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Density Functional Theory Study of the Mechanism and Origins of Stereoselectivity in the Asymmetric Simmons−Smith Cyclopropanation with Charette Chiral Dioxaborolane Ligand

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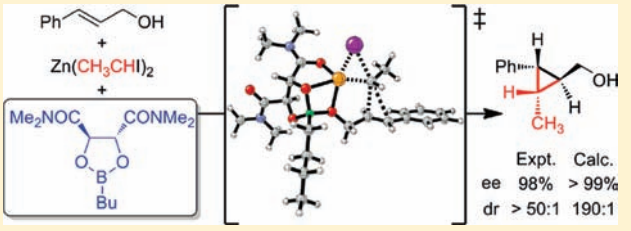
Supporting Information

ABSTRACT: Asymmetric Simmons−Smith reaction using Charette chiral dioxaborolane ligand is a widely applied method for the construction of enantiomerically enriched cyclopropanes. The detailed mechanism and the origins of stereoselectivity of this important reaction were investigated using density functional theory (DFT) calculations. Our computational studies suggest that, in the traditional Simmons−Smith reaction conditions, the monomeric iodomethylzinc allyloxide generated in situ from the allylic alcohol and the zinc reagent has a strong tendency to form a dimer or a tetramer. The tetramer can easily undergo an intramolecular cyclopropanation to give the racemic cyclopropane product. However, when a stoichiometric amount of Charette chiral dioxaborolane ligand is employed, monomeric iodomethylzinc allyloxide is converted into an energetically more stable four-coordinated chiral zinc/ligand complex. The chiral complex has the zinc bonded to the CH_2I group and coordinated by three oxygen atoms (one from the allylic alcohol and the other two oxygen atoms from the carbonyl oxygen and the ether oxygen in the dioxaborolane ligand), and it can undergo the cyclopropanation reaction easily. Three key factors influencing the enantioselectivity have been identified through examining the cyclopropanation transition states: (1) the torsional strain along the forming C−C bond, (2) the 1,3-allylic strain caused by the chain conformation, and (3) the ring strain generated in the transition states. In addition, the origin of the high anti diastereoselectivity for the substituent on the zinc reagent and the hydroxymethyl group of the allylic alcohol has been rationalized through analyzing the steric repulsion and the ring strain in the cyclopropanation transition states.



INTRODUCTION

Cyclopropane subunits are widely found in many drugs and natural products that possess important biological properties.[1] Cyclopropanes are also found to undergo a wide array of synthetically useful reactions as three-carbon components.[2] Because of these, developing new reactions to synthesize cyclopropanes is a very important field in organic chemistry.[3] Of the same importance in this field is to develop asymmetric cyclopropanation reactions.[3c,d] One reason for this is that most cyclopropane subunits in natural products are chiral. On the other hand, if precursors with chiral cyclopropanes are used in ring-opening transformations, the chirality of the cyclopropanes can be transferred to the final products in most cases. This greatly increases the utility of chiral cyclopropanes in organic synthesis.

The Simmons−Smith (SS) reaction is regarded as a general and efficient process for the synthesis of cyclopropanes from olefins.[4] The importance of chiral cyclopropanes in synthesis has intrigued many groups to develop asymmetric SS reactions with high enantioselectivity through introducing chiral ligands into the reaction system.[5] One of the most successful methods in this field is the enantioselective cyclopropanation of allylic alcohols using a stoichiometric amount of chiral dioxaborolane ligand **1**, prepared readily from tetramethyltartaric acid diamide and butylboronic acid (Scheme 1). This reaction was developed by Charette and co-workers in 1994.[6] Because of its excellent performance, this method has been successfully utilized in the total synthesis of natural products[7] and widely used to provide chiral cyclopropane building blocks for organic synthesis.[8] However, the detailed mechanism of the SS cyclopropanation with Charette chiral dioxaborolane ligand and the origins of its asymmetric induction, which are important for understanding this reaction, optimizing the reaction conditions, and developing new chiral ligands, have not been investigated.

Previous mechanistic studies have shown that the Simmons−Smith cyclopropanation using zinc carbenoids proceeds via a concerted [2 + 1] methylene transfer process.[9] For the SS reaction employing allylic alcohols as substrates, Charette and co-workers demonstrated through NMR experiments that the generation of iodomethylzinc alkoxide complexes from alcohols and $Zn(CH_2I)_2$ is the first step of this reaction.[10] Further DFT calculations by Nakamura and co-workers suggested that the

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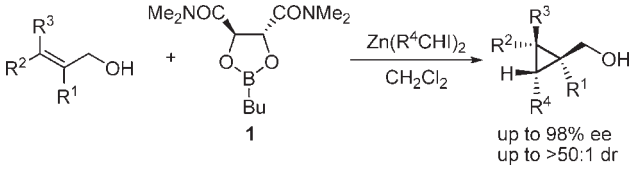
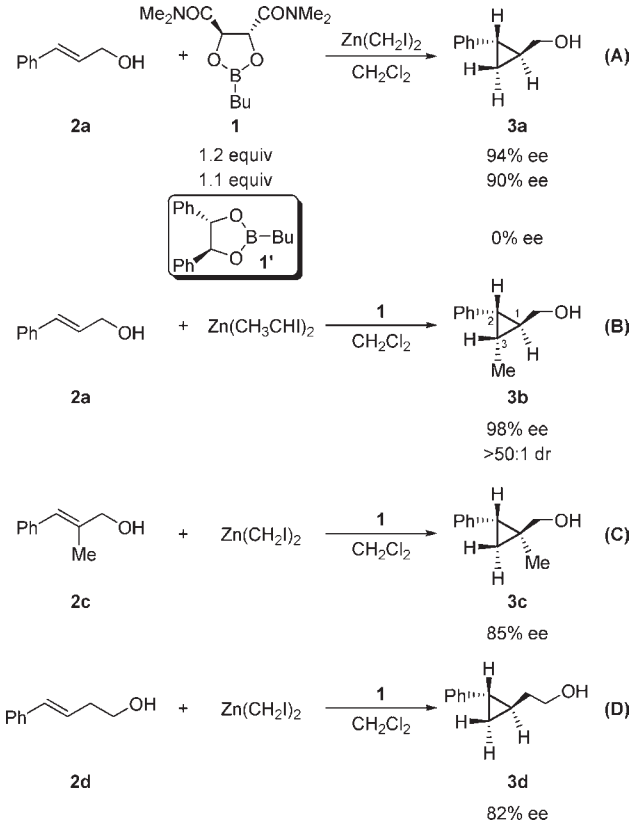
Scheme 1. Charette Asymmetric Modification of the Simmons–Smith Reaction



Scheme 2. Four Representative Reactions and Their Stereochemical Outcomes



monomeric species of halomethylzinc allyloxide is unreactive, but multimetallic aggregate (a dimer or a tetramer) is likely to be a reactive species in the racemic reaction.[9f] For the asymmetric version of this reaction shown in Scheme 1, Charette and co-workers proposed that the cyclopropanation occurs via the formation of a chiral complex between dioxaborolane **1** and iodomethylzinc allyloxide.[6a,e] They hypothesized that the acidic (boron) and basic (carbonyl oxygen of amide) sites of **1** are crucial for allowing the simultaneous complexation of the basic allyloxide and the acidic iodomethylzinc. To clarify these hypotheses and study the reaction mechanism, locating all possible stationary points in the SS reaction with the dioxaborolane ligand and analyzing their structures and energies in reaction A (Scheme 2) are required.

As mentioned above, the Charette modification of the SS reaction is very powerful because a broad scope of allylic alcohols were found to be excellent substrates for the asymmetric cyclopropanation (about 90% ee values were achieved).[6] Unfortunately, this reaction requires a stoichiometric amount of chiral ligand **1**, and its enantioselectivity is highly dependent on the quantity of ligand **1**. For example, in reaction A, when the equivalent of **1** is reduced from 1.2 to 1.1, the ee of product **3a** decreases from 94% to 90% (Scheme 2).[6e] To date, there have been no reports of a significant level of enantiocontrol using a substoichiometric amount of ligand **1**. Therefore, we hoped to use DFT calculations to understand this phenomenon.

Charette and co-workers found that the amide group on ligand **1** is crucial for obtaining high enantioselectivity. The cyclopropanation of **2a** in the presence of chiral dioxaborolane **1′** led to racemic product (see this in reaction A, Scheme 2).[6a] Therefore, our DFT study will answer why this was unsuccessful and give some guidance for the future design of chiral ligands in the asymmetric SS reaction.

In addition to addressing the aforementioned questions, the present DFT calculation results will provide insights into the origins of the stereoselectivity in the Charette modification of the SS reaction using different substrates. For example, the asymmetric SS reaction of cinnamyl alcohol gives cyclopropane **3a** as a single diastereomer with 94% ee when 1.2 equiv of chiral dioxaborolane **1** is used (reaction A, Scheme 2).[6e] However, the key factors that control the enantioselectivity of this reaction have not been disclosed.

Substituted iodomethyl zinc reagents are also suitable for the Charette asymmetric SS reaction, where it is found that both excellent enantioselectivities (90–98% ee) and high diastereoselectivities (from 10:1 to >50:1) can be achieved.[6d] For example, treatment of a mixture of cinnamyl alcohol and ligand **1** with bis(methyliodomethyl)zinc not only results in an excellent diastereomeric ratio (>50:1), but also gives an outstanding ee value (98%) of the major diastereomer **3b** (reaction B, Scheme 2).[6d] In the cyclopropane product **3b**, the methyl group from the zinc reagent is anti to the hydroxymethyl group from the allylic alcohol. However, the origin of this high anti diastereoselectivity has not been clarified either.

It is interesting to note that the cyclopropanation reactions of 2-substituted allylic alcohols and homoallylic alcohols gave relatively lower levels of enantioselectivities (around 80% ee).[6e] For instance, the asymmetric SS reactions of 2-methyl allylic alcohol **2c** and homoallylic alcohol **2d** give cyclopropanes **3c** and **3d** with 85% and 82% ee, respectively (reactions C and D, Scheme 2).[6e] To explain these experimental results, a detailed computational investigation is required.

In what follows, we report our DFT studies of the above four representative reactions A–D (Scheme 2) to address the above-mentioned mechanistic issues.

COMPUTATIONAL METHODS

All DFT calculations were performed with the Gaussian 03 software package.[11] Geometry optimization of all of the minima and transition states involved was carried out at the B3LYP level of theory.[12] Ahlrichs' SVP all-electron basis set[13] was used for the zinc atom, and the 6-31G(d) basis set[14] was used for other atoms except for the iodine atom, for which the LANL2DZ basis set[15] was used. The keyword "5D" in the Gaussian 03 program was used to specify that five (instead of six) d-type orbitals were used for all elements in the calculations. This approach has been successfully applied to investigate a series of racemic SS cyclopropanation reactions by Nakamura and co-workers.[9f,16] The vibrational frequencies were computed at the same level to check whether each optimized structure was an energy minimum or a transition state and to evaluate its zero-point vibrational energy (ZPVE) and thermal corrections at 298 K. To improve the calculation accuracy, single-point

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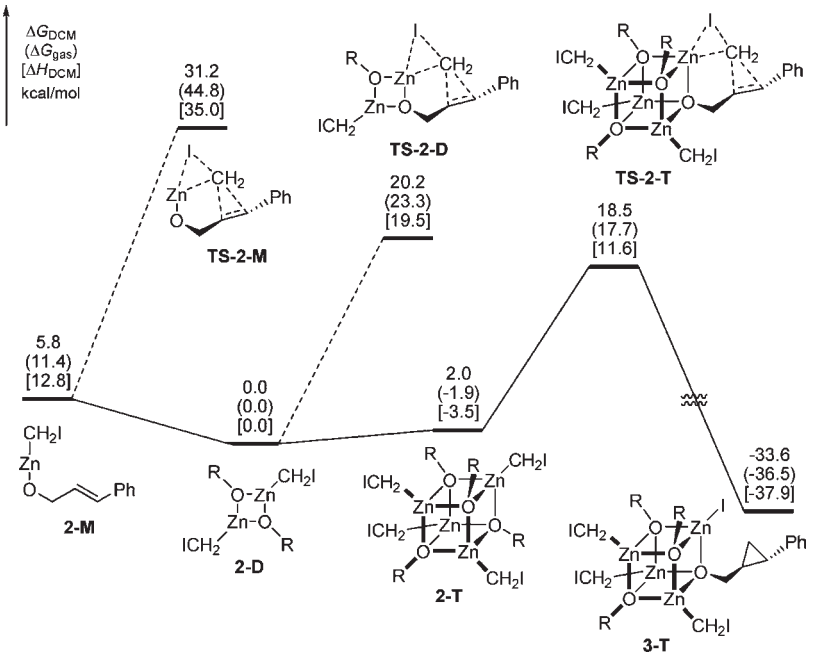

Figure 1. DFT-computed free energy surfaces for the cyclopropanation reactions of monomer **2-M**, dimer **2-D**, and tetramer **2-T** (R = (*E*)-PhCH=CHCH$_2$).

energies and solvent effects were computed at the B3LYP level of theory with the SDD basis set[17] for zinc and iodine atoms and the 6-311G(d,p) basis set[14] for the other atoms, based on the gas-phase-optimized structures.[18] Solvation energies in dichloromethane were evaluated by a self-consistent reaction field (SCRF) using the CPCM model,[19] where the simple united atom topological model (UA0) was used to define the atom radii.[20] In this Article, all discussed energies are Gibbs free energies in dichloromethane (ΔG_{DCM}) unless specified. The Gibbs free energies in gas phase (ΔG_{gas}) and the enthalpies in dichloromethane (ΔH_{DCM}) are also given for reference.

RESULTS AND DISCUSSION

1. Structures and Reactivities of Iodomethylzinc Allyloxide Complexes in the Simmons–Smith Cyclopropanation. The first step of the Simmons–Smith reaction using allylic alcohols as substrates is the generation of iodomethylzinc alkoxides from alcohols and Zn(CH$_2$I)$_2$. Charette's NMR experiments showed that this step is rapid and highly effective, as evidenced by the quantitative formation of CH$_3$I at −20 °C.[10] Further experimental studies on the structures of halomethylzinc alkoxides by Charette and co-workers suggested that the zinc species exists as a monomer in benzene but a tetramer in the solid phase.[10] However, Nakamura's computational studies on the racemic SS reaction of the allylic alcohol indicated that the monomeric species of chloromethylzinc allyloxide is quite unreactive, and a multimetallic aggregate (either a dimer or a tetramer) is likely to be a reactive species.[9f] To achieve an asymmetric reaction with high enantioselectivity, suppressing the racemic background reaction is an essential prerequisite. Therefore, to study the mechanism and provide an unambiguous understanding of the asymmetric SS reaction employing allylic alcohols as the substrates, we have to compare the racemic background reaction and the reaction using a stoichiometric amount of chiral ligand.

We first studied the structures and reactivities of the zinc species in the racemic reaction pathway. DFT-optimized structures of the monomeric iodomethylzinc alkoxide **2-M** derived from cinnamyl alcohol and its dimer **2-D** and tetramer **2-T** are given in Figure 1. Our computational results indicate that aggregates **2-D** (1/2 mol) and **2-T** (1/4 mol) in dichloromethane are more stable than **2-M** (1 mol) by 5.8 and 3.8 kcal/mol in terms of free energy, respectively. This is due to the highly coordinative unsaturation of the Zn(II) atom in monomer **2-M** with a coordination number of only two, while the coordination numbers of Zn(II) in dimer **2-D** and tetramer **2-T** are three and four, respectively. In **2-T**, four zinc and four oxygen atoms form a cubic structure, and the three Zn–O bond lengths are 2.07, 2.09, and 2.10 Å (Figure 2). This DFT-optimized tetramer structure is very close to the X-ray crystal structure of the iodomethylzinc alkoxide tetramer derived from 4-methoxylbenzyl alcohol, in which three Zn–O bond lengths are 2.04, 2.05, and 2.12 Å, respectively.[10]

To evaluate the reactivities of **2-M**, **2-D**, and **2-T** in the cyclopropanation, we located their corresponding cyclopropanation transition states **TS-2-M**, **TS-2-D**, and **TS-2-T** (Figure 1). It is found that the lowest-energy transition state among them is **TS-2-T**. This indicates that tetramer **2-T** is the most reactive species for the cyclopropanation. From this, we know that the background cyclopropanation requires an overall activation free energy of 18.5 kcal/mol (from **2-D** to **TS-2-T**). Charette and co-workers reported that the (*E*)-PhCH=CHCH$_2$OZnCH$_2$I was not stable for a long period of time at −20 °C, and its corresponding cyclopropane product appeared within 24 h.[10] This suggests that the racemic SS reaction is an easy process. The DFT-computed low energy barrier (18.5 kcal/mol) is in good agreement with this experimental observation.

In the Charette asymmetric SS reaction (Scheme 1), a stoichiometric amount of chiral dioxaborolane ligand **1** (usually 1.2 equiv) is necessary to achieve high enantioselectivity.[6] Charette and co-workers proposed that the iodomethylzinc allyloxide monomer first reacts with ligand **1** to produce a chiral zinc complex. In their proposed structure of the complex, the central zinc atom has a coordination number of three, coordinated by the carbon atom of

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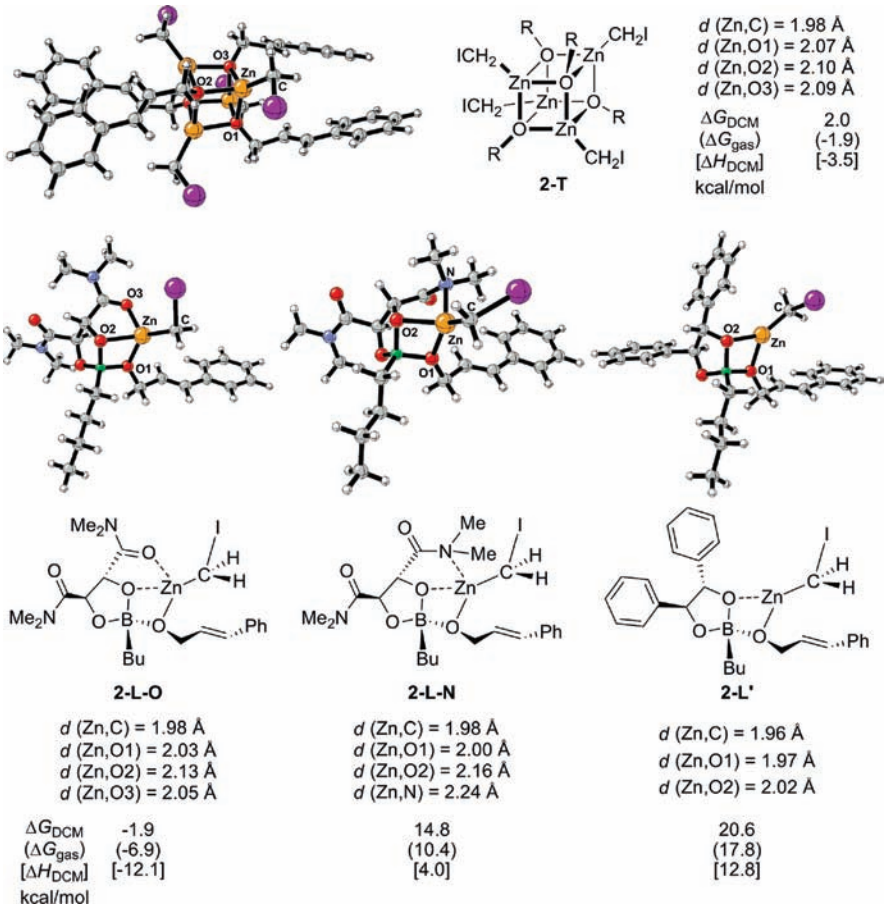

Figure 2. DFT-optimized structures of iodomethylzinc allyloxide complexes **2-T**, **2-L-O**, **2-L-N**, and **2-L′** (carbon, gray; hydrogen, white; oxygen, red; nitrogen, blue; boron, green; zinc, orange; iodine, purple; energies are given in kcal/mol; R = (*E*)-PhCH=CHCH$_2$).

the iodomethyl, the oxygen atom of the allyloxide, and the carbonyl oxygen atom of an amide group in **1**.[6e] However, there has been no experimental evidence for the exact structure of this chiral zinc complex. To better understand the structure and reactivity of this important intermediate in the asymmetric SS reaction, we located two complexes, **2-L-O** and **2-L-N**, generated from the monomeric iodomethylzinc allyloxide **2-M** and dioxaborolane **1**. In complex **2-L-O**, not only the carbonyl oxygen atom (O3) of the amide and the oxygen atom (O1) of the allyloxide coordinate to the zinc atom, but also the oxygen atom (O2) of the dioxaborolane is involved in the coordination (Figure 2). We also attempted to locate the hypothetic zinc complex without the Zn−O2 coordinate bond proposed by Charette and co-workers. However, all DFT optimizations of such hypothesized species led to **2-L-O**, implying that the four-coordinated zinc complex **2-L-O** is much more stable than the originally proposed three-coordinated one. Complex **2-L-N** is also a possible structure of the reactive intermediate, in which the nitrogen atom of the amide group works as the coordinating atom (Figure 2). Although the coordination number of the zinc atom in **2-L-N** is still four, **2-L-N** is energetically less stable than **2-L-O** by 16.7 kcal/mol. This means that the Zn−O3 bond in **2-L-O** is much stronger than the corresponding Zn−N bond in **2-L-N**, which is in accordance with the fact that the bond energy of Zn−O bond is usually higher than that of Zn−N bond.[21] As mentioned before, in the absence of ligand **1**, dimer **2-D** is the most stable zinc complex, which is in equilibrium with the reactive cyclopropanation precursor **2-T**. However, in the presence of a stoichiometric amount of ligand **1**, dimer **2-D** (1/2 mol) can be efficiently transformed to the chiral complex **2-L-O** (1 mol) because this process is exergonic by 1.9 kcal/mol in CH_2Cl_2 (Figure 3). This ensures that, under the conditions of Charette asymmetric modification, the chiral zinc complex **2-L-O** is the most stable intermediate in the reaction system.

We then located the lowest-energy cyclopropanation transition state **TS-3a** connecting **2-L-O** and the chiral product **3-L-O** (Figure 3, and for detailed discussion on the enantioselectivity of this reaction, see section 2.1). Calculations show that the activation free energy barrier for cyclopropanation from **2-L-O** is 18.3 kcal/mol, which is close to that from dimer **2-D**. As mentioned above, dimer **2-D** is 1.9 kcal/mol less stable than **2-L-O**. This means that the overall activation free energy for the generation of the racemic cyclopropane product is 20.4 kcal/mol (**2-L-O** → **2-D** → **2-T** → **TS-2-T**; Figure 3), which is 2.1 kcal/mol higher than that for the formation of the chiral product via **TS-3a**. Therefore, in the case of using a stoichiometric amount of chiral dioxaborolane ligand **1**, the racemic background SS reaction can be efficiently suppressed, making the enantioselective pathway dominant. In contrast, when substoichiometric chiral ligand **1** is used (suppose it is x equivalent, here $x < 1$), the reaction system will mainly have complexes of **2-L-O** (x equivalent) and **2-D** ($0.5 - x/2$ equivalent). In this case, **2-L-O** will give one cyclopropane product enantioselectively, while **2-D** (via **2-T**) gives a mixture of racemic products. This is because the residual achiral **2-D** (via **2-T**) in the reaction system reacts as fast

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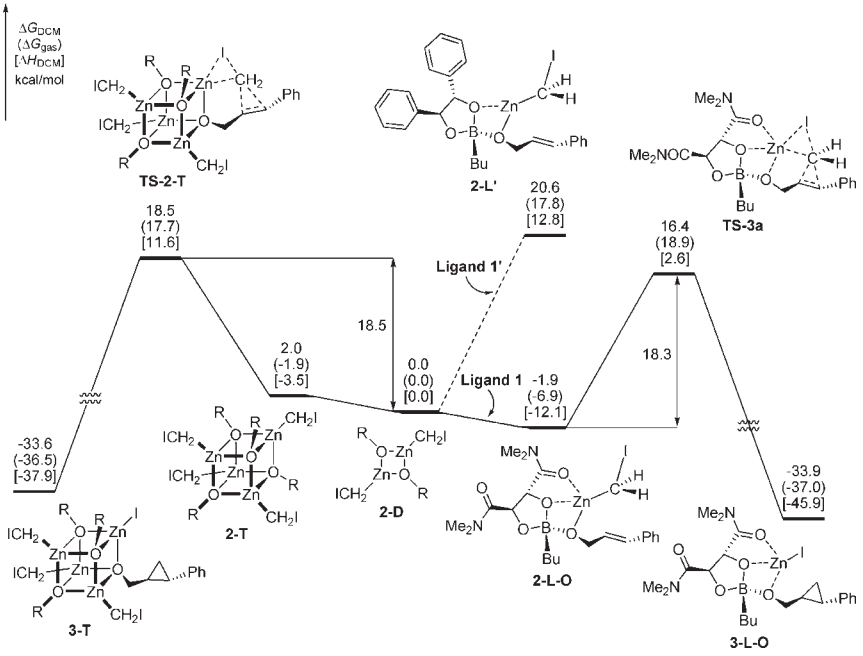

Figure 3. DFT-computed free energy surfaces for the cyclopropanation reactions of tetramer **2-T** and the chiral zinc complex **2-L-O** (R = (*E*)-PhCH=CHCH$_2$).

as the chiral complex **2-L-O** (18.5 versus 18.3 kcal/mol, Figure 3). Therefore, when using substoichiometric chiral ligand **1**, the generation of racemic cyclopropanes from the background reaction cannot be suppressed. This is the main reason why Charette asymmetric modification of the SS reaction has not been developed into a catalytic version. On the other hand, the B−O bond in product **3-L-O** is not labile. Therefore, the interchange between **3-L-O** and **2-T** to generate **2-L-O** and **3-T** may be not facile kinetically, although this process is exergonic by 3.6 kcal/mol in CH_2Cl_2.

Charette and co-workers reported that the cyclopropanation of cinnamyl alcohol employing dioxaborolane **1′** derived from chiral 1,2-diphenyl-1,2-ethanediol as ligand could only give the racemic product (reaction A, Scheme 2).[6a] To explain this phenomenon, we located the chiral zinc complex **2-L′**, which could undergo the enantioselective cyclopropanation (Figure 2). However, formation of this three-coordinated zinc complex is extremely disfavored because **2-L′** is 2.1 kcal/mol higher than transition state **TS-2-T** of the background SS reaction (Figure 3). This implies that the added chiral ligand does not take part in the cyclopropanation reaction in this case, and the reaction completely proceeds through the background cyclopropanation process (via **TS-2-T**) to give the racemic product (Figure 3). Through comparing the energies and structures of **2-L′** and **2-L-O** (Figures 2 and 3), we conclude that the strong coordination of the carbonyl oxygen on Charette ligand **1** to the Zn(II) center can greatly stabilize the chiral zinc intermediate, making the enantioselective pathway more favorable than the background reaction leading to racemic products. This is crucial for obtaining high enantioselectivity in the Charette asymmetric SS reaction. Our calculations suggest that, for a future designed chiral ligand, it must have at least two strong coordinating atoms to ensure the designed chiral ligand can form a four-coordinated zinc complex that is much more stable than tetramer **2-T**.

2. Origins of Stereoselectivity in Charette Asymmetric Modification. *2.1. Which Factors Influence the Enantioselectivity?* The asymmetric cyclopropanation of allylic alcohol **2a** gives product **3a** as a single diastereomer with 94% ee (reaction A, Scheme 2). The stereospecific formation of cyclopropane **3a** with the hydroxymethyl and phenyl group in a trans configuration is due to the concerted methylene transfer transition state, via which the stereochemical information in the alkene substrate is maintained in the product.[9] However, the key factors influencing the enantioselectivity have not been established. Therefore, we located two transition states **TS-3a** and **TS-*ent*-3a** corresponding to the generation of experimentally observed product **3a** and its enantiomer (Figure 4). It is found that **TS-3a** is 3.2 kcal/mol lower than **TS-*ent*-3a** in CH_2Cl_2 in terms of free energy, giving a predicted ee of 99%. This is close to the experimental result (94% ee).[6e]

Through examination of the structural features of transition states **TS-3a** and **TS-*ent*-3a**, we found three key factors influencing the enantioselectivity of the Charette asymmetric SS reaction (Figure 4).[22] First, the torsional strains[23] in the intramolecular cyclopropanation transition states are responsible for the experimentally observed enantioselectivity. The transition state structure **TS-3a** has a staggered conformation along the developing C2−C3 bond, as evidenced by the H1−C2−C3−C4 dihedral angle of 66°. However, in the energetically disfavored **TS-*ent*-3a**, the corresponding H1−C2−C3−C4 dihedral angle is only 33°, suggesting that the torsional strain in **TS-*ent*-3a** is much more severe than that in **TS-3a**. This claim is also supported by the H−H distances shown in Scheme 3. In **TS-*ent*-3a**, the hydrogen atom H^a on the methylene moiety experiences stronger steric repulsion[22] from H^b on the C=C double bond because the distance of H^a and H^b is 0.33 Å shorter than the H1−H^b distance in **TS-3a** (2.35 versus 2.68 Å, Scheme 3). Second, the conformation of the allyloxide chain is also an important factor in determining the enantioselectivity for this asymmetric cyclopropanation reaction. Charette and co-workers proposed that the C4−C3−C5−O6 chain adopts an *s-trans* conformation in the favored transition state.[6e] Our computational study confirmed this

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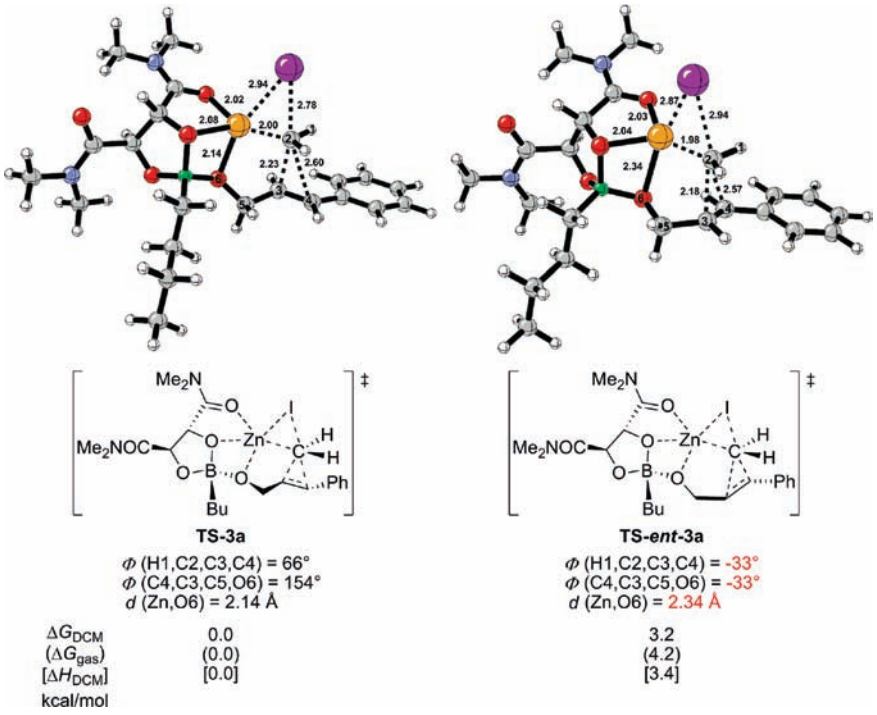
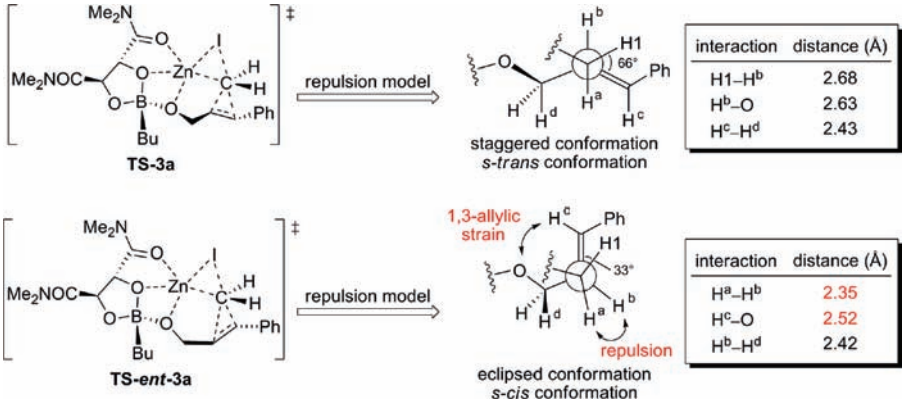


Figure 4. DFT-computed structures of cyclopropanation transition states and their relative energies in reaction A (carbon, gray; hydrogen, white; oxygen, red; nitrogen, blue; boron, green; zinc, orange; iodine, purple; energies are given in kcal/mol, and distances are given in angstroms).

Scheme 3. Repulsion Models of Transition States TS-3a and TS-*ent*-3a



hypothesis. In the energetically favored **TS-3a**, the C4−C3−C5−O6 dihedral angle is 154°, very close to an *s-trans* conformation. In contrast, the allyloxide chain in **TS-*ent*-3a** adopts an *s-cis* conformation with the C4−C3−C5−O6 dihedral angle of 33°. Because of the *s-cis* conformation of the allyloxide chain in **TS-*ent*-3a**, an extra 1,3-allylic strain[24] is experienced in this cyclopropanation transition state. A support for this conclusion can be found in Scheme 3, which shows that the H^c−O distance in **TS-*ent*-3a** is 2.52 Å, which is 0.11 Å shorter than the H^b−O distance in **TS-3a**. Third, we discovered that the ring strains generated in transition states are critical to the high enantioselectivity as well. As discussed in section 1, the distance between the zinc atom and the oxygen atom of the allyloxide is 2.03 Å in the cyclopropanation precursor **2-L-O** (Figure 2). In **TS-3a**, the corresponding Zn−O6 distance stretches to 2.14 Å because of the strain of the five-membered ring (Zn−O6−C5−C3−C2) formed in the transition state (Figure 4). It is notable that the Zn−O6 distance in **TS-*ent*-3a** becomes much longer than that in **TS-3a** (2.34 versus 2.14 Å, Figure 4). This means that **TS-*ent*-3a** suffers a stronger ring strain as compared to **TS-3a**. The aforementioned three factors exist in all asymmetric SS reactions of allylic alcohols using Charette chiral ligand, so their cumulative effect will determine the enantioselectivities of these reactions. For most allylic alcohol substrates, the effects of these three factors on the enantioselectivity are synergetic, resulting in the generation of cyclopropylmethanols with high ee values.

2.2. What Is the Origin of High Anti Diastereoselectivity? In the asymmetric SS reaction of cinnamyl alcohol with bis(methyliodomethyl)zinc, both excellent diastereomeric ratio (>50:1) and ee value (98%) are obtained (reaction B, Scheme 2). In the major diastereomer **3b**, the methyl group from the zinc reagent is anti to the hydroxymethyl group from the allylic

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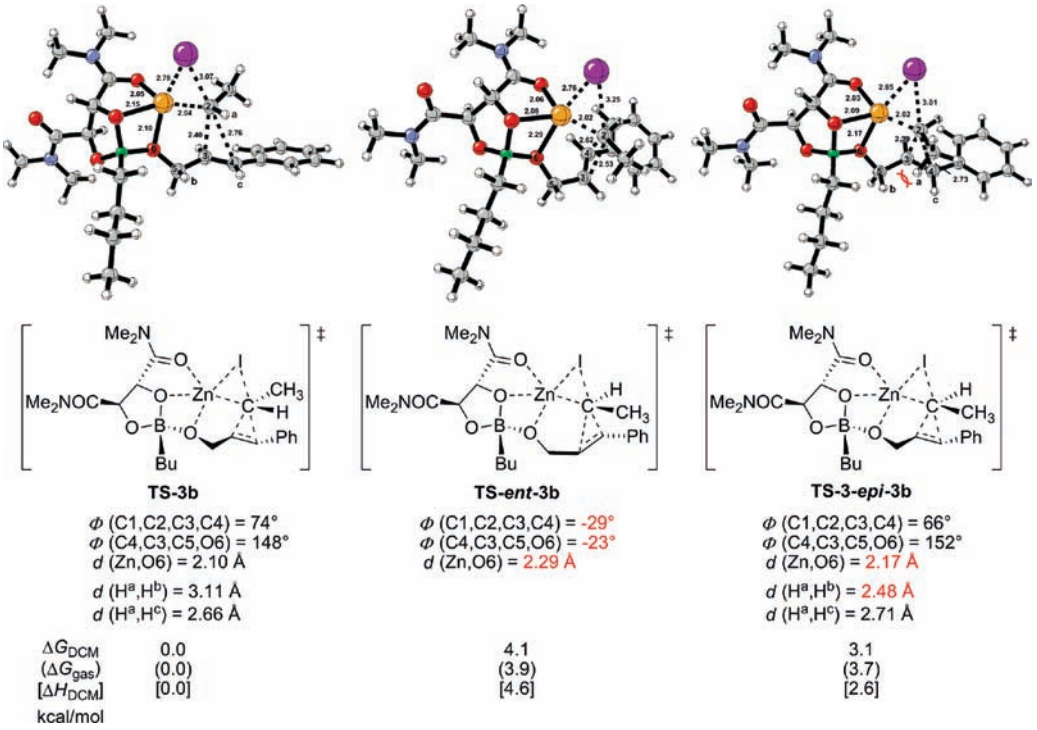

Figure 5. DFT-computed structures of cyclopropanation transition states and their relative energies in reaction B (carbon, gray; hydrogen, white; oxygen, red; nitrogen, blue; boron, green; zinc, orange; iodine, purple; energies are given in kcal/mol, and distances are given in angstroms).

alcohol. To investigate whether the aforementioned three factors still influence the enantioselectivity and rationalize the high anti diastereoselectivity of this reaction, we located three cyclopropanation transition states, **TS-3b**, **TS-*ent*-3b**, and **TS-3-*epi*-3b**, corresponding to the generation of experimentally observed product **3b**, its enantiomer, and its 3-epimer, respectively (Figure 5). The calculations show that the free energy difference between **TS-3b** and **TS-*ent*-3b** is 4.1 kcal/mol in CH_2Cl_2, predicting an enantiomeric excess of over 99%, and that the free energy difference between **TS-3b** and **TS-3-*epi*-3b** is 3.1 kcal/mol in CH_2Cl_2, giving a predicted diastereomeric ratio of 190:1. These computational results are in good agreement with the experimental values (98% ee, >50:1 dr).[6d]

Comparison between the transition states **TS-3b** and **TS-*ent*-3b** shows that the observed excellent enantioselectivity in reaction B can also be well explained by three key factors that we have found in reaction A. First, the torsional strain along the developing C2−C3 bond in **TS-*ent*-3b** is much more serious than that in **TS-3b** because the H1−C2−C3−C4 dihedral angle in **TS-*ent*-3b** is only 29° (Figure 5). Second, the allyloxide chain in **TS-*ent*-3b** adopts a less favored *s-cis* conformation, as depicted by the C4−C3−C5−O6 dihedral angle of 23° (Figure 5). Third, **TS-*ent*-3b** has a bigger ring strain, as evidenced by a longer Zn−O bond distance in this transition state (2.29 versus 2.10 Å, Figure 5). These three factors all prefer **TS-3b** to **TS-*ent*-3b**. As a result, the generation of cyclopropane **3b** via **TS-3b** is much more favorable than the formation of its enantiomer via **TS-*ent*-3b**.

When bis(methyliodomethyl)zinc is used as methylene transfer reagent, a new stereocenter is generated in the cyclopropane. The orientation of the methyl group in the transition states determines the diastereoselectivity of this reaction. In **TS-3b**, the methyl group and the C5 group are in an anti conformation, while in **TS-3-*epi*-3b**, they are in a syn conformation. Through analyzing the structures of transition states **TS-3b** and **TS-3-*epi*-3b**, we found that in **TS-3-*epi*-3b**, the distance between H^a and H^b is 2.48 Å (Figure 5), close to the sum (2.40 Å) of their van der Waals radii.[25] This indicates that there is a strong steric repulsion[22] between the methyl group on the zinc reagent and the C5 group of the allyloxide. Besides, the Zn−O6 bond distance in **TS-3-*epi*-3b** is slightly longer than that in **TS-3b** (2.17 versus 2.10 Å, Figure 5). This implies that the five-membered ring strain in **TS-3-*epi*-3b** is more severe than that in **TS-3b**. Because of these two reasons, the formation of cyclopropane **3b** with anti diastereoselectivity between the substituent of the zinc reagent and the hydroxymethyl group of the allylic alcohol is more favorable.

2.3. Why Do Cyclopropanations of 2-Substituted Allylic Alcohols Give Lower ee? In the cyclopropanation reactions of 2-substituted allylic alcohols, a relatively lower level of enantioselectivity was observed. For instance, substitution of a methyl group at the C2 position of cinnamyl alcohol decreases the ee of the product from 94% to 85% (reaction C, Scheme 2). To probe the reasons for this decrease in enantioselectivity, we located two cyclopropanation transition states **TS-3c** and **TS-*ent*-3c** corresponding to the generation of major product **3c** and its enantiomer (Figure 6). It is found that the free energy difference between these two transition states is 1.3 kcal/mol in CH_2Cl_2, giving a predicted ee of 80%. This result coincides with the experimentally observed tendency.[6e]

As mentioned in section 2.1, there are three main factors influencing the enantioselectivity of the asymmetric SS reaction using Charette ligand. For the SS reaction of cinnamyl alcohol (reaction A), three factors all prefer **TS-3a** to **TS-*ent*-3a** (Figure 4). However, in the case of 2-methyl cinnamyl alcohol (reaction C), we found only two favored factors for **TS-3c**. One is

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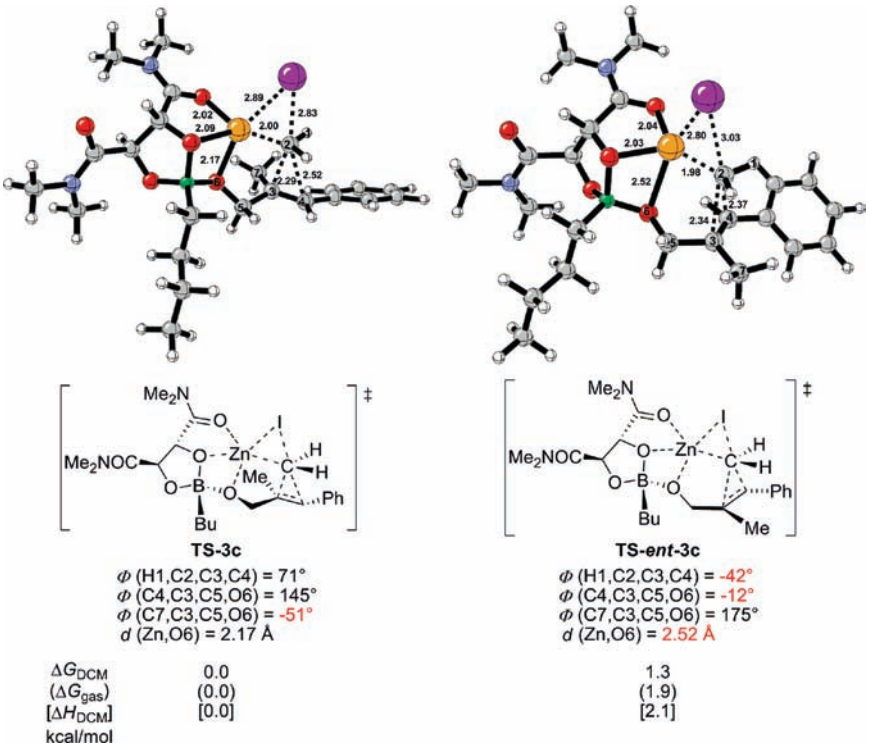
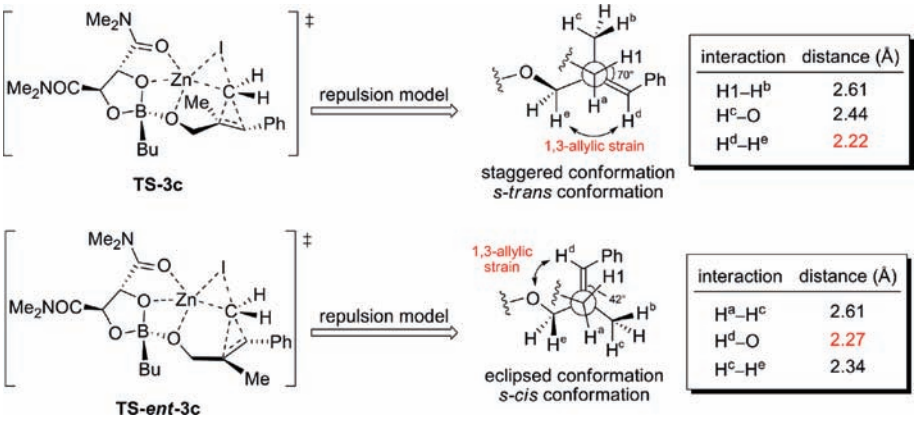


Figure 6. DFT-computed structures of cyclopropanation transition states and their relative energies in reaction C (carbon, gray; hydrogen, white; oxygen, red; nitrogen, blue; boron, green; zinc, orange; iodine, purple; energies are given in kcal/mol, and distances are given in angstroms).

Scheme 4. Repulsion Models of Transition States TS-3c and TS-*ent*-3c



the less torsional strain along the forming C2−C3 bond, as evidenced by the H1−C2−C3−C4 dihedral angle of 71° in **TS-3c** (Figure 6). The other is the less strain of the five-membered ring (Zn−O6−C5−C3−C2) generated in **TS-3c**, which is supported by the shorter Zn−O6 distance (2.17 versus 2.52 Å, Figure 6). The effect of the conformation of the allyloxide chain on the enantioselectivity becomes very limited due to the substitution of the methyl group at the C2 position of cinnamyl alcohol. In **TS-*ent*-3c**, the allyloxide chain adopts an *s-cis* conformation, resulting in an obvious 1,3-allylic strain (Scheme 4) as in **TS-*ent*-3a** (Scheme 3). Although the allyloxide chain in **TS-3c** adopts an *s-trans* conformation to avoid the unfavorable interaction between H^d and O, another 1,3-allylic strain is introduced, as evidenced by the short distance of H^d and H^e (2.22 Å, Scheme 4). Because of the absence of a contribution from the allyloxide chain conformation to control the geometry of the cyclopropanation transition states, the enantioselectivities of the SS reactions of 2-substituted allylic alcohols are lower than those of their parent allylic alcohols.

2.4. Why Are Homoallylic Alcohols Not Good Substrates? The Charette SS reaction can also be applied to the asymmetric cyclopropanation of the homoallylic alcohol substrate, but the enantiomeric excess value is not so satisfied (the ee is around 80%). For instance, treatment of a mixture of homoallylic alcohol **2d** and ligand **1** with the zinc reagent in CH_2Cl_2 gives cyclopropane **3d** with 82% ee (reaction D, Scheme 2). To better understand the origin of the enantioselectivity, we investigated the cyclopropanation transition states **TS-3d** and **TS-*ent*-3d** corresponding to the generation of experimentally observed product

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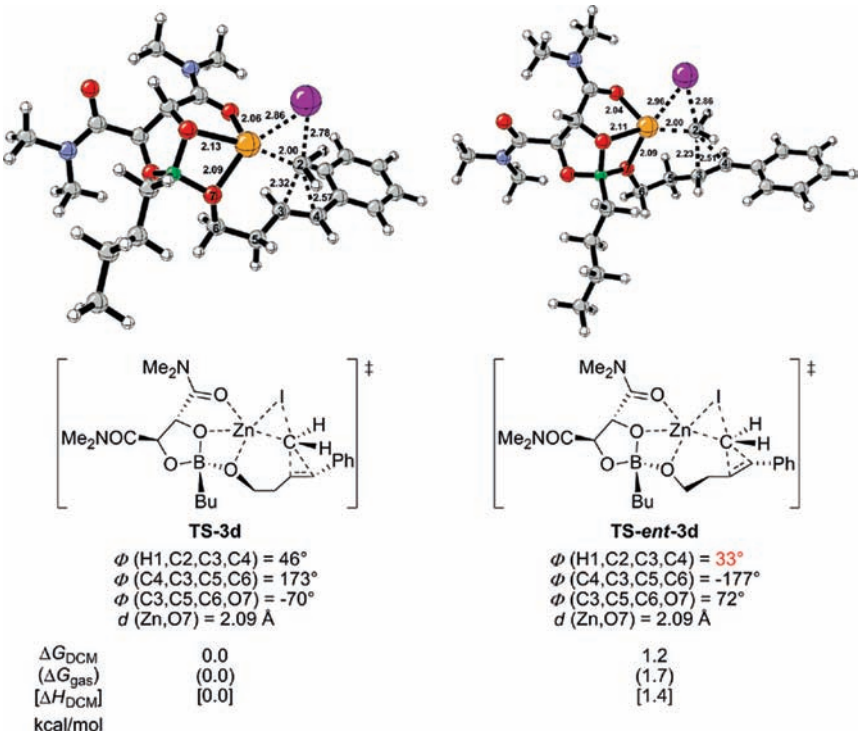

Figure 7. DFT-computed structures of cyclopropanation transition states and their relative energies in reaction D (carbon, gray; hydrogen, white; oxygen, red; nitrogen, blue; boron, green; zinc, orange; iodine, purple; energies are given in kcal/mol, and distances are given in angstroms).

3d and its enantiomer in reaction D (Figure 7). The computational results indicate that the free energy of **TS-3d** is 1.2 kcal/mol lower than that of **TS-*ent*-3d** in CH_2Cl_2, predicting an ee value of 75%. This is close to the experimentally observed ee.[6e]

The three key factors identified from the study of the Charette SS reaction of the allylic alcohol are found to be applicable toward rationalizing the enantioselectivity observed in the asymmetric SS reaction of the homoallylic alcohol. When the substrate is changed from the allylic alcohol to the homoallylic one, one more carbon atom is introduced into the carbon chain, making the homoallyloxide chain more flexible in both transition states **TS-3d** and **TS-*ent*-3d**. For example, the C4−C3−C5−C6 moieties of the homoallyloxide chain in these two transition states both adopt a stable *s-trans* conformation,[26,27] and the C3−C5−C6−O7 moieties are in a favored staggered conformation (Figure 7). Besides, a less strained six-membered ring structure (Zn−O7−C6−C5−C3−C2) is generated in the transition states. In **TS-3d** and **TS-*ent*-3d**, the Zn−O7 bond lengths are both 2.09 Å (Figure 7), which is 0.05 Å shorter than that in the favored transition state **TS-3a** for the cyclopropanation of the corresponding allylic alcohol substrate (Figure 4). Therefore, the conformation of the homoallyloxide chain and the ring strain generated in transition states have no preference for a specific transition state. The dominant factor influencing the enantioselectivity in this case is only the torsional strain along the incipient C2−C3 bond in the cyclopropanation transition states. As shown in Figure 7, the H1−C2−C3−C4 dihedral angle in the energetically disfavored transition state **TS-*ent*-3d** is only 33°, much smaller than the corresponding dihedral angle (46°) in **TS-3d**, suggesting that **TS-*ent*-3d** experiences a stronger steric repulsion than does **TS-3d**. Therefore, we conclude that when the chain is elongated, the influences of the chain conformation and the ring strain in the cyclopropanation transition states are not present, but only the torsional strain is still operational, making the two transition states close in energy. Consequently, a relatively lower level of enantioselectivity is observed using homoallylic alcohols as substrates.

CONCLUSION

In summary, the detailed mechanism and the stereoselectivity of the asymmetric Simmons−Smith cyclopropanation with Charette chiral dioxaborolane ligand have been investigated by DFT calculations. The computational studies suggest that, in the traditional SS reaction conditions, the monomeric iodomethylzinc allyloxide generated in situ from the allylic alcohol and the zinc reagent has a strong tendency to form a dimer or a tetramer. The tetramer can easily undergo an intramolecular cyclopropanation to give the racemic product. However, when a stoichiometric amount of Charette ligand is employed, the monomeric iodomethylzinc allyloxide can be efficiently converted into a four-coordinated chiral zinc/ligand complex. The strong coordination of the carbonyl oxygen on Charette ligand to the Zn(II) center plays an important role in stabilizing this chiral zinc intermediate and suppressing the racemic background reaction. From the reactive chiral zinc complex, a series of asymmetric cyclopropanation transition states toward the experimentally observed products and their stereoisomers have been located. Through examination of the transition state structures, three key factors influencing the enantioselectivity are established: (1) the torsional strain along the forming C−C bond, (2) the 1,3-allylic strain caused by the chain conformation, and (3) the ring strain generated in transition states. For most allylic alcohol substrates, the effects of these three factors on the enantioselectivity are synergetic, resulting in the generation of cyclopropylmethanols with high ee values. For 2-substituted allylic alcohols and

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homoallylic alcohols, the contribution from the chain conformation is very limited, and for homoallylic alcohols, the ring strain generated in transition states can also be neglected. Therefore, the relatively lower levels of enantioselectivities are found in the corresponding cyclopropanation reactions. In addition, the reason for high anti diastereoselectivity between the substituent on the zinc reagent and the hydroxymethyl group of the allylic alcohol is clarified by analyzing the steric repulsion and the ring strain in transition states.

■ ASSOCIATED CONTENT

Supporting Information. Computational details, full citation of ref 11, and Cartesian coordinates of computed stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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