For simplification of the calculations, Ms-tethered model substrates were used without sacrificing the reliability and efficiency of computations. Considering that the insertion step is exergonic and irreversible, the formation of either **2** or **3** depends on the relative energies of the insertion transition states **TS2a** and **TS2b** (see Scheme 4).

DFT calculations suggest that, when R = H, **TS2a-H** (the bridged [5+2] reaction pathway) is favored by 3.2 kcal mol^{-1} compared to **TS2b-H** in the normal [5+2] reaction pathway, and implies that the bridged bicyclic adduct **2-H** would be generated predominantly, and is thus consistent with the experimental findings. This is because the transition state **TS2b-H**, for *trans* insertion of the allene into the C2–Rh bond, suffers strong repulsion between internal hydrogen atoms in the allene moiety and those in the VCP moiety (the corresponding H···H distances are 2.10 Å and 2.16 Å, within the sum of van der Waals radii; see Scheme 4). In contrast, in the bridged [5+2] pathway, the transition state **TS2a-H** reduces these steric repulsions by putting the allene moiety away from the VCP moiety. Consequently, **TS2a-H** is favored over **TS2b-H**. When R = Ph, insertion of the allene in the bridged [5+2] reaction pathway via **TS2a-Ph** requires a higher activation Gibbs free energy (17.2 kcal mol^{-1} for R = Ph and 14.3 kcal mol^{-1} for R = H) because of the introduction of an additional π-lone pair repulsion between the Ph group and Cl in the present case. The activation energy for the insertion of allene in the normal [5+2] reaction does not change for R = Ph, compared to that for R = H. As a result, allene insertions by both pathways have close activation energies and both bridged and normal [5+2] cycloadducts are generated, thus agreeing with the experimental observation.

DFT calculations have also been used to rationalize why the carbon tether is not suitable for the bridged [5+2] reaction, and we found that the carbon tether experiences more steric repulsion in the transition state of the allene insertion (see the Supporting Information).

In summary, a novel rhodium(I)-catalyzed intramolecular bridged [5+2] cycloaddition of *cis*-allene-VCPs has been developed to synthesize the challenging bicyclo[4.3.1]decane skeleton. Preliminary DFT calculations revealed that the allene insertion in the expected normal [5+2] cycloaddition suffers from the repulsion between the allene and VCP moiety in the transition state. In contrast, the bridged [5+2] cycloaddition can reduce this repulsion by placing the allene away from the VCP moiety in the allene insertion transition state, thus leading to inverse allene insertion and giving finally the bridged [5+2] cycloadducts.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allenes · cycloaddition · density-functional calculations · rhodium · small ring compounds

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[26] CCDC 1535695 (**2k**) and 1535693 (**3p**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[27] The pathway of *cis* insertion was also analyzed and found to be unfavored because of steric hindrance (see the Supporting Information).

[28] The inverse insertion of the inner double bond into the Rh−C2 bond and the *trans* insertion into Rh−Cβ bond were also considered and ruled out because of a high-energy barrier. For details, see the Supporting Information.

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