

Computational Study of Mechanisms and Tether Length Effects of Rh-Catalyzed [3 + 2] and [3 + 2 + 1] Reactions of Ene/Yne-Vinylcyclopropanes

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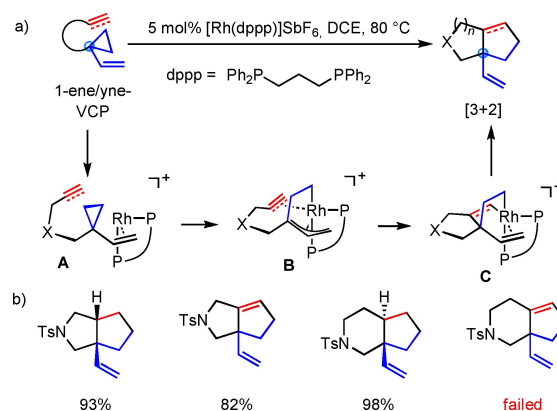
Abstract: DFT calculations have been applied to study the mechanisms of [3 + 2] and [3 + 2 + 1] reactions of ene/yne-vinylcyclopropanes (shorted as ene/yne-VCPs). The [3 + 2] reactions of ene/yne-VCPs start from C–C cleavage of cyclopropane (CP cleavage) to form six-membered rhodacycle, followed by alkene/alkyne insertion and reductive elimination. The [3 + 2 + 1] reactions have two competing pathways, one is the [3 + 2 + 1] pathway (CP cleavage, ene/yne insertion,

CO insertion and reductive elimination) and the other is the [3 + 1 + 2] pathway (CP cleavage, CO insertion, ene/yne insertion and reductive elimination). The length of tether in substrates affects the ene/yne insertion steps in these cycloadditions, making some reactions fail or changing the reaction pathways. The reasons for these tether length effects are discussed.

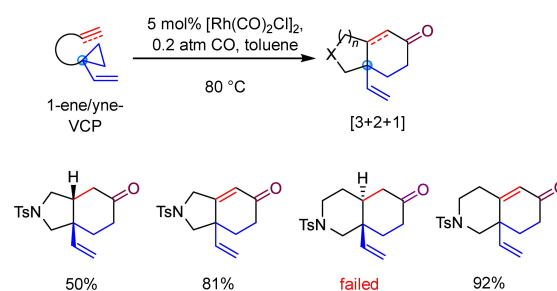
1. Introduction

Previously we developed a Rh-catalyzed [3 + 2] reaction of ene/yne-vinylcyclopropanes (Scheme 1a).^[1] The proposed pathway (Scheme 1a) for this reaction starts from the C–C cleavage of vinylcyclopropane (VCP) by the cationic rhodium catalyst, followed by intramolecular alkene/alkyne insertion and reductive elimination. This reaction can be used to synthesize 5/5 bicycles, no matter whether the 2- π component is alkynes or alkenes. However, to synthesize 6/5 bicycles, the 2- π component can only be alkenes (Scheme 1b).^[1c] Previously we used DFT calculations to study the mechanism of [3 + 2] reaction of ene/yne-VCPs for the formation of 5/5 system, but not the 6/5 system. We hypothesized that for a longer tether, the alkyne insertion is difficult so that 6/5 bicycle cannot be built. Here we report our quantum chemical calculations aiming to understand whether this hypothesis is correct or not and the reason behind this so-called tether length effect.

We have also developed a [3 + 2 + 1] cycloaddition of ene/yne-vinylcyclopropanes and CO to synthesize 5/6 and 6/6 bicyclic skeletons with a bridgehead quaternary carbon center (Scheme 2).^[2] This reaction has been applied by both our group and the Lei group in the synthesis of natural products.^[3] For yne-VCP substrates, both 5/6 and 6/6 bicyclic skeletons can be achieved. But for ene-VCPs, 5/6 but not



Scheme 1. The [3 + 2] reaction of ene/yne-VCPs.



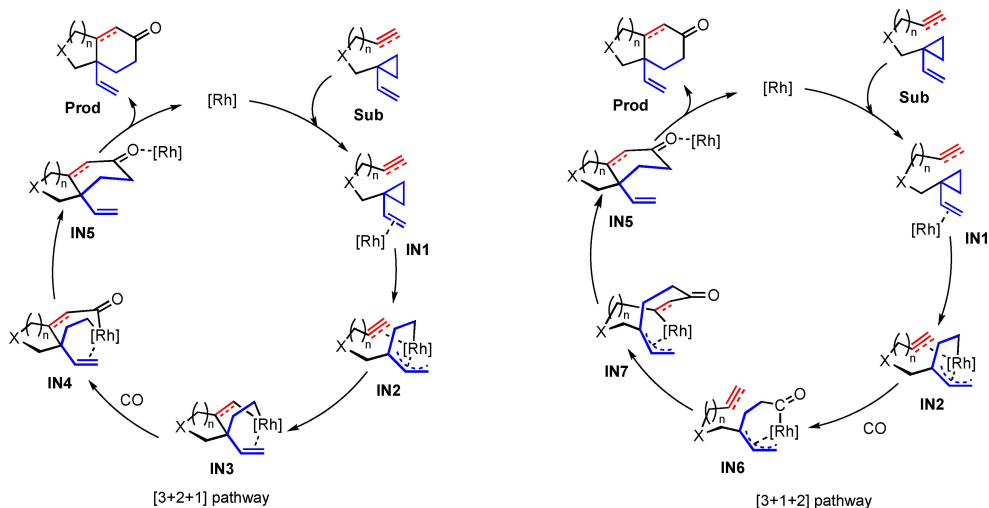
Scheme 2. The [3 + 2 + 1] reaction of ene/yne-VCPs and CO.

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6/6 bicyclic skeleton can be constructed (Scheme 2).^[4] The proposed mechanism of this reaction is shown in Scheme 3, which starts from the ring opening of VCP via C–C cleavage, alkene/alkyne insertion, CO coordination and insertion, and finally reductive elimination. We name this as the [3 + 2 + 1] pathway. We hypothesized that this [3 + 2 + 1] pathway works for the synthesis of 5/6 bicyclic skeleton, but not for the 6/6 bicyclic skeleton. As we mentioned above, the alkyne insertion for 6/5 bicycles in [3 + 2] reaction could be difficult.



Scheme 3. Two pathways for the [3+2+1] reaction of ene/yne-VCPs and CO.

If this is true, the similar step in the [3+2+1] pathway for 6/6 bicycles in [3+2+1] reaction should be difficult too and cannot be accomplished. Consequently, no [3+2+1] product could be generated. This is contradictory to our experimental observation, where [3+2+1] reaction using yne-VCPs to 6/6 bicycles worked. Therefore, we proposed a new pathway for the [3+2+1] reaction for the synthesis of 6/6 bicyclic skeleton using yne-VCPs as substrates, namely the [3+1+2] pathway, which differentiates from the [3+2+1] pathway by the relative order of CO and alkyne insertions. In the [3+2+1] pathway, alkyne insertion proceeds before CO insertion, while in the [3+1+2] pathway, an opposite order is proposed. Therefore, in this paper, we will discuss whether these hypotheses are correct or not, and the reasons behind this tether length effect. Also, we want to answer whether [3+1+2] pathway works for [3+2+1] reaction accessing to 5/6 bicyclic skeleton (Scheme 3).

2. Results and Discussion

In this part, we first discuss the mechanisms of [3+2+1] reactions of various substrates. Then we describe the mechanisms of [3+2] reactions. Finally, the tether length effects will be analyzed.

2.1. Mechanism of [3+2+1] reaction of Yne-VCPs for the synthesis of 5/6 bicyclic skeleton

Firstly, we calculated both [3+2+1] and [3+1+2] pathways of the [3+2+1] reaction of yne-VCP substrate with a short tether for the synthesis of 5/6 bicyclic skeleton (Figure 1). The catalytic species is proposed to be the monomer, similar to $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ catalyzed [5+2+1] and [4+2+1] reactions.^[5] We don't know the resting state of the reaction. We propose that this resting state will give rhodium/substrate complex,

Y-IN1, which is followed by the dissociation of one CO ligand and C–C bond activation of cyclopropane (CP cleavage) via Y-TS1. This C–C cleavage step is similar to that in the [5+2+1] reaction of ene-VCP and CO, which requires an activation free energy of 18.2 kcal/mol. The ensuing step is alkyne coordination to Rh, forming Y-IN4, which is exergonic by 16.4 kcal/mol. Then intramolecular alkyne insertion via Y-TS2 is easy, with an activation free energy of 19.5 kcal/mol. The formed Y-IN5 from this step is then coordinated by CO to form Y-IN6. The followed CO insertion reaction has an activation free energy of 14.8 kcal/mol. The final step in the [3+2+1] pathway is reductive elimination, generating Y-IN8 with an activation free energy of 18.2 kcal/mol. After that, intermediate Y-IN8, in which Rh is coordinated by two alkene moieties, can then be coordinated by another CO to form a Y-IN9 (this is exergonic by 9.2 kcal/mol). Finally, ligand exchange between this complex and substrate regenerates the resting state species and delivers the product.

We also computed the CO insertion in the competing [3+1+2] pathway. In this pathway, Y-IN3 forms a complex with CO to generate Y-IN4', which is exergonic by 13.8 kcal/mol. Then CO insertion via Y-TS2' requires an activation free energy of 25.6 kcal/mol, which is disfavored compared to the alkyne coordination and insertion steps in the [3+2+1] pathway. Therefore, the reaction of yne-VCP substrates with short tether favors [3+2+1] pathway.

The rate-determining step via [3+2+1] pathway is the cyclopropane cleavage, similar to the [5+2+1] reaction.^[5a,b] The exact activation free energy of this step is unknown because we don't know the resting state of this reaction at present.

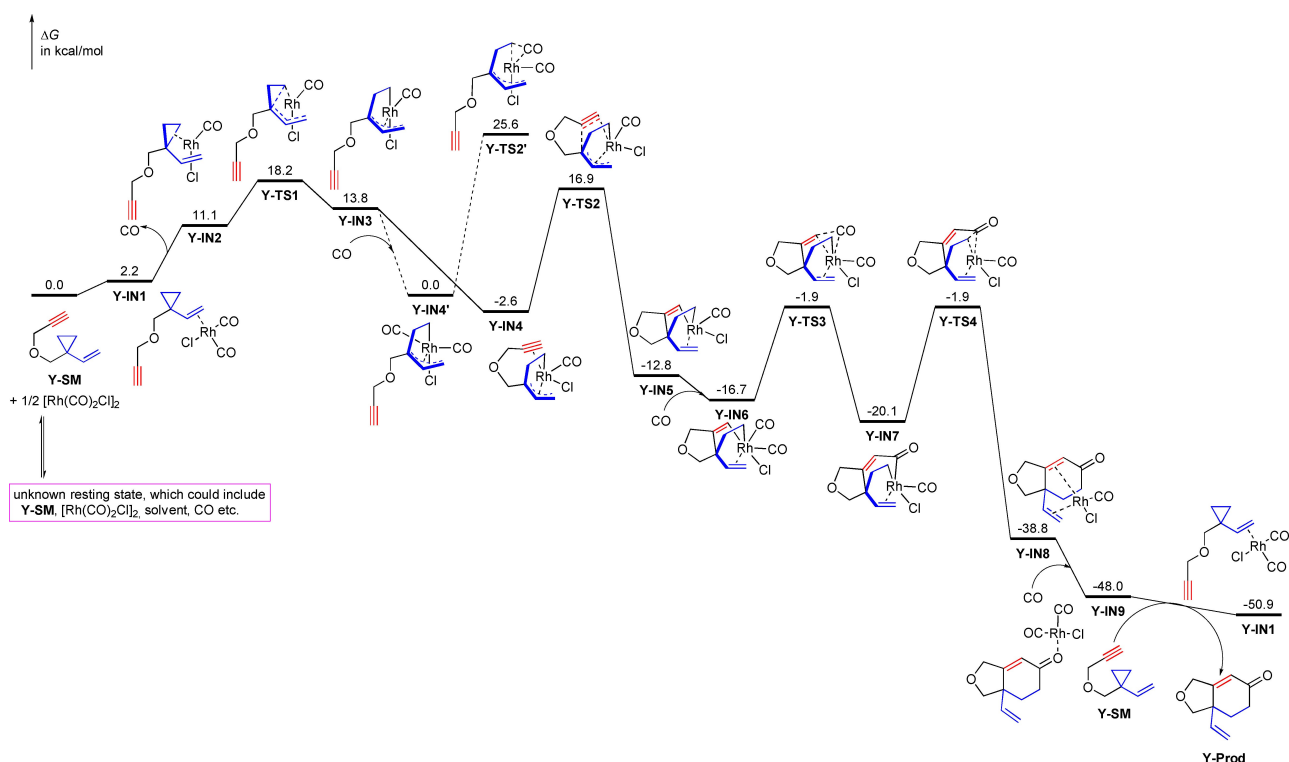


Figure 1. Reaction A: the computed free energy profiles of [3 + 2 + 1] reaction of yne-VCP forming 5/6 ring.

2.2. Mechanism of [3 + 2 + 1] reaction of Ene-VCPs for the synthesis of 5/6 bicyclic skeleton

For the [3 + 2 + 1] reaction of ene-VCPs which yielded the 5/6 bicyclic products, the [3 + 2 + 1] pathway is favored over the [3 + 1 + 2] pathway. The [3 + 2 + 1] pathway share similar

free energy profile with that of the above [3 + 2 + 1] reaction of yne-VCP (Figure 2). Here E-TS1 (VCP cleavage transition state) and E-TS2 (alkene insertion transition state) are close in energy in this reaction. We propose that VCP cleavage is still rate-determining step because the process from the

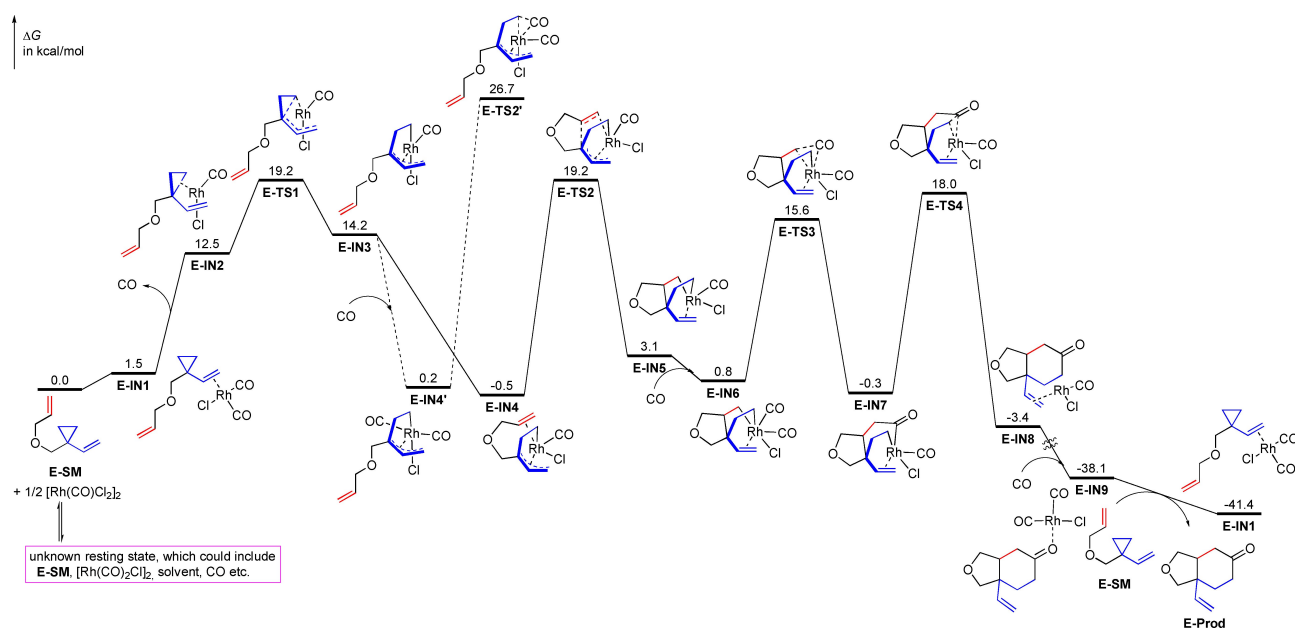


Figure 2. Reaction B: the computed free energy profiles of [3 + 2 + 1] reaction of ene-VCP forming 5/6 ring.

resting state (unknown) and E-TS1 could have an activation free energy higher than 20 kcal/mol.

2.3. Mechanism of [3 + 2 + 1] reaction for yne-VCP for the synthesis of 6/6 bicyclic skeleton

Figure 3 presents the computed profile of the favored [3 + 1 + 2] pathway of the [3 + 2 + 1] reaction of yne-VCP for accessing 6/6 bicyclic framework. After CP cleavage (via HY-TS1, 20.4 kcal/mol) to form HY-IN3, CO coordination forms HY-IN4 (exergonic by 14.1 kcal/mol). Then CO insertion via HY-TS2 with an activation free energy of 25.7 kcal/mol gives HY-IN5. After that, intramolecular alkyne coordination converts HY-IN5 to HY-IN6, which undergoes alkyne insertion subsequently via HY-TS3, with an activation free energy of 25.7 kcal/mol. This step gives intermediate HY-IN7, which is named as an endo metallacycle, as suggested in our recent [4 + 3] reaction of diene-VCPs.^[6]

Intermediate HY-IN7 can be coordinated by CO to form an 18-e complex HY-IN8, which then undergoes reductive elimination via HY-TS4. From HY-IN8 to HY-TS4, the required activation free energy is just 12.3 kcal/mol. Finally, ligand exchange between HY-IN9 and substrate gives HY-IN1 and liberates [3 + 2 + 1] product.

The competing [3 + 2 + 1] pathway is disfavored because alkyne insertion is difficult. HY-IN3 generated from CP cleavage can form HY-IN4' through intramolecular alkyne coordination, which is then followed by alkyne insertion via HY-TS2'. The activation free energy for this step is 26.4 kcal/mol. HY-TS2' is higher than CO insertion transition state HY-TS2 by 7.4 kcal/mol. Consequently, [3 + 2 + 1] pathway is disfavored.

In the present [3 + 2 + 1] reaction, the rate-determining step is proposed to be the alkyne insertion step. The required activation free energy from HY-IN5 to HY-TS3 is 29.0 kcal/mol and the overall activation energy could be this value or even higher than this if the resting state (unknown) is lower than HY-IN5.

2.4. Mechanism of [3 + 2 + 1] reaction of ene-VCP for the synthesis of 6/6 bicyclic skeleton

The [3 + 2 + 1] reaction of an ene-VCP for the synthesis of 6/6 bicycle with an elongated tether results in a complex mixture (Scheme 1). Nevertheless, we tried to calculate the reaction pathway for the [3 + 2 + 1] reaction of ene-VCP with an elongated tether, which turns out to have a reasonable energy profile because no steps with high activation free energies are involved (see the Supporting Information). We propose the failure of such a reaction shown in Scheme 1 could be caused by other unknown side reactions.

2.5. Analyzing the geometries of alkene/alkyne insertion transition states to rationalize the mechanisms of [3 + 2 + 1] reactions

It was proposed that intermolecular alkene/alkyne insertion into Rh–C bond prefers to have planar transition states.^[7] But for intramolecular cycloaddition reactions, to reach such planar transition states, the alkene or alkyne moiety has to bend to some extent, which contributes to some of the distortion energy of the transition states.^[8] For substrates with shorter tether in forming 5/6 cycloadducts, the alkyne

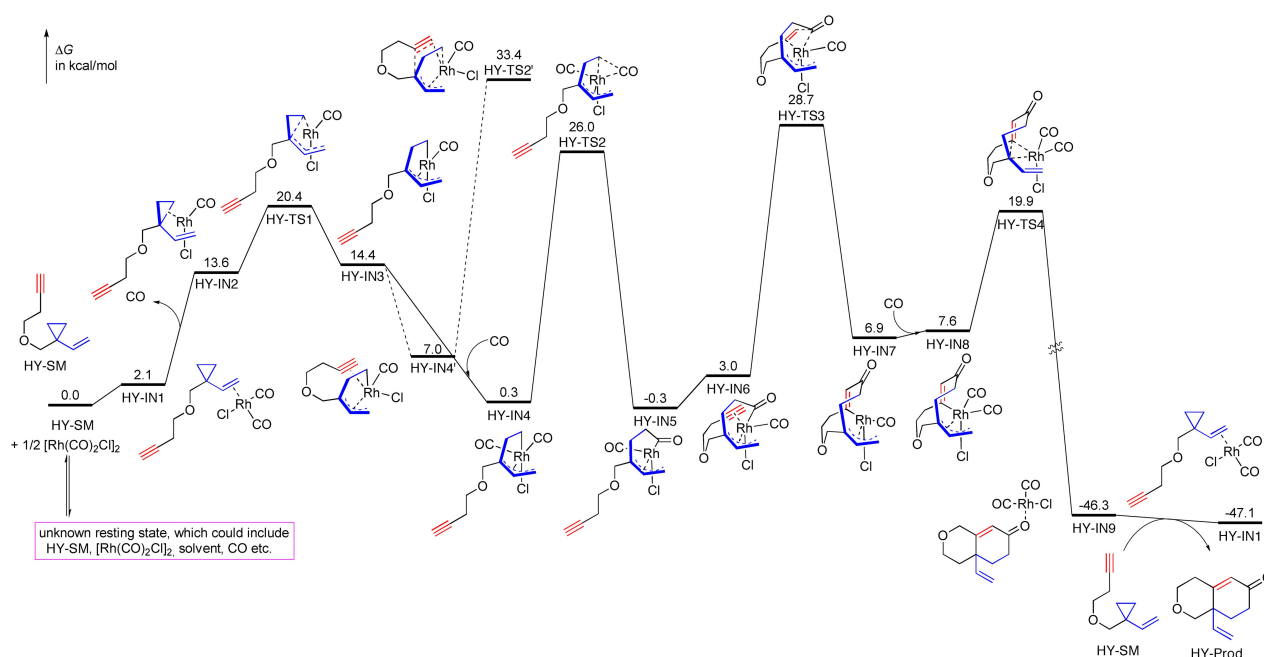


Figure 3. Reaction C: the computed free energy profiles of [3 + 2 + 1] reaction of yne-VCP and CO for forming 6/6 ring.

and alkene insertion activation free energies are 19.5 and 19.7 kcal/mol, respectively (Figure 4). But for the synthesis of 6/6 cycloadducts, the additional tether length forces the substrates to change to more distorted geometries to reach their planar transition states, requiring additional energies. For example, the alkyne insertion has an activation free energy of 26.5 kcal/mol, and the alkyne moiety in the transition state is bent to 133.2°, which is greater than that in transition state Y-TS2. In this case, the competing CO insertion step in the [3+1+2] pathways requiring less activation free energies (25.7 kcal/mol) become favored (Figure 5).

Here we want to mention why alkyne insertion in the [3+1+2] pathway is not difficult. As can be seen from Figure 5, the alkyne moiety is bent to 145.9° in the corresponding transition state HY-TS3. Because of the elongated tether, the terminal carbon of the alkyne moiety is sufficiently close to the carbonyl carbon for alkyne insertion step, generating an endo metallacycle.

2.6. Alkyne/alkene insertion step in the [3+2] reaction of ene/yne-VCPs

The above conclusion can also be applied to understand the [3+2] reactions of ene/yne-VCPs, which used cationic Rh catalyst instead. To demonstrate this, we have also computed the key alkyne/alkene insertion steps of the four types of

substrates in the [3+2] reactions catalyzed by cationic Rh catalyst, which is modeled by $[Rh(dmpp)]^+$ in the calculations (dmpp = 1,3-Bis(dimethylphosphino)propane, Figure 6). The results have similar tendency, indicating that the alkyne insertion forming 6/5 bicycles requires higher activation energy for substrates with longer tether (25.3 kcal/mol) compared to other three types of substrates with shorter tether, also due to the bending of alkyne in the alkyne insertion transition state. Due to the increased activation free energy, side reaction could become easier and then a complex mixture was obtained. These results help us to understand the different reactivity of the substrates of different tether lengths in [3+2] reactions.

3. Conclusion

The mechanisms of the [3+2] and [3+2+1] reactions of ene-VCPs with tethers of different length have been investigated by quantum chemical calculations. All these reactions start from C–C cleavage of the VCP moiety of the substrates to form six-membered metallacycles. For [3+2] reaction of ene/yne-VCPs to form 5/5 bicycles, the followed steps are alkene/alkyne insertion and reductive elimination. The above mechanism still works for ene-VCPs in the formation of 6/5 bicycles, but fails for yne-VCPs to form 6/5 bicycles, due to the greater activation free energy of the alkyne insertion

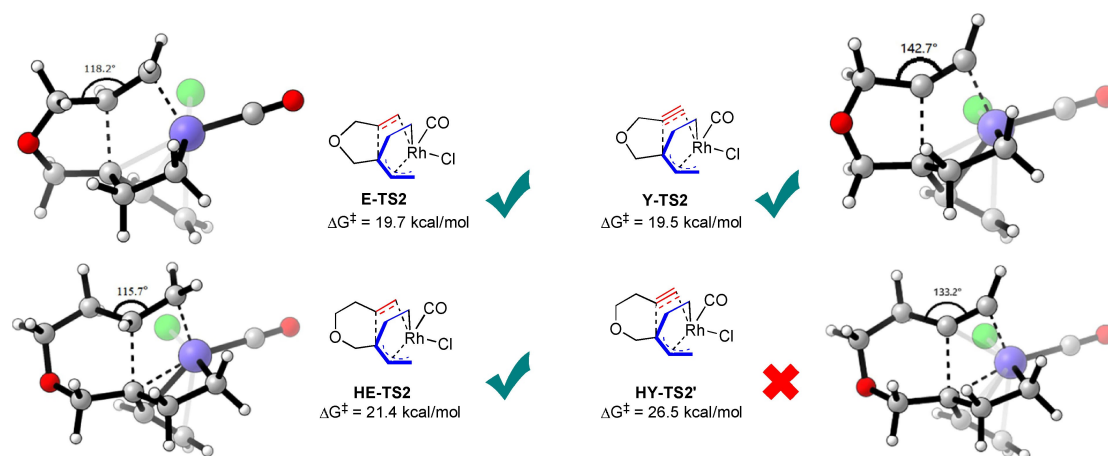


Figure 4. The alkyne/alkene insertion transition states in the [3+2+1] reactions and activation free energies.

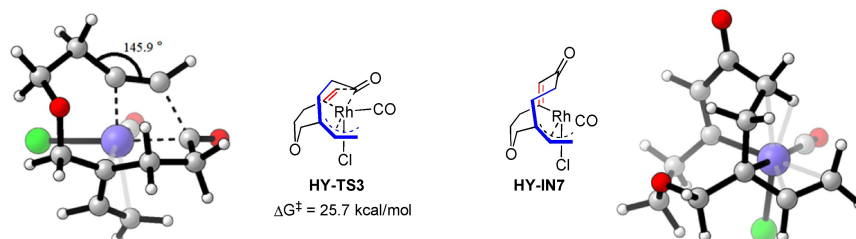


Figure 5. The intermediate and alkyne insertion transition states in the [3+1+2] pathway and its activation free energy.

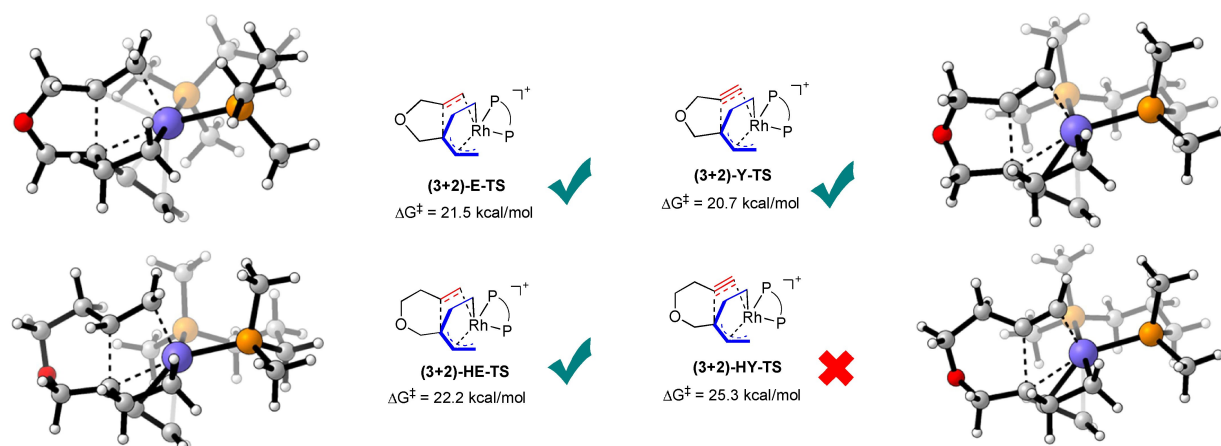


Figure 6. Comparison of intramolecular alkyne/alkene insertion transition states for [3 + 2] reaction of yne/ene-VCPs with different tethers and activation free energies.

step. In this case, side reactions could dominate and the [3 + 2] reaction became unsuccessful.

In the [3 + 2 + 1] reaction of ene/yne-VCPs and CO for the synthesis of 5/6 bicycles, cyclopropane cleavage is followed by alkene/alkyne insertion, CO insertion, and reductive elimination. This is because alkene/alkyne insertion is easier (with activation energies of about 20 kcal/mol) than CO insertion. However, for the [3 + 2 + 1] reaction of yne-VCPs with longer tether in the synthesis of 6/6 skeleton, the alkyne insertion becomes difficult (with a computed activation free energy of 26.5 kcal/mol), due to the distortion of alkyne in the alkyne insertion transition state. This is similar to the [3 + 2] reaction of yne-VCPs to form 6/5 bicycles. In this case, CO insertion proceeds ahead of alkyne insertion. Consequently, the [3 + 2 + 1] reaction follows a [3 + 1 + 2] pathway.

3.1. Computational method

The computational works were performed with Gaussian 09, E.01 program package.^[9] Geometry optimization was carried out at BMK^[10]/def2-SVP^[11] level in vacuum, using the ULTRA-FINE grid. Gibbs energies of solvation were computed at the SMD^[12]/BMK/def2-SVP level. The solvent used is toluene for the [3 + 2 + 1] reaction, and DCE for the [3 + 2] reaction. The functional was chosen according to benchmark study in our previous works.^[5b] Single-point energy refinements were performed with ORCA 5.0.3^[13] at the DLPNO-CCSD(T)^[14]/def2-TZVPP^[11] level. Standard state concentration of CO was estimated to be 1.8 mM under our reaction conditions (0.2 atm CO gas, 80 °C in toluene),^[15] and 1.0 M for all other species were used.^[16] All of the 3D structures were prepared with CYLview.^[17]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: Rhodium Catalysis · Cycloaddition Reactions · [3 + 2 + 1] · [3 + 2] · alkene/alkyne insertion · tether length effect

- [1] a) L. Jiao, M. Lin, Z.-X. Yu, *Chem. Commun.* **2010**, 46, 1059–1061; b) L. Jiao, M. Lin, Z.-X. Yu, *J. Am. Chem. Soc.* **2011**, 133, 447–461; c) M. Lin, G.-Y. Kang, Y.-A. Guo, Z.-X. Yu, *J. Am. Chem. Soc.* **2012**, 134, 398–405; d) The 2- π component of the [3 + 2] reaction can be allenenes, but in this case, the tether of substrates can be only TsN and BsN and the ligand was also different. see: C.-H. Liu, F. Li, Y. Yuan, M. Dou, Z.-X. Yu, *Asian J. Org. Chem.* **2018**, 7, 1609.
- [2] L. Jiao, M. Lin, L.-G. Zhuo, Z.-X. Yu, *Org. Lett.* **2010**, 12, 2528–2531.
- [3] a) Y. Feng, Z.-X. Yu, *J. Org. Chem.* **2015**, 80, 1952–1956; b) J. Yang, W. Xu, Q. Cui, X. Fan, L.-N. Wang, Z.-X. Yu, *Org. Lett.* **2017**, 19, 6040–6043; c) J. Wang, B. Hong, D. Hu, Y. Kadonaga, R. Tang, X. Lei, *J. Am. Chem. Soc.* **2020**, 142, 2238–2243; d) Y. Zhou, J.-L. Qin, W. Xu, Z.-X. Yu, *Org. Lett.* **2022**, 24, 5902–5906.
- [4] See ref. 2, note 12 for details.
- [5] a) Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, 129, 10060–10061; b) Y. Wang, W. Liao, Y. Wang, L. Jiao, Z.-X. Yu, *J. Am. Chem. Soc.* **2022**, 144, 2624–2636; c) Y. Yang, Z.-Y. Tian, C.-L. Li, Z.-X. Yu, *J. Org. Chem.* **2022**, 87, 10576–10591.
- [6] a) J. Yang, P. Zhang, Z.-Y. Shen, Y. Zhou, Z.-X. Yu, *Chem* **2023**, doi: 10.1016/j.chempr.2023.01.020; b) J. Zhang, X. Wang, T. Xu, *Nat. Commun.* **2021**, 12, 3022.

- [7] N. Koga, S. Q. Jin, K. Morokuma, *J. Am. Chem. Soc.* **1988**, *110*, 3417–3425.
- [8] F. M. Bickelhaupt, K. N. Houk, *Angew. Chem. Int. Ed.* **2017**, *56*, 10070–10086; *Angew. Chem.* **2017**, *129*, 10204–10221.
- [9] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, *D. J. Fox Gaussian 09 Rev. E.01*, Gaussian, Inc.: Wallingford, CT **2013**.
- [10] A. D. Boese, J. M. L. Martin, *J. Chem. Phys.* **2004**, *121*, 3405–3416.
- [11] a) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305; b) D. Andrae, U. Häußermann, M. Dolg, H. Stoll, H. Preuß, *Theor. Chim. Acta* **1990**, *77*, 123–141.
- [12] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
- [13] a) F. Neese, *WIREs Comput. Mol. Sci.* **2012**, *2*, 73–78; b) F. Neese, *WIREs Comput. Mol. Sci.* **2022**, *12*, e1606.
- [14] a) C. Riplinger, F. Neese, *J. Chem. Phys.* **2013**, *138*, 034106; b) C. Riplinger, B. Sandhoefer, A. Hansen, F. Neese, *J. Chem. Phys.* **2013**, *139*, 134101.
- [15] V. S. Nair, S. P. Mathew, R. V. Chaudhari, *J. Mol. Catal. A* **1999**, *143*, 99–110.
- [16] J. A. Keith, E. A. Carter, *J. Chem. Theory Comput.* **2012**, *8*, 3187–3206.
- [17] C. Y. Legault CYLview20; Université de Sherbrooke, 2020. <http://www.cylview.org>.

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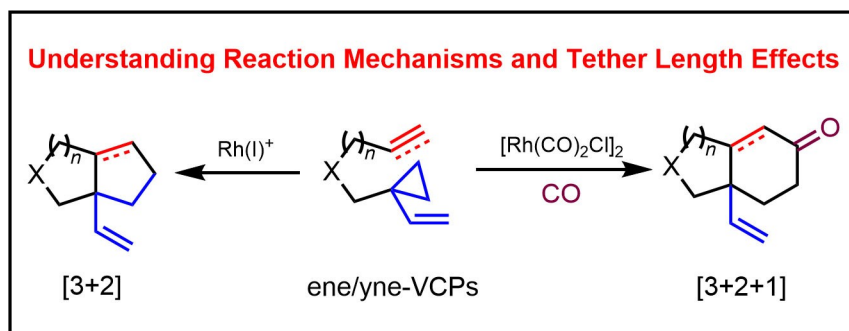
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Correction added on 06.03.2023: Correction in Schemes (1 & 2), Figures (1, 2, 3, 4, 5, 6), references and Supporting Information

RESEARCH ARTICLE



The mechanisms of [3 + 2] and [3 + 2 + 1] reactions using ene/yne-vinylcyclopropanes have been studied computationally, finding that the length of tether affects the ene/yne insertion

into Rh–C bond of the formed rhodacycles (from the cyclopropane cleavage), which in turn determines the reaction destinies and reaction pathways.

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1 – 8

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