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Experimental and Computational Studies on Rh(I)-Catalyzed Reaction of Siloxyvinylcyclopropanes and Diazoesters

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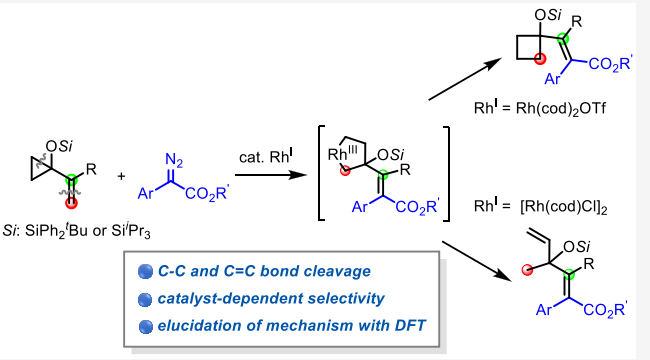
ABSTRACT: The Rh(I)-catalyzed reaction of siloxyvinylcyclopropanes and diazoesters leads to the formation of siloxyvinylcyclobutane and 1,4-diene derivatives. With $[Rh(cod)Cl]_2$ as the catalyst, the formation of 1,4-diene was favored over the formation of siloxyvinylcyclobutane. By changing the catalyst to $[Rh(cod)_2OTf]$, siloxyvinylcyclobutane derivatives are formed with excellent chemoselectivities and in moderate to good yields. The alkene products are also obtained as single *E* configured isomers. A detailed mechanism for this transformation is proposed on the basis of mechanistic experiments and DFT calculations. The effect of catalysts on the chemoselectivity of these reactions is also examined computationally.

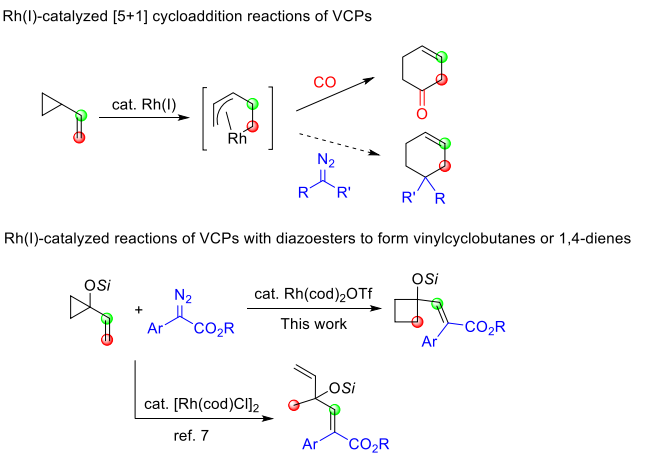


INTRODUCTION

Transition-metal-catalyzed cycloaddition reactions of vinylcyclopropanes (VCPs) and π-components have emerged as one of the efficient approaches for the synthesis of medium and large ring systems.[1] Since the first report of a Rh(I)-catalyzed intramolecular [5 + 2] reaction of β-yne-VCPs by Wender in 1995,[2] Rh(I)-catalyzed [5 + 2] cycloaddition reactions of VCPs with 2π-components such as alkynes, alkenes, and allenes have been actively studied for constructing various seven-membered rings.[3] On the other hand, Yu and co-workers have developed versatile methodology for constructing five-membered rings by using Rh(I)-catalyzed reactions of 1-ene/yne-VCPs as well as 2- and α-ene-VCPs through a [3 + 2] pathway.[4] In addition, they also introduced CO as a one-carbon coupling partner to achieve [5 + 2 + 1], [5 + 1], and [3 + 2 + 1] cycloaddition reactions of VCPs (Scheme 1).[5]

As part of our continuous interest in utilizing diazo compounds as a one-carbon synthon in transition-metal-catalyzed cross-coupling reactions,[6] and also inspired by the [5 + 1] reaction of VCPs with CO developed by Yu and co-workers,[5e] we envisioned that VCPs could potentially react with diazo compounds under Rh(I) catalysis to provide [5 + 1] products. In 2016, we reported the reaction between VCPs and diazoesters catalyzed by $[Rh(cod)Cl]_2$. Instead of the proposed [5 + 1] products, 1,4-dienes were formed in good yields.[7] During our further investigation, we discovered that when employing a cationic Rh(I) catalyst, $[Rh(cod)_2OTf]$, the reaction selectively afforded the vinylcyclobutane as the major product, along with the minor products of 1,4-dienes. Herein, we report methodology for the efficient synthesis of a variety of vinylcyclobutanes.[8] Furthermore, density functional theory (DFT) calculations were performed to study the mechanism of the reactions between VCPs and diazoesters catalyzed by $[Rh(cod)_2OTf]$ and $[Rh(cod)Cl]_2$, respectively, and shed light on the origin of the interesting catalyst-dependent chemoselectivity.

Scheme 1. Rh(I)-Catalyzed Reaction of Vinylcyclopropanes



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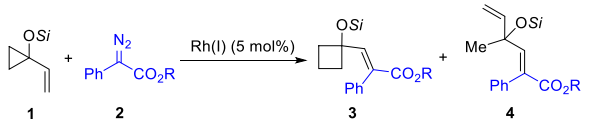
RESULTS AND DISCUSSION

Reaction Condition Optimization.[9] To begin with, we carefully re-examined the $[Rh(cod)Cl]_2$-catalyzed reaction of VCP **1** and diazo ester **2** that we have reported previously.[7] We observed that in addition to the 1,4-diene product **4**, trace amounts of cyclobutane product **3** were also formed (Table 1, entry 1). Further study indicated that **3**:**4** ratio was affected by the structure of the siloxy group. Switching the Si group from $SiMe_2{}^tBu$ to Si^iPr_3 changed the ratio of **3**:**4** from 1:20 to 1:3 (Table 1, entry 2). A more dramatic change of product ratio was observed when the Rh(I) catalyst was switched from $[Rh(cod)Cl]_2$ to $Rh(cod)_2OTf$ (Table 1, entries 3 and 4). With the cationic $Rh(cod)_2OTf$ as the catalyst, cyclobutane **3** become the major product. The four-membered ring and the *E* configuration of the double bond of product **3** in the reaction shown in entry 4 was confirmed by X-ray crystallography of its derivative (see Supporting Information for details). The ester group of the diazo substrate had a marginal effect on the yields (Table 1, entries 4−6). Because the Et group gave relatively high yield, we further modified the ester moiety with a 2,2,2-trifluoroethyl group and found that the yield was slightly improved (Table 1, entry 7). In addition, we found that adjusting the addition time of diazo substrate could slightly improve the yield (Table 1, entry 8). Finally, the reaction of VCP **1** bearing a siloxy group of $SiPh_2{}^tBu$ afforded the highest yield, whereas the **3**:**4** ratio was decreased to 10:1 (Table 1, entry 9).

Table 1. Optimization of the Reaction Conditions[a]

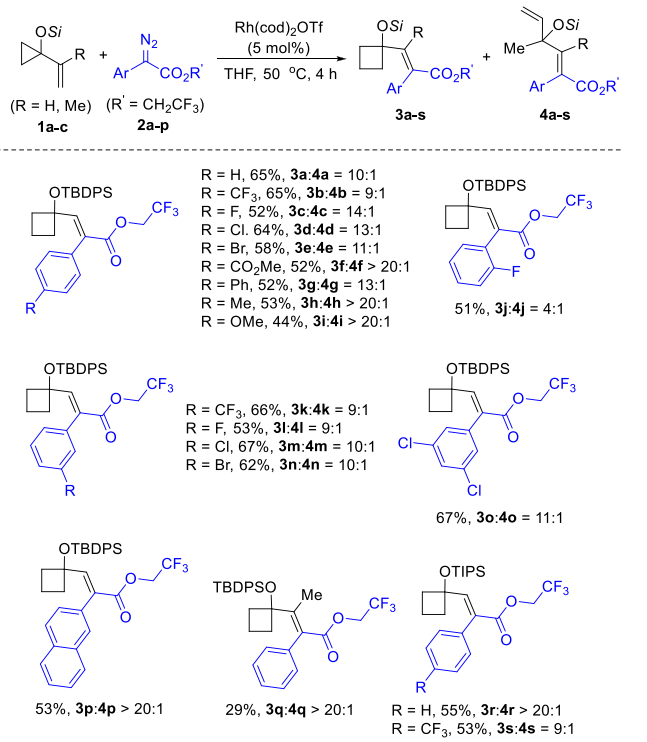


entry	*Si*	R	Rh(I)	**3**:**4**[b]	yield (%)[c]
1[d]	$SiMe_2{}^tBu$	Me	$[Rh(cod)Cl]_2$	1:20	88
2[d]	Si^iPr_3	Me	$[Rh(cod)Cl]_2$	1:3	55
3[d]	$SiMe_2{}^tBu$	Me	$Rh(cod)_2OTf$	2:1	25
4[d]	Si^iPr_3	Me	$Rh(cod)_2OTf$	>20:1	27
5[e]	Si^iPr_3	Et	$Rh(cod)_2OTf$	>20:1	43
6[e]	Si^iPr_3	^{t}Bu	$Rh(cod)_2OTf$	>20:1	31
7[e]	Si^iPr_3	CH_2CF_3	$Rh(cod)_2OTf$	>20:1	50
8[e,f]	Si^iPr_3	CH_2CF_3	$Rh(cod)_2OTf$	>20:1	55
9[e,f]	$SiPh_2{}^tBu$	CH_2CF_3	$Rh(cod)_2OTf$	10:1	65

[a]The reaction was carried out with **1** (0.1 mmol) and **2** (0.15 mmol). [b]Ratio was determined by ^{1}H NMR of the crude products. [c]Isolated yield. [d]These reactions were carried out in dioxane at 80 °C for 4 h, with slow addition of a solution of diazo substrate in dioxane. [e]These reactions were carried out in THF at 50 °C for 4 h, with slow addition of a solution of diazo substrate in THF over 1.5 h. [f]The addition of a solution of diazo substrate in THF was completed over 1.5 h with initial fast addition for 5 min. See Supporting Information for details.

Next, we proceeded to investigate the substrate scope of this reaction (Scheme 2). The reactions of **1a** with para- (**2a**−**i**), ortho- (**2j**), meta- (**2k**−**n**), and multisubstituted aryl diazoesters (**2o**) were all able to afford the corresponding vinylcyclobutane products **3a**−**o** in moderate to good yields. The ratio of **3**:**4** in these reactions ranged from 9:1 to >20:1. Reactions using aryl diazoesters bearing electron-withdrawing substituents generally gave higher yields. On the other hand, reactions with aryl diazoesters that were substituted by electron-donating groups had very high chemoselectivities but gave slightly lower yields. Naphthyl diazoester **2p** could also undergo this transformation

Scheme 2. Substrate Scope of the Rh(I)-Catalyzed Reaction[a]



[a]The reactions were carried out on 0.1 mmol scale. Yields refer to the isolated product of a mixture of **3** and **4**. TBDPS = $SiPh_2{}^tBu$, TIPS = Si^iPr_3.

with moderate yield and excellent chemoselectivity. When switching to a triisopropylsilyl substituted VCP **1b**, the reaction of **2a** with **1b** to form **3r** could achieve >20:1 chemoselectivity, but the yield was slightly lower than when **1a** was used. If a methyl-substituted VCP **1c** was used for the reaction, **3q** was selectively formed. This result showed that the C=C bond in VCP was cleaved during the course of the reaction, and that the terminal CH_2 in the vinyl group in VCP became part of the cyclobutane ring in the product.

To further confirm the structure of the vinylcyclobutane products, we converted **3r** to **3r′** through deprotection and then acylation. X-ray crystallography of **3r′** was then performed to determine it to be an *E* configured vinylcyclobutane derivative (Scheme 3). Because only one cis/trans isomer was observed in the vinylcyclobutane products, the configuration of all the other products were assigned as *E*.

To determine which position the terminal CH_2 in the vinyl group in VCP ended up in the cyclobutane ring in the product, we subjected **1d** and **1e** to the reaction. However, both reactions gave the 1,4-diene product **4′** instead of the vinylcyclcobutane products (Scheme 4). Similar type of product was observed when a 1-butyl substituted VCP **1f** was used with $[Rh(cod)Cl]_2$ as the catalyst.[7,10] To unambiguously track the terminal vinyl carbon, we then performed a deuterium labeling experiment using deuterated VCP **1g**, in which both hydrogens on the terminal vinyl carbon were 79% deuterium incorporated. ^{1}H NMR analysis of the product (**3t**) suggested that the terminal vinyl carbon in **1g** ended up at the C2-position of cyclobutane in the product.

The mechanism for the rhodium(I)-catalyzed cycloaddition reactions involving VCPs has been well studied. Theoretical studies suggest that these reactions proceed through a common

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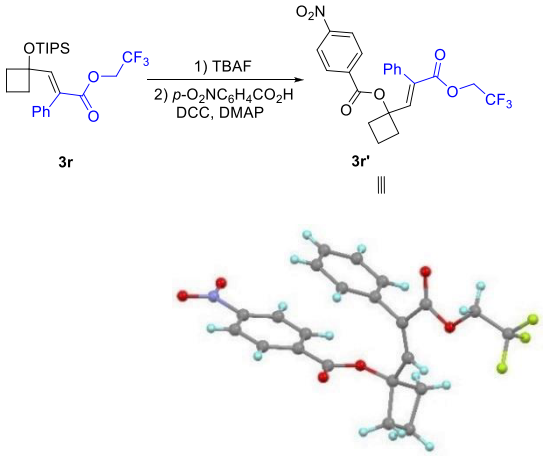
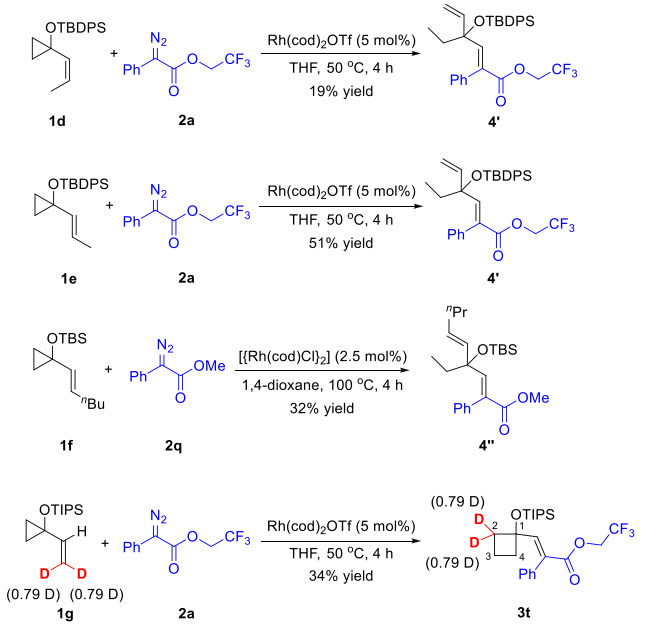
Scheme 3. Structural Determination of the Product



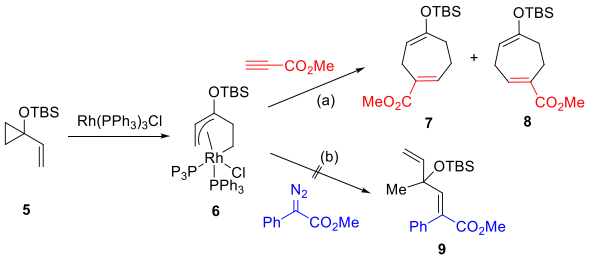
Scheme 4. Rh(I)-Catalyzed Reactions of 1-Substituted or Deuterated VCPs with Diazoester



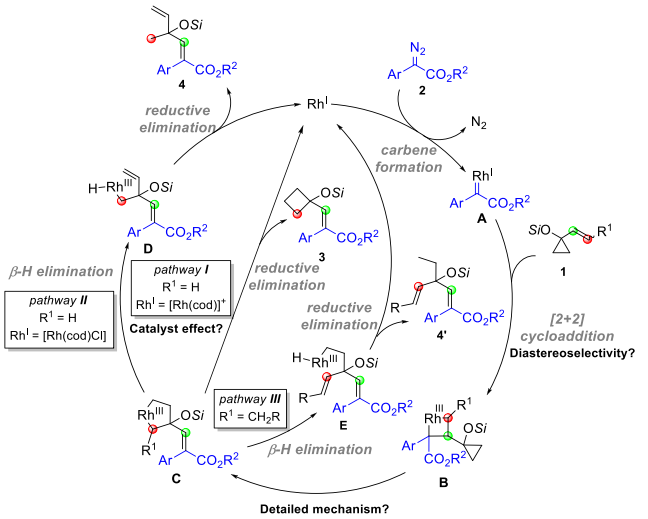
intermediate, which is a σ,η^3-allyl rhodium species generated from the oxidative addition of the Rh(I) catalyst with VCPs.[11] Recently, we successfully isolated such a σ,η^3-allyl rhodium complex **6** from the reaction of $Rh(PPh_3)_3Cl$ with VCP **5**, reacted it with alkyne, and formed the [5 + 2] products **7** and **8**, showing that such a species is very likely to be the key intermediate of the Rh(I)-catalyzed [5 + 2] reactions of VCPs (Scheme 5a).[7] However, treating the isolated σ,η^3-allyl rhodium complex **6** with diazo compound did not give the 1,4-diene product **9** (Scheme 5b), suggesting that the σ,η^3-allyl rhodium **6** is unlikely to be the key intermediate in our reactions.

On the basis of the mechanistic observations that we have so far, we propose several possible pathways for the reactions of VCPs with diazoesters catalyzed by either cationic or neutral Rh(I) catalysts (Scheme 6). First, the Rh(I) catalyst reacts with diazo compound **2** to form Rh(I) carbene **A**, which then undergoes a [2 + 2] cycloaddition with the C=C bond in VCP **1**. Next, the resulting rhodacyclobutane **B** rearranges into rhodacyclopentane **C**. For VCPs in which R^1 = H, **C** would

Scheme 5. Mechanistic Experiments of Rh(I)-Catalyzed Reaction of VCP



Scheme 6. Proposed Mechanism



undergo reductive elimination to form vinylcyclobutane **3** if $[Rh(cod)_2OTf]$ was used as the catalyst, but would reductive eliminate and then β-H eliminate to form 1,4-diene **4** if $[Rh(cod)Cl]_2$ was used instead.[12] However, if the terminal alkene position in VCP bears a substituent that has an α-H, then β-H elimination of **C** using the hydrogen from the substituent in VCP would be much more favorable as compared to β-H elimination using the hydrogen from the rhodacyclopentane ring or reductive elimination of **C**. Therefore, 1,4-diene **4′** would be selectively formed in this case regardless of the choice of catalyst. Although these proposed pathways align well with the experimental observations, several questions remain to be addressed: (i) Only *E*-vinylcyclobutane products were observed in the reactions. And because the diastereoselectivity in the [2 + 2] cycloaddition step would be completely transferred into the *E*/*Z* ratio in the product, we wanted to examine the diastereoselectivity of this step computationally. (ii) The detailed mechanism from intermediate **B** to **C** is currently unclear. (iii) The effect of the rhodium catalysts on the competition between the reductive elimination and the β-H elimination steps of **C** needs to be determined. Additionally, we need to confirm through calculations that our proposed pathway is indeed favored over oxidative cleavage of the C1−C2 or C2−C3 bond in the cyclopropane of VCP.

COMPUTATIONAL STUDIES

To gain insights into the mechanistic details, we carried out density functional theory calculations.[13] First, we computed the energy profile of the carbene formation and the [2 + 2]

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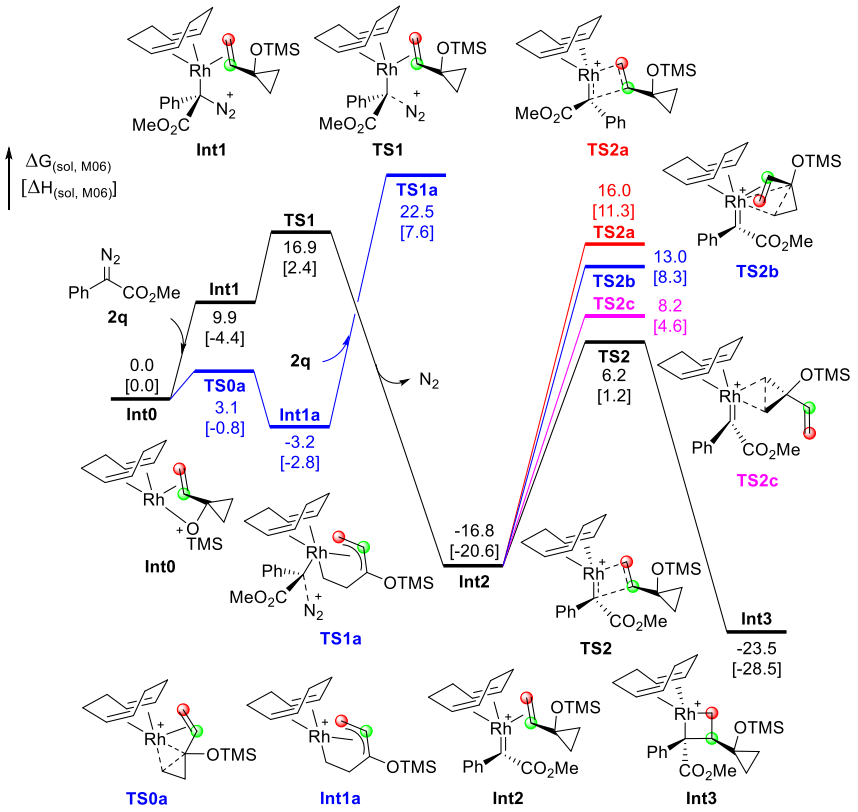

Figure 1. Energy profile of the carbene formation and the [2 + 2] cycloaddition steps for the cationic rhodium catalyzed reaction between VCP and diazoester.

cycloaddition steps in the reaction between VCP and diazoester with cationic Rh(I) as the catalyst (Figure 1). The formation of the Rh(I) carbene **Int2** involves the coordination of the diazoester **2q** to the rhodium center in **Int0** and subsequent release of N_2 via **TS1**. This step is highly exothermic and has a relatively low energy barrier. To explain why the reaction did not give our originally proposed [5 + 1] product, we also examined the scenario in which the Rh(I) catalyst undergoes oxidative addition with VCP prior to engaging with the diazoester via **TS1a**. It turns out that the oxidative addition step is fast and reversible, whereas the subsequent irreversible carbene formation step strongly favors **TS1** over **TS1a** by 5.6 kcal/mol. Therefore, Curtin−Hammett kinetics determines that the reaction should go through **TS1** to give Rh(I) carbene **Int2**, which then undergoes a [2 + 2] cycloaddition with VCP via **TS2** to form rhodacyclobutane **Int3**. The energy barrier of this step is 23.0 kcal/mol. Alternatively, the [2 + 2] cycloaddition step can go through **TS2a** to form the diastereomer of **Int3**, which will ultimately lead to the *Z*-isomer of the vinylcyclobutane product. Because the energy of **TS2a** is 9.7 kcal/mol higher than that of **TS2**, the [2 + 2] cycloaddition of **Int2** should completely proceed through **TS2** and eventually gives the *E*-alkene product exclusively. This computational prediction does match the experimental results. Moreover, the irreversible (based on results in Figure 1 and 2a) [2 + 2] pathway is energetically more favorable compared to the oxidative addition of **Int2** with either C1−C2 (**TS2b**) or C2−C3 (**TS2c**) bond in the cyclopropane of VCP.

Next, we investigated the detailed mechanism of the rearrangement from intermediate **B** to **C** in Scheme 6. After several attempts, we came up with a pathway which has a reasonable activation barrier for each step. In our computed pathway (Figure 2a), the cationic rhodium in **Int3** first serves as an electrophile to induce a reversible ring-opening of siloxycyclopropane to provide **Int4**.[14] The reverse process of this step is a methylene shift from the rhodium center to the oxocarbenium ion in **Int4** to regenerate the siloxycyclopropane ring. Because the rhodium center in **Int4** has another methylene group attached to it, this methylene group can also undergo a similar and yet more facile methylene shift to generate **Int5**. **Int5** then undergoes a nearly barrierless *β*-C elimination to give the rhodacyclopentane intermediate **Int6**. The optimized structures of each intermediate and transition state are shown in Figure 2b. We then looked into the competition between the reductive elimination and *β*-H elimination of **Int6** (Figure 3a). Both of these steps are very facile and irreversible, with the reductive elimination being favored over the *β*-H elimination step by 1.0 kcal/mol. This energy difference corresponds to a 5:1 ratio of the cyclobutane product **Int7** versus 1,4-diene **Int9**, which is in line with the chemoselectivity observed in the experiments. The overall catalytic cycle for the cationic Rh(I)-catalyzed reaction of VCP with diazoester has a reasonable Gibbs free energy span of 23.0 kcal/mol. The [2 + 2] cycloaddition of rhodium carbene with VCP constitutes the rate-determining step of this reaction. The theoretically predicted *E*/*Z* selectivity as well as the chemoselectivity of the reaction are both in good accordance with the experimentally observed selectivities. Additionally, we compared pathway I−III in Scheme 6 using 1-methyl substituted VCPs as the substrates.[9] The computed results show that pathway III is indeed the most favorable pathway for both **1d** and **1e**, which further support our proposed mechanism.

Finally, we wanted to investigate the origin of the opposite chemoselectivity obtained with the cationic and the neutral rhodium catalysts. Because the reactions of diazoesters with

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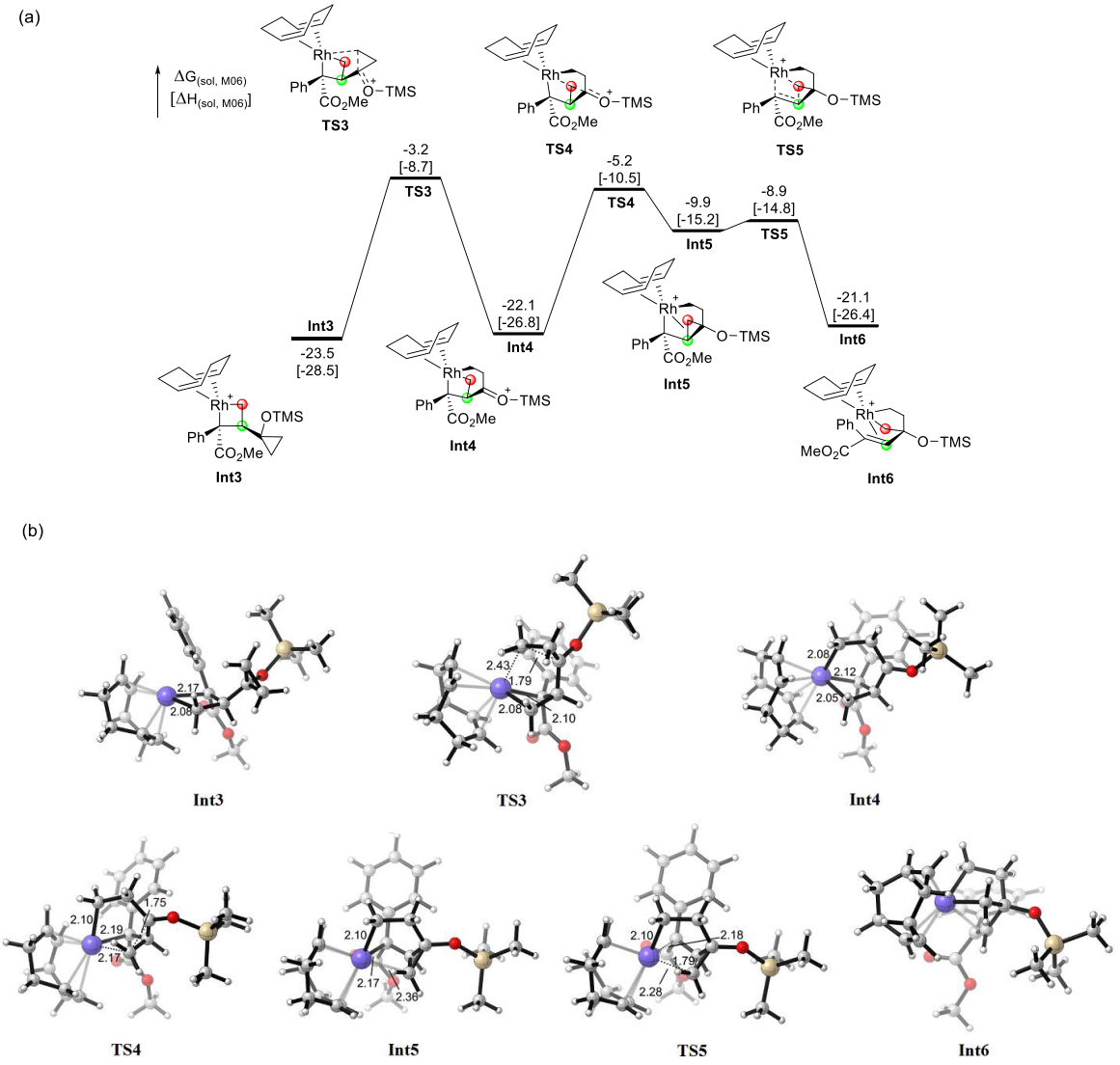

Figure 2. (a) Energy profile for the rearrangement of rhodacyclobutane **Int3** into rhodacyclopentane **Int6**. (b) Optimized structures of intermediates and transition states in the rearrangement steps.

VCPs having different substitution patterns all give the same types of products regardless of whether $[Rh(cod)_2OTf]$ or $[Rh(cod)Cl]_2$ was used as the catalyst, we expect the reaction to have the same mechanism in both cases. Therefore, we initiated our computation for the $[Rh(cod)Cl]_2$ catalyzed reaction from the rhodacyclopentane intermediate **Int10** (Figure 3b). The β-H elimination and the reductive elimination of **Int10** are both facile, but this time the β-H elimination step is reversible because the transition state (**TS9**) for the reductive elimination that follows the β-H elimination is slightly higher in energy compared to **TS8**. Because the energy of **TS8a** is 1.2 kcal/mol higher than that of **TS9**,[15] the reductive elimination to form the cyclobutane product **Int13** is still disfavored compared to the formation of the 1,4-diene product **Int12**. Again, this result matches the experimental observations.

After comparing the structures resulting from the two types of catalysts (Figure 3c), we found that a key difference between the rhodacyclopentane intermediate coming from the cationic and the neutral rhodium catalyst was that the cationic rhodium center was coordinated to the C═C bond in **Int6**, whereas the neutral rhodium center in **Int10** was not. With the neutral rhodium catalyst, the C═C bond remains uncoordinated to the rhodium center throughout the subsequent steps. But with the cationic rhodium catalyst, it is a different situation. In order for β-H elimination to occur, the C−H bond has to have an agostic interaction with the rhodium center in the transition state. Therefore, in the β-H elimination transition state **TS6a** of the cationic rhodium intermediate **Int6**, the previously coordinated C═C bond has to dissociate to give way to this C−H agostic interaction and this will require an additional energy. And yet reductive elimination of **Int6** is able to occur with the C═C bond still coordinated to the rhodium center. Therefore, β-H elimination becomes more difficult in the case of the cationic rhodium catalyst.

CONCLUSIONS

We have developed a cationic Rh(I) catalyzed reaction of VCPs with diazoesters to selectively form *E*-vinylcyclobutane derivatives in moderate to good yields. The 1,4-diene products, which was the major isomer observed in our previously reported reaction catalyzed by neutral Rh(I) catalysts,[7] now becomes the minor isomer in this reaction. The origin of this change of the

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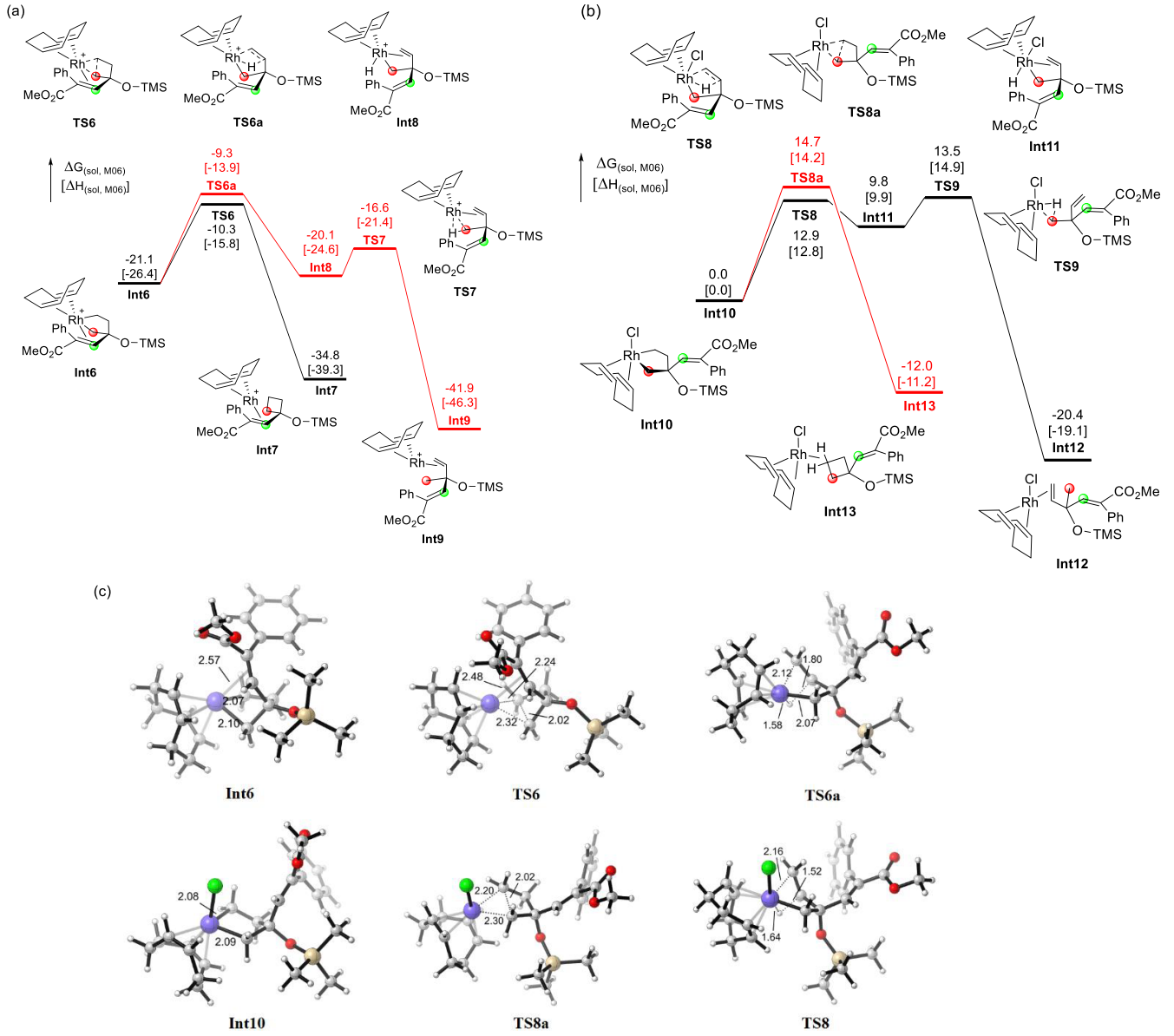

Figure 3. (a) Energy profile for the conversion of rhodacyclopentane **Int6** to vinylcyclobutane **Int7** and 1,4-diene **Int9** with $[Rh(cod)_2OTf]$ catalyst. (b) Energy profile for the conversion of rhodacyclopentane **Int10** to 1,4-diene **Int12** and vinylcyclobutane **Int13** with $[Rh(cod)Cl]_2$ catalyst. (c) Optimized structures of intermediates and transition states for the reductive elimination and β-H elimination of rhodacyclopentane with $[Rh(cod)_2OTf]$ and $[Rh(cod)Cl]_2$ catalyst.

chemoselectivity was examined computationally. Reactions performed with substituted and deuterated VCPs showed that the C═C bond in VCP was cleaved during the reaction. We proposed a mechanism in which each step is energetically plausible based on our computations. This mechanism, along with our computational results, can also help rationalize the excellent *E*/*Z* selectivity as well as the formation of the unexpected products in the reactions carried out with substituted VCPs. Through the combination of the metal carbene chemistry, we have discovered a new reaction mode of VCPs which is completely different from and is energetically favored over the traditional C−C bond activation of VCPs under transition metal catalysis. These new findings and the mechanistic insights may inspire further development of VCP chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08089.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray crystallographic data for the derivative of the cyclobutane product **3r** (CIF)

X-ray crystallographic data for the derivative of the cyclobutane product **3** (Table 1, entry 4) (CIF)

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Notes

The authors declare no competing financial interest.

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