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Mechanistic Understanding of the Divergent Reactivity of Cyclopropenes in Rh(III)-Catalyzed C−H Activation/Cycloaddition Reactions of *N*-Phenoxyacetamide and *N*-Pivaloxybenzamide

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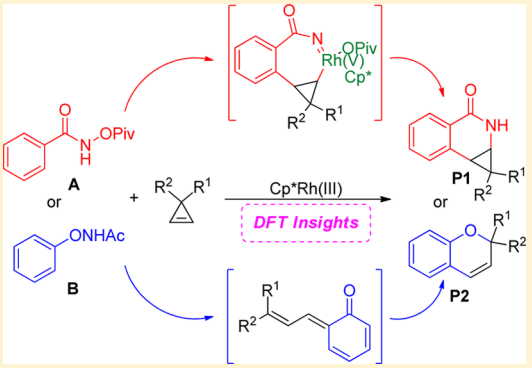
Supporting Information

ABSTRACT: Density functional theory calculations were conducted to develop a mechanistic understanding of the Rh(III)-catalyzed C−H activation/cycloaddition reactions of *N*-phenoxyacetamide and *N*-pivaloxybenzamide with cyclopropenes, and insights into the substrate-dependent chemoselectivity were provided. The results showed that the divergence originated from the different reactivity of the seven-membered rhodacycles from the insertion of cyclopropene into the Rh−C bond. In reactions of *N*-pivaloxybenzamide, such an intermediate undergoes the pivalate migration to form a cyclic Rh(V)-nitrenoid intermediate in a reaction that is easier than the opening of the three-membered ring by *β*-carbon elimination, leading finally to a tricyclic product with retention of the cyclopropane moiety by facile reductive elimination. While similar Rh(V)−nitrenoid species could also be possibly formed in Cp*Rh(III)-catalyzed reactions of *N*-phenoxyacetamide, the *β*-carbon elimination occurs more easily from the corresponding seven-membered rhodacycle intermediate and the subsequent O−N bond cleavage gives rise to an unexpected dearomatized (*E*)-6-alkenylcyclohexa-2,4-dienone intermediate. The *E*/*Z* isomerization of this intermediate is required for the final cyclization to 2*H*-chromene, and interesting metal−ligand cooperative catalysis with Rh(III) carboxylate was disclosed in the C═C double bond rotation process.



INTRODUCTION

Cyclopropenes represent one class of highly strained molecules, and their reactivity in organic transformations has been widely explored.[1] The strained structure makes the C═C bond in such small cyclic compounds much more reactive than normal olefins toward addition reactions with electrophiles.[2] Alternatively, the ring openings of cyclopropenes are quite favorable as a result of the release of the strain energy and are commonly seen in transition metal-catalyzed transformations in which the cyclopropene could be a precursor for a carbenoid intermediate or incorporated into the final product as a three-carbon synthon.[3] Thus, diverse reactivities of cyclopropenes were documented in the literature.[1−3]

In recent years, a great deal of attention has been paid to transition metal-catalyzed C−H functionalization in organic chemistry, and notable progress was achieved in directed C(sp^2)−H activations of various aromatic and olefinic compounds under the catalysis of Cp*Rh(III) complexes.[4] Thus, novel access to interesting heterocycles is achieved by the Rh(III)-catalyzed C−H activation/cycloaddition processes. Mechanistically, the insertion of an inter- or intramolecular unsaturated coupling partner into the Rh−C bond of the initially formed rhodacycle intermediate is a key step for all these transformations. In this respect, the reactivities of a diversity of unsaturated molecules, including alkene, alkyne, allene, and others,[5] were well explored in Rh(III)-catalyzed C−H activation/cycloaddition reactions; however, much less attention was paid to the reactions involving cyclopropenes.[6] Recent research from the Wang group disclosed the Rh(III)-catalyzed reactions of *N*-pivaloxybenzamide (**A**) and *N*-phenoxyacetamide (**B**) with cyclopropenes to give tricyclic lactam **P1** and 2*H*-chromene **P2**, respectively (Scheme 1a).[7] Thus, interesting substrate-dependent chemoselectivity was uncovered as the three-membered ring of the cyclopropene is retained in reaction with **A**, while ring opening reaction of cyclopropene occurred with substrate **B**.[8]

In previous theoretical works, we studied the mechanism of Rh(III)-catalyzed C−H activations of *N*-pivaloxybenzamide and proposed the Rh(V) intermediate should be important for the C−N bond formation step, and the divergence of reactions of **A** and **A′** with olefin was uncovered (Scheme 1b).[9] However, the origin of the different reactivity of cyclopropene in reactions with **A** and **B** observed by Wang et al. (Scheme 1a) is not understood. Possibly, prior to C−N bond formation to generate **P1**, a Rh(V) intermediate may be formed from rhodacycle **I** by a similar pathway as disclosed in other systems.[9,10] On the other hand, the *β*-C elimination from intermediate **I**, generating an eight-membered rhodacycle like **II**, should be favorable because of the release of the ring strain

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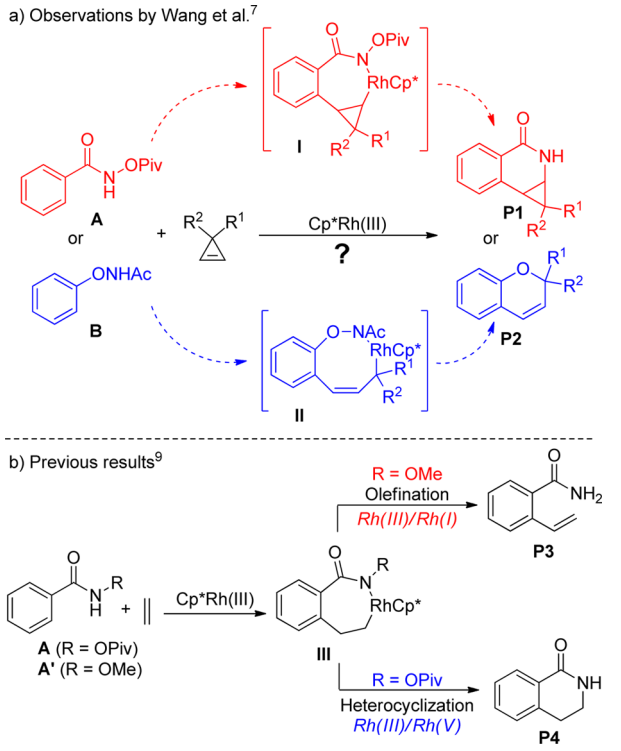
Scheme 1. Substrate-Dependent Chemoselectivity in Rh(III)-Catalyzed C−H Functionalizations



of the cyclopropane moiety.[11] In addition, the ring opening of cyclopropene by activation of the π bond was implied in the literature;[7,12] whether such a process could compete with C−H activation under Cp*Rh(III) catalysis is unknown. In addition, while the concept of external oxidant-free C−H activations becomes more and more popular,[13−15] how the O-NHAc moiety in *N*-phenoxyacetamides works as an internal oxidant is still unclear.[14m,n,16]

As a continuation of our interest in the mechanistic understanding of related transformations,[9,10,12] in this work we conducted a computational study for a detailed understanding of the substrate-dependent chemoselectivity discovered by the Wang group (Scheme 1a). For both reactions of *N*-phenoxyacetamide and *N*-pivaloxybenzamide with cyclopropene, the competition among possible pathways of β-C elimination (opening of the three-membered ring), C−X (X = N or O) bond formation, and Rh(V) formation were analyzed to show the divergence of the reactions, and interesting dearomatization of the phenyl group in *N*-phenoxyacetamide upon the Rh(III)-promoted cleavage of the O−N internal oxidant and metal−ligand cooperative catalysis for double bond rotation of the dearomatized intermediate were disclosed.[17]

COMPUTATIONAL DETAILS

All calculations were conducted by using the Gaussian 09 suite of computational programs.[18] All stationary points along the reaction coordinate were fully optimized at the DFT level using the M06 hybrid functional.[19] The 6-31G(d) basis set[20] was applied for all atoms except Rh, which was described by the Lanl2dz basis set and effective core potential implemented (BSI).[21] Frequencies were analytically computed at the same level of theory to obtain the thermodynamic corrections and to confirm whether the structures are minima (no imaginary frequency) or transition states (only one imaginary frequency). Intrinsic reaction coordinate (IRC) calculations[22] were conducted to confirm that all transition state structures connect the proposed reactants and products. The solvation effect was examined by performing single-point self-consistent reaction field (SCRF) calculations based on the SMD solvation model for gas-phase optimized structures.[23] Methanol was used as the solvent, corresponding to the original experimental conditions. All SCRF calculations were conducted at the M06 level by using a larger basis set of SDD for Rh and 6-311+G(d,p) for the rest of the elements (BSII). The relative free energies corrected by solvation effects from M06/BSII calculations are used for discussion. According to the experimental condition used by Wang et al.[7] and previous mechanistic results,[9,10] Cp*Rh(OPiv)$_2$ was used as the active catalyst in calculations, and the 3,3-dimethylcyclopropene was used to model the 3,3-dialkylcyclopropene substrates in experiments.[7] For a species that has more than one conformer, only the one having the lowest energy value is used for discussion. To further validate the computational results, geometry optimizations in a methanol solution at the M06/BS1 level were conducted for key steps, which lead to the same conclusion that is given herein (see the Supporting Information for details).

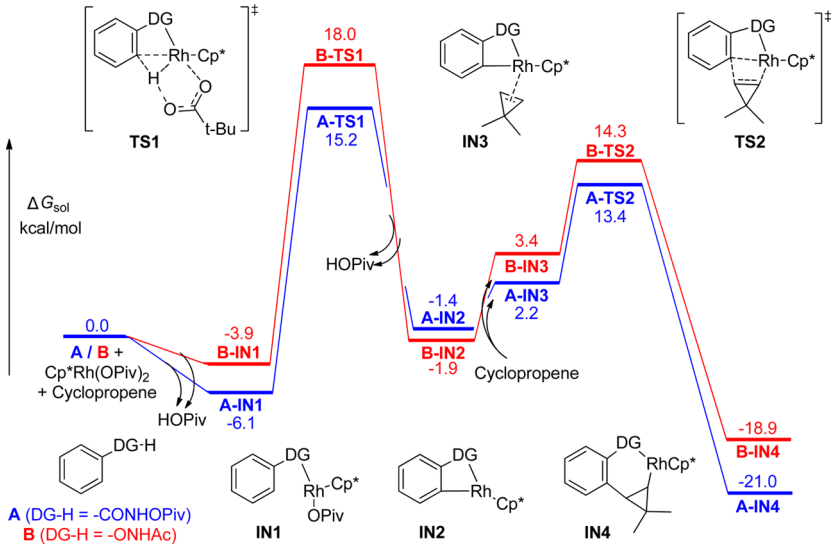


Figure 1. Potential energy surfaces for C−H activation/olefin insertion processes of **A** and **B**.

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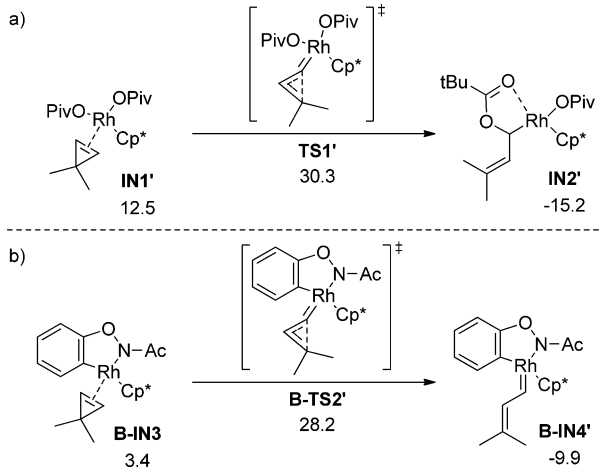
RESULTS AND DISCUSSION

Energetic Profiles for C−H Activation/Cyclopropene Insertion Steps. Figure 1 shows that the formation of **IN1** by N−H deprotonation is slightly exergonic and the following C−H activation occurs via a CMD process (**TS1**) with activation free energies of ∼22.0 kcal/mol for both **A** and **B**. Upon the formation of rhodacycle intermediate **IN2**, the incorporation of cyclopropene first forms π complex **IN3** endergonically, and then the migratory insertion occurs via **TS2**. The energy of this step is lower than that of the C−H activation step, and this step generates ring-expanded rhodacycle **IN4** exergonically. Accordingly, the different directing groups in **A** and **B** have an only marginal influence on the initial steps. Figure 1 shows **TS1** has the highest energies, and the generation of **IN4** is exergonic by ∼20 kcal/mol. In fact, the activation energies for further steps are much lower than the C−H activation step, suggesting the C−H activation is the rate-limiting step of the whole transformation. This is in good agreement with the KIE study by Wang et al.[7] As the detailed mechanism for sequential C−H activation/olefin insertion processes has been previously discussed,[9,10] the work presented here will focus on how the reaction pathways are controlled by the internal oxidants in further transformations from rhodacycle **IN4**.

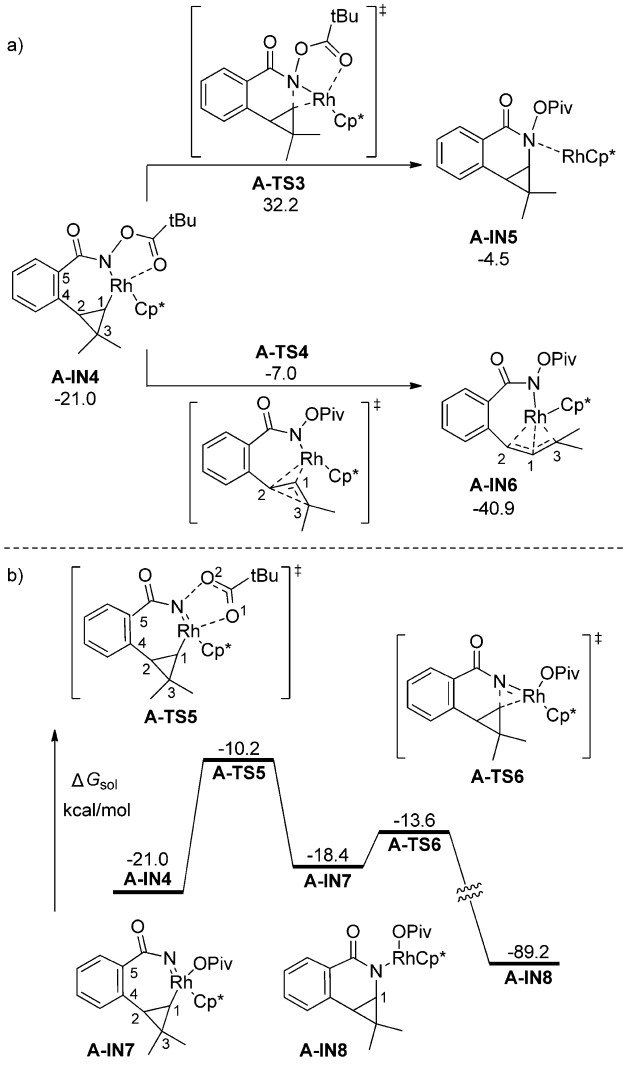
Energies for Rh(III)-Catalyzed Opening of Cyclopropene. As mentioned in the Introduction, the opening of cyclopropene could be possible when the C=C bond is electrophilically activated by Rh(III).[7,12] Results in Scheme 2a showed that the formation of π complex **IN1′** from cyclopropene and Cp*Rh(OPiv)$_2$ is endergonic by 12.5 kcal/mol, and the C−C bond cleavage via **TS1′** requires a total barrier of 30.3 kcal/mol. Instead of forming a carbenoid species, **TS1′** leads to **IN2′** exergonically with the pivalate group being bonded with the α-carbon. Thus, the Cp*Rh(OPiv)$_2$-catalyzed direct ring opening of cyclopropene is kinetically unfavorable compared with the Cp*Rh(OPiv)$_2$-catalyzed C−H bond activation of **A** or **B** (Figure 1). The opening of the cyclopropene after the C−H activation was also investigated. For example, from **B-IN3**, the energy for the ring opening of cyclopropene via **B-TS2′** is 24.8 kcal/mol (Scheme 2b), being much higher than that of the migratory insertion via **B-TS2**. Similar results were obtained for the reaction of **A-IN3** as given in the Supporting Information. Thus, the possible involvement of Rh-carbenoid species was ruled out, and the generation of **IN4** from the pathway showing in Figure 1 is confirmed as the major reaction channel.

Scheme 2. Energies for Rh(III)-Catalyzed Ring Opening of Cyclopropene



Formation of Tricyclic Lactam from A-IN4. Theoretically, the reductive elimination from **A-IN4** could give rise to **A-IN5** with retention of the three-membered ring, or the β-carbon elimination may lead to a ring-expanded intermediate **A-IN6** (Scheme 3a). The calculated energies indicate that the formation of **A-IN5** via **A-TS3** [N−C1, 1.77 Å (see geometries in Figure 2)] is unfavorable both kinetically and thermodynamically because of the difficult reductive elimination from the Rh(III) intermediate, as has been uncovered in other systems.[9,10] Instead, the β-carbon elimination via **A-TS4** requires a barrier of only 14.0 kcal/mol, leading irreversibly to **A-IN6** by opening of the cyclopropane moiety in **A-IN4**. In **A-TS4**, the C2−C3 bond (C2−C3, 2.01 Å) is breaking while the Rh(III) moiety is associated with C1−C2 (Rh−C1, 2.02 Å; Rh−C2, 2.12 Å), and the allyl moiety in **A-IN6** is delocalized and coordinated to the Rh center via the η^3 binding mode.

Scheme 3. Energies for Possible Transformations of A-IN4



While the predictions in Scheme 3a are not consistent with the experimental observations, calculations of the possible formation of a Rh(V)-nitrenoid from **A-IN4** were performed (Scheme 3b). Accordingly, the pivalate migration occurs via **A-**

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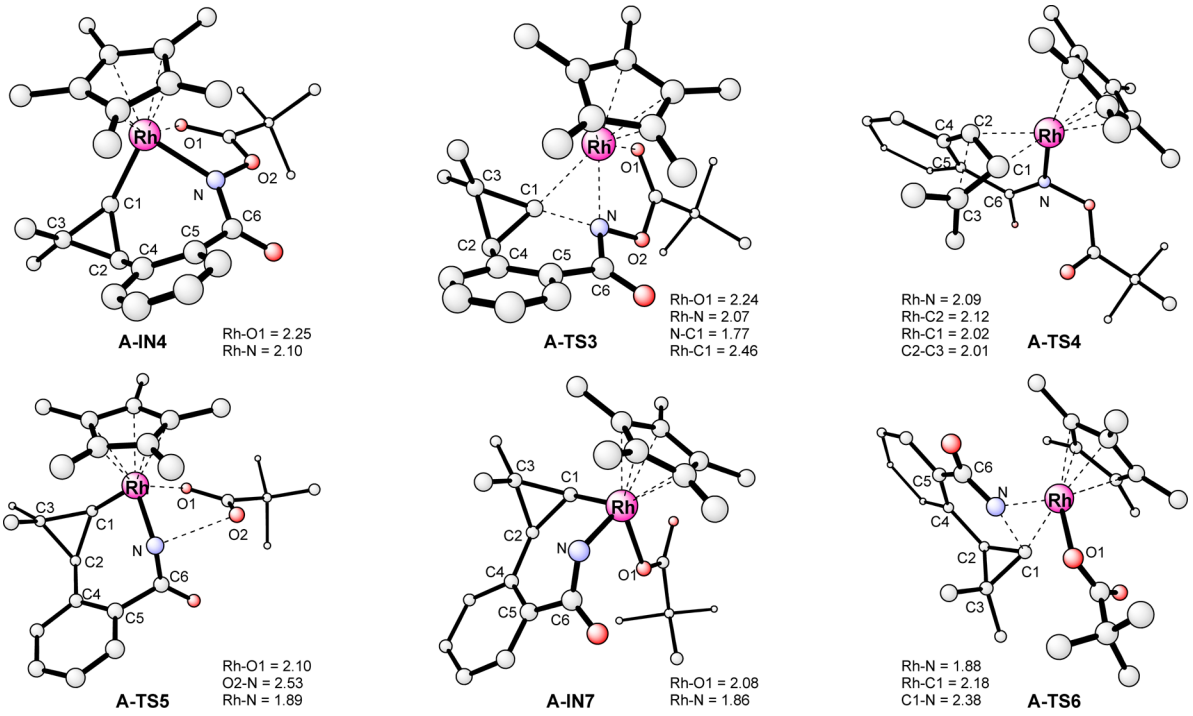


Figure 2. Geometries for key stationary points in reactions of **A**. All hydrogen atoms have been omitted for the sake of clarity. Selected distances are given in angstroms.

TS5 (O2−N, 2.53 Å; Rh−N, 1.89 Å) requires a barrier of 10.8 kcal/mol, generating the Rh(V)-nitrenoid **A-IN7** (Rh−N, 1.86 Å) slightly endergonically. From **A-IN7**, C−N bond formation occurs readily via **A-TS6** (C1−N, 2.38 Å) with a barrier of only 4.8 kcal/mol, forming **A-IN8** highly exergonically. The catalytic cycle will be finished by a further protonation step from **A-IN8**. Thus, the facile pivalate migration (via **A-TS5**) is 3.2 kcal/mol more kinetically favorable than the *β*-carbon elimination (via **A-TS4**), explaining how the C−N bond was formed to give rise to the lactam product and why the cyclopropane moiety was retained in this system.

Possible Reaction Channels from B-IN4. Possibly, tricyclic intermediate **B-IN4** may undergo reductive elimination reaction to form Rh(I) intermediate **B-IN5** containing a cyclopropane moiety. However, transition state **B-TS3** is 59.0 kcal/mol above **B-IN4**, blocking this possibility as a productive pathway (Scheme 4). This is consistent with the experiments in which no heterocycle product containing both O and N atoms was observed.[14m,n,7,16]

Following our previous studies of the generation of Rh(V) intermediates by pivalate migration for efficient C−N bond formation in C−H activation/cyclization of benzamide derivatives,[9,10] we wondered if a similar Rh(V) species is also involved in the Rh(III)-catalyzed C−H activation reactions of *N*-phenoxyacetamide. As the O−N bond is an internal oxidant, migration of the N−Ac moiety by O−N bond cleavage oxidizes the Rh(III) center in **B-IN4** to a Rh(V)-nitrenoid in **B-IN6**. As shown in Figure 3, this process is possible with a barrier of 20.8

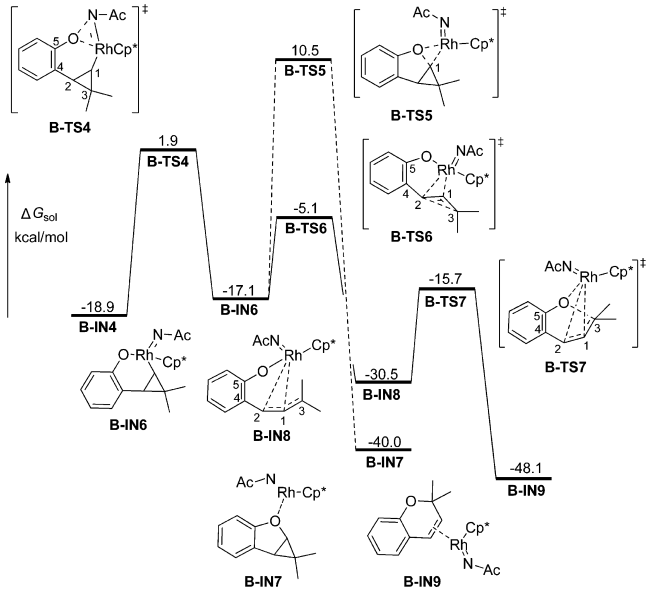
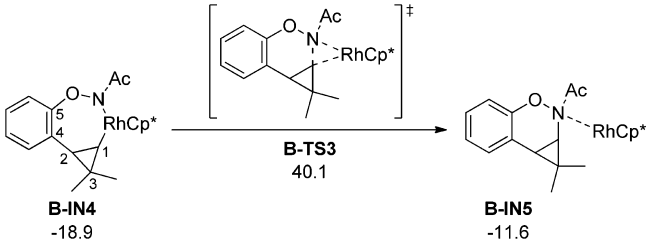


Figure 3. Formation of Rh(V)-nitrenoid from **B-IN4** and further transformations.

Scheme 4. Possible Reductive Elimination from B-IN4



kcal/mol via **B-TS4** [Rh−O, 2.19 Å; Rh−N, 1.94 Å; O−N, 2.20 Å (Figure 4)], and **B-IN6** (Rh−O, 2.04 Å; Rh−N, 1.85 Å) is only slightly unstable relative to **B-IN4**. From **B-IN6**, the possible reductive elimination for C−O bond formation was calculated and showed that **B-TS5** is 27.6 kcal/mol above **B-IN6**, indicating the retention of the three-membered ring and formation of a tricylic product is relatively difficult. This is

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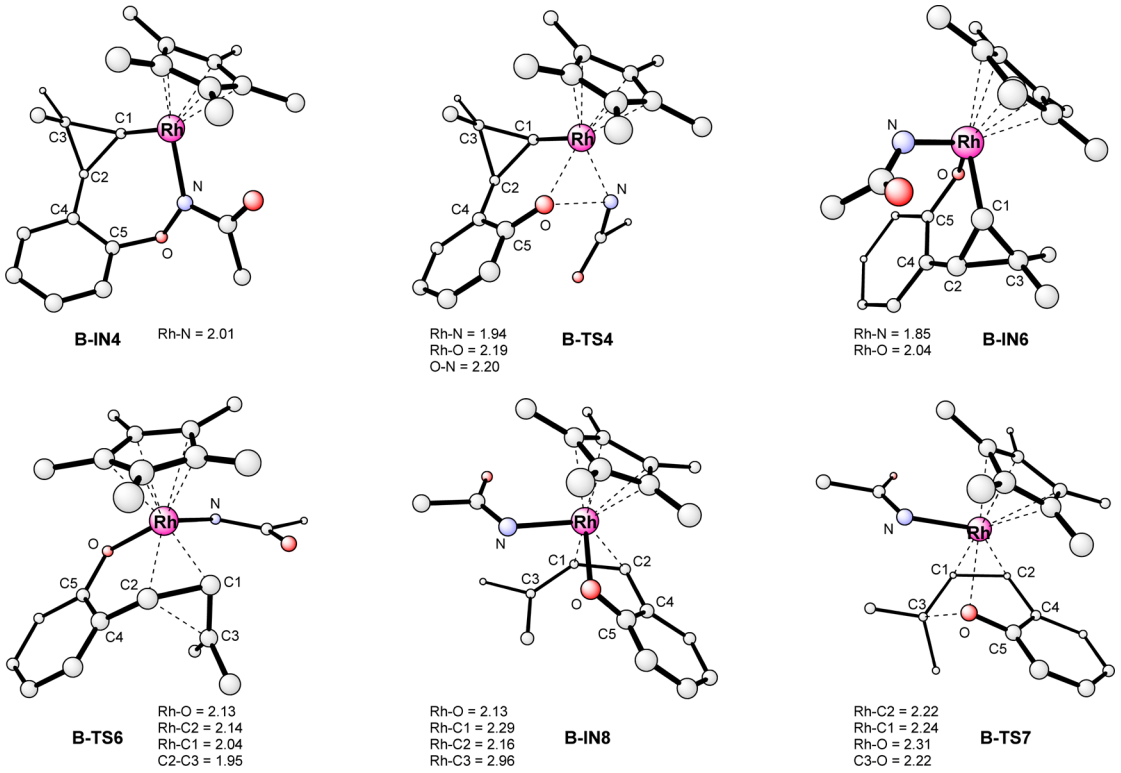

Figure 4. Geometries for key stationary points in reactions of **B** in Figure 3. All hydrogen atoms have been omitted for the sake of clarity. Selected distances are in angstroms.

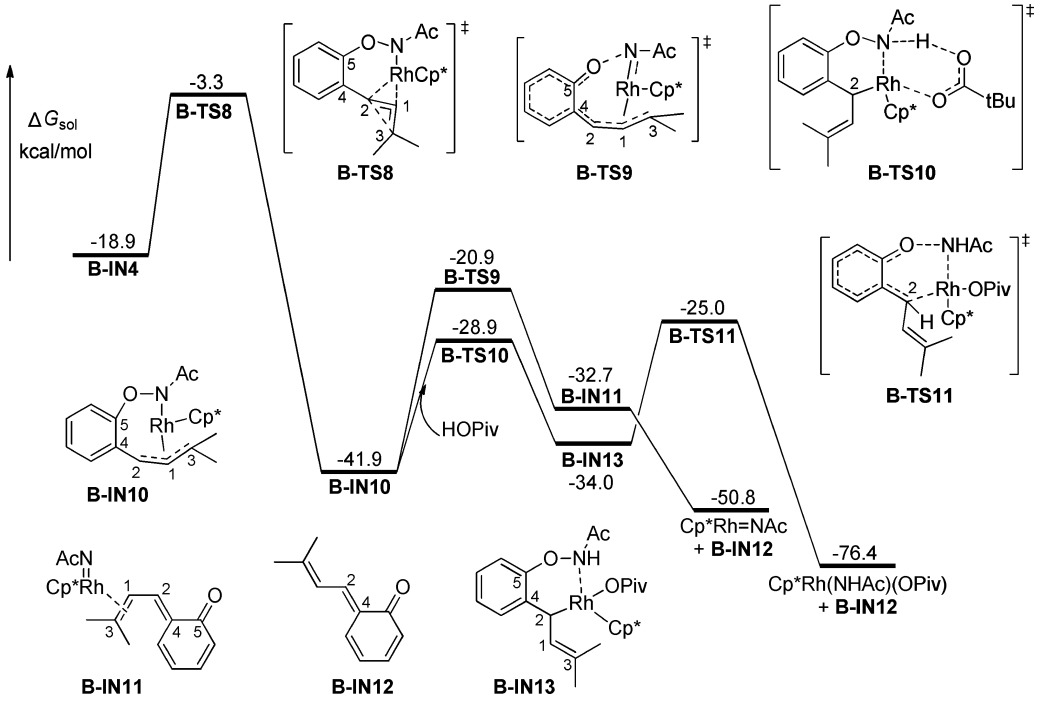

Figure 5. Potential energy surface for the sequential β-C elimination/O−N bond cleavage process from **B-IN4**.

different from the reactivity of **A-IN7** in which the nitrenoid moiety is involved in the reductive elimination for C−N bond formation (Scheme 3b). Alternatively, ring opening of the cyclopropane moiety via β-carbon elimination (via **B-TS6**) requires a barrier of only 12.0 kcal/mol. The geometry of **B-TS6** indicates that the breaking C2−C3 bond is at a distance of 1.95 Å and the Rh−C1 and Rh−C2 distances are 2.04 and 2.14 Å (Figure 4), respectively, being quite similar to the structure of **A-TS4** (Figure 2). Instead of the formation of the expected η^3-coordinated Rh-allyl species, the geometry of **B-IN8** indicates that the Rh atom has interactions with C1 and C2 (Rh−C1, 2.29 Å; Rh−C2, 2.16 Å) that are much stronger than those with C3 (Rh−C3, 2.96 Å), probably because of the steric effect between the nitrenoid moiety and the methyl groups at C3. In

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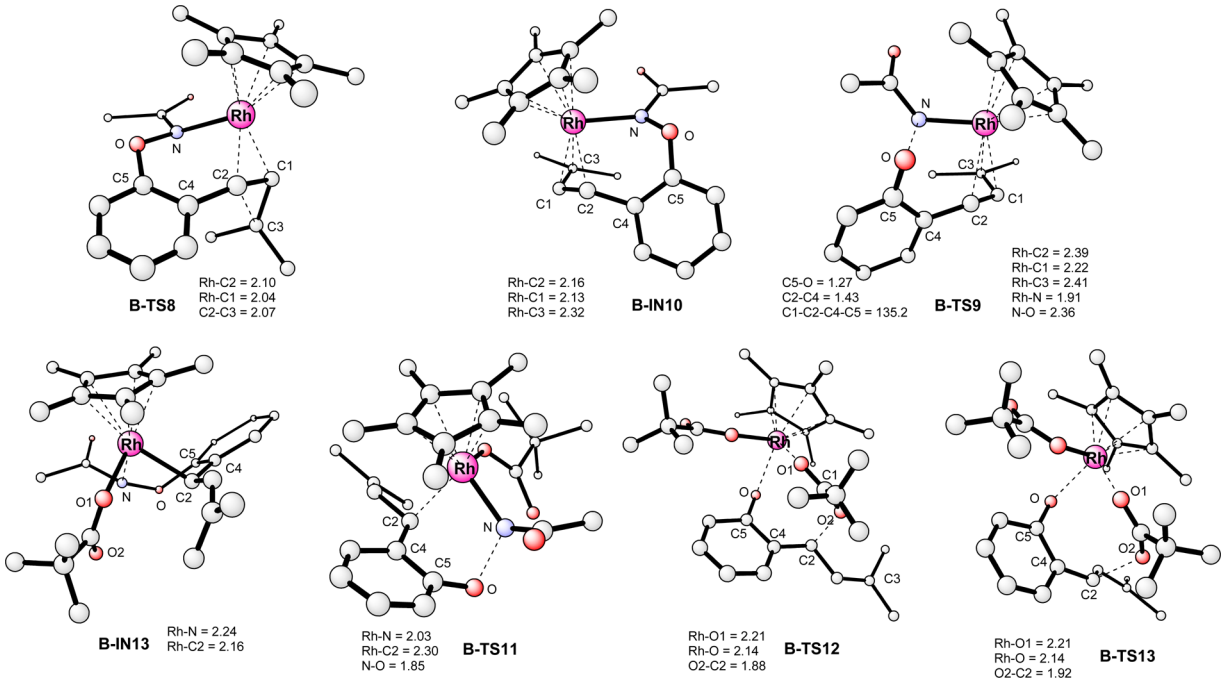

Figure 6. Geometries for key stationary points in the *β*-C elimination, dearomatization, and C2═C4 bond rotation processes from **B-IN4**. All hydrogen atoms have been omitted for the sake of clarity. Selected distances are in angstroms.

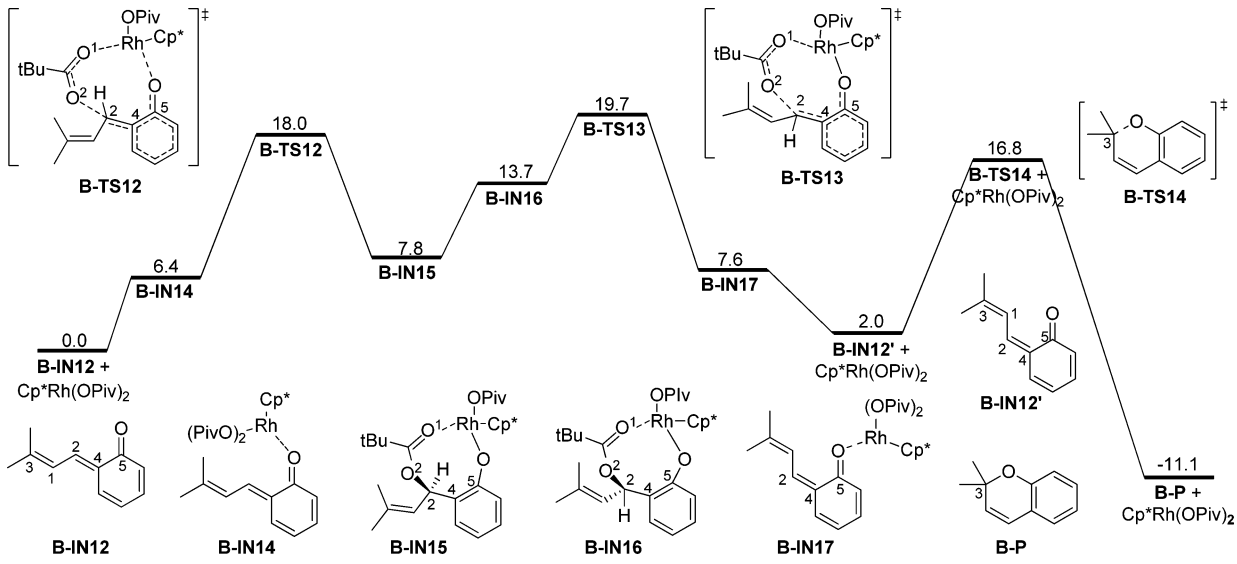

Figure 7. Potential energy surface for the C2═C4 bond rotation and C−O bond formation processes.

the following step, C3−O bond formation is facile with a barrier of 14.8 kcal/mol via **B-TS7**. In this transition state, the forming C3−O distance is 2.22 Å while both Rh−C2 and Rh−O distances are slightly prolonged versus those in **B-IN8**, corresponding to the reductive elimination of this Rh(V)-nitrenoid intermediate. Finally, the formation of 2*H*-chromene product and regeneration of Cp*Rh(OPiv)$_2$ catalyst will be easy by reaction of intermediate **B-IN9** with HOPiv formed in the C−H activation process. Thus, upon generation of Rh(V)-nitrenoid **B-IN6** by first cleavage of the O−N bond via **B-TS4**, the following *β*-carbon elimination/C3−O bond formation will give rise to the observed product irreversibly (Figure 3).

Although the Rh(III)/Rh(V) mechanism described above looks quite reasonable for 2*H*-chromene formation, the opening of the three-membered ring prior to O−N bond cleavage from **B-IN4** should be evaluated.[11] Indeed, the energy profile in Figure 5 shows that the *β*-carbon elimination via **B-TS8** is 5.2 kcal/mol more favorable kinetically than the Rh(V)-nitrenoid formation via **B-TS4** (Figure 3), and the formation of **B-IN10** is irreversible as the energies of the following transition states are much lower than that of **B-TS8**. The structures in Figure 6 show that in **B-TS8** the Rh atom is coordinated by C1 and C2 (Rh−C1, 2.04 Å; Rh−C2, 2.10) while the C2−C3 (2.07 Å) bond is breaking, and the allyl group in **B-IN10** is delocalized (Rh−C1, 2.13 Å; Rh−C2, 2.16 Å; Rh−C3, 2.32 Å). From **B-IN10**, it was envisioned that cleavage of the O−N bond to generate a phenoxide should facilitate C3−O bond formation that was required in the 2*H*-chromene product. Instead of forming another Rh(V) species with formal insertion of the Rh(III) into the O−NAc moiety, O−N bond cleavage

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transition state **B-TS9** (N−O, 2.36 Å) leads unexpectedly to a dearomatized species **B-IN11**, in which the Rh(III)-nitrenoid moiety is coordinated to the C1=C3 bond. Cyclohexa-2,4-dienone **B-IN12** and nitrenoid Cp*Rh=NAc are generated favorably by dissociation of **B-IN11**. Interestingly, the newly formed double bond defined by C2 and C4 in both **B-IN11** and **B-IN12** adopts the *E* configuration. In fact, only the *E* isomer is afforded from the O−N bond cleavage via **B-TS9**, in which the dearomatization of the phenoxy moiety (C5−O, 1.27 Å) and the *E* configuration of the forming C2=C4 bond [C2−C4, 1.43 Å; C1−C2−C4−C5, 135.2° (dihedral angle)] have already been defined, and the energy of the TS leading to the *Z* isomer is 1.5 kcal/mol higher than that of **B-TS9**. The stereoselectivity in this step could be attributed to steric factors. While the mechanism for generation of 2*H*-chromene from **B-IN12** is still unknown, a more favorable pathway leading to **B-IN12** was found when one molecule of HOPiv was involved.[24] Thus, protonation of the N atom in **B-IN10** via **B-TS10** requires a barrier of 13.0 kcal/mol, forming the η^1-allyl Rh(III) intermediate **B-IN13** (Rh−C2, 2.16 Å) endergonically. In the next step, O−N bond cleavage occurs via **B-TS11** (N−O, 1.85 Å), which is 3.9 kcal/mol higher in energy than **B-TS10** and leads to **B-IN12** and Cp*Rh(NHAc)(OPiv) exergonically. Hence, the overall barrier for generating **B-IN12** by first protonation of **B-IN10** is 16.9 kcal/mol, being 4.1 kcal/mol lower than that of O−N bond cleavage via **B-TS9**.[25]

Thus, Figure 5 shows that regardless of whether HOPiv is involved, dearomatized intermediate **B-IN12** could be formed irreversibly from **B-IN4**. To realize C−O bond formation, *E*/*Z* isomerization of **B-IN12** is required. As the direct rotation of the C2=C4 bond is difficult under normal conditions, we found the formation of stereoisomer **B-IN12′** could be facilitated by the Cp*Rh(OPiv)$_2$ catalyst, which could be formed easily by reaction of the previously formed Cp*Rh(NHAc)(OPiv) (or Cp*Rh=NAc) with HPOiv,[26] and cooperative catalysis by metal and ligand was disclosed for facile double bond rotation (Figure 7). In this process, the first coordination of Cp*Rh(OPiv)$_2$ to the carbonyl oxygen of **B-IN12** to form σ-complex **B-IN14** is endergonic by 6.4 kcal/mol, and then via **B-TS12** [O2−C2, 1.88 Å (Figure 6)], Michael addition of one of the pivalate anions to C2 requires a barrier of 11.6 kcal/mol from **B-IN14** and generates phenoxide **B-IN15** slightly endergonically. Although **B-IN15** adopts a cyclic geometry with the Rh atom being coordinated by O1, rotation of the C2−C4 single bond could be achieved by first dissociation of the Rh−O1 interaction, and stereoisomer **B-IN16** is expected before the elimination via **B-TS13** (O2−C2, 1.92 Å), leading to complex **B-IN17**. Thus, *Z* isomer **B-IN12′** could be formed with an overall barrier of 19.7 kcal/mol from **B-IN12**. Finally, the electrocyclization of the conjugated 6π system occurs easily via **B-TS14** with a barrier of 14.8 kcal/mol, forming the experimentally observed 2*H*-chromene product **B−P**. Thus, generation of **B-IN12** and the following double bond rotation are key steps uncovered by theoretical calculations; however, it is not surprising that a dearomatized product (**B-IN12**) was not observed in experiments, because it is formed after the rate-determining step and its consumption is much faster than its formation.

CONCLUSIONS

In summary, the divergence between Cp*Rh(III)-catalyzed C−H activation reactions of *N*-pivaloxybenzamide and *N*-phenoxyacetamide with cyclopropene was rationalized on the basis of DFT calculations. Different reactivities were disclosed upon the formation of seven-membered rhodacycles from insertion of cyclopropene into the Rh−C bond. For the *N*-pivaloxy-containing intermediate, the sequential pivalate migration and C−O bond formation steps are more facile than the β-carbon elimination for opening of the cyclopropane moiety, suggesting the retention of the three-membered ring in the lactam product should be attributed to the facile formation and reductive elimination of the Rh(V)-nitrenoid intermediate. On the other hand, β-carbon elimination from the seven-membered rhodacycle intermediate in reactions of *N*-phenoxyacetamide is the most kinetically favorable among possible channels and leads to a dearomatized (*E*)-6-alkenylcyclohexa-2,4-dienone intermediate by followed O−N bond cleavage. The *E*/*Z* isomerization of this intermediate is required for the final cyclization to 2*H*-chromene and is realized by the metal−ligand cooperative catalysis with Rh(III) carboxylate. These results provided a detailed mechanistic understanding of the interesting experimental observations of Wang et al.[7] In addition, the Rh(V)-nitrenoid species was predicted to be kinetically less favorable in Rh(III)-catalyzed reactions of *N*-phenoxyacetamide; however, this mechanism should have implications in other systems where β-carbon elimination is not involved.[14m,n,16]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01201.

Other possible pathways, calculated energies, and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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(24) The possible pathways by reactions of HOPiv with other intermediates were also studied, and higher energies were obtained. See the Supporting Information for details.
(25) According to the original mechanism of Wang et al.,[7] possible cleavage of the N−O bond by protonation of the N atom in **B-IN13** with HOPiv was calculated; however, much higher activation barriers (>50 kcal/mol) are required.[24]
(26) Energies for regeneration of Cp*Rh(OPiv)$_2$ are given in the Supporting Information.

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