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Rh(I)-Catalyzed [4+3]/[4+1] Cycloaddition of Diene-Vinylcyclopropanes and Carbon Monoxide to Access Angular 5/7/5 Tricycles

Jun Yang,[a] Pan Zhang,[a] Zeyuan Shen,[a] and Zhi-Xiang Yu*[a]

Report here is a Rh-catalyzed [4+3]/[4+1] cycloaddition of diene-vinylcyclopropanes (diene-VCPs) and carbon monoxide to access compounds with angular 5/7/5 tricyclic skeleton found in natural products. The reaction has broad scope and further transformation of the [4+3]/[4+1] cycloadduct was also investigated. How this [4+3]/[4+1] reaction occurs and why its competing [4+3] reaction is disfavored have been investigated computationally.

Introduction

Angular m/n/p tricyclic skeleton, also known as [m.n.p]fenestrane, serves as a prevalent scaffold in a vast array of natural products with diverse biological activities.[1] Figure 1 shows natural products with 5/7/5 skeleton such as intricarene,[2] laurenene,[3] and daphniphyllum alkaloids.[4] Constructing 5/7/5 skeleton is challenging due to the presence of seven-membered ring and bridgehead quaternary carbon. To date, only limited strategies have been applied for this. For example, Wender built the seven-membered ring first and then employed an arene-alkene photocycloaddition to access the target skeleton;[5] Tsunoda,[6] Crimmins[7] and Paquette[8] forged the angular triquinane scaffold, and then established the seven-membered ring through intramolecular aldol condensation; Trauner[9] and Pattenden[10] used intramolecular [5+2] cyclo-addition to synthesize intricarene. In this paper, we report an intriguing Rh-catalyzed [4+3]/[4+1] cycloaddition (shown in Scheme 1, together with an schematic description of this reaction), which enables the direct and efficient construction of 5/7/5 skeleton from readily synthesized Z-diene-VCPs. The functional alkene and carbonyl groups in the cycloadducts can enable further transformations. Additionally, ab initio calculations were applied to study the mechanism of this reaction.

Results and Discussion

Reaction Optimization

We previously disclosed a rhodium catalyzed intramolecular [4+3] cycloaddition of Z-diene-VCPs, accessing 5/7-bicycles bearing various substituents on seven-membered ring (Scheme 1).[11] We were curious to know whether a [4+3+1]

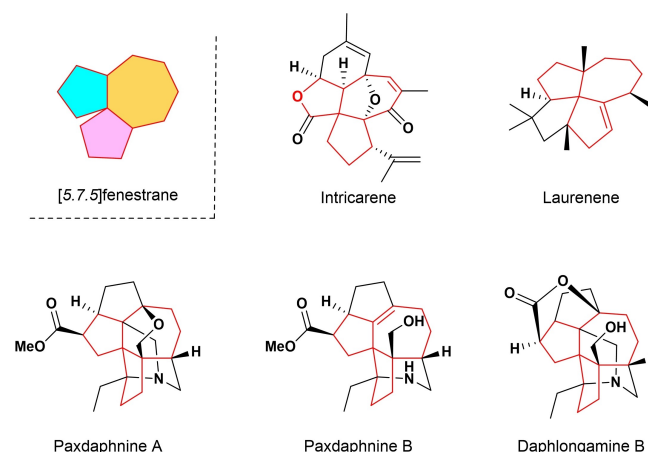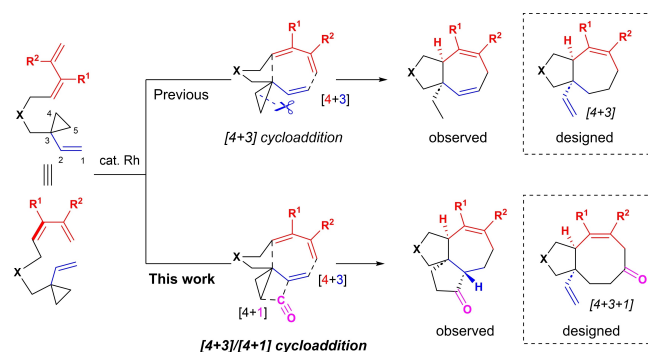**Figure 1.** Representative examples of natural products with [5.7.5]fenestrane frameworks.

[a] Dr. J. Yang, Dr. P. Zhang, Z. Shen, Prof. Dr. Z.-X. Yu
Beijing National Laboratory for Molecular Sciences (BNLMS)
Key Laboratory of Bioorganic Chemistry and
Molecular Engineering of Ministry of Education
College of Chemistry
Peking University Beijing 100871 (China)
E-mail: yuzx@pku.edu.cn

Scheme 1. Previous [4+3] and the present [4+3]/[4+1] cycloadditions.

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reaction (C3, C4, C5 in VCP as 3-Carbon synthon) would take place to yield 5/8-fused bicycles if treating the same substrate under CO atmosphere (Scheme 1).
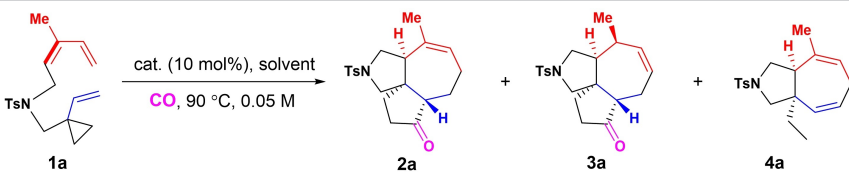
To our surprise, the reaction of **1a** with CO under the [Rh(CO)$_2$Cl]$_2$ catalyst gave two tricyclic carbonylative [4+3]/[4+1] products, **2a** and **3a**, while the expected [4+3+1] cycloadduct was not observed (Table 1, entry 2). Product **3a** was proposed to be generated from alkene isomerization from product **2a**. Both **2a** and **3a** were confirmed by X-ray crystallography analysis (see Supporting Information for details). In comparison to entry 1, the presence of CO atmosphere completely suppressed the [4+3] reaction (no [4+3] product **4a** was observed), indicating that CO migration insertion is faster than β–H elimination in the [4+3]/[4+1] reaction (This was further confirmed by subsequent DFT calculations, see later on discussion).[11] To improve reaction selectivity and yield, further optimization of reaction conditions was performed. Solvent screening indicated that dioxane was better than toluene and DCE, giving a similar reaction yield but much higher selectivity of **2a** over **3a** (entries 2–4). Reducing CO pressure had no influence on the reaction yield, but resulted in low selectivity (entry 5). Lowering catalyst loading was not beneficial to the reaction yield (entry 6). Variations in reaction concentration had little effects on the reaction yield and selectivity (entries 7 and 8). It's worth noting that neither Wilkinson's catalyst nor cationic Rh catalyst of Rh(PPh$_3$)$_3$SbF$_6$ can catalyze the cycloaddition reaction (entries 9 and 10). Thus, the optimal reaction conditions, which was used in later on study of reaction scope, include: using 10 mol% [Rh(CO)$_2$Cl]$_2$ as catalyst, 2 mL dioxane as solvent under 90 °C for 24 h, on a 0.1 mmol scale for substrate (entry 3, Table 1).

Reaction Scope

Investigation of the reaction scope of [4+3]/[4+1] cycloaddition is summarized in Scheme 2. For substrates with different alkyl groups in the diene part, the target cycloadditions occurred smoothly. When R^1 was an ethyl group, the isolated yield of the final cycloadduct **2b** was 72%. Isopropyl substituted substrate **1c**, which imposed steric hindrance to the reaction, gave unexpected and exceptionally high reaction yield (92%). Substrate **1d** with a CH$_2$OBn functional group delivered product **2d** in 78% yield. Unexpectedly, the phenyl group in diene moiety of the substrate seemed to have some peculiarity because the carbonylative reaction delivered two products, **2e** (in 58% yield) and **5e** (in 18% yield). Their structures were both confirmed by X-ray crystallography analyses (see Supporting Information for details). When tri-substituted diene substrate was subjected upon the reaction conditions, tricycle **2f** with tetra-substituted alkene was obtained in 90% yield.
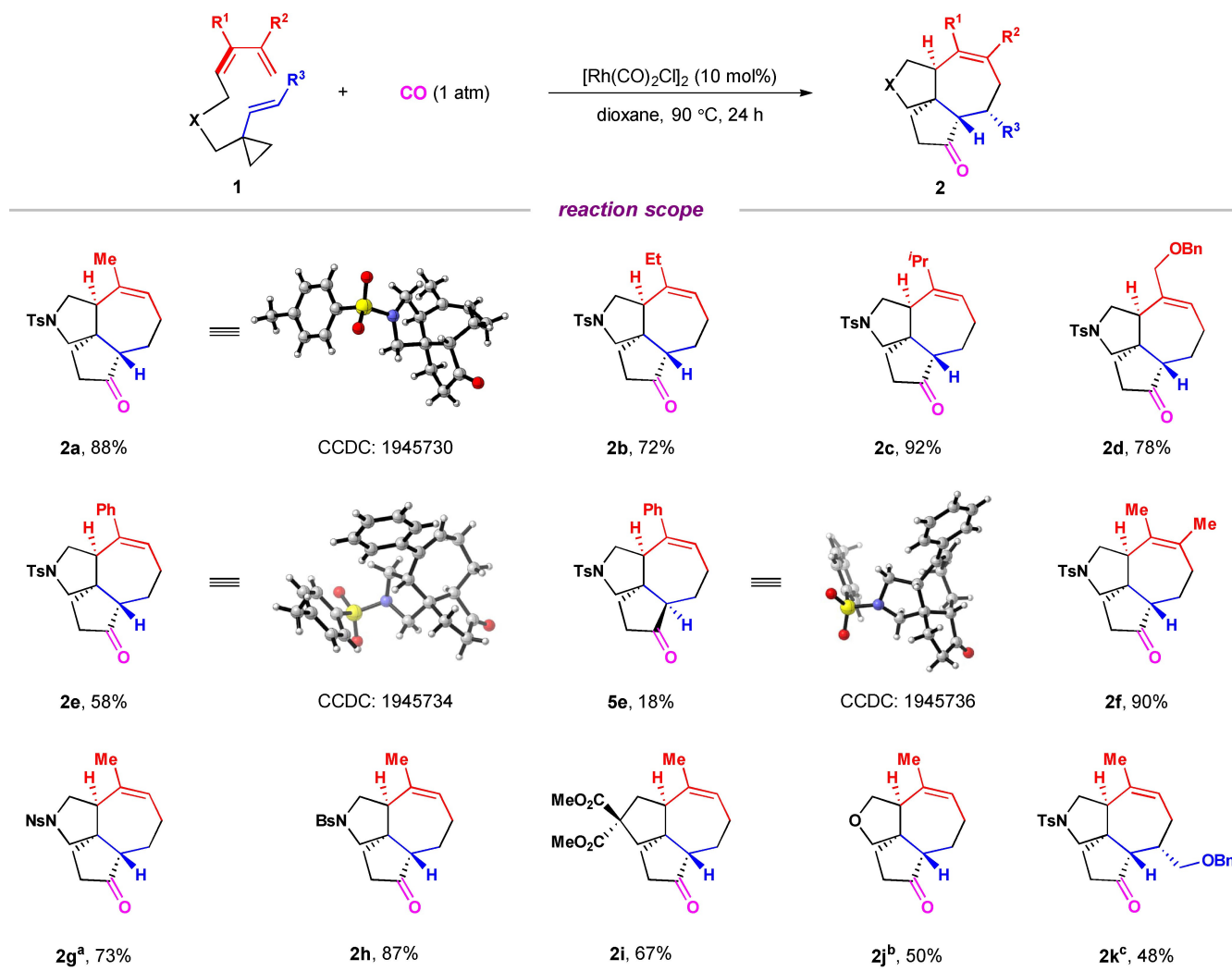
Next, we examined how the tether connecting the dienes and VCPs affected the reaction outcomes. Substrates with NNs and NBs tethers smoothly generated their products **2g** and **2h**, respectively. Substrate **1i** with a dimethyl malonate tether can provide full carbon skeleton **2i** in 67% yield, indicating potential utility in synthesizing natural products. Oxygen-tethered substrate **1j** delivered **2j** in 50% yield. Surprisingly, substrate **1k** with a substituent in the terminal position of its VCP moiety was also suitable to the cycloaddition reaction, affording **2k** in 48% yield, even though elevated reaction temperature (100 °C) and an extended reaction time (36 h) were both required. The harsher conditions for this reaction were likely a consequence of the steric hindrance within the substrate. It is worth noting that product **2k** has consecutive four stereo carbon centers with a single diastereomer, suggest-

Table 1. Optimization of reaction conditions for [4+3]/[4+1] cycloaddition.[a]

Entry	Catalyst	Solvent	CO/atm	Time/h	Product	Yield[b]	2a:3a:4a[c]
1	[Rh(CO)$_2$Cl]$_2$	Toluene	–	12	**4a**	76%	1.3:1:8.4
2	[Rh(CO)$_2$Cl]$_2$	Toluene	1.0	48	**2a+3a**	81%	11.5:1:0
3[d]	[Rh(CO)$_2$Cl]$_2$	Dioxane	1.0	24	**2a+3a**	88%	>20:1:0
4	[Rh(CO)$_2$Cl]$_2$	DCE	1.0	24	**2a+3a**	88%	7.6:1:0
5	[Rh(CO)$_2$Cl]$_2$	Dioxane	0.2	12	**2a+3a**	88%	3.8:1:0
6[e]	[Rh(CO)$_2$Cl]$_2$	Dioxane	1.0	24	**2a+3a**	63%	>20:1:0
7[f]	[Rh(CO)$_2$Cl]$_2$	Dioxane	1.0	24	**2a+3a**	87%	>20:1:0
8[g]	[Rh(CO)$_2$Cl]$_2$	Dioxane	1.0	24	**2a+3a**	87%	>20:1:0
9	Rh(PPh$_3$)$_3$Cl	Dioxane	1.0	24	–	NR	–
10	[Rh(PPh$_3$)$_3$]SbF$_6$	Dioxane	1.0	12	–	CM	–

[a] 0.1 mmol substrate was used. [b] Isolated yield. [c] Confirmed by crude ^{1}H NMR. [d] Average yield of two runs. [e] Catalyst loading: 5 mol%. [f] Reaction concentration: 0.025 M. [g] Reaction concentration: 0.1 M. cat. = catalyst, NR = no reaction, CM = complex mixture.

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Scheme 2. Reaction Scope of [4+3]/[4+1] Cycloadditions. The reaction was performed in a 0.1 mmol scale and 2 mL dioxane was used. The yield is the average yield of two runs. [a] Reaction time was 48 h. [b] Reaction time was 31 h. [c] Reaction was performed at 100 °C and reaction time was 36 h.

ing that [4+3]/[4+1] cycloaddition is extremely stereospecific. More discussion of the stereochemistry of **2k** in which the CH₂OBn group is in a *trans* configuration with respect to its adjacent hydrogen atom at the bridgehead position, is given in the Supporting Information.

To our disappointment, substrates **1l** with a methyl group on the VCP, **1m** with no substituent on the diene, and **1n** with a longer chain did not yield [4+3]/[4+1] products (Scheme 3). For **1l** and **1n**, most of unreacted starting materials were recovered, but trace impurity was observed in ¹H NMR of recycled starting material. For **1m**, only 32% of raw materials were recycled, indicating that reaction was decomposed under the standard conditions.

We also examined how *E*-diene-VCPs reacted under the same conditions. To our surprise, an unanticipated [5+1] (but not [4+3]/[4+1]) cycloaddition occurred (Scheme 3). Our previous study suggested that neutral catalyst [Rh(CO)₂Cl]₂ cannot catalyze the [5+1] cycloaddition for simple VCPs substrates.[12] The successful [5+1] cycloaddition of *E*-diene-
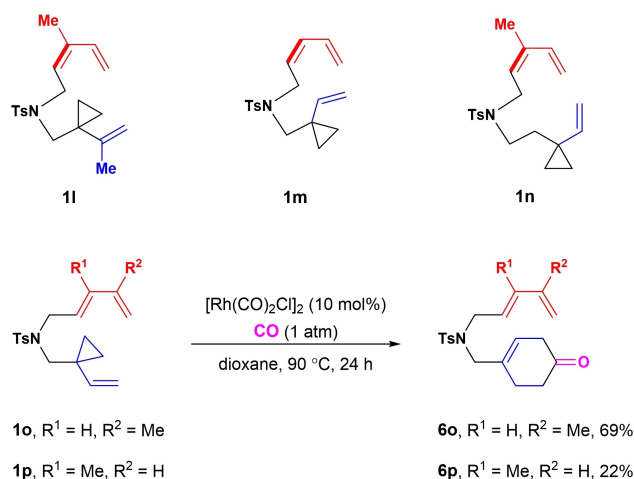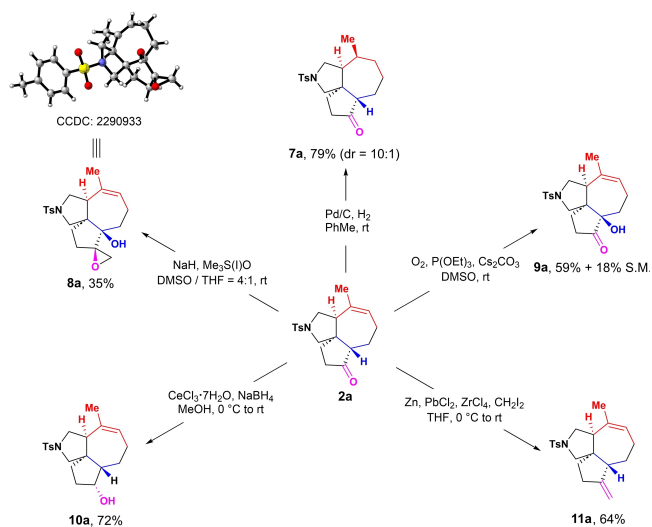

Scheme 3. Substrates **1l–n** failed in [4+3]/[4+1] reaction while substrates **1o** and **1p** as *E*-diene-VCPs underwent [5+1] reaction.

VCPs here indicated that diene moiety on the substrates somehow facilitated [5＋1] cycloaddition by providing coordination (the exact reason for this is unknown at the present stage).

Product Transformation

Next, some transformations were carried out to obtain diversified molecules using cycloadduct **2a** (Scheme 4). The alkene bond in **2a** was reduced by H_2 using Pd/C as the catalyst, delivering **7a** in 79% yield with good diastereoselectivity. We tried to convert the carbonyl group in **2a** to an epoxide via Corey–Chaykovsky reaction.[13] Surprisingly, not only the
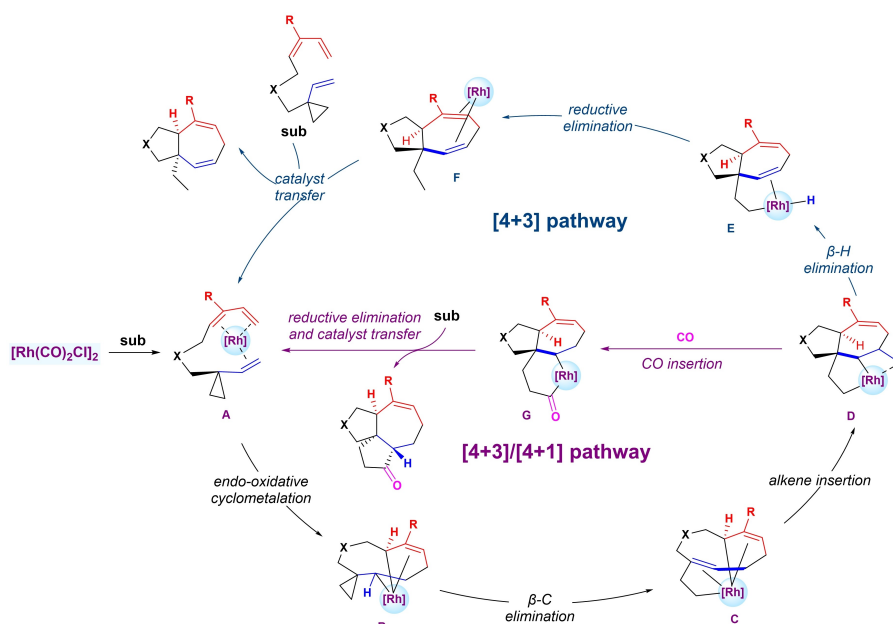
epoxidation took place, but also α-hydroxylation of the carbonyl group occurred, giving rise to **8a** as a major product in 35% yield. The structure of **8a** was confirmed by X-ray crystallography analysis (see Supporting Information for details). Inspired by this result, we then tried to achieve the tertiary C–H hydroxylation by using Jiao's protocol.[14] To our delight, the reaction proceeded smoothly and the desired α-hydroxycarbonyl compound **9a** was obtained in 59% yield, together with 18% of **2a** recovered in the reaction. **9a** could also be converted into **8a** using the Corey–Chaykovsky condition (see Supporting Information for details). The carbonyl group in **2a** could be reduced to alcohol. After several attempts of using different reaction conditions, we found that Luche's condition[15] gave **10a** in an excellent diastereoselectivity and 72% yield. We have also carried out a methenylation reaction. However, applying the classic Wittig conditions (t-BuOK, Ph_3PMeBr) failed, possibly because the tertiary carbon adjacent to the carbonyl group isomerized to give some unknown side products under the basic reaction conditions. Due to this, we turned to utilize the Zr-based Takai-Lombardo condition for the reaction (Zn, CH_2I_2, $PbCl_2$, $ZrCl_4$),[16a,b] finding that the desired product **11a** was be obtained in 64% yield.

Reaction Mechanism

We then carried out computational study to understand how the [4＋3] reaction of Z-diene-VCP is changed to [4＋3]/[4＋1] reaction. The catalytic cycle of the [4＋3] reaction is shown in the big circle in Scheme 5. Firstly, the substrate/Rh complex **A** undergoes endo-OCM (oxidative cyclometalation) to give intermediate **B**. Then, **D** is generated after β–C elimination and alkene insertion. Subsequently, β–H elimination in **D** gives Rh–H spices **E**, which finally affords the [4＋3] product via

Scheme 4. Further transformations of **2a**.

Scheme 5. Proposed mechanisms of [4＋3]/[4＋1] and [4＋3] cycloadditions.

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reductive elimination and catalyst transfer.[11] However, when CO is present, CO insertion from intermediate **D** gives **G**, which then undergoes reductive elimination to generate [4+3]/[4+1] product.

Scheme 6 shows the competition of [4+3] and [4+3]/[4+1] pathways (computed at DLPNO-CCSD(T)[17]/def2-TZVPP:[18] SMD(dioxane)[19]//BMK[20]/6-31G(d)[21]/LANL2DZ[22] using Gaussian[23] and ORCA[24] software packages and **1j** as model substrate). In the [4+3]/[4+1] pathway, **IN1**, which is a shared intermediate in both [4+3]/[4+1] and [4+3] pathways (see its generation in previous study[11]), is firstly coordinated by CO to give **IN2**. This coordination step is exergonic by 5.0 kcal/mol. The subsequent CO migratory insertion via **TS1** has an activation free energy of 9.6 kcal/mol, affording **IN3'** (see this in Supporting Information), which is coordinated by another CO to give **IN3**. CO insertion at the other tertiary C position is not favored (see Supporting Information for details). Finally, reductive elimination of **IN3** gives the product/catalyst complex **IN4** via **TS2** with an activation free energy of 14.3 kcal/mol.

In the [4+3] pathway, intermediate **IN5**, generated from **IN1** via isomerization, firstly undergoes β–H elimination via **TS3** to give a Rh–H complex **IN6**. This step required an activation

free energy of 9.6 kcal/mol. Subsequently, an easy reductive elimination from **IN6** via **TS4** gives the product/catalyst complex **IN7**. The selectivity between [4+3]/[4+1] and [4+3] pathway is determined by the relative energy of **TS2** and **TS3**. Our calculations found that [4+3]/[4+1] pathway is 3.0 kcal/mol more favored than the [4+3] pathway. Thus, generating [4+3]/[4+1] product is dominant, consistent with the experiments.

Conclusions

In summary, we have developed an unexpected Rh(I)-catalyzed [4+3]/[4+1] cycloaddition of Z-diene-VCPs and CO, enabling the construction of complex 5/7/5 tricyclic framework with consecutive stereo centers. This one-step carbonylative cycloaddition represents a significant advancement in terms of atom-economy, step-economy, and green chemistry for building complex skeletons. This novel cycloaddition also features highly diastereoselectivity, good substrate tolerance, mild reaction conditions, and moderate to excellent reaction yields. The configuration of diene plays a significant role to the success
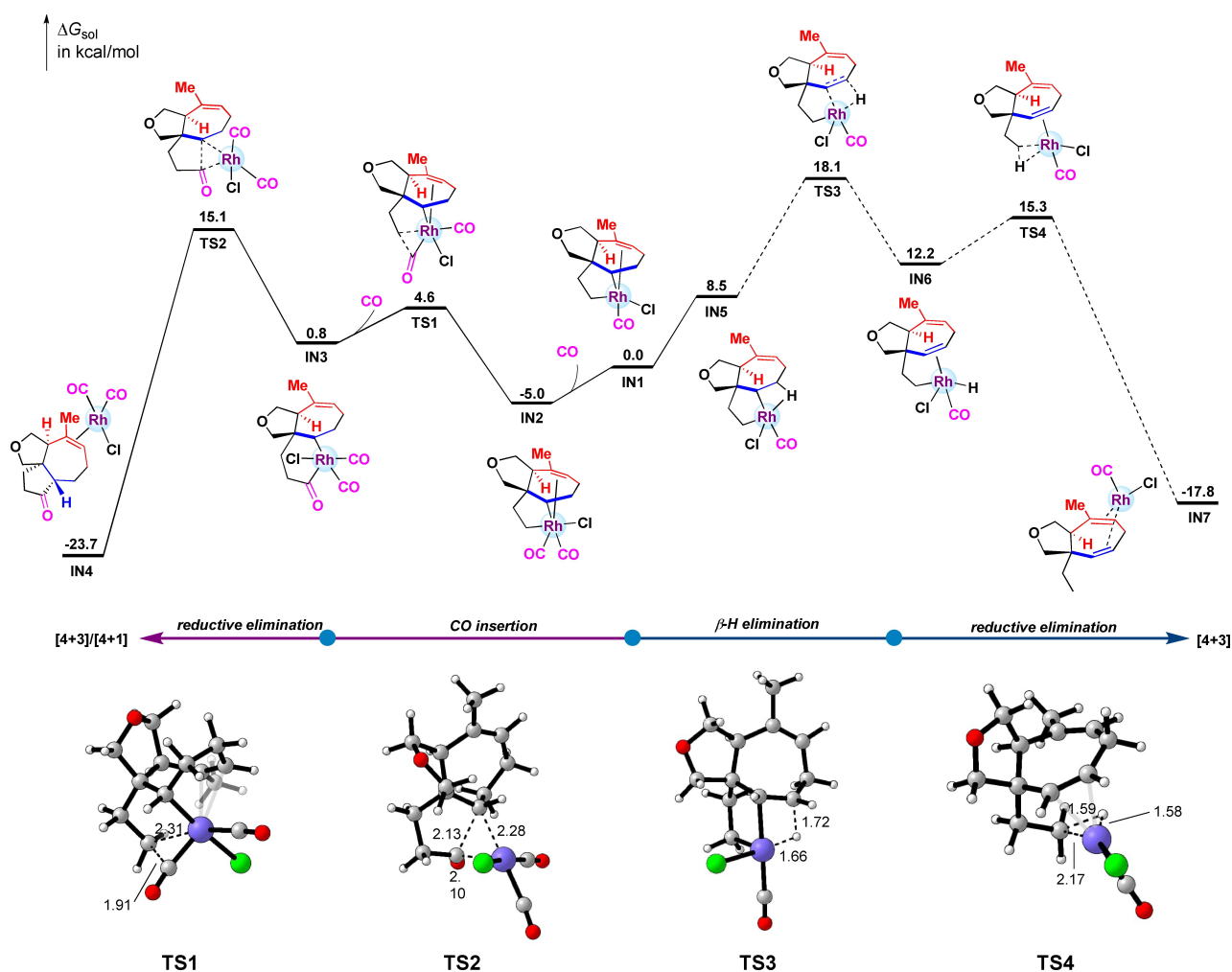
Scheme 6. Gibbs energy profile for the competing [4+3]/[4+1] and [4+3] pathways. Bond distances are reported in Å.

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of [4+3]/[4+1] cycloaddition, where endo oxidative cyclization[11] is required. Quantum chemical calculations have also been performed to rationalize the reaction selectivity, showing that β–H elimination is disfavored with respect to CO insertion and this changes the previous [4+3] reaction into the present [4+3]/[4+1] reaction.

Experimental Section

For all experimental details, including some kinetic studies, see the Supporting Information. Additional references are cited within the Supporting Information.[25–29]

Supporting Information

The authors have cited additional references within the Supporting Information.[25–29]

Conflict of Interests

The authors declare no conflict interests.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article. CCDC deposition Number(s) 1945730 (for **2a**), 1945733 (for **3a**), 1945734 (for **2e**), 1945736 (for **5e**), 2290933 (for **8a**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[1] a) A. Boudhar, M. Charpenay, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2013**, *52*, 12786–12798; b) D. Das, T. K. Chakraborty, *Tetrahedron Lett.* **2016**, *57*, 3665–3677.

[2] J. Marrero, A. D. Rodríguez, C. L. Barnes, *Org. Lett.* **2005**, *7*, 1877–1880.

[3] R. E. Corbett, D. R. Lauren, R. T. Weavers, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1774–1790.

[4] a) C.-Q. Fan, S. Yin, J.-J. Xue, J.-M. Yue, *Tetrahedron* **2007**, *63*, 115–119; b) C.-S. Li, Y.-T. Di, S.-Z. Mu, H.-P. He, Q. Zhang, X. Fang, Y. Zhang, S.-L. Li, Y. Lu, Y.-Q. Gong, X.-J. Hao, *J. Nat. Prod.* **2008**, *71*, 1202–1206.

[5] P. A. Wender, T. W. Von Geldern, B. H. Levine, *J. Am. Chem. Soc.* **1988**, *110*, 4858–4860.

[6] T. Tsunoda, M. Amaike, U. S. Tambunan, Y. Fujise, S. Ito, M. Kodama, *Tetrahedron Lett.* **1987**, *28*, 2537–2540.

[7] M. T. Crimmins, L. D. Gould, *J. Am. Chem. Soc.* **1987**, *109*, 6199–6200.

[8] L. A. Paquette, M. E. Okazaki, J. C. Caille, *J. Org. Chem.* **1988**, *53*, 477–481.

[9] P. A. Roethle, P. T. Hernandez, D. Trauner, *Org. Lett.* **2006**, *8*, 5901–5904.

[10] B. Tang, C. D. Bray, G. Pattenden, *Tetrahedron Lett.* **2006**, *47*, 6401–6404.

[11] J. Yang, P. Zhang, Z. Shen, Y. Zhou, Z.-X. Yu, *Chem* **2023**, *9*, 1477–1494.

[12] G.-J. Jiang, X.-F. Fu, Q. Li, Z.-X. Yu, *Org. Lett.* **2012**, *14*, 692–695.

[13] a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364; For mechanism, see: b) Y. Xiang, X. Fan, P.-J. Cai, Z.-X. Yu, *Eur. J. Org. Chem.* **2019**, 582–590.

[14] Y.-F. Liang, N. Jiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 548–552.

[15] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

[16] a) K. Takai, T. Kakiuchi, Y. Kataoka, K. Utimoto, *J. Org. Chem.* **1994**, *59*, 2668–2670; b) E. A. Colby, K. C. O'Brie, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 998–999.

[17] 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.

[18] a) F. Weigend, F. 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.

[19] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[20] A. D. Boese, J. M. L. Martin, *J. Chem. Phys.* **2004**, *121*, 3405–3416.

[21] W. J. Hehre, L. Radom, P. V. R. Schleyer, J. A. Pople, Ab Initio *Molecular Orbital Theory*; Wiley: New York, **1986**.

[22] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270–283.

[23] 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. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. 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*, revision E.01; Gaussian, Inc.: Wallingford, CT, **2013**.

[24] a) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2012**, *2*, 73–78; b) F. Neese, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2017**, *8*, e1327.

[25] J. Burés, *Angew. Chem. Int. Ed.* **2016**, *55*, 2028–2031.

[26] J. Burés, *Angew. Chem. Int. Ed.* **2016**, *55*, 16084–16087.

[27] Y. Wang, W. Liao, Y. Wang, L. Jiao, Z.-X. Yu, *J. Am. Chem. Soc.* **2022**, *144*, 2624–2636.

[28] E. Veleckis, D. S. Hacker, *J. Chem. Eng. Data* **1984**, *29*, 36–39.

[29] C. Y. Legault, *CYLview20*; Université de Sherbrooke, **2020**; http://www.cylview.org (accessed 24 January, 2021).

RESEARCH ARTICLE

One-step construction of [5.7.5]fenestrane
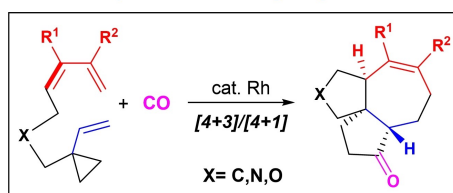
Schematic of [4+3]/[4+1]
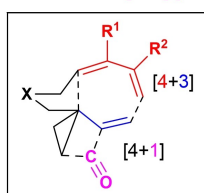
An unexpected [4+3]/[4+1] reaction of diene-vinylcyclopropanes (diene-VCPs) and carbon monoxide to access challenging 5/7/5 tricycles was developed, together with its mechanistic study by using ab initio calculations.

Dr. J. Yang, Dr. P. Zhang, Z. Shen, Prof. Dr. Z.-X. Yu*

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Rh(I)-Catalyzed [4+3]/[4+1] Cycloaddition of Diene-Vinylcyclopropanes and Carbon Monoxide to Access Angular 5/7/5 Tricycles