

Theoretical study on the Rh-catalyzed C-C activation of cyclopropanol to construct diketone or monoketone

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June 8, 2020

Abstract

The mechanisms of C-C activation of 1-Benzylcyclopropan-1-ol to produce 1,6-diketone have been investigated by density functional theory (DFT) calculations. The catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive Ag_2CO_3 play an important role in controlling the selectivity. By employing $[\text{Cp}^*\text{RhCl}_2]_2$ as catalyst and Ag_2CO_3 as additive, the product is 1,6-diketone, whereas the β -hydride elimination product could not be obtained. The product would become monoketone in the absence of $[\text{Cp}^*\text{RhCl}_2]_2$. In addition, the combination of catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive AgOAc would also lead to monoketone. The observed selectivity could be attributed to the electronic effect.

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ABSTRACT:The mechanisms of C-C activation of 1-Benzylcyclopropan-1-ol to produce 1,6-diketone have been investigated by density functional theory (DFT) calculations. The catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive Ag_2CO_3 play an important role in controlling the selectivity. By employing $[\text{Cp}^*\text{RhCl}_2]_2$ as catalyst and Ag_2CO_3 as additive, the product is 1,6-diketone, whereas the β -hydride elimination product could not be obtained. The product would become monoketone in the absence of $[\text{Cp}^*\text{RhCl}_2]_2$. In addition, the combination of catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive AgOAc would also lead to monoketone. The observed selectivity could be attributed to the electronic effect.

KEYWORDS: DFT; 1,6-diketone; selectivity; β -hydride elimination

1. INTRODUCTION

As one of the important carbon synthons to prepare pharmaceutically relevant and biologically active five- and six-membered carbo- and heterocyclic compounds,^[1-3] 1,6-diketones and other acyclic long-chain diketones have attracted increasing attention in recent years. Although a lot of synthetic methods have been reported to yield 1,6-diketones, many of them were less efficiency and selectivity, and used non-readily obtainable substrates and synthetically harsh reaction conditions.^[4,5] Thus, a more general and efficient methodology to construct 1,6-diketones is highly desirable.

Transition-metal-catalyzed ring opening and cross-coupling reactions have been widely employed to synthesize 1,6-diketones from small carbocyclic rings. The intrinsic strain of small carbocyclic rings has been successfully exploited for the C-C bond activation,^[6] by releasing of strain compensates to overcome the reachable thermodynamic barrier. Nevertheless, catalytic self-coupling of metal homoenolates using rhodium-homoenolate derived from β -carbon elimination (C-C activation) of cyclopropanol is often restricted,^[7-10] due to the possible facile β -hydride elimination and isomerization pathways.^[11]

Recently, Ravikumar *et al* reported a rhodium-catalyzed C-C activation of readily available cyclopropanols for one-step access to diverse 1,6-diketones at room temperature.^[12] The catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive Ag_2CO_3 play an important role in controlling the selectivity. As shown in Scheme 1, by employing $[\text{Cp}^*\text{RhCl}_2]_2$ as catalyst and Ag_2CO_3 as additive, 1-Benzylcyclopropan-1-ol (**R**) would furnish 1,6-diketone **P1**, whereas the β -hydride elimination product monoketone **P1'** could not be obtained (reaction A). In contrast, the product would become monoketone **P2** in the absence of $[\text{Cp}^*\text{RhCl}_2]_2$ (reaction B). In reaction C, the combination of catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive AgOAc would also lead to monoketone **P2**.

SCHEME 1 C-C activation of cyclopropanol reported by Ravikumar

et al

To account for the distinct regioselectivity, Ravikumar group postulated possible reaction mechanisms that are summarized in Scheme 2. $[\text{Cp}^*\text{RhCl}_2]_2$ firstly reacts with Ag_2CO_3 to generate active catalyst Cp^*RhCO_3 (**cat**), which is followed by the ligand exchange with cyclopropanol **R** to afford alkoxide compound **I**. From **I**, there exist two possible pathways (path a or path b). In path a, β -carbon elimination would take place to afford alkyl-rhodium homoenolate **II**. Then, with the participant of another molecule of cyclopropanol, the successive ligand exchange and β -carbon elimination occur to give dialkyl-rhodium species **IV**. In contrast, the ligand exchange with the second molecule of cyclopropanol prior to β -carbon elimination would yield species **IV** through compound **II'** (path b). Finally, reductive elimination from species **IV** leads to 1,6-diketone **P**. It should be noted that the β -hydride eliminated product **P'** could not be obtained in this reaction. As shown in Scheme 2, in the absence of $[\text{Cp}^*\text{RhCl}_2]_2$, cyclopropanol would undergo the ring-opening to give monoketone product catalyzed by Ag_2CO_3 .

SCHEME 2 Possible reaction mechanisms proposed by Ravikumar's group

Although the plausible mechanistic pathway has been proposed by the Ravikumar group, some key issues still need to be addressed: (1) In this experiment, the role of the catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ and additive Ag_2CO_3 is still unclear; (2) It is unclear which steps determine the selectivity and what are the origins of that observation in this experiment; (3) The β -hydride eliminated product was not obtained in reaction A – it would be interesting to investigate the corresponding factors. To address these questions, a theoretical investigation of the detailed reaction mechanisms is needed. Herein, we report our detailed density functional theory (DFT) calculations on the reaction mechanisms, in order to gain insight into the interesting experimental observations and distinct selectivity. We expect that this work will help to understand the detailed reaction mechanisms and to design new related reactions.

2. COMPUTATIONAL DETAILS

All structures were optimized at the B3LYP^[13-15]/BSI level (BSI designates the basis set combination of LanL2DZ^[16-18] for Rh atom, and 6-31G(d,p) for main group elements) in the gas phase. Harmonic vibrational frequencies were also calculated at the same level of theory to identify all stationary points as minima (zero imaginary frequencies) or transition states (one imaginary frequency). Intrinsic coordinate reaction

(IRC)^[19-21] calculations were carried out to examine the connectivity of a transition state with its backward and forward minima when necessary. The energetic results were then further refined by single-point calculations at the M06^[22,23]/BSII level with solvation effects accounted for by the SMD^[24-28] solvent model using TFE as solvent according to the experimental conditions, where BSII denotes the basis set combination of SDD^[29-31] for Rh atom, and 6-311++G(d,p) for main group elements. Natural bond orbital (NBO) analyses were performed at the B3LYP/BSII level on selected systems with the NBO code included in Gaussian 09.^[32] In all of the figures that contain energy diagrams, calculated relative Gibbs free energies are presented. For reference, relative enthalpic energies are also given in parentheses. All the energies are given in kcal/mol. Unless otherwise stated, Gibbs free energies are used for the discussion of reaction mechanisms. All the calculations were performed with the Gaussian 09 software package.^[32]

It should be noteworthy that the ideal gas-phase model intrinsically overestimates the entropic contributions, and thus the development of general schemes to correct the overestimation of entropic contributions is desired. Yu *et al.*^[33,34] have carried out a comparison between the entropies experimentally determined and those computed with the ideal gas model, and demonstrated that the latter could overestimate entropic contribution by 50-70% as compared to the former. In view of the overestimation of entropies with ideal gas-phase model, we applied a scaling factor of 0.5 to the gas phase entropic contributions as to correct the free energies for 2:1 and 1:2 transformations. Such a correction has been applied in other theoretical studies.^[35-44]

3. RESULTS AND DISCUSSION

3.1 Reaction A

The free energy diagrams for the ligand exchange and β -carbon elimination in reaction A are calculated and shown in Figure 1. At the entrance of the reaction, **R** firstly coordinates with **cat** and Ag₂CO₃ to yield the intermediate **1^A** by exoergic of 32.2 kcal/mol. The inaccessible direct ring-opening of **R** with the assistance of Ag₂CO₃ is given in Figure S1 in Supporting Information (**TS1-P2-1^A**). Then the ligand exchange takes place to generate an alkoxide intermediate **2^A** via transition state **TS1^A** with a facile barrier of 0.2 kcal/mol. In the following step, **2^A** undergoes the β -carbon elimination to form an alkyl-rhodium homoenolate **3^A** by overcoming the barrier of 20.5 kcal/mol (**TS2^A**). The possible ring-opening processes from **2^A** and **3^A**, respectively, caused by the protonation, were also calculated and precluded due to the high barriers (**TS1-P2-2^A** and **TS1-P2-3^A** in Figure S1 in Supporting Information).

FIGURE 1 Free energy diagrams for the ligand exchange and β -carbon elimination steps in reaction A. The relative free energies and relative enthalpic energies (in parentheses) are given in kcal/mol

FIGURE 2 Free energy diagrams for the second ligand exchange, second β -carbon elimination, and reductive elimination steps in reaction A. The relative free energies and relative enthalpic energies (in parentheses) are given in kcal/mol

With the coordination of another molecule of **R**, **3^A** transforms into intermediates **4-cis^A** and **4-tran^A**, respectively, according to the relative position of two moieties of **R** (Figure 2). The subsequent ligand exchange then occurs to result into intermediates **5-cis^A** and **5-tran^A**, respectively. The unfavorable β -hydride elimination from **3^A** was excluded (**TS3-P1'-1^A** in Figure S2 in Supporting Information). In the next step, another β -carbon elimination from **5-cis^A** and **5-tran^A** takes place to bring about intermediates **6-cis^A** and **6-tran^A**, through transition states **TS4-cis^A** and **TS4-tran^A**, respectively. The corresponding barriers are 19.0 and 22.1 kcal/mol. Finally, the C-C reductive elimination occurs to produce the product-coordinated complexes **7-cis^A** and **7-tran^A**, by overcoming the barriers of 47.7 and 28.1 kcal/mol (**TS5-cis^A** and **TS5-tran^A**), respectively. Another infeasible β -hydride elimination from **6-tran^A** was also considered and put into Figure S2 in Supporting Information (**TS5-P1'-1^A**). Ravikumar *et al* also proposed an alternative pathway (path b as shown in Scheme 2), but this possibility is precluded due the high barrier (Figure S3 in Supporting Information).

As suggested in Figures 1 and 2, the rate-determining step for reaction A is the C-C reductive elimination

and the overall barrier is 28.1 kcal/mol. The *cis* - or *tran* -selectivity is controlled by the competition between **TS5-cis^A** and **TS5-tran^A**. The lower **TS5-tran^A** indicates that the *tran* -product is the main product in reaction A. The steric effect could account for the regioselectivity. As shown the structures of **TS5-cis^A** and **TS5-tran^A** in Figure 3, the strong repulsion of Rh...C1 interaction at 2.64 Å in **TS5-cis^A** destabilizes it and restricts the subsequent process.

FIGURE 3 The optimized structures of transition states of **TS5-tran^A** and **TS5-cis^A**. The bond distances are given in Å

FIGURE 4 NBO charges (e) in the optimized structures of transition states **TS3-P1-1'^A** and **TS5-P1-1'^A**

In this reaction, the β -hydride elimination product monoketone **P1'** was not found. The electronic effect could account for this selectivity. As indicated in the given NBO charges of corresponding β -hydride elimination transition states depicted in Figure 4, the strong attraction between C^β and H^β , and repulsion between Rh and H^β restrain the β -hydride elimination jointly.

3.2 Reaction B

The free energy diagrams leading to **P2** catalyzed by Ag_2CO_3 in reaction B are shown in Figure 3. In the absence of **cat**, **R** would coordinate to Ag_2CO_3 firstly,^[45] which is followed by the ligand exchange to transform into intermediate **2^B** with a barrier of 3.9 kcal/mol (**TS1^B**). The subsequent ring-opening would furnish **P2**-coordinated complex **3^B**, requiring the barrier of 14.9 kcal/mol (**TS2^B**). The infeasible ring-opening process is given in Figure S4 in Supporting Information. In contrast, from **2^B**, the β -carbon elimination could also take place to lead to **P1** (red line in Figure 3), but the relative higher barrier of **TS2-P1^B** restricts this pathway. These calculated results are consistent with the experimentally observed selectivity.

FIGURE 5 Free energy diagrams leading to **P1** and **P2** in reaction A. The relative free energies and relative enthalpic energies (in parentheses) are given in kcal/mol

3.3 Reaction C

As reported in this experiment, under the catalysis of **cat** and $AgOAc$, **P2** is the product. As presented in Figure 6, the ring-opening caused by the protonation of $HOAc$ (**TS1-P2^C**) is much favorable than the β -carbon elimination pathway (**TS1-P1^C**), suggesting **P2** is the product, in agreement with the experimental observation. The reversion on the selectivity, caused by different additives, could be attributed to the electronic effect. As the NBO charges shown in Figures 6 and 7, compared with HCO_3^- , the stronger acidity of $HOAc$ could give the proton more easily and facilitate the ring-opening process.

FIGURE 6 The optimized structures of transition states of **TS1-P1^C** and **TS1-P2^C**. The NBO charges are given in

e

FIGURE 7 NBO charges (e) in the optimized structures of transition states **TS1-P2-2^A** and **TS1-P2-3^A**

4. CONCLUSIONS

In this study, DFT calculations were employed to study the mechanism of C-C activation of 1-Benzylcyclopropan-1-ol to yield 1,6-diketone. The catalyst $[Cp^*RhCl_2]_2$ and additive Ag_2CO_3 play an important role in controlling the selectivity. In reaction A, the product is 1,6-diketone, whereas the β -hydride elimination product **P1'** could not be obtained. The electronic effect could account for the selectivity. In contrast, the product becomes monoketone in reaction B and C. NBO charge calculation was performed to reveal the origin of the selectivity, which could be attributed to be the electronic effect.

ACKNOWLEDGEMENTS

This work was supported by the Natural Science Foundation of Shandong Province (No. ZR2019MB069).

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