ORGANIC LETTERS

2002
Vol. 4, No. 4
517−520

Theoretical Analysis of the Reaction Pathway and the Effect of the Axial Ligand for 3-Oxobutylideneaminatocobalt(II)-Catalyzed Cyclopropanation

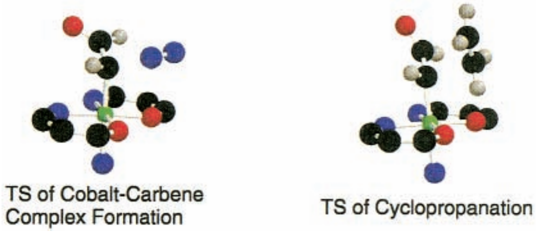
Taketo Ikeno, Izumi Iwakura, Satoshi Yabushita, and Tohru Yamada*

Department of Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

yamada@chem.keio.ac.jp

Received November 27, 2001

ABSTRACT



The reaction pathway of the cyclopropanation catalyzed by the 3-oxobutylideneaminatocobalt(II) complex was analyzed by the density functional method to reveal that the axial donor ligand produced two prominent effects. One is that the activation energy for the formation of the cobalt carbene complex was reduced and that the activation energy for the cyclopropanation step was increased. The other is that the distance of the carbene carbon above the ligand plane was shortened during the cyclopropanation step.

The 3-oxobutylideneaminatocobalt(II) complexes derived from 1,3-dicarbonyl compounds and 1,2-diarylethylenediamines have been developed as efficient catalysts for enantioselective reactions and applied to the highly enantioselective borohydride reduction of ketones,[1] imines,[2] and α,β-unsaturated carbonyl compounds[3] and the highly enantioselective hetero Diels−Alder reaction.[4] These complex catalysts were also successfully used for the enantioselective cyclopropanation of styrenes and diazoacetates.[5] For the cobalt-catalyzed cyclopropanation, it was revealed that the addition of a catalytic amount of *N*-methylimidazole had a significant effect on both the enantioselectivity and reaction rate.

Since the catalytic enantioselective cyclopropanation of olefins with diazoacetate was reported in 1966,[6] a wide variety of transition-metal catalysts have been developed and several efficient catalysts have achieved high diastereo- and enantioselectivities to date.[7] Their design has mainly been based on an empirical method; however, theoretical analyses of the reaction pathway of the catalytic cyclopropanation have been only slightly investigated.[8] Therefore, an under-

---

(1) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145.

(2) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, 493.

(3) Yamada, T.; Ohtsuka, Y.; Ikeno, T. *Chem. Lett.* **1998**, 1129.

(4) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2000**, 824.

(5) (a) Yamada, T.; Ikeno, T.; Sekino, H.; Sato, M. *Chem. Lett.* **1999**, 719. (b) Ikeno, T.; Sato, M.; Yamada, T. *Chem. Lett.* **1999**, 1345. (c) Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* **2001**, 406. (d) Ikeno, T.; Sato, M.; Sekino, H.; Nishizuka, A.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2139. (e) Ikeno, T.; Iwakura, I.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2151.

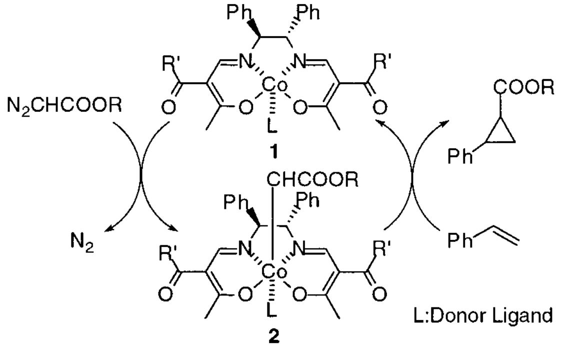
(6) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239.

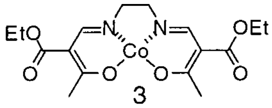
10.1021/ol017129d CCC: $22.00

standing of the reaction based on a theoretical analysis should provide fruitful information for the rational design of the complex catalyst. In this Letter, we describe a theoretical analysis of the cyclopropanation reaction pathway and the axial-ligand effect for the 3-oxobutylideneaminatocobalt(II)-catalyzed system.

The reaction pathway of the 3-oxobutylideneaminatocobalt(II)-catalyzed cyclopropanation was considered to be that shown in Scheme 1. The cobalt(II) complex **1** reacted with diazoacetate and was transformed into the cobalt carbene complex **2**, which then reacted with styrene to regenerate the cobalt(II) complex **1**. The following experiment indicated that the cobalt carbene complex **2** was generated as an intermediate; to a THF solution of an equimolar amount of the cobalt complex **3** and a two-fold molar amount of *N*-methylimidazole was added a THF solution of ethyl diazoacetate. The reaction mixture immediately turned a brown color, and the evolution of an almost equimolar amount of dinitrogen gas was observed. The real system for the cyclopropanation catalyzed by the cobalt complex was too large to directly analyze its reaction pathway by the density functional calculation; therefore, a model structure was extracted while maintaining the electronic effect of the reaction. The model cobalt(II) complexes **4a**−**4c** (Figure 1) consisted of planar coordination as a simple acacen-type complex but without an ethylene bridge[9] instead of the 3-oxobutylideneaminato ligands and one of its vacant axial positions was occupied by water or ammonia as a model axial ligand in place of methanol[5c] or *N*-methylimidazole. Diazoacetoaldehyde and ethylene were used for the reactant instead of diazoacetate and styrene, respectively. The calculations[10] were performed using the density functional theory at the UB3LYP/LANL2DZ[11] and UB3LYP/6-31G* level.

Scheme 1,. Catalytic Cycle of the Cyclopropanation





3

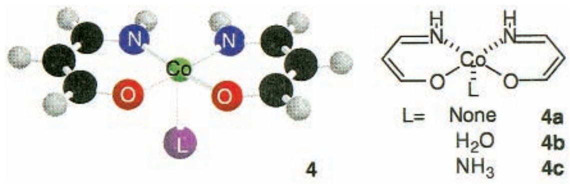


Figure 1. Model cobalt complexes **4a**−**4c**. In each molecular model, hereafter, the cobalt atom is colored green, nitrogen blue, oxygen red, carbon black, and hydrogen gray.

The calculated reaction pathway of the 3-oxobutylideneaminatocobalt(II)-catalyzed cyclopropanation is shown in Figure 2.[12,13] The cobalt(II) complexes **4a**−**4c** reacted with diazoacetoaldehyde to generate the cobalt carbene complexes **6a**−**6c** via the transition state **5a**−**5c** in which dinitrogen was released by bisecting an O−Co−O angle.[14] On the potential energy surface for the rotation of the carbene moiety around the cobalt−carbene carbon bond as an axis in complexes **6a**−**6c**, four energy minimums were found. Each rotational isomer was optimized to produce the most stable isomer, with the carbonyl group of the carbene moiety bisecting an O−Co−O angle.

---

(7) For reviews of the transition-metal-catalyzed cyclopropanations, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998. (b) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. For examples of the cobalt-catalyzed cyclopropanation, see: (d) Nakamura A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443. (e) Fukuda, T.; Katsuki T. *Synlett* **1995**, 825. (f) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647.

(8) For recent examples of the theoretical analysis of the cyclopropanation, see: (a) Fraile J. M.; Garcia J. I.; Martinez-Merino V.; Mayoral J. A.; Salvatella L. *J. Am. Chem. Soc.* **2001**, *123*, 7616. (b) Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2001**, 2151.

(9) Preliminary calculations using diazomethane instead of diazoacetoaldehyde at UB3LYP/LANL2DZ indicated that the ethylene bridge had little effect on the reaction pathway and energy profile, because the ligand plane in the doublet states was flat during the reaction.

(10) Frisch, M. J.; et al. Gaussian 98, Revision A.6; Gaussian, Inc., Pittsburgh, PA, 1998.

(11) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(12) The quartet states of all the complexes except for **4b** and **4c** were optimized at the UB3LYP/LANL2DZ level. As for **4b** and **4c**, reasonable optimized structures could not be obtained. The energies of the quartet states of all the species were higher than those of the corresponding doublet states. Hence, it was considered that the reaction proceeded throughout in the doublet states and no spin crossing occurred. The S^2 values of the reactant, TS_1, cobalt carbene complexes, and TS_2, were slightly greater than 0.75. This suggested that the quartet states might be sufficiently higher in energy and were not mixed with the doublet states (**4a**: 0.7635, **4b**: 0.7582, **4c**: 0.7593, **5a**: 0.7772, **5b**: 0.7697, **5c**: 0.7687, **6a**: 0.7824, **6b**: 0.7808, **6c**: 0.7791, **7a**: 0.7919, **7b**: 0.7900, **7c**: 0.7886, **8b**: 0.8201, **8c**: 0.7667, **9b**: 0.9198, **9c**: 0.9423.)

(13) A similar energy profile was obtained when ZPE was included in the correction of energy or when single point calculations were performed at the UB3LYP/6-311+G** level using the optimized structures at the UB3LYP/LANL2DZ level.

(14) The transition states **5a**−**5c** possessed rotational isomers, in which dinitrogen was released bisecting an N−Co−N angle. Although these isomers were slightly more stable than **5a**−**5c** (0.9 kcal mol^{-1} for **5a**, 0.5 kcal mol^{-1} for **5b**, and 0.0 kcal mol^{-1} for **5c** at UB3LYP/LANL2DZ) in the model system, the real system including aryl groups on the diimine part and their isomers must be less stable due to the steric repulsion between the aryl groups and the diazoacetate. Hence, the transition states **5a**−**5c** were accounted for. The other directions for the dinitrogen release were unstable.

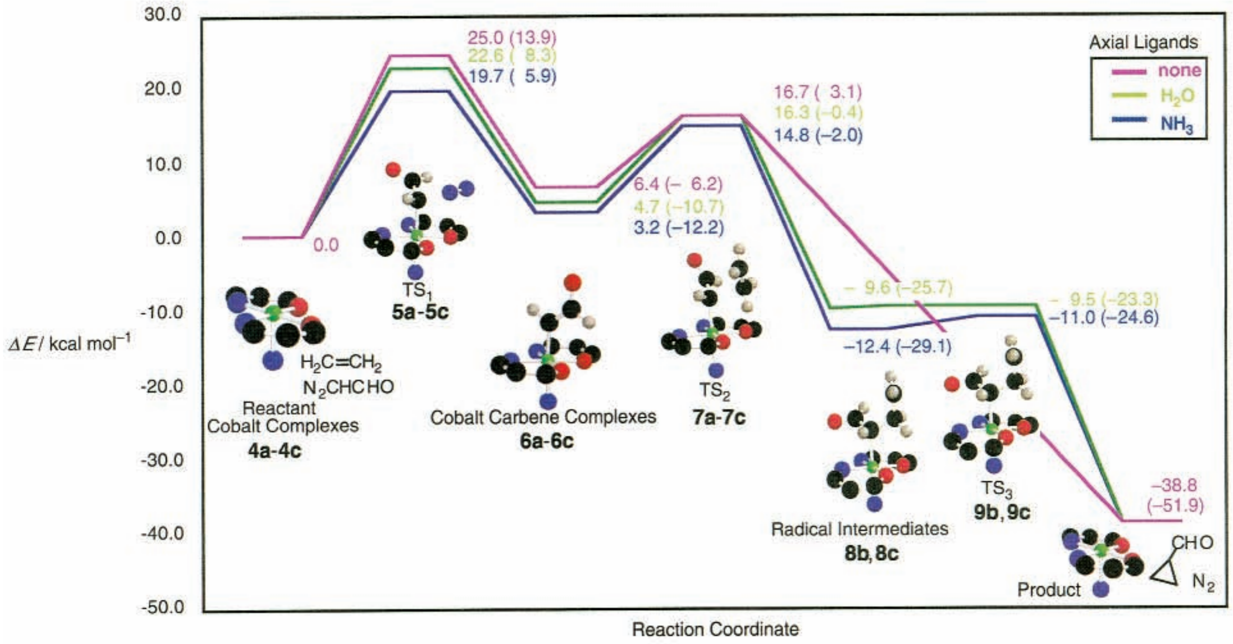


Figure 2. Reaction pathway of cobalt complex catalyzed cyclopropanation with axial ligands at UB3LYP/LANL2DZ//UB3LYP/LANL2DZ. Results at UB3LYP/6-31G*//UB3LYP/6-31G* are shown in parentheses.

The ethylene molecule approached the complex **6a**−**6c** from the direction bisecting an O−Co−O angle to finally afford the product via the transition states **7a**−**7c**. When ethylene approached from the direction bisecting an N−Co−N or N−Co−O angle, the corresponding transition states could be found, though they were calculated to be 2.5−3.8 kcal mol^{-1} less stable than the transition states **7a**−**7c** at UB3LYP/LANL2DZ. Therefore, it is reasonable that the other isomers were omitted and the transition states **7a**−**7c** were employed for further calculations. The radical intermediates **8b** and **8c** could be optimized, though the potential energy surface seemed very flat around the species. Hence, the activation energies of the ring-closing step from the intermediates **8b** and **8c** were investigated and found to be small. Concerning the formation of cyclopropane from the intermediate **6a**, no radical intermediates could be found. During the asymmetric cyclopropanation, the absolute configuration of the 1-position of the product was generally the same for the diastereomeric *trans*- and *cis*-isomers. On the basis of these results, it should be concluded that the stereoselectivities of the cyclopropanation were regulated at the transition states **7a**−**7c**.

Table 1 summarizes the activation energies of each step for the respective axial ligand. The formation step of the cobalt carbene complex **6a** required the highest activation energy, while it was calculated that the axial ligands (H_2O or NH_3) clearly reduced the activation energy from 25.0 (none) to 22.6 (H_2O) or 19.7 (NH_3) kcal mol^{-1} at the UB3LYP/LANL2DZ level and from 13.9 (none) to 8.3 (H_2O) or 5.9 (NH_3) at the UB3LYP/6-31G* level. This prediction was consistent with the experimental results in the presence of a donor ligand, such as *N*-methylimidazole.[5,7] The evolution of nitrogen gas was actually measured for the reaction of ethyl diazoacetate and the complex **3** in the presence of *N*-methylimidazole and for the reaction without *N*-methylimidazole.[15] These experiments revealed that the dinitrogen evolution in the presence of *N*-methylimidazole was about seven times faster than without *N*-methylimidazole at 10 °C. These observations could be ascribed to the fact that *N*-methylimidazole should coordinate the cobalt atom as an axial ligand to reduce the activation energy of the formation of the cobalt(II) carbene complex. It was predicted in their transition states, **5a**−**5c**, that the elongation of the carbene carbon and the nitrogen bonds and the increase in the electron density on the carbene carbon and the nitrogen

Table 1. Transition State Energies for Various Axial Ligands[a,b]

entry	axial ligand	Δ*E*(**5**−**4**)/ kcal mol^{-1}	Δ*E*(**7**−**6**)/ kcal mol^{-1}	Δ*E*(**9**−**8**)/ kcal mol^{-1}
1	none	25.0 (13.9)	10.3 (9.3)	*c*
2	H_2O	22.6 (8.3)	11.6 (10.3)	0.1 (2.4)
3	NH_3	19.7 (5.9)	11.6 (10.1)	1.4 (4.5)

[a] Optimizations and energy calculations of the ground and transition ssstates were performed at UB3LYP/LANL2DZ. [b] Energies of UB3LYP/6-31G*//UB3LYP/6-31G* are shown in parentheses. [c] A radical intermediate could not be obtained.

---

(15) To a solution of the cobalt(II) complex **3** (158.8 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) were added *N*-methylimidazole (63.8 μL, 0.8 mmol) and then ethyl diazoacetate (47.5 μL, 0.4 mmol) at 10 °C. The volume of the evolution of nitrogen vs time was measured. Without *N*-methylimidazole, the same procedure was performed except for the addition of *N*-methylimidazole.

atom were caused by the axial ligand (Figure 3);[16] the donative ligand increases the electron density of the d_{z^2} orbital of the cobalt atom to enhance the interaction between the d_{z^2} orbital and σ^* orbital of the carbene carbon−nitrogen bond and the delocalization weakens the bond. These mechanistic considerations seemed similar to the push effect of the axial ligand on the O−O bond of the acylperoxoiron(III) porphyrin.[17]

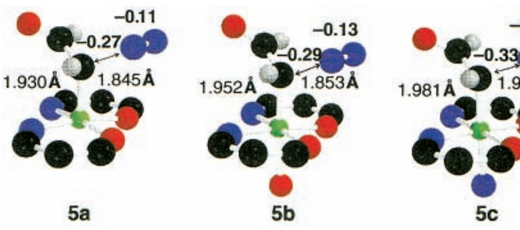
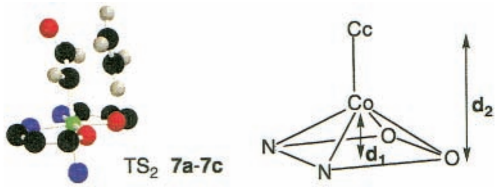


Figure 3. Charge and bond length of the transition states **5a**−**5c**.

For the next step in the cyclopropane formation from the cobalt carbene complexes **6a**−**6c** and ethylene, on the contrary, the axial ligand clearly increased its activation energy from 10.3 (**7a**) to 11.6 (**7b** and **7c**) kcal mol^{-1} at UB3LYP/LANL2DZ and from 9.3 (none) to 10.3 (H_2O) and 10.1 (NH_3) at UB3LYP/6-31G*. These destabilizations of the transition states by the axial ligand could be qualitatively explained as follows: the electron density of the carbene carbon was increased by the donative axial ligand, and electronic repulsion between the carbene carbon and approaching olefin was enhanced.[18]

An increase in the activation energy would lead to the transition state later. From the simple consideration, the diastereoselectivity would be improved but the enantioselectivity would be worse, since the olefin would approach closer to the carbene carbon but the cobalt−carbene carbon bond would be elongated. As shown in Table 2, the Co−carbene carbon bond was actually elongated from 1.92 (none) to 1.94 (H_2O) and 1.96 Å (NH_3). However, the distance of the cobalt atom above the ligand plane was significantly shortened by the axial ligand from 0.18 (none) to 0.10 (H_2O) and 0.06 Å (NH_3) and as a result, the distance of the carbene carbon above the plane was shortened from 2.10 (none) to 2.04 (H_2O), and 2.02 Å (NH_3), respectively. Therefore, the stereoselection caused by the steric demanding groups in the chiral diamine was effectively enhanced by the addition of some axial ligands. These phenomena of the axial ligand are well-known. For example, an X-ray structure analysis of salen oxochromium(V) complexes revealed that the distance of the chromium atom above the ligand plane in the 6-coordinate (with axial ligand) was shorter than that in the 5-coordinate (without axial ligand).[19]

Table 2. Length of the Cobalt−Carbene Carbon Bond and the Distances of the Cobalt and Carbene Carbon Above the Ligand Plane in the TS_2[a]



entry	axial ligand	Co−C_c	d_1 (Å)	d_2 (Å)
1	none	1.92	0.18	2.10
2	H_2O	1.94	0.10	2.04
3	NH_3	1.96	0.06	2.02

[a] Optimizations were performed at UB3LYP/LANL2DZ.

In summary, the reaction pathway of the cyclopropanation catalyzed by the 3-oxobutylideneaminatocobalt(II) complex was fully analyzed by the density functional method to reveal that the axial donor ligand produced two prominent effects. One is that the activation energy for the formation of the cobalt carbene complex was reduced and that the activation energy for the cyclopropanation step was increased. The other is that the distance of the carbene carbon above the plane was shortened during the cyclopropanation step. From these results, the axial donor ligand effects, enhancing reactivity and improving the diastereo- and enantioselectivities, in the 3-oxobutylideneaminatocobalt(II)-catalyzed asymmetric cyclopropanation could be clearly explained.

Acknowledgment. We thank the Information Technology Center of the Faculty of Science and Technology, Keio University, and Computer Center of the Institute for Molecular Science, Japan for their support of the DFT calculations.

OL017129D

---

[16] The distances of the cobalt−carbene carbon bond ranged from 1.88 to 1.91 Å in complexes **6a**−**6c** and from 1.93 to 1.98 Å in the TS_1 (**5a**−**5c**). On the other hand, the bond distances of the carbene carbon−nitrogen of the diazo moiety ranged from 1.85 to 1.90 Å in the TS_1 and that of diazoacetoaldehyde was 1.32 Å. Therefore, TS_1 was considered to be a late transition state and the bond formation of the cobalt−carbon was almost accomplished and then the bond fission of the carbon−nitrogen proceeded in the TS_1. This might indicate that the dinitrogen release mainly produced the activation barrier for this step.

[17] Yamaguchi, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1993**, *115*, 4058.

[18] Another qualitative explanation based on the stability of **6a**−**6c** was possible. The cobalt−carbene complexes **6b** and **6c** were stabilized compared to complex **6a** because of electron delocalization from the donative axial ligand to the electron deficient carbene moiety.

[19] Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606.