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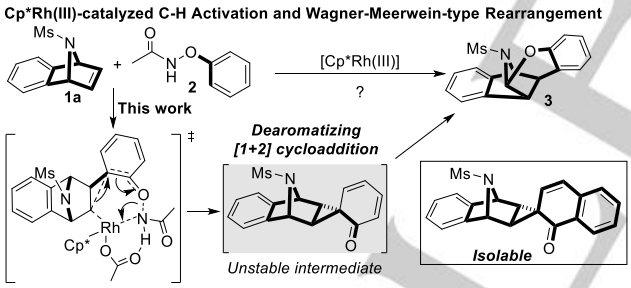
Unprecedented Dearomatized Spirocyclopropane in a Sequential Rh(III)-catalyzed C–H Activation and Rearrangement Reaction

Xiaoming Wang,[†§] Yingzi Li,[‡§] Tobias Knecht,[†] Constantin G. Daniliuc,[†] K. N. Houk,[*‡] Frank Glorius[*†]

Abstract: An unprecedented dearomatized spirocyclopropane intermediate was discovered in a sequential Cp*Rh(III)-catalyzed C–H activation and Wagner–Meerwein-type rearrangement reaction. How the oxidative O–N bond is cleaved and the role of HOAc were uncovered in this study. Furthermore, a Cp*Rh(III)-catalyzed dearomatization reaction of *N*-(naphthalen-1-yloxy)acetamide with strained olefins was developed, affording a variety of spirocyclopropanes.

Rh(III)-catalyzed C–H activation is an attractive mode of catalysis for the synthesis of small molecules.[1] The use of oxidizing directing groups (DG^{ox}), which function as both the directing group and the internal oxidant, has become a powerful strategy in this area.[2] While the concept of oxidizing directing groups has become more widely popular, it is crucial to understand their underlying mechanisms of action for the further development of novel catalysis on a rational basis. In our previous work, we coupled *N*-phenoxyacetamides with an internal oxidizing O–NHAc bond[3] and 7-azabenzonorbornadienes to deliver bridged polycyclic molecules via an unexpected Wagner–Meerwein-type rearrangement (Scheme 1).[4] This methodology provided an efficient way to construct the highly complex polycyclic products. However, the underlying causes driving force for the rearrangement and how the O–N bond is cleaved, remains unclear.



Scheme 1. The discovery of the dearomatized spirocyclopropane intermediate.

Herein, we report our new finding in the Cp*Rh(III)-catalyzed reaction of *N*-phenoxyacetamide with 7-azabenzonorbornadiene. An unconventional reactivity for Rh(III)-catalysis was revealed (Scheme 1). The *N*-phenoxyacetamide derivatives act as a formal one-carbon component in an unexpected [1 + 2] annulation giving an unprecedented dearomatized spirocyclopropane intermediate which undergoes further intramolecular rearrangement reaction. To the best of our knowledge, this is the first time that the coupling of a phenol-derived precursor and an olefin leads to a dearomatized spiro structure with a cyclopropane unit.[5,6] Both experimental and DFT studies suggest that protonation of an olefin-insertion intermediate by HOAc, followed by intramolecular attack, are the key steps for the formation of the dearomatized spirocyclopropane intermediate. Inspired by this finding, a Cp*Rh(III)-catalyzed dearomatization reaction of *N*-(naphthalen-1-yloxy)acetamide with strained olefins was successfully developed, affording a variety of spirocyclopropanes.

A stable cyclometalated Rh(III) complex **A** was synthesized upon treatment of the substrate **2** with $[RhCp^*Cl_2]_2$. Our first objective was to gain insight into the formation and the reactivity of the olefin-insertion intermediate **B** (Scheme 2). To our delight, the reaction of complex **A** with one equivalent of olefin **1a** at -40 °C afforded the expected intermediate **B** in 91% yield as determined by ^{1}H NMR.[7] However, this complex was consumed almost completely when the temperature was increased to room temperature and ~15% NMR yield of the complex **4** was detected.[8] No rearrangement product **3** was formed. During the formation of the Rh(III) complex **A**, HOAc is also formed. To probe the potential role of HOAc in this reaction, two equivalents of HOAc were added to the solution of intermediate **B** in NMR tube at -40 °C. To our surprise, the formation of a new species **5** was immediately observed at -40 °C and **B** was fully converted into this new species at -20 °C in 90% yield (Scheme 2). The spirocyclopropane structure of **5**, which was formed via the dearomatization of the phenol ring, was elucidated by 2D-NMR. This new species **5** was stable at 26 °C for ~30 min. Afterwards the final rearrangement product **3** was formed slowly. After 48 h, the product **3** was detected in 85% yield. These results illustrated that **B** must first react with HOAc to form the key intermediate **5**, which ultimately forms the final rearrangement product **3**. A catalytic reaction using $Cp^*Rh(OAc)_2 \cdot H_2O$ (2 mol%) as catalyst also shown the formation of **5** and the subsequent consumption of **5** to **3** in the NMR tube (For details, see the Supporting Information (SI)). Unfortunately, neither isolation of **5** or traps with further transformations failed, and only the final product **3** could be isolated. The investigation of the electronic effects on the stability of the spirocyclopropane intermediate suggested that both the electron-withdrawing group on the *N*-phenoxyacetamide and the electron-donating group on the olefin part could destabilize the intermediate and promote the further rearrangement (see SI).

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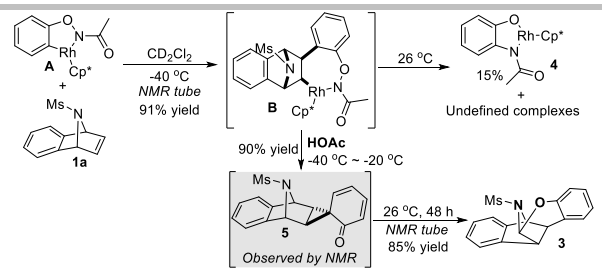
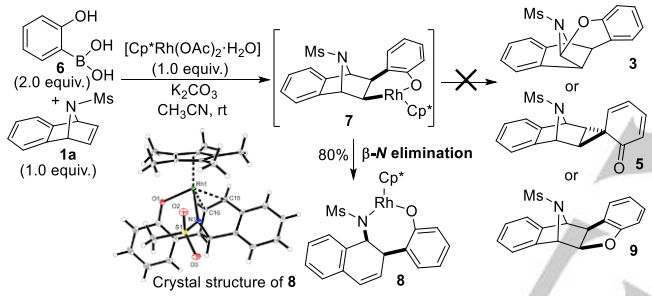


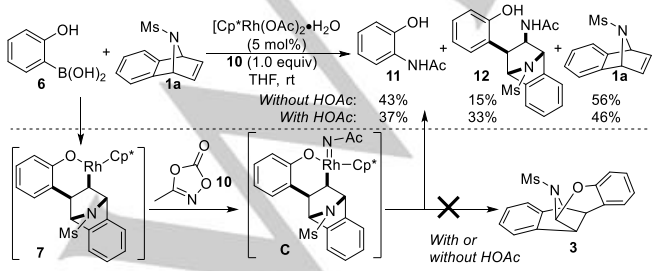
Scheme 2. The discovery of the formation of the dearomatized intermediate **5**.

To learn about the process for the formation of this key intermediate **5**, we investigated the reactions of (2-hydroxyphenyl)boronic acid **6** and the olefin **1a** with stoichiometric amounts of Cp*Rh(OAc)$_2$•H$_2$O (Scheme 3). A rhodium(III) complex **7** was proposed to be formed from the transmetalation of the arylboronic acid followed by the olefin-insertion. However, a new rhodium complex **8** was observed in 80% NMR yield which is formed by the β-*N* elimination of the complex **7**. The structure was confirmed by single-crystal X-ray diffraction. No rearrangement product **3**, dearomatized intermediate **5** or C–O bond reductive elimination product **9** was detected in this case, suggesting that the in-situ generated Rh(III) species **7** prefers to undergo the β-*N* elimination.[9,10]



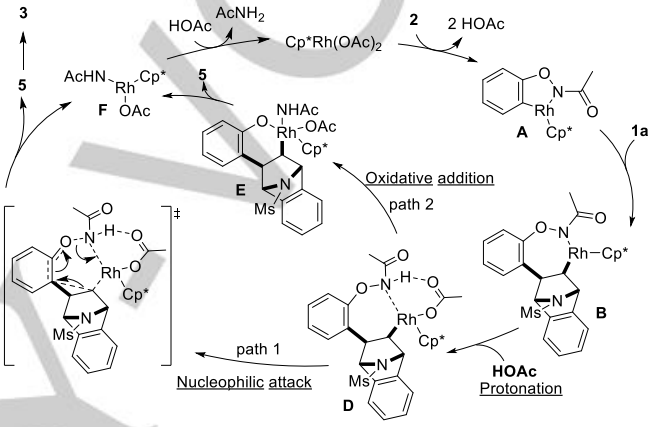
Scheme 3. The reactivity of the in-situ generated complex **7**.

To study the possibility of a Rh(V) pathway[11-13] involving the Rh(V) nitrenoid intermediate **C** (Scheme 4), we investigated the reactions of (2-hydroxyphenyl)boronic acid **6** and olefin **1a** with the amidation reagent **10**[13] using Cp*Rh(OAc)$_2$•H$_2$O as the catalyst. In the Cp*Rh(III)-catalyzed C–H amidation using **10**, a key Rh(V) nitrenoid intermediate was proposed by Chang.[12] As shown in Scheme 4, the reaction afforded the amidation product **11** in 43% NMR yield and the olefin carboamidation product **12** in 15% yield.[8] In the presence of HOAc, the reactions still gave similar results. These results indicate that intermediate **7** could react with **10** to form a Rh(V) nitrenoid intermediate **C** which can further give the amidation product **11** and **12**. These also suggest that the intermediate **5** is unlikely to be generated from a Rh(V) species.



Scheme 4. The investigation of the possible Rh(V) pathway.

DFT calculations (see SI for computational details) were also conducted to understand the reaction mechanism. On the basis of the experiments, two possible pathways have been proposed in Scheme 5. After C–H activation and the generation of rhodacycle **A**, olefin insertion forms the seven-membered rhodacycle **B**. The protonation of **B** by acetic acid to afford the intermediate **D** was proposed to be the next step because the dearomatized intermediate **5** is formed from the interaction of the intermediate **B** with HOAc according to the experiments. In pathway 1, intermediate **D** is proposed to undergo an intramolecular nucleophilic attack reaction to afford the spirocyclopropane product **5**. In pathway 2, the N–O bond cleavage in complex **D** by oxidative addition is proposed to deliver a Rh(V) species **E**. Reductive elimination of the C–C bond from **E** would release the product **5** and the same intermediate **F** in which rhodium is reduced to Rh(III).



Scheme 5. The plausible mechanisms.

The free energy profiles of the two possible pathways for the formation of spirocyclopropane intermediate **5** are given in Figure 1. **B** is formed from the insertion of the rhodacycle **A** into the olefin. Protonation of **B** by one acetic acid can readily proceed via transition state ts-1 with a barrier of 6.0 kcal/mol. Intermediate **cp2** can subsequently undergo an intramolecular attack to give the cyclized product **5** with an overall barrier (17.6 kcal/mol) from intermediate **B**. The O−N bond cleaves simultaneously in this cyclopropanation step.[11] The formation of the spiro-product **5** requires minimal distortion of CP2. In path 2, the N−O bond oxidative addition via transition state ts-3 leads to the formation of a Rh(V) intermediate **cp4**. However, the overall barrier reaches up to 54.7 kcal/mol, which is 37.1 kcal/mol higher than that in path 1. Thus it is clearly disfavored in comparison to the intramolecular attack step in path 1. In addition, we cannot locate a transition state for an intramolecular attack of C–Rh bond to O atom to deliver the product **12** from **cp2**.[3] It is essentially a S$_N$Ar reaction, with C1-C2 bond formation accompanying N−O cleavage.[14] Direct attack of C1 on O1 would require a disfavored frontside S$_N$2 process. In addition, as the natural population analysis (NPA) charge of the carbon C2 in intermediate cp2 is -0.039, which suggests the nucleophilic attack of carbon C1 (-0.339) toward C2 via ts-2 could generate the spirocyclopropane product facilely. The strong nucleophilicity of both C1 (-0.339) and O1 (-0.422) indicates that the cyclization should not occur to form **12**. In order to further understand the role of HOAc in the reaction, we also performed calculations on the possible pathways without the protonation of **B** (See Figure S5 in SI). O−N oxidative addition can occur to generate a Rh(V) nitrenoid complex **C** with a high barrier of 28.6 kcal/mol from the intermediate **B**. However, this

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intermediate prefers to afford a *N*-(2-hydroxyphenyl)acetamide product and carbon-amidation product which is in line with the results in Scheme 4. Furthermore, an acid-promoted rearrangement of the intermediate **5** to the product **3** is proposed (For details, see SI). The aromatization of the cyclohexadienone unit by the cleavage of C–C bond and a Wagner–Meerwein-type rearrangement of the bicyclic framework are thought to be the key steps.

Our calculations show that the reaction of complex **B** is greatly facilitated by protonation with an additional HOAc, followed by the subsequent intramolecular attack. This pathway is much more favorable than the O–N bond oxidative addition in complex **B** or **cp2** by Rh(V) pathways. These results are consistent with the experimental observation that the addition of HOAc is necessary for the formation of **5** from the intermediate **C**. These also fit the results shown in Scheme 4 that the intermediate **5** is

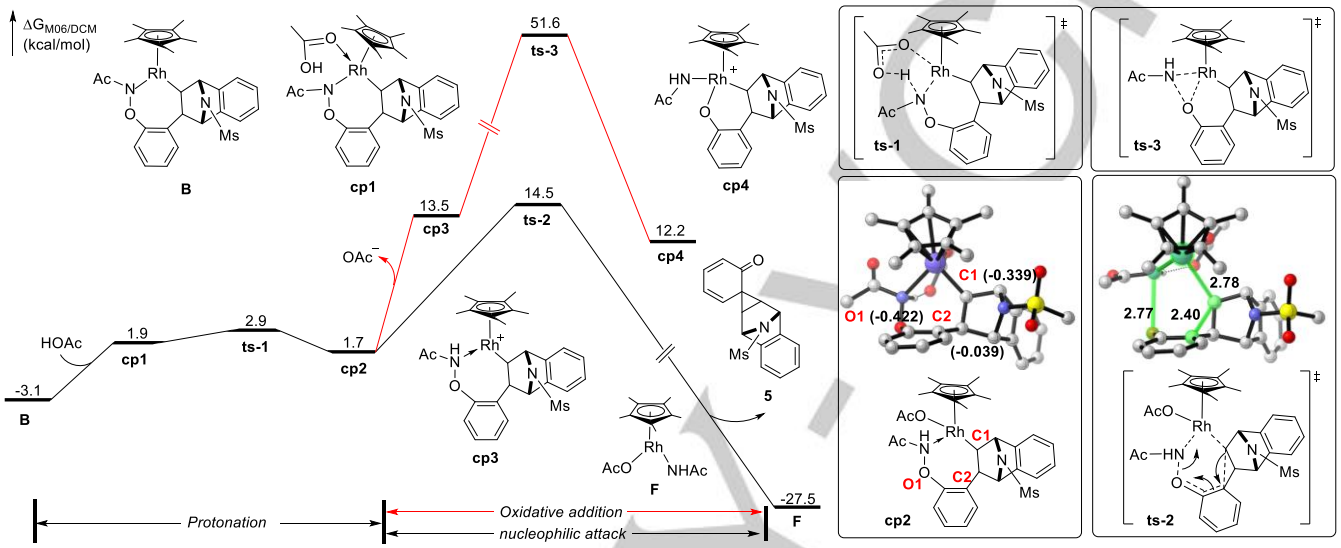
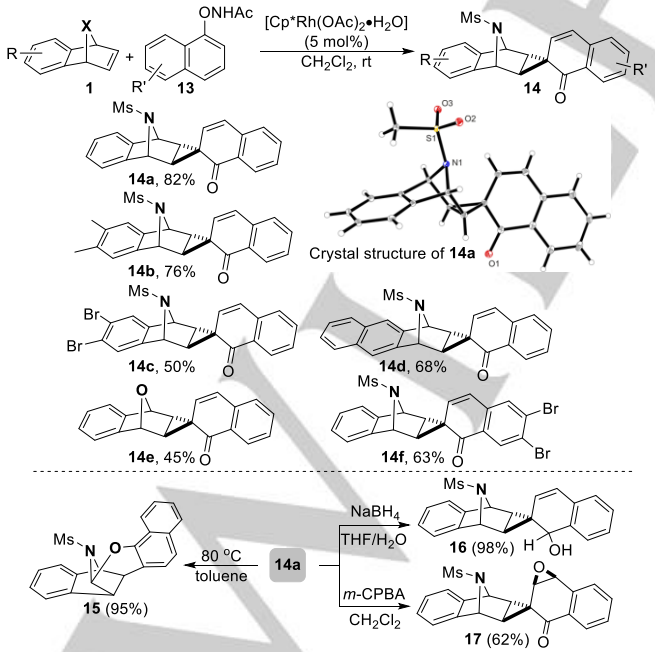


Figure 1. Free energy profiles for the formation of the spirocyclopropane

unlikely to be generated from Rh(V) species. Moreover, O–N bond is proposed to cleave through an intramolecular attack during the cyclopropanation step. Combining the experimental and DFT results, path 1 in Scheme 5 is the most reasonable mechanism.



Scheme 6. Cp*Rh(III)-catalyzed dearomatization reaction of *N*-(naphthalen-1-yloxy)acetamide with strained olefins. For details, see the supporting information.

Due to the wide occurrence of spirocyclopropanes in drugs and pharmaceutically active compounds,[15] it is highly desirable to develop the dearomatized spirocyclopropane reactions based on the above mentioned finding. In order to isolate a stable dearomatized product, we explored a starting material from α-naphthol as this motif can easily undergo a dearomatization process.[5] To our delight, the reaction between **13a** and the olefin **1a** indeed afforded a stable and isolable product **14a** in 82% yield (Scheme 6). Crystal structure of **14a** clearly showed that the molecule adopts a structure analogous to that proposed for intermediate **5**. A spirocyclopropane unit is found in this structure, wherein the naphthol ring is dearomatized to a naphthalen-1(2H)-one motif. Two new C–C bonds are formed in the key cyclopropanation step and thus the starting material acts as a formal one-carbon component in this [1 + 2] annulation reaction. 7-azabenzonorbornadienes with different groups on the arene, including methyl-, bromo- and benzo-structure, performed well affording the corresponding products in moderate yields. The reaction with 7-oxabenzonorbornadiene as coupling partner delivered the product **14e** in 45% yield. However, norbornene was tested in this reaction and only led to a complex reaction mixture. The dibromo substituted starting material also afforded the product **14f** in 63% yield. In addition, further transformations of the product were investigated. **14a** could rearrange to the product **15** by heating it to 80 °C in toluene. The ketone could be easily reduced to alcohol and the double bond could be transferred to an oxirane unit without the destruction of the spirocyclopropane scaffold.

Experimental and DFT investigations have elucidated the mechanism of Cp*Rh(III)-catalyzed C–H activation followed by Wagner–Meerwein-type rearrangement. *N*-phenoxyacetamide functions as a formal one-carbon component in a [1 + 2] annulation with 7-azabenzonorbornadiene, to afford an unprecedented dearomatized spirocyclopropane intermediate. Inspired from this finding, a Cp*Rh(III)-catalyzed dearomatization reaction of *N*-(naphthalen-1-yloxy)acetamide with strained olefins affording several spirocyclopropanes was successfully developed.

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Keywords: Rh(III)-catalysis • Spirocyclopropane • Oxidizing directing groups • Strained olefins

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[16] CCDC-1579105 (**8**) and CCDC-1579103 (**14a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif.

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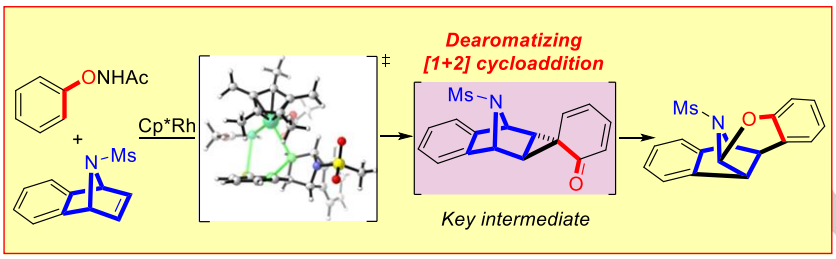

Unprecedented dearomatized spirocyclopropane intermediate was discovered in the sequential Cp*Rh(III)-catalyzed C–H activation and Wagner–Meerwein-type rearrangement reaction. *N*-phenoxyacetamide was found to act as a formal one-carbon component in this unexpected Rh(III)-catalyzed [1 + 2] annulation process.

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