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Computational Revisit to the β-Carbon Elimination Step in Rh(III)-Catalyzed C−H Activation/Cycloaddition Reactions of *N*-Phenoxyacetamide and Cyclopropenes

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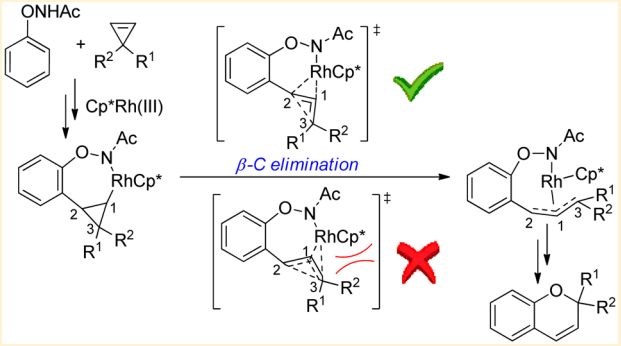
Supporting Information

ABSTRACT: This computational study uncovered the origin of the contradicting results in two recent DFT studies of the Rh(III)-catalyzed C−H activation/cycloaddition reactions between *N*-phenoxyacetamide and cyclopropenes. It was found that the β-carbon elimination of the tricyclic intermediate occurs very faciely via a conformer in which the opening of the three-membered ring is trans to the Cp* ligand so that the steric repulsion between the two moieties is avoided. Thus, the conclusions of our previous study were reconfirmed.



With the enormous growth of computer speed and the development of accurate theoretical methods, in silico study has been shown to play increasingly important roles in every aspect of chemical research, providing an important supplement to experimental chemistry with added insights or uncovering as yet unknown chemical outcomes. Notable progress has been achieved in the mechanistic understanding of organic reaction and catalysis by computational methods in recent decades[1,2] in which a comprehensive comparison of well-depicted potential energy surface of possible reaction channels is generally required for a full justification of the mechanism. To this end, carefully chosen computational methods and model reactions are essential to obtain reliable structures and energies for analysis.[3] However, due to the inherent complexity in mechanisms of transition-metal-catalyzed organic transformations,[4] sometimes the researcher's experience in mechanistic hypothesis and technical ability become more crucial for accurate and reliable predictions, which we would like to emphasize in this report by a computational revisit to the mechanism of the title reaction.

The Rh(III)-catalyzed C−H activation/cycloaddition reactions of *N*-phenoxyacetamide (**1**) and cyclopropenes (**2**) leading to 2*H*-chromene (**3**) was originally reported by the Wang group (Scheme 1a).[5] This methodology is featured with external oxidant-free reaction conditions, facile ring-opening of cyclopropene, and unique chemoselectivity as compared with the C−H activation of *O*-pivaloyl benzhydroxamine (**1′**), making it interesting from both synthetic and mechanistic aspects.[6] To understand the mechanism of this transformation, we previously carried out DFT calculations to answer how the O-NHAc moiety in **1** works as an internal oxidant and why different reactivity of cyclopropenes was observed in reactions with **1** and **1′**.[7] Our study suggested that the reaction for *N*-phenoxyacetamide (**1**) is initiated by the formation of 5-membered rhodacycle **IN1** (Scheme 1b). After the insertion of cyclopropene (simplified as **2a**) into the Rh−C bond, tricyclic intermediate **IN2** is involved as a key intermediate for further transformations. Computational results indicated that the opening of the 3-membered ring by β-carbon elimination (**aTS1**, 15.7 kcal/mol) to form the Rh(III) η^3-allylic complex **aIN3** is more favorable than the N−O cleavage (**aTS2**, 20.8 kcal/mol) to form Rh(V) species **aIN4**,[8] and the following steps from both intermediates are irreversible.[7] Further transformations from **aIN3** were also rationalized, in which an unexpected dearomatization intermediate **aIN5** was suggested and its isomerization to **aIN6** could be facilitated by the Rh(III) catalyzed-double bond rotation. Finally, the 2*H*-chromene product is formed by a 6π-electrocyclization.

After the publication of our results,[7,8] another computational work was reported by Li et al.,[9] in which the same reaction of *N*-phenoxyacetamide by the Wang group was studied with similar procedures. Interestingly, a totally different pathway was suggested by the later study (Scheme 1b). A quick comparison found that both studies used the M06 functional and similar basis sets,[10] but in the later work a more complicated cyclopropene derivative, the 3-(2′-phenyl)ethyl-3-methylcyclopropene (**2b**), was used as a model reactant. To our surprise, however, the β-carbon elimination from **bIN2** requires a very high activation energy of 49.0 kcal/mol (**bTS1**), being 25.6 kcal/mol higher than the N−O cleavage mechanism (**bTS2**).

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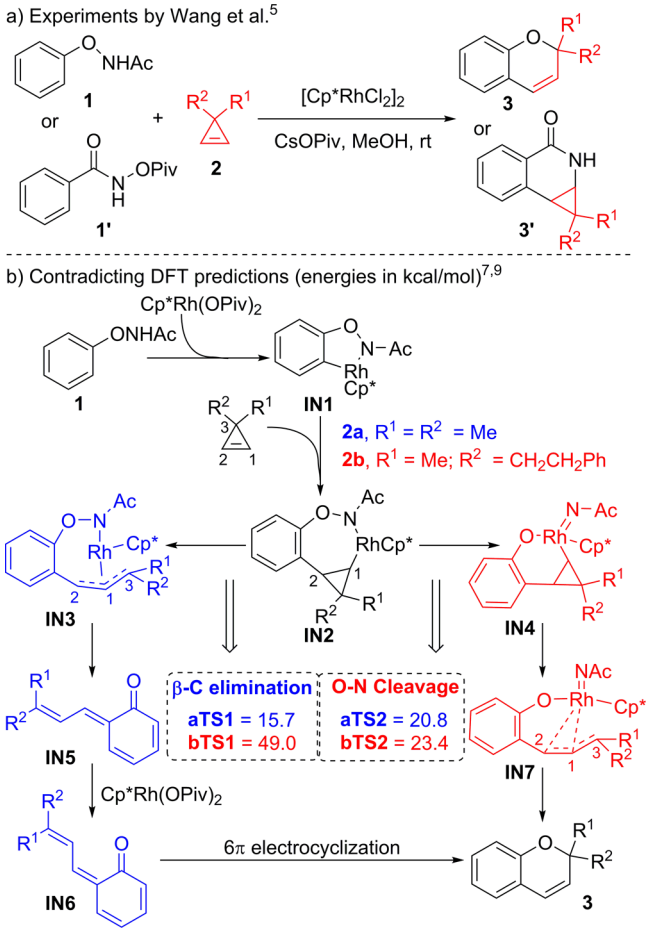
Scheme 1. Previous Experimental and Theoretical Results



Accordingly, a Rh(III)/Rh(V) catalytic cycle[8] was thought to be the favorable pathway and was highlighted in Li's report.[9]

The contradicting conclusions from the above computational studies prompted us to reinvestigate the mechanism of the Rh(III)-catalyzed reaction between *N*-phenoxyacetamide and cyclopropenes, and herein we uncovered the details of the *β*-carbon elimination and reconfirmed the mechanism of our previous study.[11]

To uncover the reason for the dramatic difference in activation barriers of the *β*-carbon eliminations in previous studies, the computed energies in reaction of **1** with **2a** were first presented. According to Figure 1, **aIN2** is a key intermediate in the reaction between **1** and **2a**,[7] from which the *β*-carbon elimination may occur. Via calculations at the (SMD)M06/6-311+G(d,p)-SDD//M06/6-31G(d)-LanL2DZ ((SMD)M06/BS2//M06/BS1) level[12] by running Gaussian 09,[13] two conformational isomers for the TS of this process, namely **aTS1** (15.7 kcal/mol) and **aTS1′** (25.3 kcal/mol), were located. The major difference between these two structures is that the Rh atom is coordinated by C1 and C2 in **aTS1** and the opening of the cyclopropyl moiety occurs trans to the Cp* ligand, while in **aTS1′** the Rh center is coordinated by C1 and C3. Hence, the higher energy of the latter conformer could be attributed to the steric repulsion between the substituents on C3 and the Cp* ligand.

Next, the key TS and intermediates in reaction of **1** and **2b** were analyzed to see if there are dramatic differences in energies and geometries compared with those given in Figure 1.

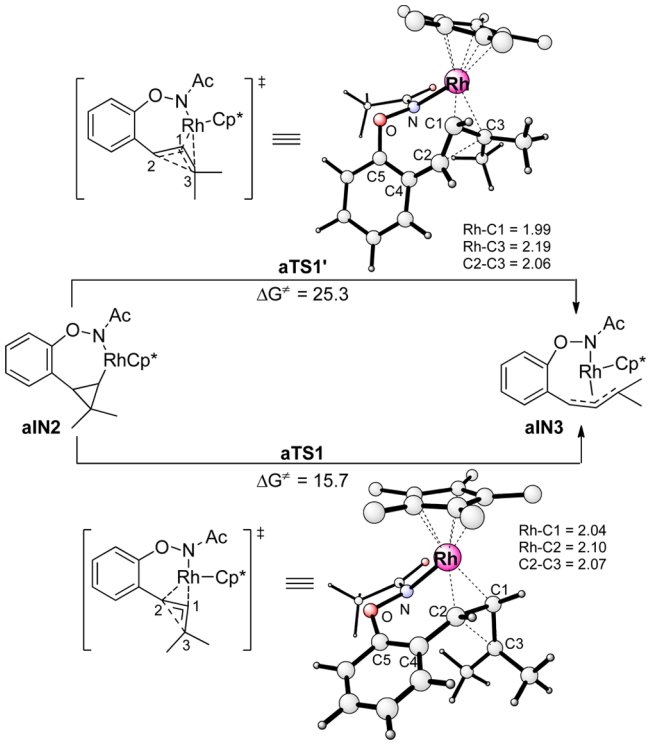


Figure 1. Possible *β*-carbon eliminations from aIN2. In all geometries, the hydrogen atoms on the Cp* ligand are omitted for the sake of clarity. Energies and selected distances are given in kcal/mol and angstroms, respectively.

To repeat the results of Li et al.,[9] the structures for **bIN2** and **bTS1** in their report (originally labeled as **H′** and $\mathbf{TS_{H'\text{-}G'}}$ in ref 9; generated from the Cartesian coordinates in their Supporting Information) were recalculated with our method, and an energy difference of 50.4 kcal/mol was predicted, consistent with the reported barrier of 49.0 kcal/mol (Figure 2).[9] However, it was quickly found that **bIN2′**, a conformational isomer of **bIN2**, is lower in energy by 1.8 kcal/mol with the benzyl moiety being away from the three-membered ring moiety (Figure 2a). In **bTS1**, the orientation of the benzyl group is the same as that in **bIN2**, and this TS is similar to **aTS1′** with the Rh being coordinated by C1 and C3, but why the reaction with a longer chain at C3 requires a much higher activation energy of over 50 kcal/mol is unknown. A closer examination found the orientation of the benzyl moiety in **bTS1** may increase its steric repulsion with the Cp* ligand (Figure 2b). In fact, by a simple rotation of the C3−C6 single bond, the relative energy for **bTS1′** could be lowered dramatically to 24.5 kcal/mol. This clearly confirms that the repulsive interaction between the Cp* and the substituents on C3 makes **bTS1** highly unfavorable. Thus, it is not surprising that Li et al.[9] reached a different conclusion because this highly unfavorable conformer was regarded as the TS for *β*-carbon elimination.[4g] As **aTS1** is the more favorable conformer in our model reaction (Figure 1),[7] a similar TS (**bTS1″**) was calculated by using the more complicated model system in Li's study, from which the opening of the cyclopropyl moiety actually requires a barrier of only 18.2 kcal/mol.

The above results show that the *β*-carbon elimination for opening of the three-membered ring could occur easily from the tricyclic intermediate and the use of a simplified cyclopropene derivative (**1a**) for modeling could reach this

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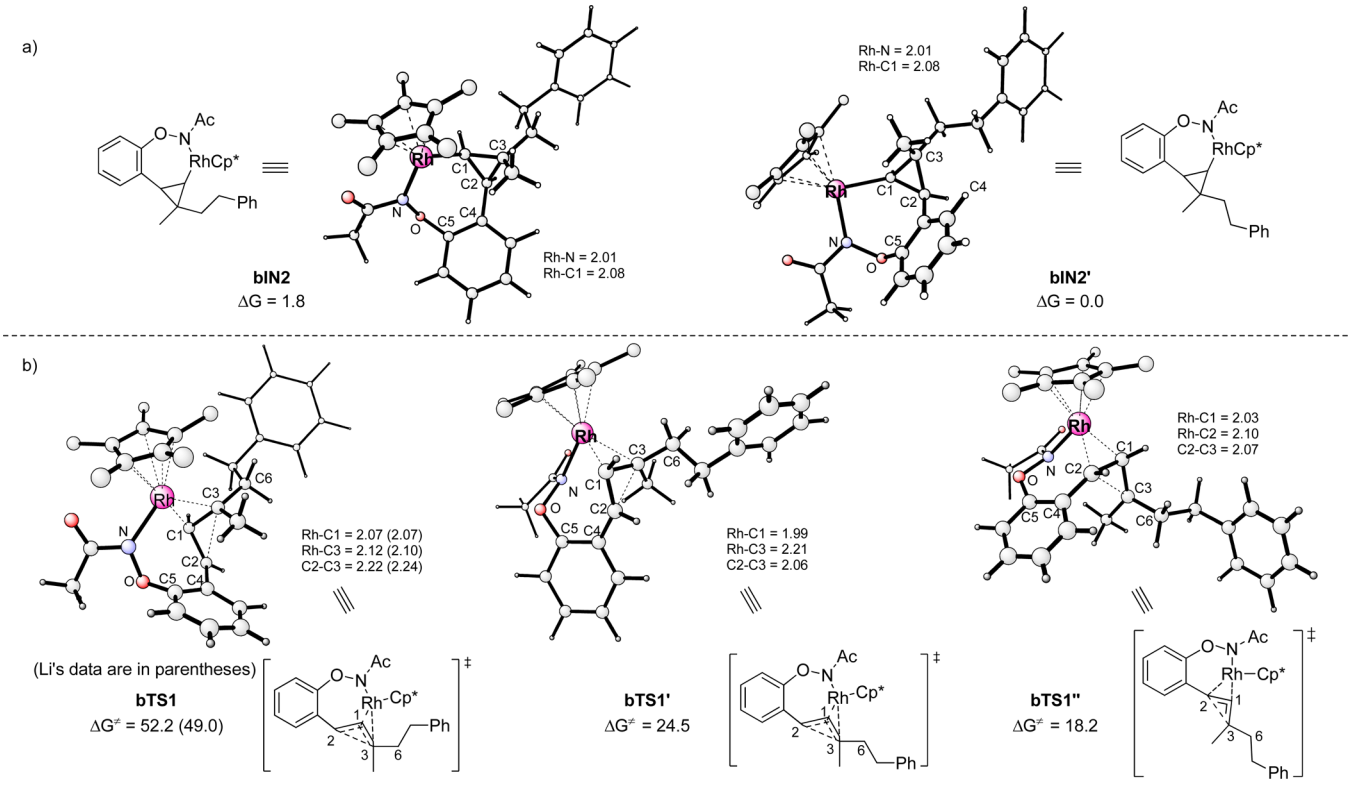
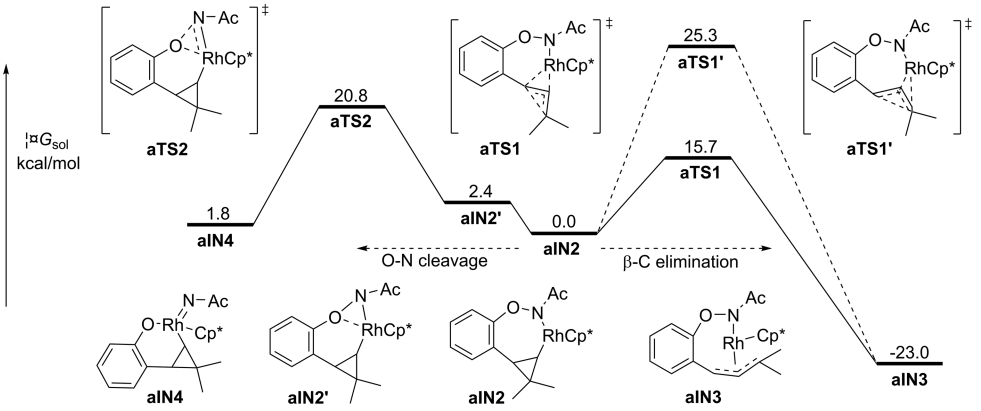


Figure 2. Possible β-carbon eliminations in reaction of **1** with **2b**. In all geometries, the hydrogen atoms on the Cp* ligand are omitted for the sake of clarity. Energies and selected distances are given in kcal/mol and angstroms, respectively.



Method	aTS1	aTS1'	aIN3	aTS2	aIN4
M1	16.5	23.9	-22.4	22.4	1.9
M2	15.4	23.4	-22.4	24.3	5.1
M3	19.0	26.5	-23.8	27.6	5.2
M4	19.6	25.4	-22.8	24.4	5.8
M5	19.0	24.5	-23.0	22.8	1.1
M6	17.5	24.9	-24.1	24.2	2.3
M7	13.8	19.9	-24.9	14.4	-9.1
M8	13.2	19.3	-26.3	13.3	-8.5
M9	15.8	24.9	-24.1	21.7	2.6
M10	17.2	23.4	-22.6	22.8	3.9

M1: (SMD)M06/BS2//M06/BS3;
M2: PCM)M06/BS1; **M3**: M06/BS1
M4: M06/BS4; **M5**: B3LYP/BS1;
M6: B3PW91/BS1; **M7**: BP86/BS1
M8: TPSSTPSS/BS1
M9: (SMD)M06/BS1//BP86/BS1
M10: (SMD)M06/BS1//TPSSTPSS/BS1

Figure 3. Free energy profile for different pathways from aIN2.[12]

conclusion more efficiently with smaller systems and reduced conformational freedom. Calculations confirmed that such simplification in the cyclopropene substrate does not lead to considerable differences in energies for the O−N bond cleavage mechanism, as such processes from **aIN2** and **bIN2′** require quite similar activation barriers of 20.8 (**aTS2**) and 20.9 kcal/mol (**bTS2**), respectively.

Accordingly, the calculated free energy profile at the (SMD)M06/BS2//M06/BS1 level for the key steps from **aIN2** suggested that the β-carbon elimination occurs more favorably via conformer **aTS1** (15.7 kcal/mol) than via **aTS1′** (25.3 kcal/mol), leading exergonically to Rh(III)−allyl intermediate **aIN3** (Figure 3). On the other hand, the N−O bond cleavage could occur from **aIN2′**, formed slightly endergonically by isomerization of **aIN2**, is unfavorable because the **aTS2** is 5.1 kcal/mol higher in energy than **aTS1** and the generated Rh(V) species **aIN4** is slightly less stable than **aIN2**. Based on previous results that indicate further transformations from **aIN3** via intermediacy of **IN5** and **IN6** (Scheme 1) are irreversible,[7,9] we could judge that no change of the oxidation state of the Rh(III) catalyst is required during the reaction.

To confirm if the calculated energy values are method-dependent, key stationary points from **aIN2** were calculated at different levels of theory and shown in the right part of Figure 3 (a full energy table is given in the Supporting Information).[12] When geometry optimizations were done at a higher level of M06/BS3 combined with solvation corrections at (SMD)M06/BS2 (**M1**), the reaction energies and activation barriers for generating **aIN3** and **aIN4** are almost the same as those given in the left part of Figure 3, indicating only marginal variation of the energy profile is observed with high-level calculations. Calculations at the (PCM)M06/BS1 level were done to test if

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the inclusion of solvation effects in geometry optimizations leads to different outcomes (**M2**); however, the **aTS2** (24.3 kcal/mol) becomes even more unfavorable than **aTS1** (15.4 kcal/mol). If no solvation correction is included, the gas-phase energies calculated by the M06 functional combined with a smaller basis set (M06/BS1, **M3**) are quite close to those calculated at a higher level of M06/BS4 (**M4**), and both calculations lead to the same conclusions as predicted by **M1** and **M2**. The preference of β-carbon elimination over N−O bond cleavage is also supported by the gas-phase calculations with other prevalent functionals such as B3LYP and B3PW91 (**M5** and **M6**). It should be noted that the gas-phase predictions at the BP86/BS1 and TPSSTPSS/BS1 levels lead to quite close free energies for **aTS1** and **aTS2** (**M7** and **M8**). These seem to suggest that both pathways are possible if they are irreversible; however, when the energies were corrected by single-point solvation calculations at the (SMD)M06/BS1 level, **aTS2** became unfavorable and consistent results were obtained (**M9** and **M10**). In addition, all calculations suggested that **aTS1′** is obviously higher in energy than **aTS1** and the ring-opening intermediate **aIN3** is thermodynamically favored by over 22.0 kcal/mol.

CONCLUSION

In summary, the mechanism of the Cp*Rh(III)-catalyzed C−H activation/cyclization reaction between *N*-phenoxyacetamide and cyclopropenes was revisited computationally. On the basis of the contradicting results of two recent DFT studies,[7,9] the reactivity of the tricyclic intermediate was studied to find that the β-carbon elimination is the most favorable when the opening of the three-membered ring occurs trans to the Cp* ligand of the Rh center to avoid steric repulsion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00003.

Computational details, IRC plots for **aTS1** and **aTS1′**, and calculated energies and Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Computational details are given in the Supporting Information. BS1−4 in Figure 3 are 6-31G(d)/LanL2dz, 6-311+G(d,p)/SDD, 6-31+G(d)/SDD, and 6-31G(d)/LanL2dz-1d+1f, respectively.

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