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Dual Activation Strategy to Achieve C−C Cleavage of Cyclobutanes: Development and Mechanism of Rh and Zn Cocatalyzed [4 + 2] Cycloaddition of Yne-Vinylcyclobutanones

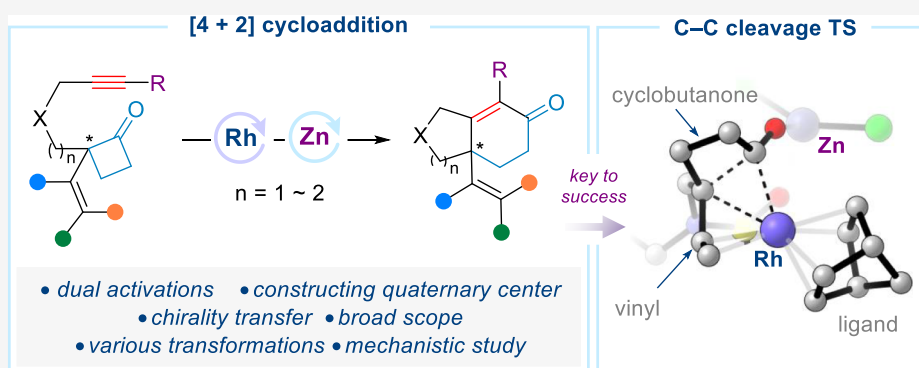Guan-Yu Zhang,[†] Pan Zhang,[†] Bing-Wen Li,[†] Kang Liu, Jun Li, and Zhi-Xiang Yu*

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ABSTRACT: Reported here is the Rh and Zn cocatalyzed [4 + 2] cycloaddition of newly designed yne-vinylcyclobutanones, which can generate 5/6 or 6/6 bicyclic products with an all-carbon quaternary bridgehead center. The reaction has a broad scope and can realize chirality transfer from enantioenriched substrates to the cycloadducts. The key to the success of this [4 + 2] reaction is the introduction of a vinyl group to cyclobutanones, which helps the C−C cleavage of vinylcyclobutanones via oxidative addition. This C−C cleavage step is synergistically aided by Zn coordination to the carbonyl group of vinylcyclobutanones. Of the same importance, visual kinetic analysis and computational studies have been carried out to support the dual activation in the rate-determining C−C cleavage, to derive the rate law of the [4 + 2] reaction, to understand another role of Zn in helping the in situ generation of the cationic Rh catalyst and preventing catalyst deactivation, and to analyze the key transition states and intermediates involved.

INTRODUCTION

Transition metal-catalyzed cycloadditions of [m + n], [m + n + o], [m + n + o +...], and so on have been becoming important and useful tools for chemists in synthesizing cyclic molecules.[1] Developing more such reactions is highly demanded in that these new reactions can complement/surpass the previous ones and, consequently, increase efficiency of synthesis of functional molecules. One of the common strategies to develop transition metal-catalyzed cycloadditions for the synthesis of carbocycles is to use strained molecules as all-carbon synthons through the C−C cleavage strategy,[2,3] which, under metal catalysis, react with other synthons such as alkenes, alkynes, and CO to generate various cycloadducts. In this line, one of the widely applied strained molecules for cycloadditions is vinylcyclopropanes (VCPs), and examples of cycloaddition reactions of VCPs include transition metal-catalyzed [5 + 2],[4] [5 + 2 + 1],[5] [3 + 2],[1a,6] [3 + 2 + 1][7,8] reactions, and others. In these VCP-participated reactions, the vinyl group is critical to assist the C−C cleavage through coordinating to the transition metal of the catalyst, followed by forming a key intermediate of

metallacycle via oxidative addition, as exemplified by the proposed mechanism of the [3 + 2 + 1] reaction of ene/yne-VCPs and CO developed by us[7] (Scheme 1a). Another commonly used strained molecule in cycloaddition reactions is cyclobutanones,[9,10] where the carbonyl group is critical to help C−C activation by the catalyst (or by using Lewis acids acting as either cocatalysts or additives) through coordination/ oxidative addition or transient group-assisted oxidative addition. Many pioneering research studies using cyclo-butanones have been achieved by Ito and Murakami,[11] Wender,[12] Dong,[13] and Cramer.[14] Scheme 1b shows Dong's intramolecular [4 + 2] reaction of ene/yne-cyclobutanones (R^1 = H),[13b−d] which provides a powerful method for synthesizing
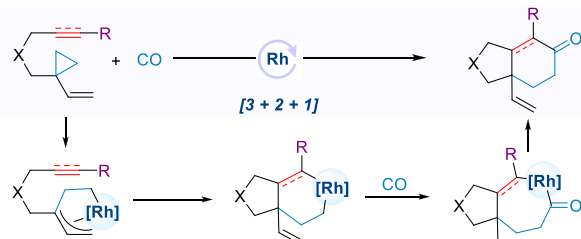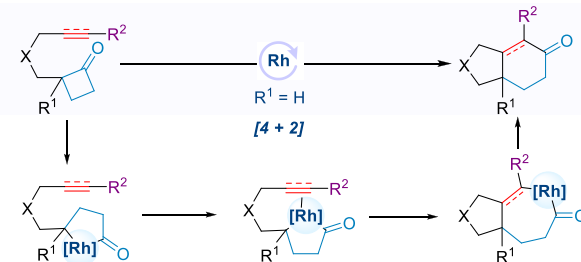
Scheme 1. Reported [3 + 2 + 1] and [4 + 2] Cycloadditions and Design of a New [4 + 2] Reaction
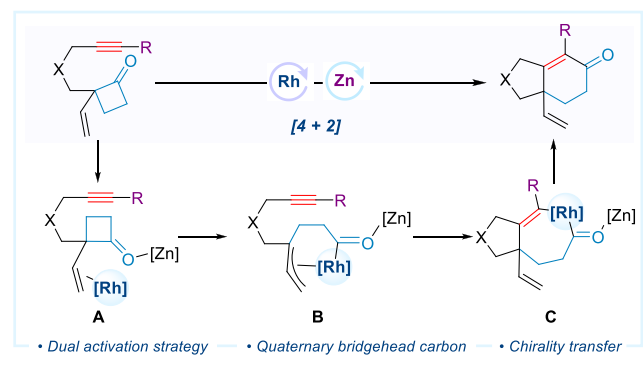
a. Rh catalyzed [3 + 2 + 1] cycloaddition of ene/yne-VCPs and CO (Yu)

b. Rh catalyzed [4 + 2] cycloaddition of ene/yne-cyclobutanones (Dong)

c. Rh and Zn cocatalyzed [4 + 2] cycloaddition of yne-VCBOs (This work)

• Dual activation strategy   • Quaternary bridgehead carbon   • Chirality transfer

5/6 and 6/6 rings and others. However, we noticed that Dong's [4 + 2] reactions have not been used to access bicycles or tricycles with substrates of R[1] being other substituents instead of hydrogen.

Considering the facts that bi- or multicyclic molecules containing a six-membered ring with an all-carbon bridgehead quaternary carbon center widely exist in nature, and the synthesis of these molecules is still posing difficulties to the synthetic community,[15] realization of such a [4 + 2] cycloaddition in Scheme 1b with R[1] = alkyl or other groups would greatly advance the science of synthesis.[16] We tested one substrate with R[1] = ethyl group under Dong's conditions,[13c] finding that no [4 + 2] product was observed (see later on discussion and the Supporting Information (SI) for details). This suggested that a new strategy to overcome this hurdle is required to realize the [4 + 2] reaction between cyclobutanones and 2π synthons (such as alkynes and alkenes), which can then afford final cycloadducts with a bridgehead quaternary carbon.

Inspired by the transition metal-catalyzed cycloaddition reactions of VCPs, where the vinyl group is critical to help the C−C cleavage,[17] we wondered whether such an activation mode by a vinyl group can be extended to cyclobutanones (Scheme 1c). The corresponding vinylcyclobutanones (VCBOs)[12,18] can now have two functional groups, and a

dual activation strategy to achieve a transition metal and Lewis acid cocatalyzed [4 + 2] reaction could then be realized. In this new design, we hypothesized that VCBOs could be coordinated/activated by Rh and ZnX$_2$ (or other Lewis acids) to form **A**, which then undergoes the C−C cleavage to form intermediate **B**. After that, the alkyne moiety of the substrate coordinates to the Rh atom and then inserts into the Rh−C bond to give **C**. Finally, intermediate **C** undergoes reductive elimination to deliver the [4 + 2] cycloadduct. This new [4 + 2] reaction can be regarded as an equivalent of the previous [3 + 2 + 1] reaction[7] because the same intermediate **C** (without coordination by a Lewis acid) is involved (Scheme 1a), which is another reason for attracting us to test whether this variant is possible or not.

The application of our [3 + 2 + 1] reaction in synthesis of natural products has been demonstrated,[7] and we expected this new [4 + 2] reaction in Scheme 1c, if successful, could also become a useful tool for synthetic chemists. Another advantage of this designed [4 + 2] reaction is that an asymmetric [4 + 2] version could be realized when using enantioenriched substrates, expecting that the chirality transfer from substrates to products could be fulfilled. Consequently, this [4 + 2] reaction could then complement our previous [3 + 2 + 1] reaction, which unfortunately does not have its asymmetric version so far.

Here, we report our development of this [4 + 2] reaction, which has a broad scope and can realize chirality transfer from substrates to products. The proposed mechanism and dual activation strategy in this reaction, which has been investigated by visual kinetic analysis, density functional theory (DFT) calculations, and experiments, are also disclosed in this paper.

■ RESULTS AND DISCUSSION

Discovery and Optimization of the [4 + 2] Reaction. We tested our idea of the new [4 + 2] reaction using substrate **1a** under the catalysis of several Rh complexes without/with Lewis acids (Table 1). We were delighted to find that the reaction of substrate **1a** with chloro(1,5-cyclooctadiene)-rhodium(I) dimer ([Rh(COD)Cl]$_2$) as a catalyst, with addition of silver salt, can generate the desired product, albeit in low yields, while no reaction occurred at all without silver salt (entries 1−2). Changing the Rh catalyst to chloro(2,5-norbornadiene)rhodium(I) dimer ([Rh(NBD)Cl]$_2$) did not further increase the yield (entry 3). If the cationic catalyst of bis(norbornadiene)rhodium(I) tetrafluoroborate ([Rh-(NBD)$_2$]BF$_4$) was used alone, the reaction yield decreased slightly, as shown in entry 4. A later kinetic study showed that catalyst deactivation was the major reason for the low reaction yield here.

Inspired by Dong's work,[10d,e,13d] various Lewis acids were added, among which zinc chloride showed the most promising result. We proposed that one role of ZnCl$_2$ here was to generate a low concentration of the cationic Rh as a catalyst so that deactivation can be prohibited and the reaction yield can then be increased, which was also supported by kinetic and computational studies of the reaction mechanism (*vide infra*). Raising the reaction temperature to 80 °C improved the reaction yield (entry 8). We then screened solvents, finding that neither strongly coordinating solvent acetonitrile (entry 10) nor the nonpolar solvent heptane (entry 11) can give a satisfactory yield. Weakly coordinating dimethoxyethane (DME) as the solvent can slightly increase the yield of the [4 + 2] product (entry 12). We hypothesized that the role of

Table 1. Optimization of Reaction Conditions[a]
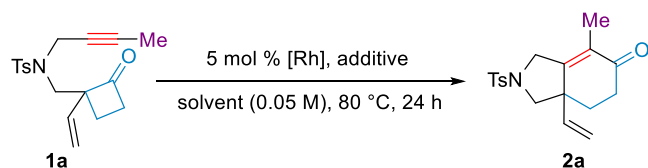
entry	[Rh]	additive	solvent	yield (brsm)%
1[b]	[Rh(COD)Cl]₂	none	CDCl₃	<5
2[b]	[Rh(COD)Cl]₂	10% AgSbF₆	CDCl₃	37 (59)
3	[Rh(NBD)Cl]₂	10% AgSbF₆	DCE	37
4[c]	[Rh(NBD)₂]BF₄	none	DCE	27
5[b]	[Rh(COD)Cl]₂	1 equiv InCl₃	DCE	20 (22)
6[b]	[Rh(COD)Cl]₂	1 equiv ZnCl₂	DCE	21 (88)
7[b]	[Rh(COD)Cl]₂	1 equiv GaCl₃	DCE	11 (12)
8	[Rh(COD)Cl]₂	1 equiv ZnCl₂	DCE	51 (73)
9	[Rh(COD)Cl]₂	1 equiv ZnCl₂	dioxane	8 (40)
10	[Rh(COD)Cl]₂	1 equiv ZnCl₂	MeCN	<5
11	[Rh(COD)Cl]₂	1 equiv ZnCl₂	heptane	31 (63)
12	[Rh(COD)Cl]₂	1 equiv ZnCl₂	DME	57 (65)
13	[Rh(CO)₂Cl]₂	1 equiv ZnCl₂	DCE	40 (62)
14	[Rh(COE)₂Cl]₂	1 equiv ZnCl₂	DCE	36
15[d]	[Rh(COD)Cl]₂	1 equiv ZnCl₂	DCE/DME	72 (92)
16[d]	[Rh(COD)Cl]₂	3 equiv ZnCl₂	DCE/DME	63 (81)
17[d]	[Rh(COD)Cl]₂	20% ZnCl₂	DCE/DME	94
18[c]	Rh(PPh₃)₃Cl	20% ZnCl₂	DCE	85
19[c]	RhH(CO)(PPh₃)₃	20% ZnCl₂	DCE	76
20	[Rh(NBD)Cl]₂	20% ZnCl₂	DCE	94
21	[Rh(NBD)Cl]₂	20% ZnI₂	DCE	91[e]

[a]Nuclear magnetic resonance (NMR) yield using dimethyl terephthalate (δ = 8.10) as the internal standard. [b]60 °C. [c]10 mol % catalyst was used for monomeric rhodium catalyst. [d]A mixture of DCE and DME (9:1) was used as the solvent. [e]Isolated yield. brsm: based on the recovered starting material.

DME was to increase the solubility and activity of the used Lewis acid. An attempt of carrying out the [4 + 2] reaction in a mixture of DCE and DME (9:1) did give a better result (entry 15). Using 3 equiv ZnCl₂ was detrimental to the reaction (entry 16), but using 20 mol % ZnCl₂ gave an excellent result (the reaction yield was 94%, entry 17).

Screening of other rhodium catalysts was then carried out, showing that [Rh(NBD)Cl]₂ gave the highest yield of 94% for the [4 + 2] reaction (entries 13 and 14 and 18−20). Even though conditions in entry 20 were suitable for 1a, we later found that these conditions were not good enough for phenyl-substituted substrate 1g. Therefore, we investigated again to find reaction conditions that could work for both 1a and 1g. To our delight, by just changing ZnCl₂ to ZnI₂, the [4 + 2] reaction outcomes for both substrates were very good (91 and 79% yields for 1a and 1g, respectively). Therefore, we chose entry 21 as the optimal conditions for the [4 + 2] reaction (for more information of reaction optimization for both substrates 1a and 1g, see the SI).

Scope of the [4 + 2] Cycloaddition. Figure 1 collects the data aiming to explore the scope of the [4 + 2] reaction. Substrates 1a and 1b with alkyl substituents of Me, n-Bu groups underwent the [4 + 2] reaction with full conversions, giving cycloadducts in high yields of 90 and 80%, respectively. Substrate 1c with a sterically more hindered cyclopropyl substitution in the alkyne moiety gave a moderate reaction yield of 47%. We did not see other spots except the desired

product 2c in TLC, suggesting that no significant amounts of byproducts were generated. Unfortunately, substrate 1d with a 3-chloropropyl group stayed intact under the standard conditions. To our delight, raising reaction temperature to 120 °C while using the cationic Rh catalyst alone (without adding ZnI₂) gave a moderate yield of 68%, implying that Lewis acid could have some unexpected effect on the Cl atom in 1d. Substrate 1e with a terminal alkyne, under the standard conditions, gave only 13% yield of the [4 + 2] product with partial starting materials recovered. Unfortunately, elevating reaction temperature to 120 °C (1,2-dichlorobenzene as the solvent) for 1e still gave a low yield of the target cycloadduct (29%) with almost no starting materials recovered. We hypothesize that substrate 1e with a terminal alkyne may undergo side reactions other than our [4 + 2] reaction, probably accompanied by catalyst deactivation, because of the unique reactivities of terminal alkynes, such as formation of alkynyl Rh species,[19a−c] polymerization,[19a−c] dimerization,[19d,e] cyclotrimerization,[19e−i] and cyclotetramerization.[19j] To overcome this shortcoming, we tested substrate 1f with a silyl-protected alkyne group, which is regarded as equivalent to the terminal alkyne group, finding that the final product can be obtained in 79% yield. Substrates with various aryl groups in their alkyne moiety had also been tested for the present [4 + 2] reaction. Phenyl-substituted substrate 1g generated 2g in 78% yield, albeit the yield was slightly lower than that of 2a. Different substitutions on the phenyl group can also be tolerated. For example, substrate 1h with an electron-deficient para-nitro group, 1i with a para-cyano group, 1j with a para-methoxycarbonyl group, 1k with a para-acyl group, 1l with a para-amide group, and 1m with a para-bromo group tolerated the optimal reaction conditions very well, giving their corresponding products 2h−2m in moderate to high yields. However, substrate 1n with a para-methoxy group behaved poorly, and its reaction was messy (only a 17% yield was obtained in this case). In addition to the para-substitution, this reaction also works for other substitution patterns of the substrates. For example, both 1o with an ortho-Cl group and 1p with a meta-methyl group gave reaction yields comparable to that of 1g. It is worth mentioning that ortho-chlorophenyl-substituted product 2o has a new chirality axis because rotation of the bond between the phenyl ring and cyclohexenone ring in this product is restricted.

Similar to 1n, substrates with electron-rich heteroaryl rings either gave poor reaction yields or even did not react under the [4 + 2] reaction conditions. For example, substrate 1q with a 2-thiophenyl group gave cycloadduct 2o in 24% yield, while substrate 1r with a 2-furyl group completely decomposed under the standard reaction conditions. We hypothesized that these substrates with electron-rich heteroaryl could not tolerate the used Lewis acid. To our further disappointment, treating substrate 1r using just cationic [Rh(NBD)₂]BF₄ as the catalyst without adding ZnI₂ still gave a decomposed mixture, prompting us to conclude that the present reaction was not suitable for substrate 1r.

To our delight, substrates 1s and 1t containing conjugated enyne groups can give [4 + 2] products in 64 and 42% yields, respectively. Unfortunately, extending the reaction time for some of the studied substrates, which gave either low or moderate yields under the original optimal conditions, did not give improved results, as demonstrated by the reactions of substrates of 1c and 1t. Substrate 1u with a longer NNs tether gave 6/6 bicyclic product 2u with a moderate yield of 62%. In

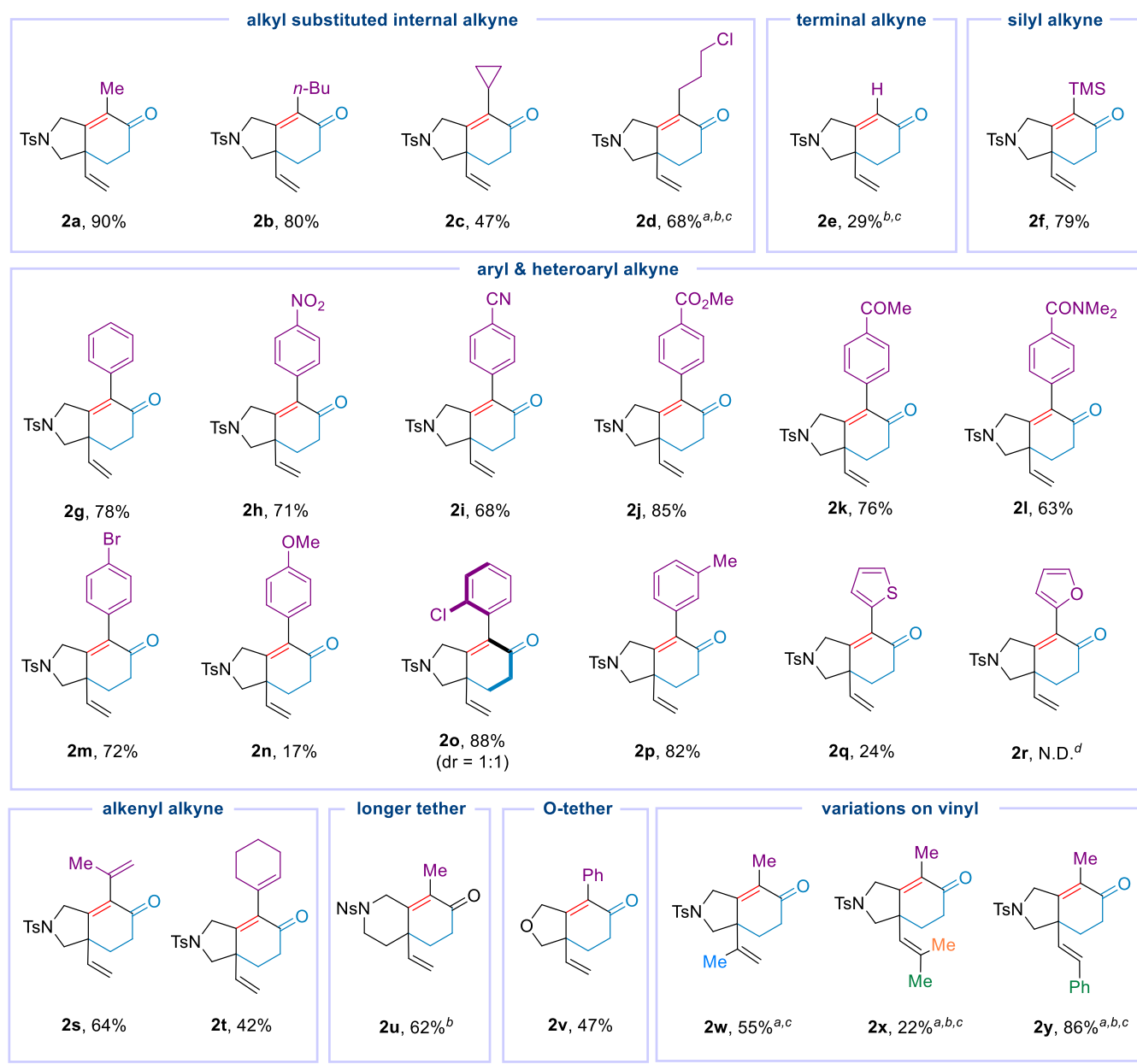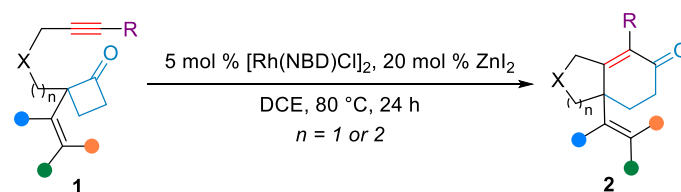**Figure 1.** Substrate scope of the [4 + 2] reaction. The reactions were conducted in 0.2 mmol scale in 2 mL DCE with 5 mol % $[Rh(NBD)Cl]_2$ and 20 mol % ZnI_2 as catalysts, unless otherwise specified. All the yields given above are average of two runs. [a]10 mol % $[Rh(NBD)_2]BF_4$ (without ZnI_2) was used instead. [b]The reaction was conducted in 0.1 mmol scale in 1 mL of solvent. [c]The reaction was conducted at 120 °C in o-DCB. [d]Substrate decomposed; N.D., not detected.

addition, we found that substrate **1v** with an oxygen tether reacted smoothly, giving **2v** in 47% yield.

Substrates with different substitutions on their vinyl group of the cyclobutanone moiety were also scrutinized. Substrate **1w** with a propen-2-yl group reacted smoothly, under the cationic Rh catalytic conditions, to give **2w** in 55% yield. Similarly, **1x** with dimethyl substituted vinyl also gave **2x**, albeit in a low

yield (22%). Delightfully, **1y** with an (E)-styryl group, under the cationic Rh catalytic conditions, gave **2y** in a high yield of 86%. We noticed that all these [4 + 2] reactions of substrates with substituents on the vinyl group needed to be performed at an elevated temperature (120 °C), suggesting that these substituents decrease the reactivity of their substrates, possibly due to the steric reason.

Chirality Transfer of the [4 + 2] Cycloaddition and the Gram-Scale Experiment. Furthermore, we synthesized an enantioenriched substrate **1z** using Toste's method[18d] to test whether the chirality in the substrate can be transferred to the final product (a proof-of-concept experiment, Scheme 2a).

Scheme 2. Experimental Tests of Chirality Transfer, Gram Scale of [4 + 2] Reaction, Importance of the Vinyl Group in the Substrate, and Intermolecular [4 + 2] Reaction[a]
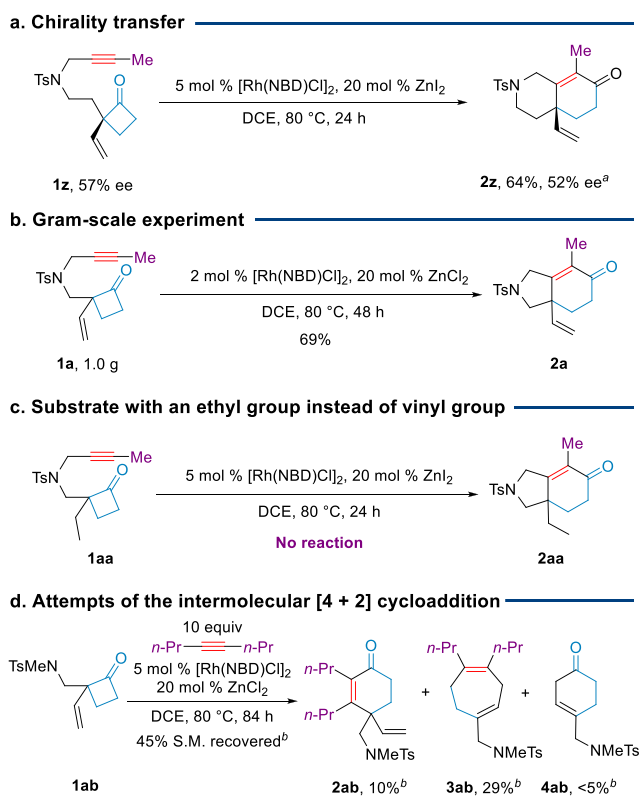
[a]The reaction was run in 0.1 mmol substrate scale in 1 mL of solvent. The yield and ee value given above are average of two runs. [b]The reaction was run in 0.4 mmol substrate scale in 4 mL of solvent.

To our delight, the reaction of enantioenriched **1z** (57% ee) can generate [4 + 2] product **2z** in 64% yield and 52% ee, demonstrating that the present [4 + 2] reaction can realize its asymmetric version when using enantioenriched substrates (this suggests that stereochemistry of the substrate is kept in all C−C cleavage, alkyne insertion, and reductive elimination steps, see mechanistic part). In addition, the gram-scale [4 + 2] reaction of **1a** (using 2 mol % Rh catalyst and 20 mol % ZnCl₂) was also tested, finding that the target cycloadduct can be obtained in 69% yield (Scheme 2b).

Experimental Demonstration of the Importance of the Vinyl Group in the Present [4 + 2] Cycloaddition. To demonstrate the importance of the vinyl group in the substrates, we tested the [4 + 2] reaction of substrate **1aa** with an ethyl group instead of a vinyl group (Scheme 2c). Nearly full recovery of the substrate was observed. We found that **1aa** did not work under Dong's conditions either (see the SI for experimental details). All these indicated that the vinyl group in the substrates is critical for the success of the present [4 + 2] reaction, supporting our initial hypothesis of the reaction design. We found that **1a** did not work under Dong's

conditions either, implying that Dong's [4 + 2] reaction has a different mechanism compared to that of the present Rh and Zn cocatalyzed [4 + 2] reaction.

Tests of the Intermolecular [4 + 2] Reaction. With the above success, we then tried to develop an intermolecular [4 + 2] cycloaddition using **1ab** and an internal alkyne as the substrates (Scheme 2d). However, three products, **2ab**, **3ab**, and **4ab**, were isolated under similar conditions. The intermolecular [4 + 2] product **2ab** had an NMR yield of 10%. The [6 - 1 + 2] cycloaddition product **3ab**, as an equivalent of Wender's [5 + 2] product,[4d] had an NMR yield of 29%. Product **4ab**, which is an equivalent of our previous [5 + 1] reaction,[20] was just the isomerized product and had an NMR yield of less than 5%. Unfortunately, the reaction of **1ab** without adding alkyne only gave an unidentified mixture under the standard conditions.

Further Transformation of the [4 + 2] Cycloadducts. The above study of the reaction scope reveals that substrates with various vinyl groups can work for the [4 + 2] reaction, demonstrating that many 5/6 and 6/6 with different bridgehead quaternary substituents can be accessed by this reaction. Previous application of the [3 + 2 + 1] reaction from our group and Lei group in total synthesis[7] also implies that the [4 + 2] products here can also be applied for achieving similar transformations. To show further the impacts of the present [4 + 2] reaction (as well as the previous [3 + 2 + 1] reaction) in synthesis, we explored other different transformations[21] using [4 + 2] adduct **2a** (Scheme 3). We found

Scheme 3. Transformation of the [4 + 2] Cycloadduct to Other Compounds[a]
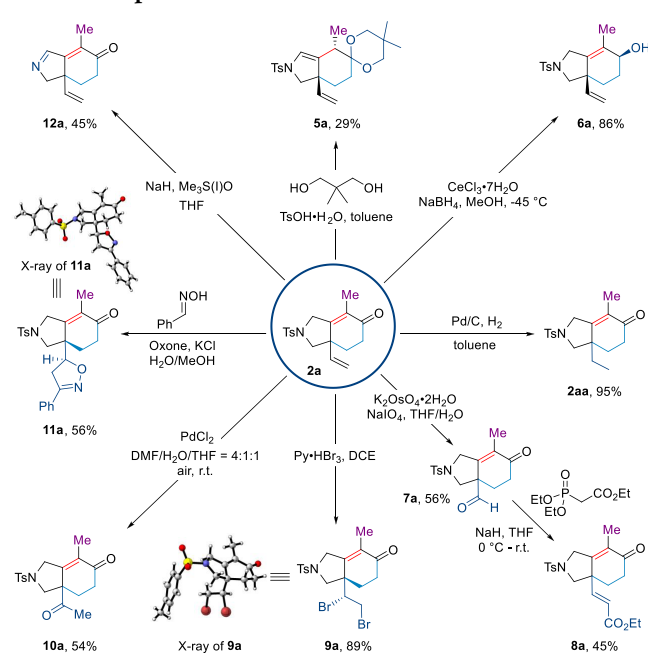
[a]All the yields are average of two runs.

that the carbonyl group in **2a** can be protected by 2,2-dimethylpropane-1,3-diol to form the corresponding ketal product **5a** (double bond isomerization also occurred here). In addition, Luche reduction[21a] can be utilized to transform **2a** to **6a** in 86% yield. The relative stereochemistry of **6a** was assigned according to the X-ray structure of its ester derivative (see the SI for details). The quaternary vinyl group in the [4 +
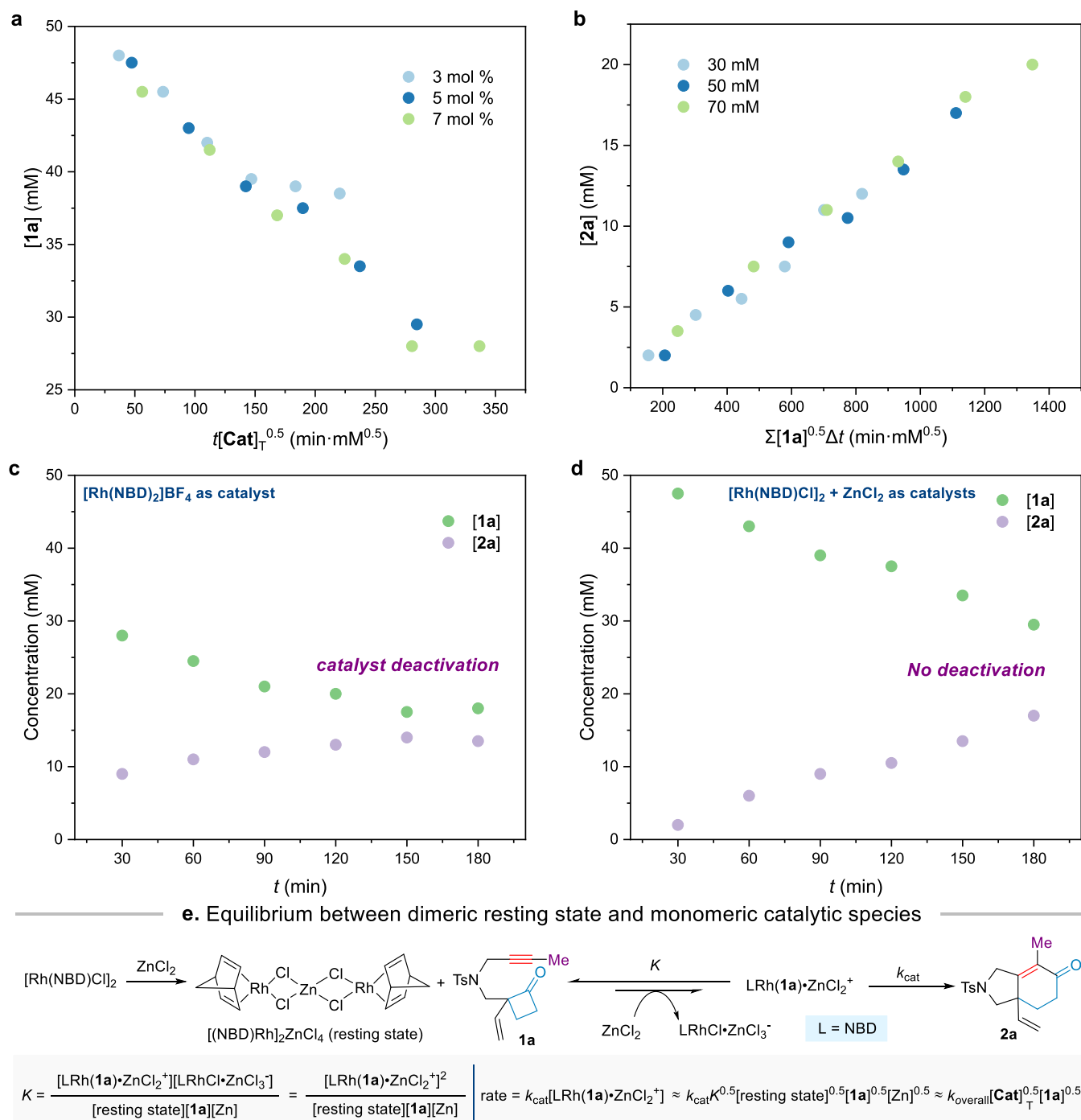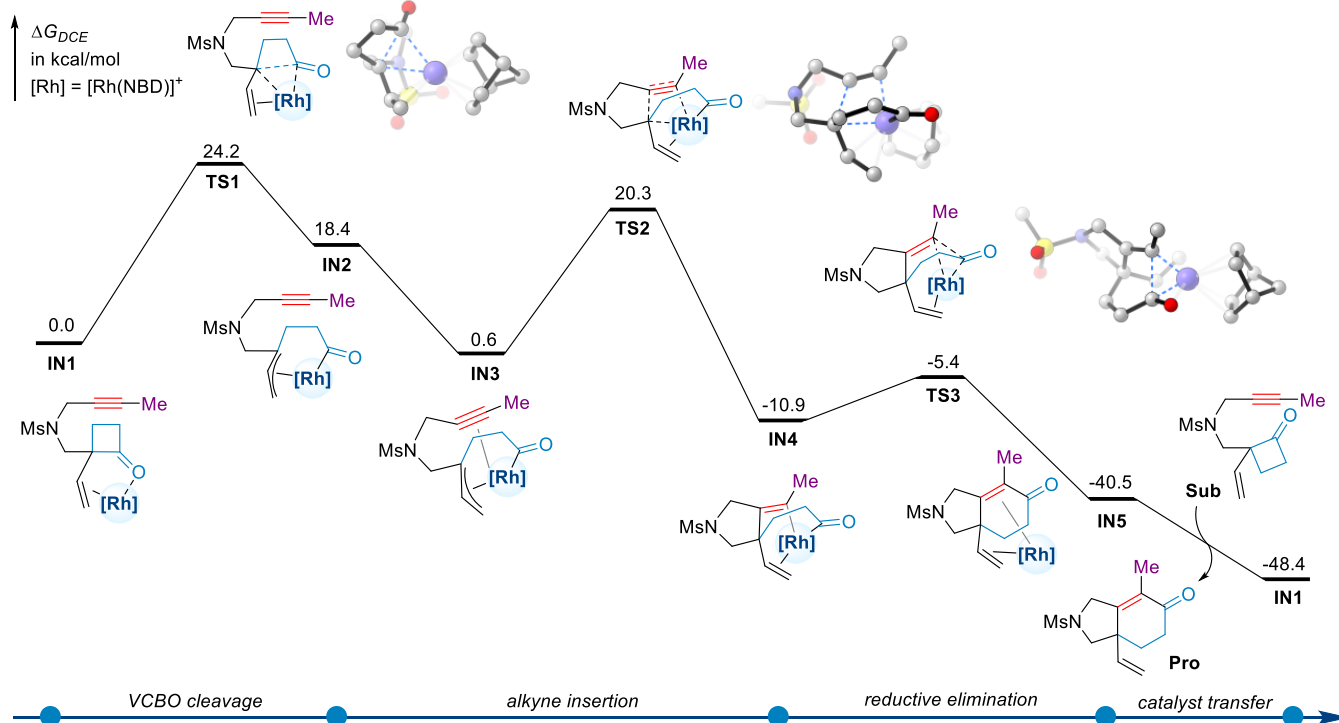
Figure 2. Visual kinetic analysis on the cycloaddition of substrate **1a** (a−d) and equilibrium between dimeric resting state and monomeric catalytic species (e). Reaction conditions: (a) **1a** (50 mM), and ZnCl$_2$ (20 mol %), [Rh(NBD)Cl]$_2$ (3, 5, 7 mol %), 60 °C; (b) **1a** (30, 50, 70 mM), and ZnCl$_2$ (20 mol %), [Rh(NBD)Cl]$_2$ (5 mol %), 60 °C; (c) **1a** (50 mM), [Rh(NBD)$_2$]BF$_4$ (10 mol %), 60 °C; (d) **1a** (50 mM), and ZnCl$_2$ (20 mol %), [Rh(NBD)Cl]$_2$ (5 mol %), 60 °C. [**Cat**]$_T$ is the total concentration of catalyst added.

2] cycloadduct can be reduced to the ethyl group by using Pd/C and H$_2$ (95% yield, see **2aa**). Synthetically useful product **7a** with a quaternary aldehyde group can be obtained by oxidative cleavage[21b] in 56% yield. This aldehyde can be further converted to other products in principle. Here, we used the Horner−Wadsworth−Emmons reaction[21c] to convert **7a** to α,β-unsaturated ester **8a**. We failed in synthesizing **8a** directly from [4 + 2] cycloadduct **2a** (several Ru olefin metathesis catalysts have been tested in both catalytic and stoichiometric fashions).[21d] We hypothesized that the vinyl group of **2a** lying

in the 5/6 bridgehead position is in a sterically hindered environment that prevents the bulky Ru catalysts from approaching.[21e] Dibromonation[21f] of **2a** can be executed smoothly to generate **9a** in 89% yield by using pyridinium hydrobromide perbromide (Py·HBr$_3$). The structure of **9a** was unambiguously confirmed by X-ray crystallography. Stoichiometric Wacker oxidation[21g] and 1,3-dipolar cycloaddition[21h] can also occur, giving quaternary ketone product **10a** and [3 + 2] adduct **11a**, respectively. The stereochemistry of **11a** was also confirmed by X-ray crystallography. We expected that **11a**

Figure 3. Gibbs energy profiles of model reactions I (a) and II (b). Computed at the SMD(DCE)/BMK/def2-TZVPP//BMK/def2-SVP level. For clarity, hydrogen atoms were omitted for 3D molecular structures.

can be further converted to many other compounds considering that the rich chemistry of isoxazolines exists.[22] We also tried to convert the α,β-unsaturated carbonyl in **2a**

into a cyclopropane via the Corey−Chaykovsky reaction,[21i] but surprisingly we found that the reaction did not give what we expected. Instead, the tosyl (Ts) group was eliminated and the

imine product **12a** was generated, implying that the present reaction can serve as a deprotection method here.

Kinetic Study of the Reaction Mechanisms. We used visual kinetic analysis[23] developed by Burés to understand the present [4 + 2] reaction first. Experimentally, we used NMR to monitor the [4 + 2] reaction of **1a** in the presence of [Rh(NBD)Cl]$_2$ and ZnCl$_2$. For Lewis acid, ZnCl$_2$ was used in the later ab initio calculations because the [4 + 2] reaction can take place by using either ZnCl$_2$ or ZnI$_2$ (while using ZnCl$_2$ in calculations can save computational time). The visual kinetic results shown in Figure 2a,b indicate that the orders of both the Rh catalyst and the substrate are 0.5, respectively. We did not measure the reaction order of zinc chloride because this Lewis acid was barely soluble in DCE (solubility of ZnI$_2$ is low too). The kinetic data suggest that an off-cycle resting state in the [4 + 2] reaction consists of a dimeric rhodium species (Figure 2e). We propose that two Rh centers and one ZnCl$_4$ bridge are involved in the resting state (similar structure has been reported[24]). This resting state can heterolyze in a disfavored equilibrium to a cationic rhodium species,[25] which coordinates to substrate and enters the catalytic cycle as active catalytic species (NBD)Rh(**1a**)·ZnCl$_2^+$, together with an off-cycle anionic species, which is a complex between the monomer of the catalyst and ZnCl$_3^-$. Another support of the cationic Rh catalyst came from experimental observation that neutral Rh(I) catalysts tested did not catalyze the reaction.

The rate equation can be deduced from intermediate (NBD)Rh(**1a**)·ZnCl$_2^+$, which has the same concentration of the off-cycle anionic species and thus [(NBD)Rh(**1a**)·ZnCl$_2^+$]^2 is presented in the equation as in Figure 2e. This explains the 0.5th order for both the substrate and the Rh catalyst.

We also monitored the [Rh(NBD)$_2$]BF$_4$-catalyzed [4 + 2] reaction of **1a**. To our surprise, the reaction conversion was 44% and yield of **2a** was 18% in the first 30 min, suggesting that unknown side reactions happened when only cationic Rh was used as the catalyst (Figure 2c). The cationic Rh-catalyzed [4 + 2] reaction was much faster (and had more side reactions as well) than the Rh and Zn cocatalyzed [4 + 2] reaction, which had only 5% conversion and 4% of **2a** in the first 30 min (Figure 2d). In addition, deactivation of Rh catalyst was observed for the cationic Rh-catalyzed [4 + 2] reaction without Lewis acid, as indicated by the fact that, in the next two hours only another 20% substrate was consumed (Figure 2c). These results explain why the yield of [4 + 2] reaction catalyzed by [Rh(NBD)$_2$]BF$_4$ was low (entry 4, Table 1). In some substrates such as **1d**, the deactivation was possibly not significant and reasonable yields can be achieved. The possible reasons for a faster cationic Rh-catalyzed [4 + 2] reaction (no off-cycle resting state and two cationic Rh species as catalysts) were proposed and discussed in the SI.

DFT Study of the Reaction Mechanisms. DFT calculations have also been carried out to further understand the reaction mechanisms. In our DFT calculations, the Ts group in the substrate was replaced by a mesyl (Ms) group for just reducing computational cost, but still keeping the calculation results reasonable. We first computed the free energy profile of the Rh-catalyzed [4 + 2] reaction (model reaction I), which represents the [Rh(NBD)$_2$]BF$_4$ catalyzed [4 + 2] reaction (entry 4, Table), also named Rh-catalyzed [4 + 2] reaction here. Then we investigated the mechanism of the Rh and Zn cocatalyzed [4 + 2] reaction (model reaction II).

In the model reaction I (Figure 3a), formation of intermediate **IN1** from substrate and catalyst is the first step.

Then **IN1** undergoes C−C cleavage to form **IN2** via **TS1**, with an activation free energy of 24.2 kcal/mol. **IN2** then isomerizes to the alkyne-coordinated complex, **IN3** (this step is exergonic by 17.8 kcal/mol). Subsequently, alkyne insertion occurs via **TS2** to give **IN4** with an activation free energy of 19.7 kcal/mol. After that, reductive elimination reaction (via **TS3**) converts **IN4** to **IN5**, a complex of Rh catalyst and [4 + 2] product **Pro**, with an activation free energy of 5.5 kcal/mol. The final step is the catalyst transfer process regenerating **IN1** and releasing **Pro**, which is exergonic by 7.9 kcal/mol. The rate-determining step in this reaction is the C−C cleavage. We must emphasize here that calculations on model reaction I using one cationic Rh catalyst only serve to understand how this differs from model reaction II which uses two catalytic species, Rh and Zn. In principle, model reaction I could use two cationic Rh catalysts, activating both the vinyl and carbonyl groups in the substrate, which was discussed in the SI.

Model reaction II was used to understand the present Rh and Zn cocatalyzed [4 + 2] reaction (Figure 3b), in which the catalysts are Rh(NBD)$^+$ and ZnCl$_2$. The first step in model reaction II is the formation of intermediate **d-IN1**, in which Rh coordinates to the vinyl group of the substrate and ZnCl$_2$ binds to the carbonyl group of the substrate. The C−C cleavage via **d-TS1** in this case becomes easier than model reaction I does, with an activation free energy of 17.7 kcal/mol, giving rise to **d-IN2**. This indicates that ZnCl$_2$ can help the C−C cleavage process. After that, isomerization converting **d-IN2** to **d-IN3** happens. The next step is alkyne insertion, with an activation free energy of 21.3 kcal/mol (this value is close to that of the same step in model reaction I). What follows is a reductive elimination process via **d-TS3** to afford **d-IN5**. Finally, catalyst transfer from **d-IN5** to **Sub** regenerates **d-IN1** and liberates [4 + 2] product **Pro** (this process is exergonic by 13.3 kcal/mol). Here, we propose that the rate-determining step is C−C cleavage considering that there is an endergonic process from the resting state of the reaction to **d-IN1** (Figure 4), not the alkyne insertion step from **d-IN3** to **d-TS2** with an activation free energy of 21.3 kcal/mol, a value too low to account for a reaction at 80 °C.
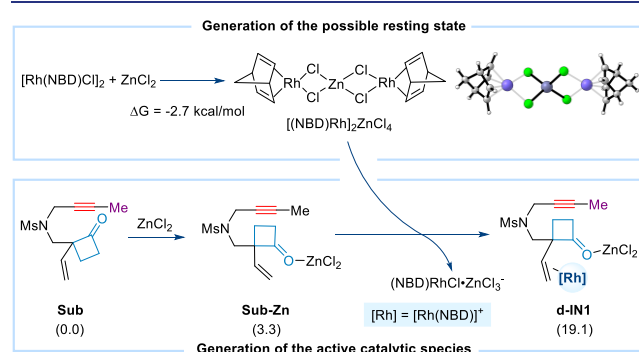
Figure 4. Generation of the possible resting state and catalytic active species **d-IN1**. Relative Gibbs energies computed at the SMD(DCE)/BMK/def2-TZVPP//BMK/def2-SVP level are reported in kcal/mol.

We have calculated the generation process of **d-IN1**, which is endergonic by 19.1 kcal/mol (from **Sub** to **d-IN1**). This suggested that the C−C bond cleavage in the [4 + 2] reaction would need 36.8 kcal/mol, which is too high for the [4 + 2] reaction at 80 °C. This discrepancy with experiments comes from the inaccuracy of calculations here. The first reason is

that, we do not know the exact form of ZnCl$_2$ in the solution, which means that representing it simply as a single molecule in an implicit solvation model is not accurate. In addition, calculations of thermodynamics for a reaction of generating charged species (from **Sub-Zn** and [Rh(NBD)]$_2$ZnCl$_4$, to **d-IN1** and (NBD)RhCl·ZnCl$_3$$^-$) in the solution are not accurate[26] (more discussions are given in the SI). Therefore, we only conclude that the generation of reactive **d-IN1** from the resting state dimeric rhodium species is endergonic and possible, which make the C—C cleavage step as the rate-determining step with activation free energy greatly larger than 17.7 kcal/mol (from **d-IN1** to **d-TS1**).

Summary of the Reaction Mechanism. Based on the kinetic study and DFT calculations, we propose the mechanism as shown in Figure 5. Active catalytic species **A**
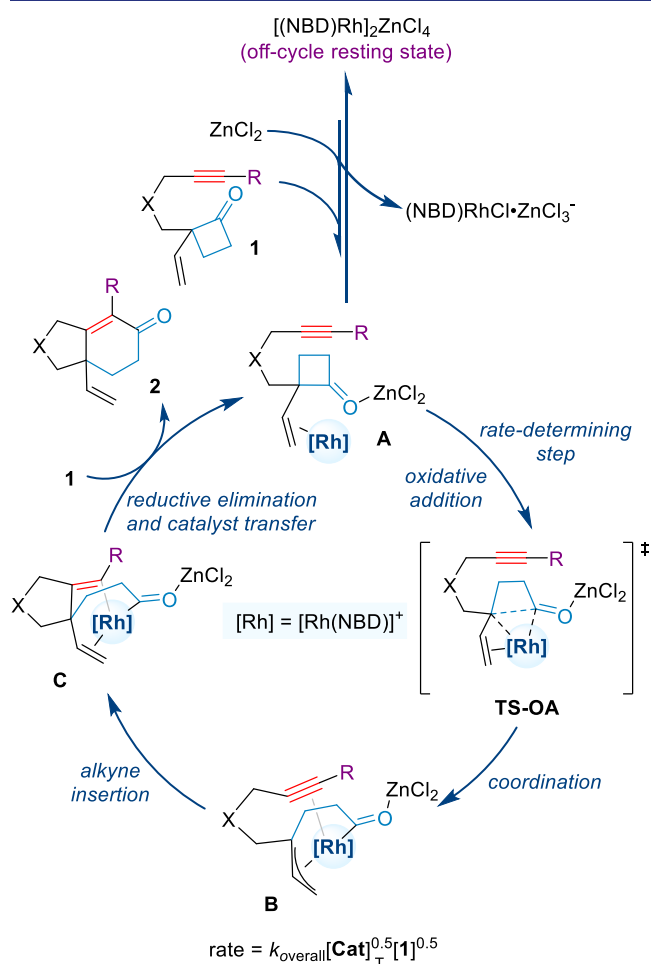

Figure 5. Proposed mechanism supported by the kinetic study and DFT calculations.

is generated via dissociation of dimeric off-cycle resting state. Then turnover limiting oxidative addition (VCBO cleavage) occurs via **TS-OA**, generating **B** after alkyne coordination. After that, alkyne insertion, reductive elimination and catalyst transfer deliver cycloadduct **2**. It is proposed that ZnCl$_2$ plays two roles. One helps the C—C activation step (Figure 3b), and the other is to form in situ the active cationic Rh species through the equilibrium (from [(NBD)Rh]$_2$ZnCl$_4$ to **A** in Figures 2e and 4), preventing the deactivation of catalytic species in the reaction.

CONCLUSIONS

In summary, we have developed an intramolecular [4 + 2] cycloaddition reaction of newly designed yne-vinylcyclobutanones to generate fused 5/6 or 6/6 ring products with an all-carbon bridgehead quaternary center. Chirality transfer can be successfully realized when an enantioenriched substrate was used. Various transformations can be achieved to convert the [4 + 2] cycloaddition products into different compounds. Computational and kinetic study suggested that the cationic Rh monomer and Lewis acid synergistically participate in the rate-determining C—C cleavage of the cyclobutanone in the [4 + 2] reaction, namely, through Rh's coordination to the vinyl group and then oxidative addition to cleave C—C bonds, and Zn's coordination to the carbonyl group. The used Lewis acid plays another role, helping in situ generation of the active cationic Rh species, suggested by the kinetic study of the Rh and Zn cocatalyzed [4 + 2] reaction. The key to the success of the present [4 + 2] reaction is introducing the vinyl group in the cyclobutanones so that the C—C bond cleavage in the four-membered ring can be realized through oxidative addition. We believe that such a new strategy to activate four-membered rings would inspire the development of more reactions using C—C cleavage chemistry. The application of this [4 + 2] reaction can be also envisioned.

COMPUTATIONAL METHODS

DFT calculations were performed with the Gaussian 09 software package.[27] Pruned integration grids with 99 radial shells and 590 angular points per shell were used for all calculations. In our previous benchmark study, we found that the BMK[28] functional has a good performance on rhodium-catalyzed cycloaddition reaction systems.[29] Therefore, our geometric optimizations of intermediates and transition states were calculated at the BMK/def2-SVP[30] level, with the default ECP applied to rhodium atoms. Unscaled harmonic frequency calculations were also performed at the same level to validate each structure as either a minimum or a transition state and to evaluate its zero-point energy and thermal corrections at 298 K. Standard state concentration of 1.0 mol/L was used for all species. Based on the optimized structures, Gibbs energies of solvation in DCE were computed at the SMD[31]/BMK/def2-SVP level, and single-point energies were calculated at the BMK/def2-TZVPP level. All of the 3D structures were prepared with CYLview.[32]

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c04244.

Experimental procedures, characterization data, copies of NMR spectra, and computational details (PDF)

Accession Codes

CCDC 2206772, 2206774, and 2208579 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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