# Theoretical Studies on Diastereo- and Enantioselective Rhodium-Catalyzed Cyclization of Diazo Compound *via* Intramolecular C–H Bond Insertion

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Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de or from the author.

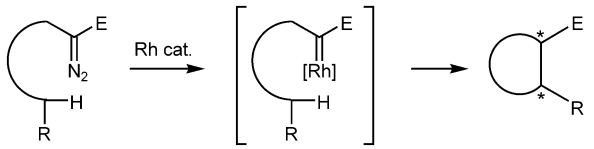
**Abstract:** Theoretical studies on the stereoselectivity of the dirhodium tetracarboxylate (carboxamidate)-catalyzed intramolecular C–H insertion reaction, which gives a variety of carbo- or heterocyclic compounds, have been performed by the following procedure. First, the C–H insertion mechanism of simple systems was studied by the hybrid density functional theory (B3LYP) calculations. On the basis of these B3LYP structures, stereoselectivities of the reactions of realistic substrates were examined by the PM3 calculations with some structural constraints. The origin of the diastereo- and enantioselectivities in the four- and five-membered ring formation reactions with an achiral or a chiral Rh catalyst has thus been elucidated.

**Keywords:** C–H activation; carbene complex; cyclization; diazo compounds; rhodium; stereoselectivity; theoretical calculation

## Introduction

Carbon-carbon bond forming reactions that rely on activation of a C–H bond have achieved a remarkable progress in recent years.[1,2] Among these, a dirhodium tetracarboxylate-catalyzed intramolecular C–H insertion reaction of an α-diazocarbonyl compound has proved to be one of the most reliable methods for carbo- and heterocycle construction that goes through activation of an $sp^3$ C–H bond.[3] In an ideal case, a new C–C bond between two $sp^3$ carbon centers is created in a highly diastereo- and enantioselective manner (Scheme 1).[4]

This class of reaction has already become a standard method for laboratory scale synthesis, and is being considered as a promising protocol for commercial processes.[5] Although a high level of stereoselectivity is often achieved in the reaction, the origin of the selectivity is not clearly understood owing to the lack of precise knowledge about the reaction mechanism and the transition state (TS) of the C–H bond activation/C–C bond formation process. For further improvement of the reaction, such information is obviously indispensable.




**Scheme 1.** Stereoselective cyclization *via* intramolecular C–H insertion of a Rh-carbene complex.

Recently, we reported the first thorough analysis of the reaction pathways of intermolecular C–H insertion reaction between a Rh-carbene complex and an alkane as revealed by hybrid density functional calculations (Scheme 2).[6] It was found that the reaction proceeds *via* a three-centered transition state involving simultaneous cleavage of the alkane C–H bond and the formation of the new C–C bond. We report herein the results of our theoretical studies to probe the TSs of the intramolecular C–H insertion reactions and the origin of the diastereo- and enantioselectivities in the cyclization process.

Numerous examples of successful cyclization reactions have been reported. To define the scope of the present studies, some representative experimental results are listed and briefly discussed below. Whenever there are possibilities of four-, five- and six-membered ring formation, five-membered ring formation is generally preferred if the reactivities of the corresponding C–H bonds are not very much different. In the early stage of the experimental studies, the $Rh_2(OAc)_4$-catalyzed reactions of disubstituted diazo compounds **1** were examined by Taber[7] and Doyle[8], Eq. (1). They

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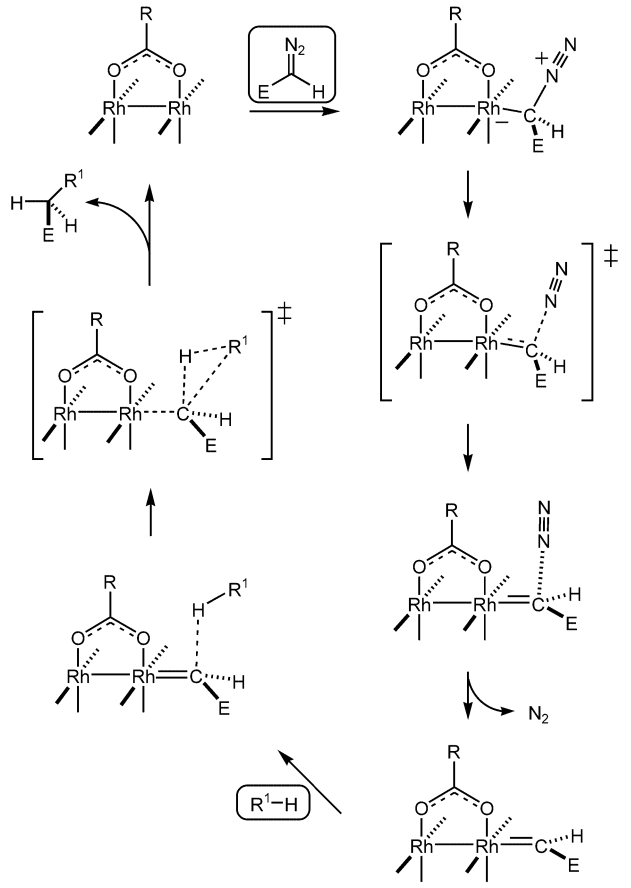
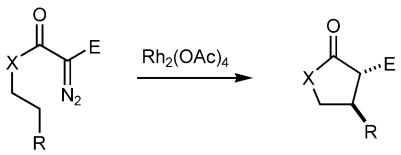
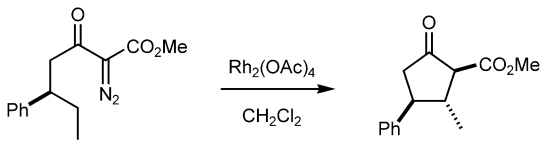


**Scheme 2.** The reaction pathway of the $Rh_2(O_2CR)_4$-catalyzed C–H insertion reaction of a diazo compound and an alkane.

found that the C–C bond formation proceeds in a *trans* fashion to give cyclopentanone derivatives ($X = CH_2$, $E = CO_2R$) or γ-lactones ($X = O$, $E = COR$) **2**. The reactions were found to be diastereoselective for the newly formed C–C bond and for the remote stereogenic center. A representative example is shown in Eq. (2).[7b] The $Rh_2(OAc)_4$-catalyzed cyclization of **3** gives the all *trans* cyclopentanone **4**.

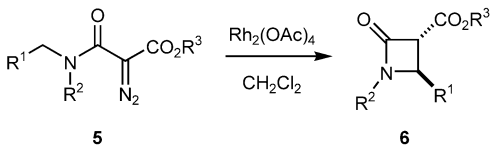


**1** **2** (1)

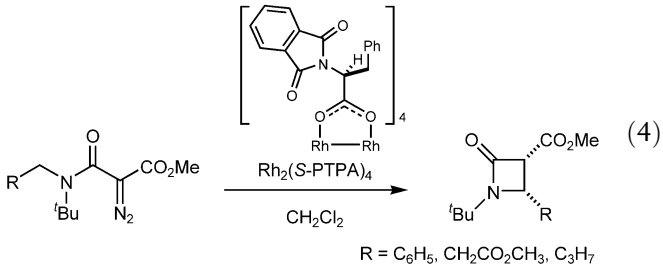


**3** **4** (2)

The reaction is effective also for four-membered ring construction. A β-lactam **6** is formed by the reaction of an *N*-alkyldiazoacetamide **5** with a catalytic amount of $Rh_2(OAc)_4$, Eq. (3). This reaction takes place with exclusive *trans* selectivity ($R^1 = C_6H_5$, $R^2 = C_6H_5$ and $R^3 = C_2H_5$).[9] Interestingly, a thermodynamically unfavorable *cis* product was obtained exclusively in the asymmetric β-lactam formation with a $Rh_2$(*S*-PTPA)$_4$ (PTPA: *N*-phthaloylphenylalaninate) catalyst, Eq. (4).[10]

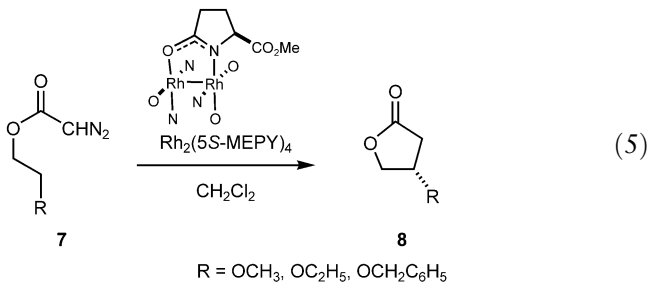


**5** **6** (3)



(4)

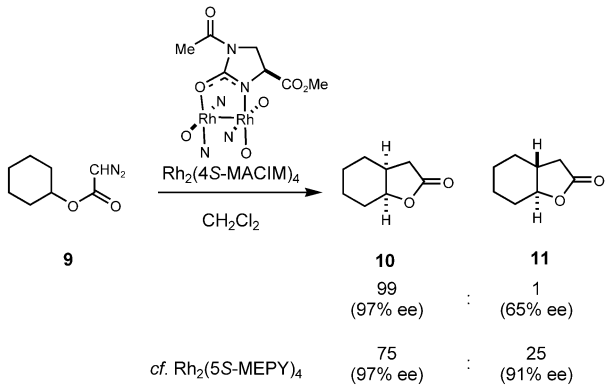
A Rh catalyst having chiral carboxylate or carboxamidate ligands has been used for asymmetric C–H insertion reactions. A highly enantioselective intramolecular C–H insertion reaction was reported by Doyle et al. in 1991, Eq. (5).[11] The chiral $Rh_2$(5*S*-MEPY)$_4$ (MEPY: methyl 2-pyrrolidone-5-carboxylate) complex catalyzes the cyclization of an α-diazoester **7** to the *S*-enantiomer of a γ-lactone **8** with good enantioselectivity (~90% ee).



**7** **8** (5)

The best example to illustrate the power of the enantio- and diastereocontrol by a chiral Rh complex is the reaction of a cycloalkyl diazoacetate, which affords a fused bicyclic compound, Eq. (6). Doyle has achieved excellent diastereo- (*cis*) and enantiocontrol by using a $Rh_2$(4*S*-MACIM)$_4$ (MACIM: methyl 1-acetylimidazolidin-2-one-4-carboxylate) catalyst. In contrast, $Rh_2$(5*S*-MEPY)$_4$ gives poor diastereoselectivity.[12]




(6)

The stereoselectivity of these reactions has been discussed often by schematic molecular modeling[7b, c,12b,13] and sometimes by molecular mechanics or semi-empirical calculations based on a hypothetical transition structure.[8,14] Although some of them were successful in explaining individual experimental observations, more realistic mechanistic models are undoubtedly desirable for further improvement of catalysts and substrates. We focused in the present studies on three topics: Diastereoselectivity in five-membered ring (cyclopentanone and γ-lactone derivatives) formation catalyzed by an achiral Rh catalyst [Eqs. (1) and (2)], diastereoselctivity in four-membered ring (β-lactam) formation [Eqs. (3) and (4)], and enantio- and diastereoselectivity in γ-lactone formation catalyzed by Doyle's catalysts $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MACIM})_4$ [Eqs. (5) and (6)].

## Results and Discussion

### Computational Details

The studies were carried out in two stages since the highly substituted realistic substrates and catalysts are too large for treatment with a high level of theory. Transition structures of cyclization of unsubstituted substrates were first calculated with the density functional theory (DFT) method using the B3LYP hybrid functional[15] as in our previous work.[6] Structures were optimized with the basis set (denoted as 631LAN) consisting of the LANL2DZ basis set including a double-ζ valence basis set with the Hay and Wadt effective core potential (ECP)[16] for Rh and the 6–31G(d) basis set[17] for C, H, N and O. As in the previous studies,[6] dirhodium tetraformate was employed as a Rh catalyst in the interest of computational time. Transition structures were adequately characterized by normal coordinate analysis (one imaginary frequency for a transition structure). To estimate the activation barrier of the reaction, the starting Rh-carbene complex precursors were partially optimized at the same level of theory (until the energy change becomes less than 0.01 kcal/mol).

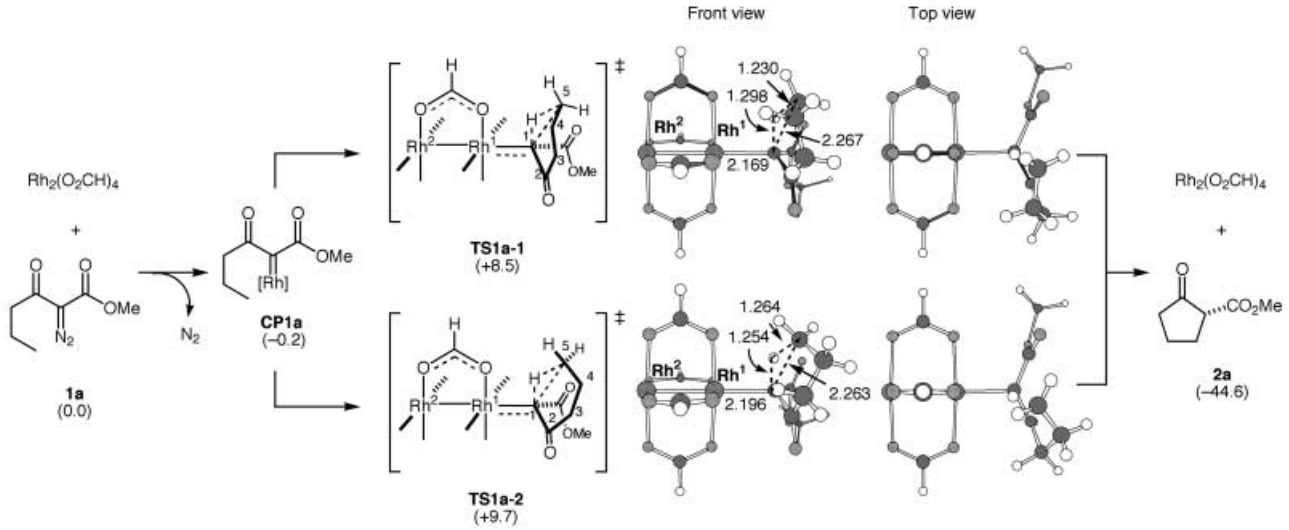
In the second stage, appropriate substituents were attached to the optimized transition structure of the simple models to investigate the stereoselectivity of cyclization. These structures were optimized at the PM3(tm)[18] level: The rhodium carboxylate (carboxamidate) was fixed throughout the calculation because the PM3 method does not give correct geometry for $Rh_2(O_2CH)_4$. The interatomic distances among the carbene carbon and the carbon and the hydrogen atoms of the reacting C–H bond are also fixed, since the C–H insertion transition structure depends very much on the theory used.[19] The Rh-carbene bond was allowed to rotate, however. With these structural constraints (denoted as PM3/B3LYP model), the PM3-optimized structures showed reasonable agreement with the B3LYP-optimized structures (differences of bond lengths and bond angles are $< 2\%$ and $< 4\%$, respectively). Structures of chiral complexes $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MACIM})_4$ were taken from Cambridge Crystallographic Database. For these systems, the Rh atoms and the pyrrolidone (or the imidazolidinone) moieties were fixed throughout the calculations. DFT and semi-empirical calculations were performed with a Gaussian 98[20] package and MacSpartan Pro ver. 1.0.2 program,[21] respectively. Cartesian coordinates and pdb files of the B3LYP-optimized TSs and the step-by-step procedures for the semi-empirical calculations are described in the Supporting Information.

A comment on the accuracy of the calculated stereoselectivity is given before describing the results. The agreement between the theory and the experiment was good, while the theoretical selectivity was always much better than reality with a few exceptions. This seems to arise from two factors: One is the structural constraints imposed on the computational models, which would work against a sterically disfavored transition state which may relax in the absence of the constraints. The other is the fact that the selectivity calculation is based on potential energy, not on free energy. The calculated activation energy is small ( $\sim 10$ kcal/mol) and hence the entropy contribution must be quite large in reality.

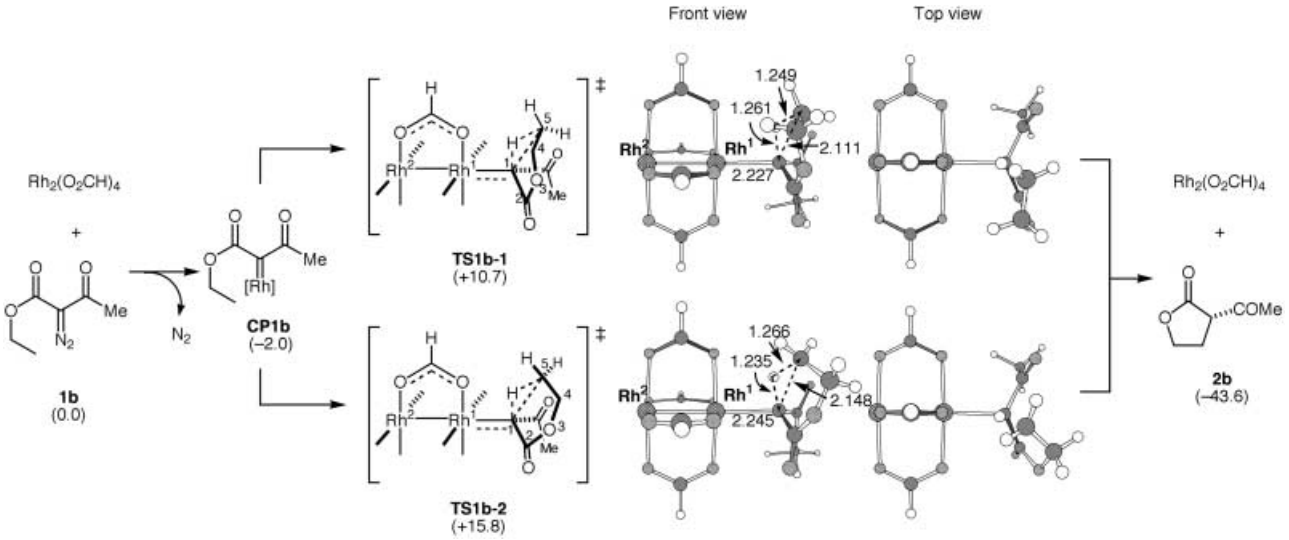
#### *1. Diastereoselectivity in Five-Membered Ring Formation Catalyzed by Achiral Rh Complex*

The cyclization of a model compound **1a** ($E = CO_2Me$, $X = CH_2$, $R = H$) into 2-methoxycarbonylcyclopentanone was first examined at the B3LYP/631LAN level, and two isomeric TSs (half-chair **TS1a-1** and boat **TS1a-2**) were located (Scheme 3). In both TSs, the reaction center takes a six-membered cyclic structure involving the transferred hydrogen atom. The activation energies of cyclization are small (8.7 and 9.9 kcal/mol for **TS1a-1** and **TS1a-2**, respectively). As suggested by the previous




**Scheme 3.** The reaction pathways of the cyclization of a diazocarbonyl compound **1a** into a cyclopentanone **2a**. The numbers in parentheses refer to the energies relative to [**1a** + $Rh_2(O_2CH)_4$ – $N_2$] (kcal/mol). The numbers in 3-D structures refer to bond lengths in Å.




**Scheme 4.** The reaction pathways of the cyclization of a diazocarbonyl compound **1b** into a γ-lactone **2b**. The numbers in parentheses refer to the energies relative to [**1b** + $Rh_2(O_2CH)_4$ – $N_2$] (kcal/mol). The numbers in 3-D structures refer to bond lengths in Å.

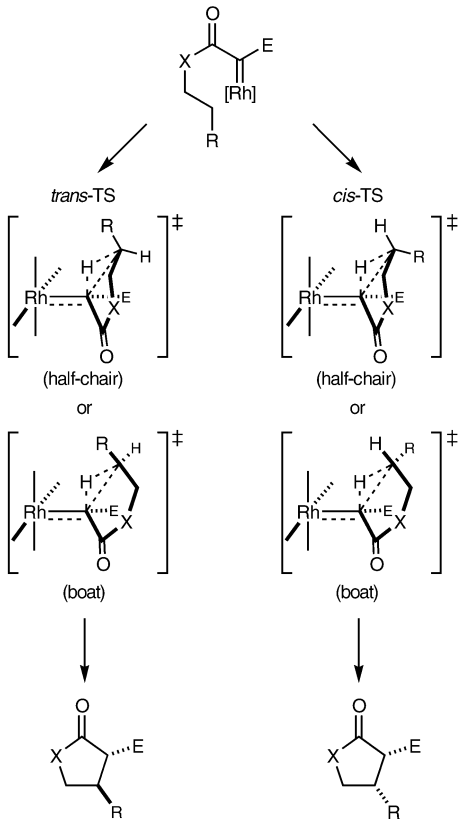
work, these values will significantly decrease when an alkyl substituent is attached on the C5 atom (ca. 5 kcal/mol decrease per one alkyl group).[6] Thus, the activation energy for the real system would be around (or less than) 5 kcal/mol, and the entropy contribution to the Gibbs free energy must be very large.

Similarly, cyclization of **1b** (E = COMe, X = O, R = H) into a γ-lactone was examined also at the B3LYP/631LAN level, and two isomeric TSs (**TS1b-1** and **TS1b-2**) were obtained (Scheme 4). The activation barriers for the half-chair TS (**TS1b-1**) and the boat TS (**TS1b-2**) are 12.7 and 17.8 kcal/mol, respectively. The large difference of the activation energy would arise from the fact that the $Rh^1$-$C^1$-$C^2$=O dihedral angle changes more in the transformation of **CP1b** to **TS1b-2** (91.6° to 64.0°) than in that to **TS1b-1** (91.6° to 83.5°).[6]

With the above structures in hand, the experimentally observed diastereoselectivity was examined by the PM3/B3LYP method for a variety of substituents listed in Table 1. Four isomeric structures were examined for each substituent (Scheme 5). Structures were optimized at the PM3(tm) level with the rhodium carboxylate and the reaction center frozen at the B3LYP geometry (see Computational Details section).[22]

The results are shown in Table 1. In all cases, the most stable TS was the *trans*-TS with half-chair conformation.



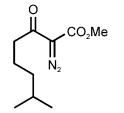
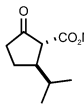
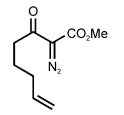
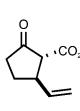
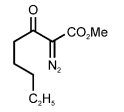
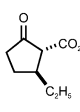
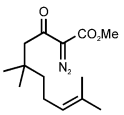
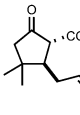
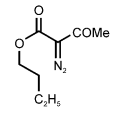
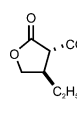
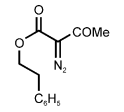
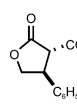

**Scheme 5.** Four diastereomeric TSs of five-membered ring formation.

Product ratio was calculated with energy differences ($\Delta\Delta E^{\ddagger}$) and reaction temperatures described in the literature. In entries 1, 3, 4 and 5, the *trans*/*cis* ratios were calculated to be $>98:2$, which agree with the experimental fact that only the *trans* products were observed in these reactions.

The origin of the diastereoselectivity is illustrated by the analysis of the *trans*- and *cis*-TSs for the case in entry 1 [$R = CH(CH_3)_2$]. Figure 1 shows 3-D structures of the half-chair *trans*-TS and *cis*-TS. In *trans*-TS, the isopropyl group occupies the sterically favored equatorial position of the six-membered ring. On the other hand, in the *cis*-TS, the isopropyl group is in the axial position and suffers from 1,3-diaxial repulsion. Therefore the *trans*-TS becomes favorable compared to the *cis*-TS.

When the substituent is a vinyl or a phenyl group (entry 2 or 6), the *trans*-TS is more stable than the *cis*-TS by only 1.3 and 1.5 kcal/mol, respectively. The calculated *trans*/*cis* ratios are $\sim 91:9$, while only the *trans* product was observed experimentally. This discrepancy would arise from the fixed C–H bond in the present calculations. As suggested by previous studies,[6] the vinyl and the phenyl group should stabilize the cationic carbon of the reacting C–H bond, and hence the cleaving C–H bond would become longer in the TS. This effect would certainly reduce the steric repulsion in the *trans*-TS (but not taken into account in the PM3/B3LYP model).

**Table 1.** PM3/B3LYP modeled relative energies (kcal/mol) of five-membered ring formation TSs (half-chair conformers; boat conformers in parentheses). Product ratios were calculated based on these energy differences.

| Entry | Starting material | Product | *trans*-TS[a] | *cis*-TS[a] | Ref. |
|---|---|---|---|---|---|
| 1[b] |  |  | 0.0 (+4.5) | +4.9 (+4.9) | [7a] |
| | | | > 99.9 : | 0.1 | |
| 2[b] |  |  | 0.0 (+1.3) | +1.3 (+3.8) | [7a] |
| | | | 90.9 : | 9.1 | |
| 3[b,c] |  |  | 0.0 (+3.5) | +2.5 (+7.4) | [7a] |
| | | | 98.5 : | 1.5 | |
| 4[b] |  |  | 0.0 (+2.9) | +6.7 (+2.9) | [7a] |
| | | | 99.2 : | 0.8 | |
| 5[c,d] |  |  | 0.0 (+5.1) | +3.0 (+8.2) | [8] |
| | | | 98.6 : | 1.4 | |
| 6[d] |  |  | 0.0 (+1.3) | +1.5 (+5.3) | [8] |
| | | | 91.0 : | 9.0 | |

[a] Relative energies of half-chair and boat TSs (kcal/mol) are shown in plain and in parentheses, respectively.
[b] The product ratio was calculated with T = 300 K (reaction conditions: $CH_2Cl_2$, rt).
[c] An *n*-octyl group was replaced by an ethyl group.
[d] The product ratio was calculated with T = 350 K (reaction conditions: $C_6H_6$, reflux).

Rh-catalyzed intramolecular C–H insertion can also set three contiguous stereogenic centers in a five-membered ring. A few cases in the literature were examined (Table 2). Since the C–C bond formation sets *trans* geometry as to the forming C–C bond as discussed in the previous paragraphs, only the *trans*/*cis* diastereoselectivity with respect to the existing stereogenic center was considered (Scheme 6).[23]

For the linear substrate in entry 1 of Table 2, the calculations showed good agreement with the experiment. *trans*-*trans*-TSs are much more stable than *trans*-*cis*-TSs, which gives a product ratio of $>99.9:0.1$. As shown in Scheme 7, *trans*-*cis*-TSs are disfavored due to the steric repulsion between the phenyl group and the

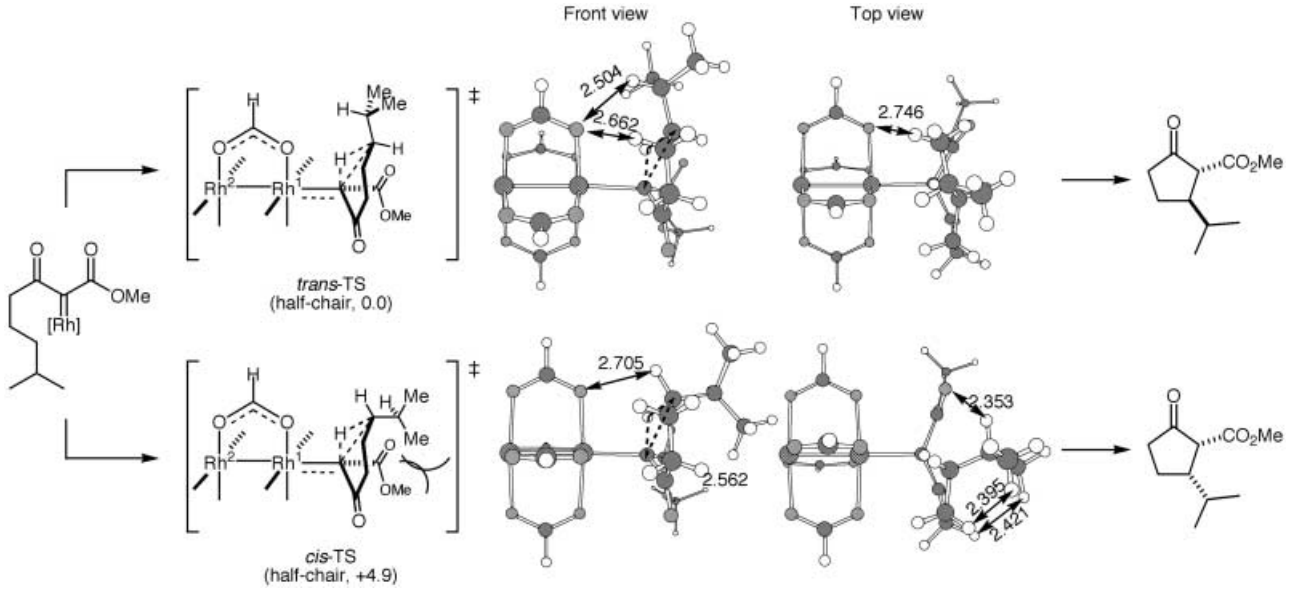
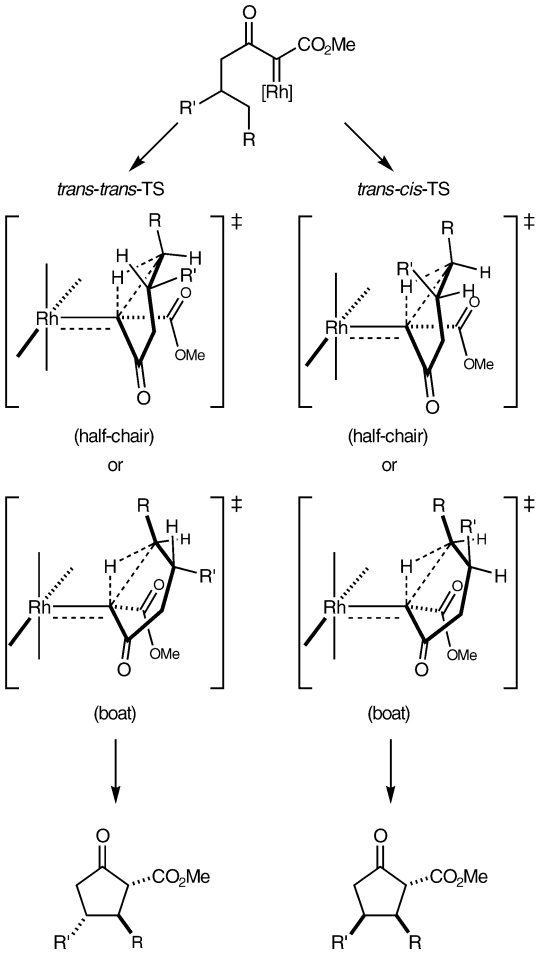
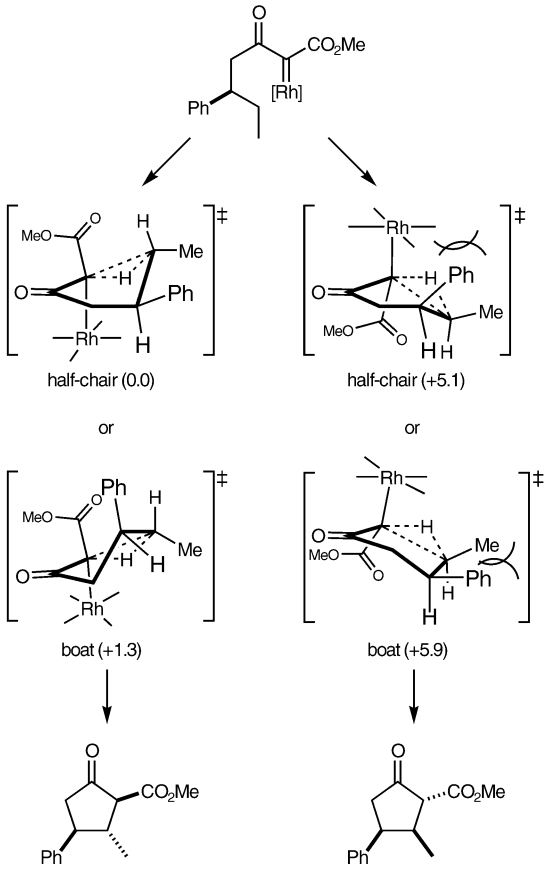



**Figure 1.** 3-D structures of *trans*-TS and *cis*-TS (half-chair conformers) in Table 1, entry 1. The numbers refer to atomic distances in Å.



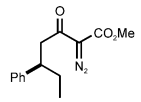
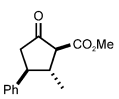
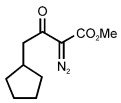
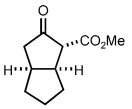
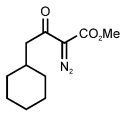
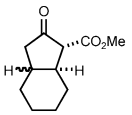

**Scheme 6.** Four diastereomeric TSs of five-membered ring formation with *trans* configuration of the forming C–C bond.




**Scheme 7.** Schematic representation of diastereomeric TSs of cyclization (Table 2, entry 1).

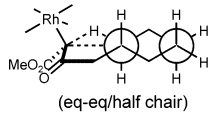
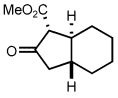
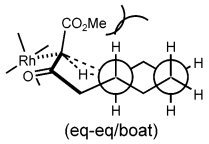
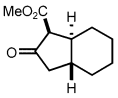
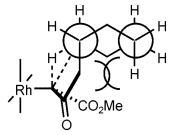
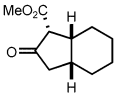
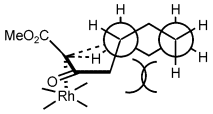
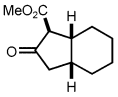
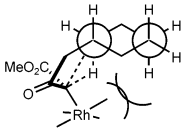
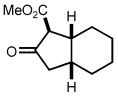
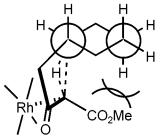
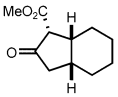
**Table 2.** PM3/B3LYP modeled relative energies (kcal/mol) of five-membered ring formation TSs (half-chair conformers; boat conformers in parentheses).

| Entry | Starting material | Product(s) | *trans-trans* TS[a] | | *trans-cis* TS[a] | Ref. |
|---|---|---|---|---|---|---|
| 1[b] |  |  | 0.0 (+1.3) | | +5.1 (+5.9) | [7b] |
| | | | > 99.9 | : | 0.1 | |
| 2[b] |  |  | 0.0 (–) | | –6.0 (–4.9) | [7c] |
| | | | < 0.1 | : | 99.9 | |
| 3[b] |  |  *trans*:*cis* = 3:1 | 0.0 (–) | | +2.0 (+2.8) | [7c] |
| | | | 95.7 | : | 4.3 | |

[a] Relative energies of half-chair and boat TSs (kcal/mol) are shown in plain and in parentheses, respectively.

[b] The product ratio was calculated with T = 300 K (reaction conditions: $CH_2Cl_2$, rt).

**Table 3.** PM3/B3LYP modeled relative energies (kcal/mol) of all possible conformers of bicyclo[4.3.0] ring formation TS.

| Entry | TS | Relative energy | Product |
|---|---|---|---|
| 1 |  (eq-eq/half chair) | +0.0 |  |
| 2 |  (eq-eq/boat) | +5.4 |  |
| 3 |  (ax-eq/half chair) | +1.8 |  |
| 4 |  (ax-eq/boat) | +2.8 |  |
| 5 |  (eq-ax/half chair) | +2.0 |  |
| 6 |  (eq-ax/boat) | +6.5 |  |

catalyst (half-chair conformer) or the methyl group (boat conformer).

Entries 2 and 3 of Table 2 illustrate the applications to fused bicyclic ring formation reactions. Calculations and experiment showed good agreement in the formation of bicyclo[3.3.0]octane, which gives the *cis*-fused product predominantly (entry 2). The selectivity reflects the product stability, which is so large that it manifests itself already in the TS of C–C bond formation (*cis*-fused product is calculated to be more stable than *trans*-fused one by *ca.* 13 kcal/mol). On the other hand, the diastereoselectivity of the bicyclo[4.3.0] system is a subtle matter (entry 3). The theoretically predicted *trans*/*cis* ratio (95.7:4.3) is consistent with but overestimates trend of *trans*-rich product (*trans*:*cis* = 3:1).

Since the bicyclo[4.3.0] system is a very important ring structure in organic chemistry, it is discussed in more detail. There are *a priori* three approaches of the Rh-carbene to the C–H bond (Figure 2), which are (i) equatorial Rh-carbene inserting to equatorial C–H bond, (ii) axial Rh-carbene to equatorial C–H bond and (iii) equatorial Rh-carbene to axial C–H bond (Figure 4). While the approach (i) gives the *trans*-fused product, the approaches (ii) and (iii) lead to the *cis*-fused product. For each approach, there takes place a facial selection of the Rh-carbene, where the conformation of the reaction center (half-chair or boat) and relative configuration of the newly formed C–C bond are determined. Thus, there are in total six diastereomeric TSs of cyclization (Table 3). Among them, the eq-eq TS with a half-chair conformation (entry 1) is the most stable and gives the *trans-trans* product. The origins of higher energies of other TSs would be unfavorable boat conformation of the reaction center (entries 2, 4, 6), 1,3-diaxial repulsion (entries 3, 4) and steric repulsion between the cyclohexane ring and the Rh carboxylate (entry 5) or the methoxycarbonyl group (entries 2, 6). Precise evaluation of the energetics of all pathways is evidently impossible at the present time because of the lack of theoretical method to accurately evaluate such energetics in terms of free energy.

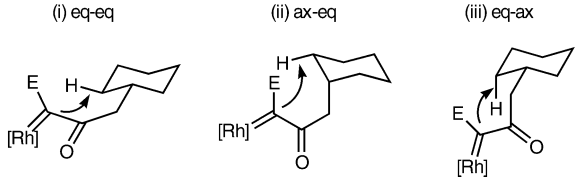



**Figure 2.** Three approaches of the Rh-carbene to the cyclohexane C–H bond.

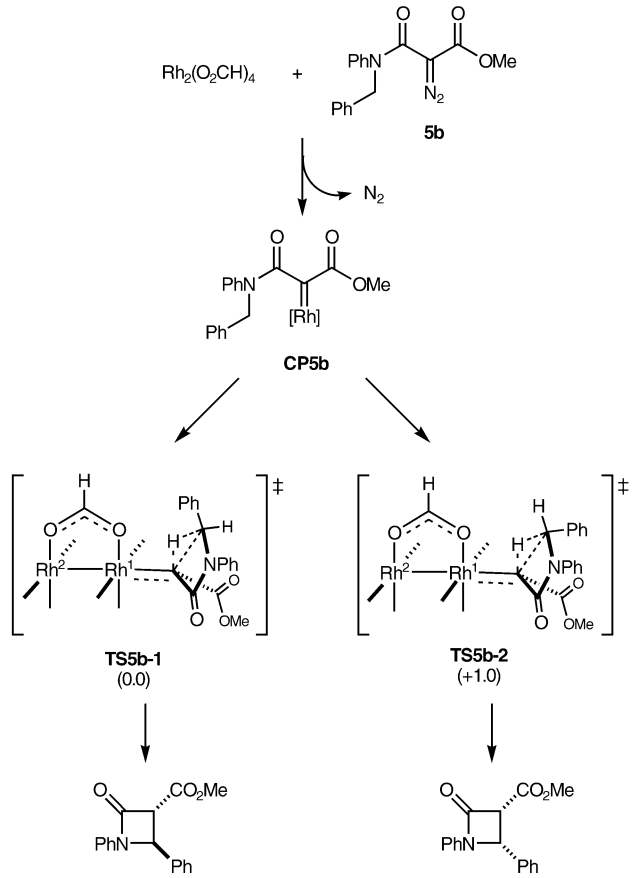
  

*2. Diastereoselectivity in Four-Membered Ring Formation Catalyzed by Achiral Rh Complex*

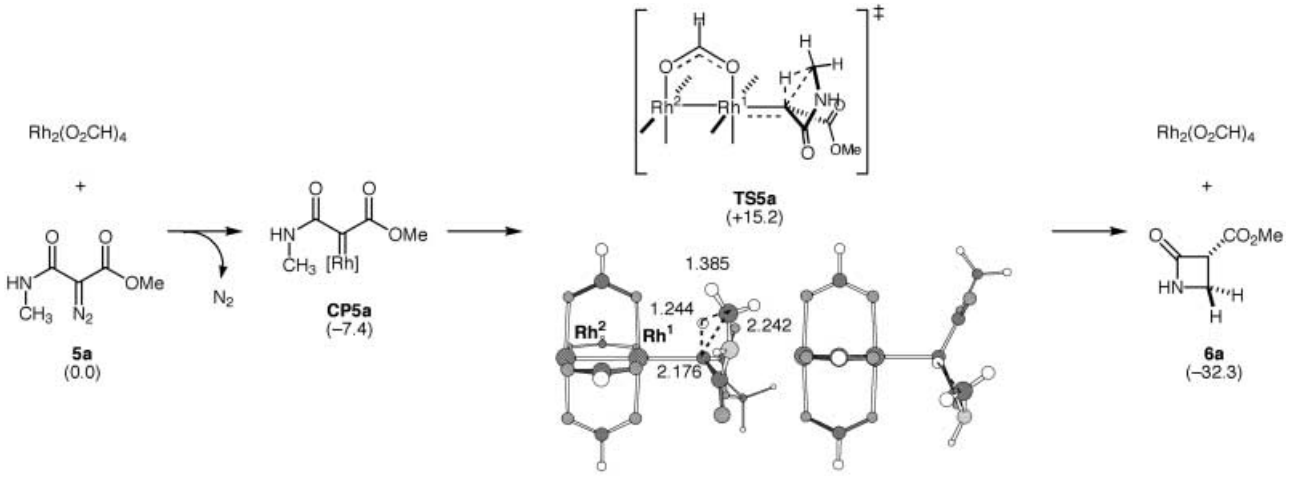
Diastereoselectivity in the β-lactam forming reaction such as the one shown in Eq. (3) was next studied. Cyclization of a model compound **5a** ($R^1 = H$, $R^2 = H$ and $R^3 = CH_3$) was examined at the B3LYP/631LAN level (Scheme 8). A five-membered cyclic transition structure (**TS5a**) was obtained. Although the activation energy of this model is high (22.5 kcal/mol) compared with the five-membered ring formation (*vide supra*), it will decrease as (cation-stabilizing) substituents are attached.

Calculations of the more realistic model ($R^1 = C_6H_5$, $R^2 = C_6H_5$ and $R^3 = CH_3$) **5b** were performed with the PM3/B3LYP modeling (Scheme 9). Although the TS into the *trans*-β-lactam (**TS5b-1**) was more stable than the one into the *cis* isomer (**TS5b-2**), the energy difference (1.0 kcal/mol, corresponding to the *trans*/*cis* ratio of 84 : 16) was too small in the light of the experiment. The disagreement of the calculations and the experiment is similar to the cases of five-membered ring forming reactions involving a vinyl or a phenyl substituent (Table 1, *vide supra*). The steric repulsion in the **TS5b-1** may be overestimated because of the fixed C–H bond in the present calculations.

In the asymmetric β-lactam formation reported by Hashimoto et al., exclusive *cis*-selective cyclization was observed [Eq. (6), $R = C_6H_5$, $CH_2CO_2CH_3$, $C_3H_7$]. This reversal of the stereoselectivity upon changing the achiral catalyst to the chiral one can be understood by the transition structures of cyclization illustrated below (Figure 3). Replacement of the formate ligand with a bulky *S*-PTPA ligand causes significant steric repulsion between the R group (phenyl in Figure 3b) and the benzyl group of the carboxylate ligand in the *trans*-TS. Such repulsion does not occur in the *cis*-TS (Figure 3a). Therefore the thermodynamically unfavorable *cis*-β-lactam is predominantly formed.[24]




**Scheme 9.** Diastereomeric TSs of β-lactam formation from **5b**.




**Scheme 8.** The reaction pathway of the cyclization of a diazocarbonyl compound **5a** into a β-lactam **6a**. The numbers in parentheses refer to the energies relative to [**5a** + $Rh_2(O_2CH)_4$ – $N_2$] (kcal/mol). The numbers in 3-D structures refer to bond lengths in Å.

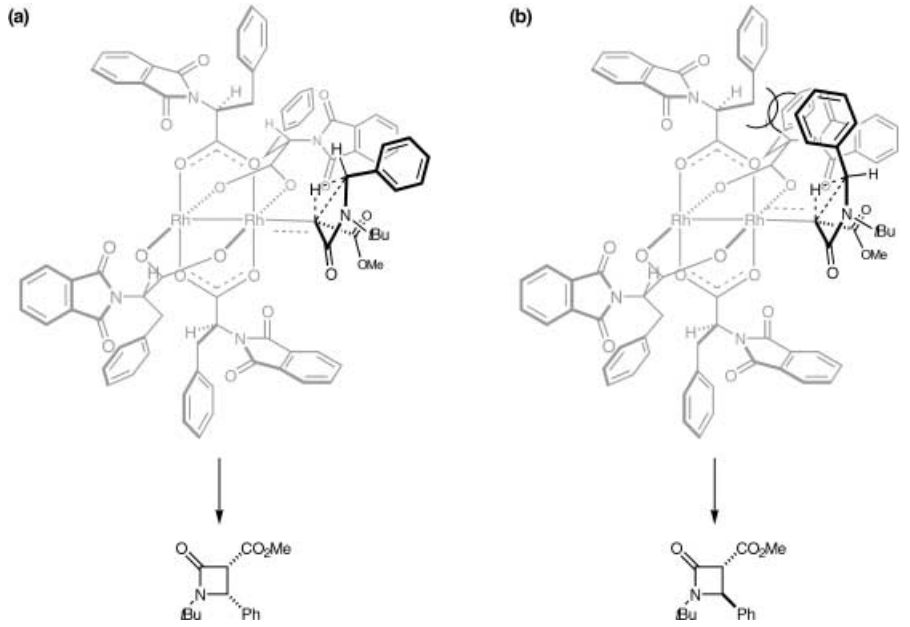
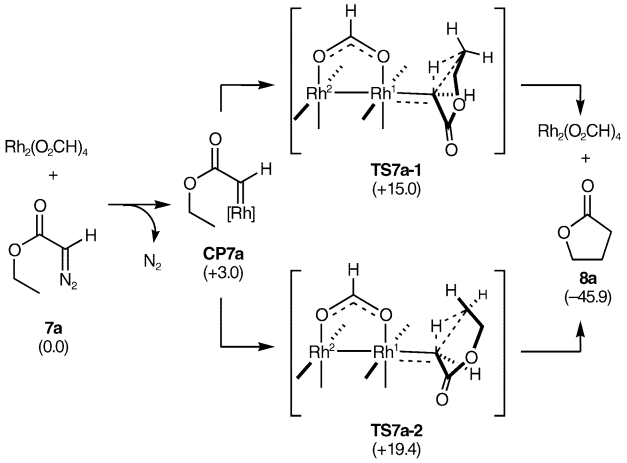



**Figure 3.** Schematic representation of β-lactam formation TSs with $Rh_2$(*S*-PTPA)$_4$ complex.

### *3. Enantio- and Diastereoselectivity in Five-Membered Ring Formation Catalyzed by Chiral Rh Complex*

Enantioselective cyclization is an important topic as illustrated in Eqs. (5) and (6), where γ-lactone derivatives are obtained. To model these reactions, cyclization of an unsubstituted diazoacetate **7a** (R = H) with $Rh_2(O_2CH)_4$ was examined first at the B3LYP/631LAN level (Scheme 10). Both a half-chair TS (**TS7a-1**) and a boat TS (**TS7a-2**) were located, and the energy difference between them was 4.4 kcal/mol. On the basis of these structures, cyclization of **7b** (R = $OCH_3$) with the $Rh_2$(5*S*-MEPY)$_4$ complex was examined with the PM3/B3LYP modeling.

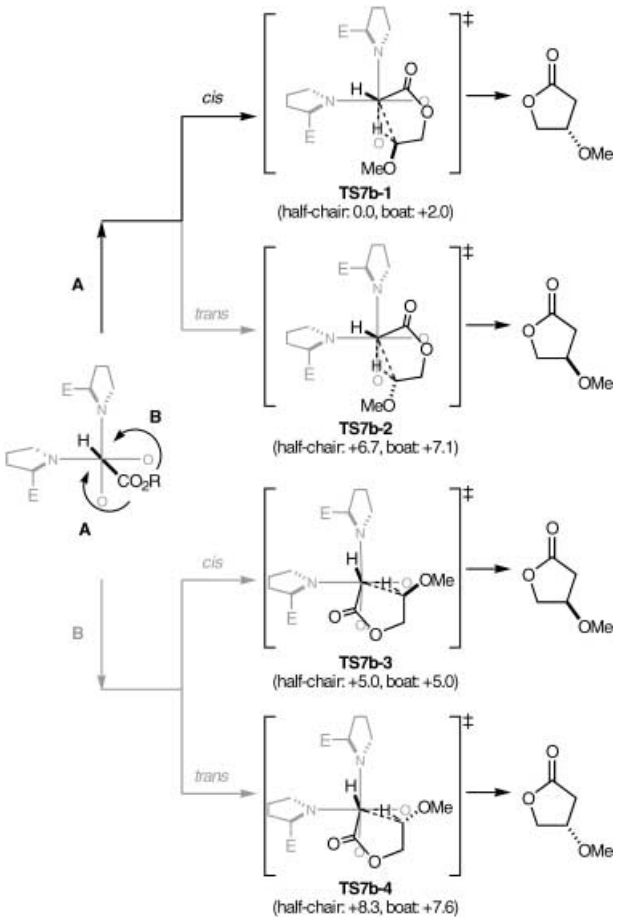
The carbene complex derived from $Rh_2$(5*S*-MEPY)$_4$ and **7b** is shown in Figure 4. The ester group of the carbene ligand is placed in a sterically less hindered position. Unlike an achiral Rh carbene complex, the two faces of the chiral carbene complex are no longer in equal environment. Thus, there are two approaches of the reacting C–H bond (**A** and **B**, Figure 4). For each approach, the methoxy group can be either *cis* or *trans* with respect to the hydrogen atom bonded to the carbene carbon. In addition, both half-chair and boat conformers are possible. Thus, there exist eight transition structures of cyclization as illustrated in Scheme 11. Among them, the most stable transition structure takes the approach **A**, *cis* configuration and half-chair conformation, and gives the *S*-enantiomer of the γ-lactone (Scheme 11, **TS7b-1**). The most stable *R*-enantiomer forming TS was 5.0 kcal/mol higher in energy (**TS7b-3**, the approach **B** and *cis* configuration). Thus, these calculations qualitatively agree with the experiments.




**Scheme 10.** The reaction pathways of the cyclization of a diazocarbonyl compound **7a** into a γ-lactone **8a**. The numbers in parentheses refer to the energies relative to [**7a** + $Rh_2(O_2CH)_4 - N_2$] (kcal/mol).

From Scheme 11, one can find that the face (**A**/**B**) and *cis*/*trans* selectivities are equally critical factors of the enantioselectivity. The conformation of the cyclic TS is less important because the change of the conformation does not cause much energy change while changes of other factors need more energy. The selectivity for the path **A** can be rationalized by the relative orientation of the carbonyl group of the substrate and the ester substituent of the MEPY ligand (Figure 5). In the path **B**, the carbonyl group of the substrate is projected toward the ester substituent of the ligand (Figure 5b), while they lie apart from each other in the path **A** (Figure 5a). Thus, the former TS suffers from steric and




**Scheme 11.** Schematic representation of the carbene complex and the cyclization TSs of **7b** with $Rh_2(5S\text{-MEPY})_4$, which are illustrated along with the C (carbene)-Rh-Rh axis (E = $CO_2Me$, R = $CH_2CH_2OCH_3$, The Rh metals are therefore "hidden" behind the carbene moiety). Relative energies (kcal/mol) of TSs are shown in parentheses.

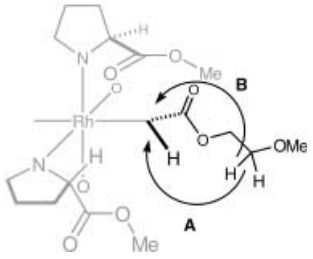



**Figure 4.** Schematic representation of a carbene complex derived from $Rh_2(5S\text{-MEPY})_4$ and **7b**.

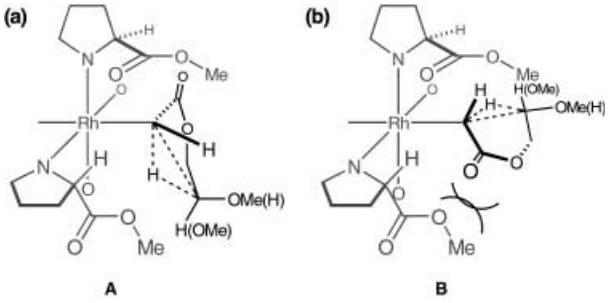



**Figure 5.** Schematic illustration of the face (**A**/**B**) selectivity in the $Rh_2(5S\text{-MEPY})_4$-catalyzed cyclization of **7b**.

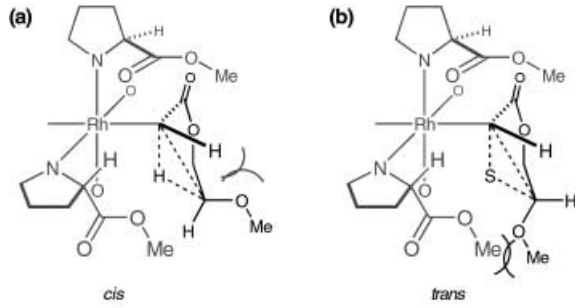



**Figure 6.** Schematic representation of *cis*- and *trans*-TSs (approach **A**) in $Rh_2(5S\text{-MEPY})_4$-catalyzed cyclization of **7b**.

electrostatic repulsion between these polar functionalities.[25]

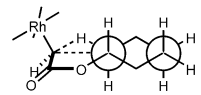
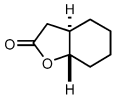
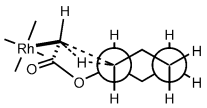
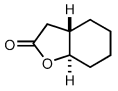
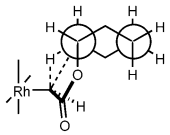
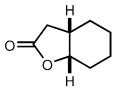
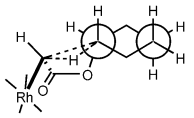
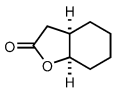
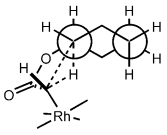
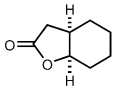
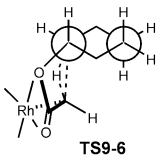
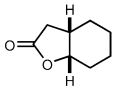
The *cis* selectivity of the present reaction stands in contrast to the *trans* selectivity in the reactions catalyzed by an achiral Rh catalyst (see Section 1). This is due to the change of both the ligand and the substrate. The larger steric bulk of the MEPY ligand destabilizes the *trans*-TS (Figure 6b). In addition, the change of the substituent on the carbene carbon (from a methoxycarbonyl group to a hydrogen) reduces the 1,3-diaxial repulsion in the *cis*-TS and makes it less unstable (Figure 6a). The latter change should play an important role since so far enantioselective intramolecular C–H insertion of disubstituted diazo compounds is not as successful as that of monosubstituted diazo compounds.[26]

Next, bicyclo[4.3.0] ring formation reaction was studied for both the $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MACIM})_4$ complexes [Eq. (4)]. As already described in Section 1, there are six diastereomeric TSs of the bicyclo[4.3.0] ring formation with an achiral Rh complex. When a chiral Rh complex is used, two faces of the carbene carbon become diastereotopic (see Figure 4, path **A** and **B**) and there result twelve diastereometric TSs. Results are shown in Table 4. Similarly to the above results, the path **A** was favored compared with the path **B**. The most stable transition structure (**TS9 – 3**), where the axial-bound Rh carbenoid inserts into the equatorial C–H bond, gives the experimentally dominant *cis*-fused (3a*S*,7a*S*) product (entry 3). As for *trans* ring fusion, the most stable TS (**TS9 – 1**) is 2.8 and 7.0 kcal/mol higher in energy in the MEPY system and the MACIM system, respectively. This is in agreement with the experimental observation that $Rh_2(MACIM)_4$-catalyzed reaction is much more *cis*-selective (99:1) than $Rh_2(MEPY)_4$-catalyzed one (75:25).

The enhancement of *cis* selectivity in the $Rh_2(4S\text{-MACIM})_4$-catalyzed reaction can be rationalized by the

**Table 4.** PM3/B3LYP modeled relative energies (kcal/mol) of bicyclo[4.3.0] ring formation TSs with $Rh_2$(5*S*-MEPY)$_4$ or $Rh_2$(4*S*-MACIM)$_4$ catalyst. The illustration shows TSs of the path **A** and their product. Energies of TSs of the path **B** are shown in parentheses.

| Entry | TS[a] | Relative energy[b] 5*S*-MEPY | 4*S*-MACIM | Product[a] |
|---|---|---|---|---|
| 1 |  TS9-1 | +2.8 (+6.5) | +7.0 (+11.3) |  |
| 2 |  TS9-2 | +7.1 (+12.0) | +9.7 (+20.6) |  |
| 3 |  TS9-3 | 0.0 (+7.7) | 0.0 (+10.1) |  |
| 4 |  TS9-4 | +4.0 (+11.0) | +8.3 (+15.8) |  |
| 5 |  TS9-5 | +4.0 (+10.7) | – (–)[c] |  |
| 6 |  TS9-6 | +6.2 (+11.1) | +7.8 (+15.3) |  |

[a] TSs and products through the path **A** are illustrated.

[b] Energies relative to **TS9-3** (path **A**). Energies of TSs through the path **B** are shown in parentheses.

[c] Calculations were not performed because of inevitable overlap of the ligands and the cyclohexane ring.

analysis of structures of **TS9 – 1** and **TS9 – 3** (Figure 7). Being similar to the $Rh_2$(5*S*-MEPY)$_4$-catalyzed reaction of **7b** (Scheme 11), the chiral environment created by the 4*S*-MACIM ligands places the cyclohexane ring on the same side with the *N*-acetyl group of the ligand. Thus, significant steric repulsion between the cyclohexane ring and the acetyl group results in **TS9 – 1**. In fact, the acetyl group in **TS9 – 1** is significantly distorted to avoid the cyclohexane ring (Figure 7b). This should make *trans* ring fusion much less favorable.

It is also noted that the enantiomeric excess in the *trans*-fused product is lower in the MACIM system (65% ee) than in the MEPY system (91% ee) [Eq. (6)]. In fact, the energy difference between **TS9 – 1** and **TS9 – 2** is larger in the MEPY system (4.3 kcal/mol) than in the MACIM system (2.7 kcal/mol). This fact can be rationalized as follows: As described above, in the MACIM system, **TS9 – 1** is much destabilized by the steric repulsion between the acetyl group and the cyclohexane ring. On the other hand, **TS9 – 2** is not as much destabilized as **TS9 – 1** because the distance between the cyclohexane ring and the acetyl group is longer. In fact, the distortion of the acetyl group is smaller in **TS9 – 2** than in **TS9 – 1** (Figure 7b). Therefore the energy difference between them becomes smaller than that of the MEPY system.

## Conclusions

In summary, the present studies have addressed the origin of diastereo- and enantioselectivity in several cyclization reactions of diazo compounds that proceed *via* intramolecular C–H insertion of Rh-carbene complexes. A *n*-membered ring formation reaction proceeds *via* [n + 1]-membered cyclic transition state involving the transferred hydrogen atom. The stereoselectivities are controlled by the conformation of the [n + 1]-membered ring, the substitution pattern of the substrate and the steric environment created by the ligands, and these factors are closely engaged with each other. Although still unsatisfactory for precise prediction of experimental results, the calculations succeeded in reproducing the experimental selectivities in a semi-quantitative manner. The present work has provided a computational procedure and model structures that may be utilized by bench chemists who explore the Rh-catalyzed intramolecular C–H insertion reactions. While admittedly incomplete, the present theoretical procedure (see Supporting Information) will be useful to make predictions of the enantioselectivity by a new chiral ligand.

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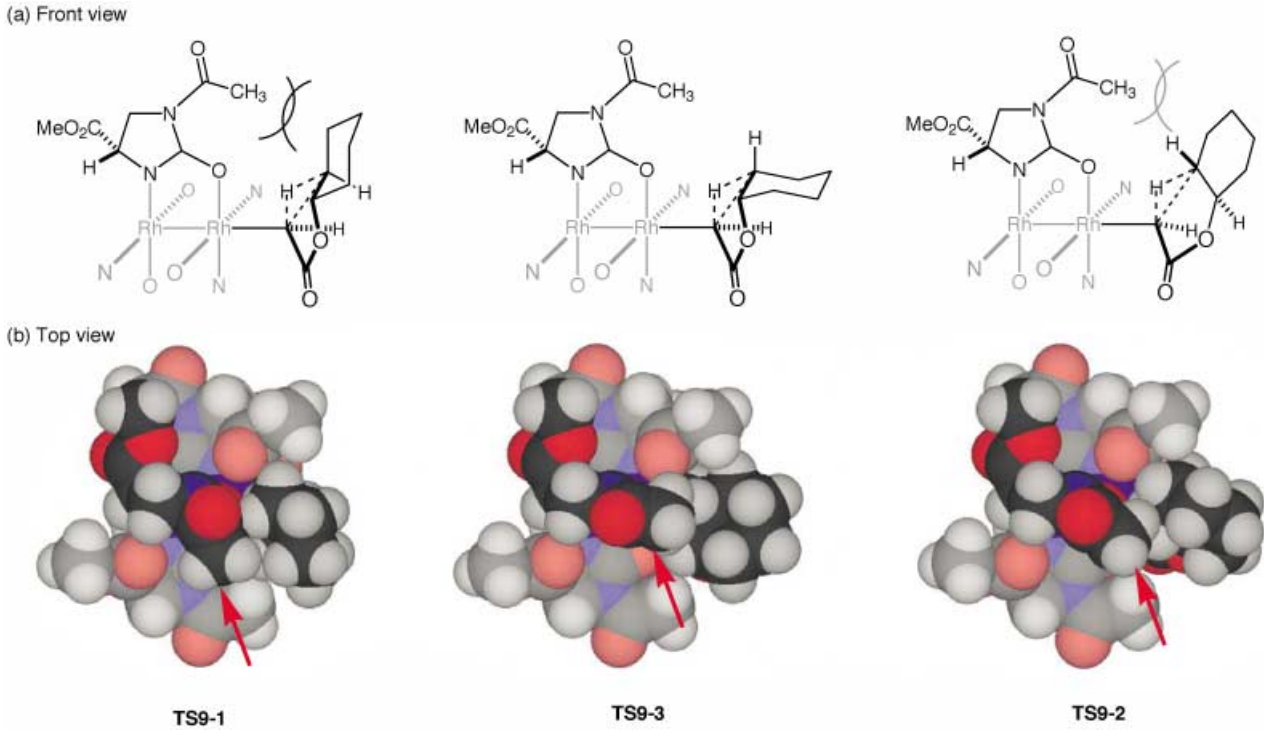


**Figure 7.** (**a**) Schematic representations and (**b**) space-filling models of the bicyclo[4.3.0] ring formation TSs with $Rh_2$(4*S*-MACIM)$_4$ complex. The deep-colored moieties of the space-filling models correspond to the parts of schematic representations drawn by black lines. Arrows indicate the acetyl group.

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[23] The *cis-trans* and *cis-cis* TSs were also examined, and *trans*/*cis* selectivities with respect to the forming C–C bond were calculated to be 98.8:1.2 (entry 1), 98.7:1.3 (entry 2) and 95.3:4.7 (entry 3), which qualitatively reproduced the experimental results.
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