

A Theoretical Study on the Mechanism and Diastereoselectivity of the Kulinkovich Hydroxycyclopropanation Reaction

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Abstract: A detailed mechanism for the Kulinkovich hydroxycyclopropanation reaction has been explored with density functional theory calculations on the reactions between $R^1\text{COOMe}$ and $\text{Ti}(\text{OMe})_2(\text{CH}_2\text{CHR}^2)$ (R^1 and R^2 are hydrogen and alkyl groups). Addition of ester to titanacyclopropane is found to be fast, exothermic, and irreversible. It has a preference for the α -addition manifold over the β -addition manifold in which its cycloinsertion transition states suffer from the steric repulsion between the R^2 and ester. The following intramolecular methoxy migration step is also exothermic with reasonable activation energy. The cyclopropane-forming step is the rate-determining step, which affords the experimentally observed *cis*- R^1/R^2 diastereoselectivity in the α -addition manifold by generating *cis*- R^1/R^2 1,2-disubstituted cyclopropanol when R^1 is primary alkyl groups. On the contrary, the unfavored β -addition manifold offers the diastereoselectivity contradicting the experimental observations. The effects of R^1 and R^2 on the regio- and stereoselectivity are also discussed.

Introduction

The Kulinkovich hydroxycyclopropanation reaction^{1–8} is an efficient synthetic method that allows esters to react with dialkoxytitanacyclopropanes, readily generated in situ from Grignard reagents and $\text{XTi}(\text{O}-i\text{-Pr})_3$ ($X = \text{O}-i\text{-Pr}$, Cl , and Me),

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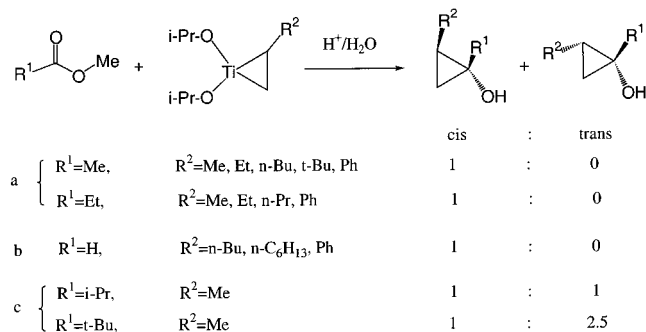
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Scheme 1



or even with subsequent alkene ligand exchange,^{1f,5,6b–d,h} to yield valuable organic intermediate cyclopropanols.⁹ Both intermolecular and intramolecular Kulinkovich reactions have been well developed. In addition to its easy operation, another salient feature of the Kulinkovich reaction is attributed to its *intrinsic* *cis*- R^1/R^2 diastereoselectivity obtained in the absence of any chelating substituents in the substrate: When R^1 is hydrogen or primary alkyl groups, the final 1,2-disubstituted cyclopropanol has its R^1 and R^2 in a *cis* relationship, regardless of the size of R^2 group, as exemplified by several examples shown in Scheme 1a^{2b,c,h,3,7,10} and b.^{2b,c,10} However, when R^1 becomes secondary or tertiary alkyl groups, a mixture of *cis*

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and trans 1,2-disubstituted cyclopropanols can be observed (Scheme 1c¹⁰). Corey et al. have also explored an enantioselective version of this reaction by using a chiral dialkoxytitanacyclopropane catalyst.³

A detailed understanding of the reaction mechanism is necessary to rationalize the observed diastereoselectivity and enantioselectivity, and to design better catalysts with higher enantioselectivity. Figure 1 summarizes the proposed reaction mechanism in the literature by Kulinkovich^{1a,2b,c} and Corey³ along with our own thoughts.

The catalytic version of the Kulinkovich reaction is initiated by the ligand-exchange reaction of Grignard reagent with Ti(OR)₄ affording a metastable dialkyl titanium complex, which, in turn, undergoes β -hydride elimination to produce the reactive species of titanacyclopropane and the corresponding alkane (Figure 1).¹¹ Like other metal-alkene and -alkyne complexes of Ti and Zr, the dialkoxytitanacyclopropane complex is still a putative species. Nevertheless, its rich chemistry has been exploited intensively in organic synthesis.^{1,12–15}

The following reaction between ester and titanacyclopropane is the key part of the Kulinkovich hydroxycyclopropanation, which is assumed to start with a formation of complex (COM), followed by cycloinsertion reaction to produce an oxatitanacyclopentane intermediate (IN1). An intramolecular methoxy migration from the former carbonyl carbon atom to the titanium atom then transforms IN1 to a second intermediate (IN2). Finally, an intramolecular cyclopropane-forming step converts IN2 to titanium cyclopropanolate (TCP) complex (Figure 1). To complete the catalytic cycle, the TCP reacts with alkylmagnesium bromide to regenerate dialkyl titanium complex with a concomitant liberation of magnesium cyclopropanolate, which is eventually hydrolyzed to the ultimate product, cyclopropanol.

When R² \neq H, the formation of IN1 has two distinctive manifolds, α -addition and β -addition, leading to α -IN1 and β -IN1, respectively. The regiochemistry encountered in this step

could be critical since the two intermediates could potentially result in very different diastereoselectivities. At present, there is no solid evidence to prefer one to the other. For example, Kulinkovich first preferred β -addition manifold^{2c} and later favored the α -addition manifold.^{2f} Corey preferred the β -addition manifold primarily based on the observation that zirconium-catalyzed carbomagnesiation of olefins occur in a β -addition fashion.¹⁶

In this paper, we present a detailed theoretical study on the mechanism of the Kulinkovich hydroxycyclopropanation reaction. Detailed reaction potential energy surfaces have been obtained to support the preference of the α -addition over the β -addition manifold. The rate-determining cyclopropane-forming step is also the stereo-determining step, which reproduces the experimentally observed cis-R¹/R² diastereoselectivity to give cis 1,2-disubstituted cyclopropanol in the α -addition manifold. In contrast, the cyclopropane-forming step offers the opposite diastereoselectivity in the unfavored β -addition manifold.

Computational Strategy and Details

Four reactions have been studied, as shown in Scheme 2. For the reactions I and II, the detailed mechanism was explored. Each structure was fully optimized with the B3LYP^{17–19} method using the HW3 basis set according to Frenking's definition,²⁰ which was constructed by the contraction scheme [3311/2111/311] + ECP²¹ on a 10-electron core for the titanium atom and the 6-31G* basis set for carbon, oxygen, and hydrogen atoms. Harmonic vibrational frequencies were calculated for each structure of reaction I.²² For reaction II, this calculation was limited to several key species, including **10c**, **11c**, **14**, **15c**, **15t**, **17t**, **18t**, **22c**, and **22t** (see Figure 4 for the labeling of these stationary points), to understand the features of the regio- and stereoselectivities.

For reactions III and IV, calculations were carried out for several structures related to their respective regio- and stereochemistry.

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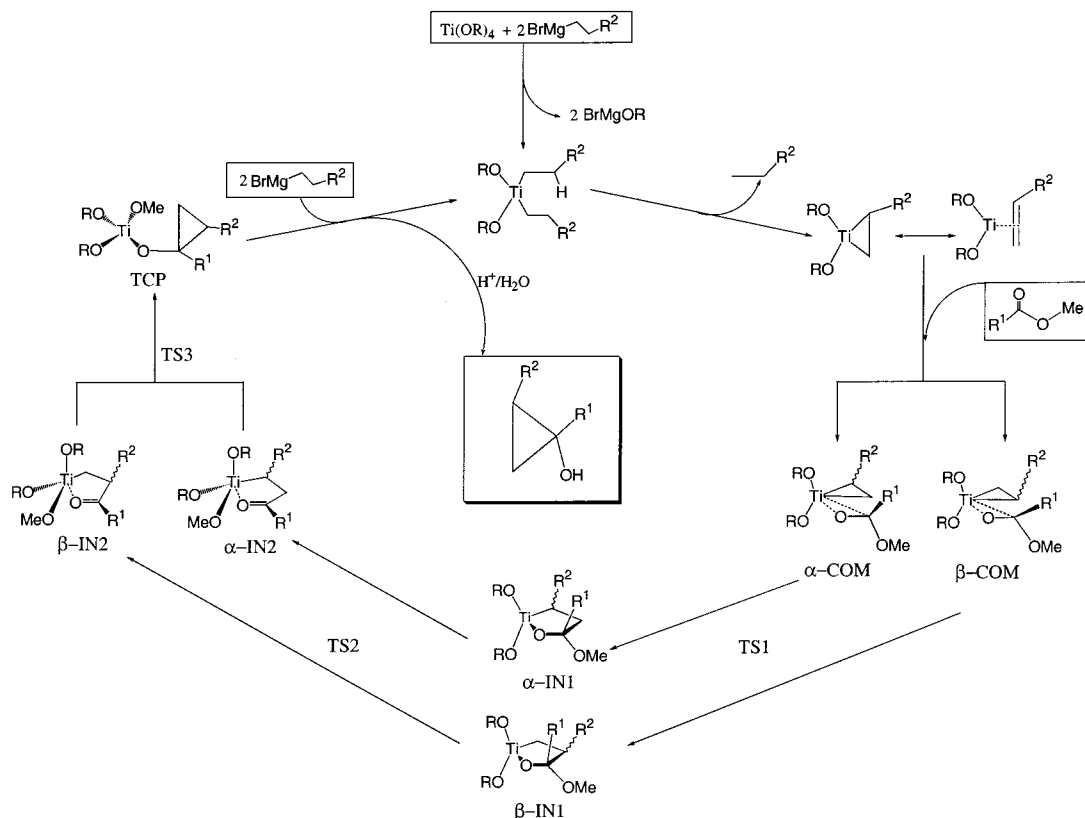


Figure 1. Proposed reaction mechanism for the Kulinkovich hydroxycyclopropanation carried out between $R^1\text{COOMe}$ and 2 equiv of $\text{BrMgCH}_2\text{CH}_2\text{R}^2$ in the presence of $\text{Ti}(\text{OR})_4$.

Scheme 2

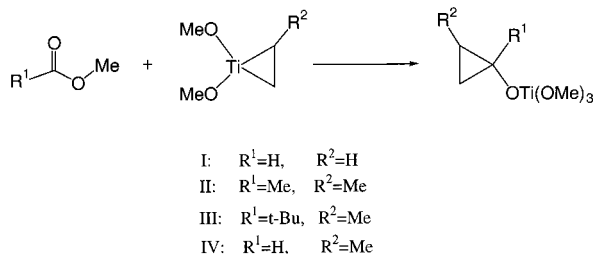


Table 1. B3LYP/HW3 Computed Reaction Parameters for the Stationary Points of Reaction I with $R^1 = R^2 = \text{H}^a$

	1 + HCOOMe	2	3	4	5	6	7	8
ΔE_{ele}	0.0	-15.8	-15.1	-39.5	-22.9	-43.4	-26.8	-56.0
ΔE_0	0.0	-13.8	-12.9	-36.1	-20.9	-42.1	-25.7	-54.1
ΔH_{298}	0.0	-14.0	-13.7	-36.9	-22.0	-42.2	-26.3	-55.0
ΔG_{298}	0.0	-1.6	0.1	-22.8	-6.1	-28.8	-11.6	-41.9

^a ΔE_{elec} , ΔH_{298} , and ΔG_{298} are the electronic energy, enthalpy, and free energy ($T = 298.73$ K), respectively, while ΔE_0 is ZPE corrected electronic energy.

Bond orders reported are the Wiberg bond indices^{23a} calculated by means of natural bond orbitals (NBO).^{23b,c} The charges reported are Mulliken atomic charges (hydrogen atoms are summed into heavy atoms). All calculations were carried out with the Gaussian 98 program package.²⁴

Results and Discussion

The Cartesian coordinates and energies of all of the species for the reactions I–IV are provided in the Supporting Informa-

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tion. Unless otherwise mentioned, all relative energies discussed within this context are free energies at 298 K (denoted as ΔG_{298}).

Reaction I ($R^1 = \text{H}$, $R^2 = \text{H}$). The geometries and relative energies of all of the stationary points of the reaction of $\text{Ti}(\text{OMe})_2(\text{CH}_2\text{CH}_2)$ (**1**) + HCOOMe are given in Figure 2 and Table 1, respectively. Meanwhile, the potential energy surface for this reaction both in unscaled zero-point energy (ZPE) corrected electronic energy (ΔE_0) and free energy (ΔG_{298}) are given in Figure 3.

$\text{Ti}(\text{OMe})_2(\text{CH}_2\text{CH}_2)$ **1.** While dialkoxytitanacyclopropanes are key species involved in the Kulinkovich hydroxycyclopropanation and other reactions,^{14–15} their structures have not been reported except for those of their analogues.²⁵ The B3LYP/HW3 optimized $\text{Ti}(\text{OMe})_2(\text{CH}_2\text{CH}_2)$ **1** displays a distorted tetrahedral structure (near C_{2v} symmetry) with the C–C bond length of 1.482 Å, close to that of a C–C single bond (1.54 Å) but significantly longer than that of a C=C double bond (1.34 Å), suggesting that this species is best described as titanacyclopropane rather than titanium(II)–olefin complex, in agreement with

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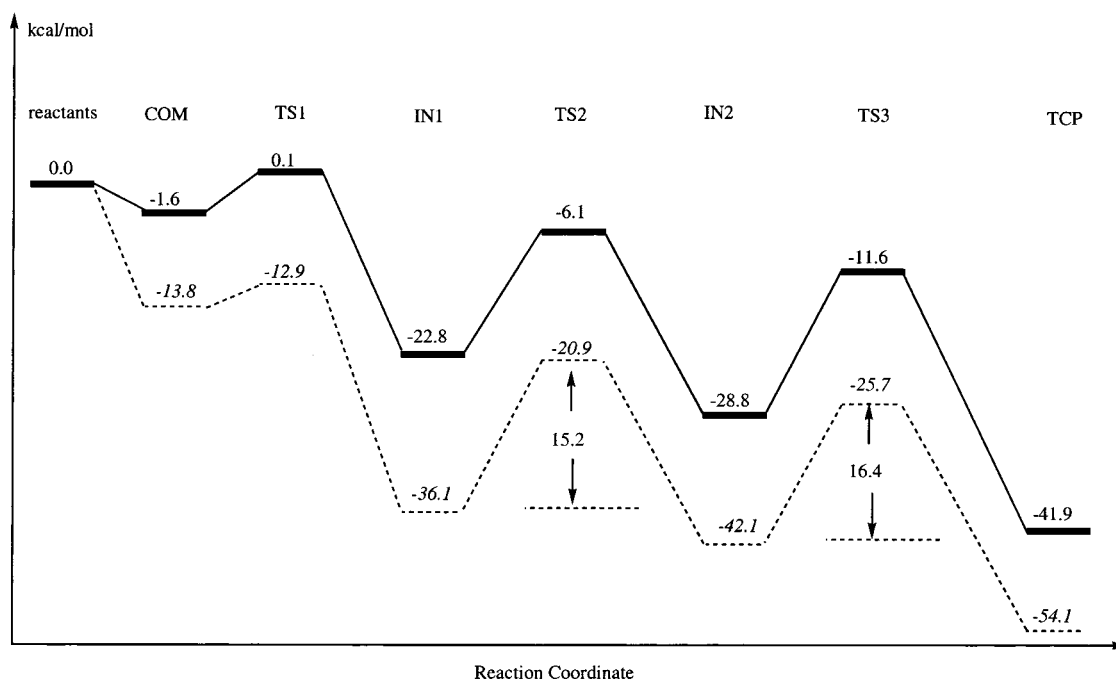
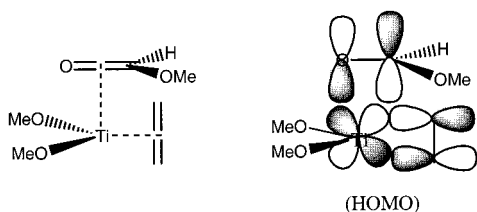


Figure 3. Potential energy surface of the reaction between $\text{Ti}(\text{OMe})_2(\text{CH}_2\text{CH}_2)$ (**1**) computed with the B3LYP/HW3 method. Solid and dashed lines represent free energies (ΔG_{298}) and ZPE corrected electronic energies (ΔE_0) relative to the reactants, respectively.

Scheme 3



$\text{O}_5\text{-C}_3$ bond (1.865 Å) almost broken while the Ti-O_5 bond (2.009 Å) formed to a large extent. IN2 **6** is a pentacoordinated Ti(IV) complex with a distorted trigonal bipyramidal (TBP) structure, where C_1 , O_5 , and O_9 form its equatorial plane while O_4 and O_7 occupy the two axial apices. It is observed that in IN2 **6**, oxygen O_4 uses its lone pair to coordinate to Ti to form a five-membered ring with an envelope conformation, in which Ti, O_4 , C_3 , and C_2 lie in the same plane (the dihedral angle is 1.7°) while C_1 is somewhat out of this plane with dihedral angle of $\text{C}_1\text{-C}_2\text{-C}_3\text{-O}_4 = 13.4^\circ$. It is important to note that the three alkoxy groups in IN2 **6** arrange around the titanium center in a clockwise fashion to avoid the lone pair interactions between neighboring oxygen atoms, as substantiated by the fact that full optimization starting from the geometry with one methoxy orientating anticlockwise converges to the geometry of IN2 **6** shown in Figure 2.

Our calculations predict that this step has activation and reaction energies of 15.2 and -6.0 kcal/mol with respect to IN1 **4** in terms of ΔE_0 . In terms of ΔG_{298} , the activation barrier is increased to 16.7 kcal/mol, still a very reasonable value even for those Kulinkovich reactions performed below room temperature. Energy release of only 6 kcal/mol for the migration step is understandable. This step does not have a net formation of a Ti-O single bond as the dative Ti-O_4 bond in IN2 **6** is substantially weaker compared to a Ti-O single bond.

Intramolecular Cyclopropane-Forming Step. The cyclopropane-forming reaction leading to the formation of TCP can be envisioned as a Lewis-acid assisted intramolecular nucleophilic addition, where Ti, C_1 , and C_3 atoms in IN2 **6** act as

Lewis acid, nucleophile, and electrophile, respectively (see their Mulliken charges in Figure 2).

The nucleophilic attack of C_1 to C_3 not only needs the C_1 and C_3 distance to be shortened to some extent in the transition state, but also requires the carbonyl group to rotate by about 90° so that it becomes nearly parallel to the equatorial plane. As shown in Figure 2, the cyclopropane-forming transition state²⁹ **7** still possesses a distorted TBP structure, in which the envelope conformation of the five-membered ring has the $\text{C}_1\text{-C}_2\text{-O}_4\text{-Ti}$ plane nearly perpendicular to the carbonyl plane of $\text{C}_2\text{-C}_3\text{-O}_4\text{-H}_{\text{R1}}$. The forming $\text{C}_1\text{-C}_3$ bond in TS3 **7** has a length of 2.003 Å, and the attack angle of $\text{C}_1\text{-C}_3\text{-O}_4$ is about 109.6° .³⁰ Meanwhile, the Ti-C_1 bond in TS3 **7** is elongated to 2.285 Å from 2.152 Å in IN2 **6**.

Another striking feature of TS3 **7** is that its two hydrogen atoms attached to C_1 become quite different. The $\text{H}_{1\text{t}}\text{-C}_1\text{-Ti}$ and $\text{H}_{1\text{c}}\text{-C}_1\text{-Ti}$ are about 91° and 112° , respectively, differing by about 21° . The $\text{H}_{1\text{t}}\cdots\text{Ti}$ distance is 2.546 Å, while the $\text{H}_{1\text{c}}\cdots\text{Ti}$ distance is 2.876 Å. In addition, the $\text{C}_1\text{-H}_{1\text{t}}$ bond (1.095 Å) is somewhat longer than the $\text{C}_1\text{-H}_{1\text{c}}$ bond (1.089 Å). All of these indicate that there is an agostic effect involving the $\text{C}_1\text{-H}_{1\text{t}}$ bond and the Ti center.³¹ Mulliken charge analyses give some support to this interaction. The $\text{H}_{1\text{t}}$ has a positive charge of 0.22 units, while that of the $\text{H}_{1\text{c}}$ is 0.19 units (both of them have a positive charge of 0.17 units in IN2 **6**). Furthermore,

(29) Another TS3 corresponding to the rotation of the carbonyl group to the opposite direction has similar geometry and energy to TS3 **7**.

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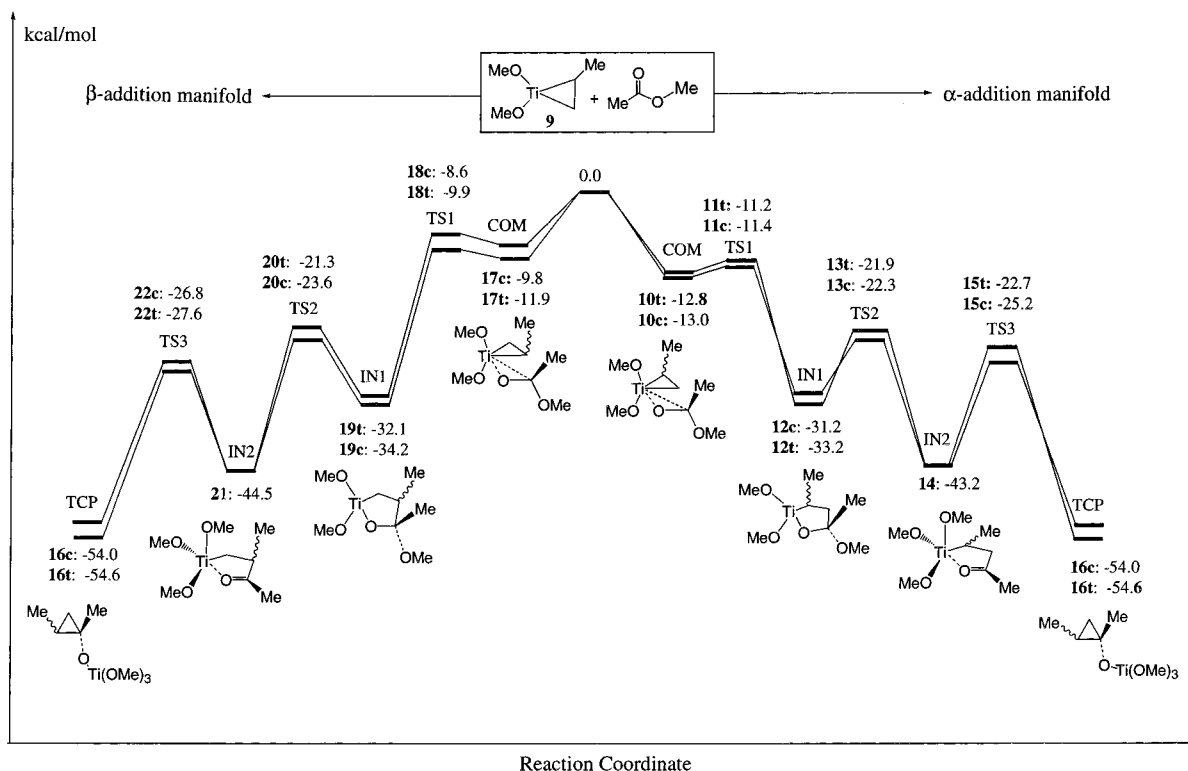


Figure 4. Potential energy surface of the reaction II computed with the B3LYP/HW3 method. All energies are electronic energies without ZPE corrections (ΔE_{ele} , kcal/mol) with respect to the reactants. The t and c stand for the trans and cis relationship of the R^1 and R^2 groups in each species, respectively.

the bond orders for Ti to H_{1t} and H_{1c} are 0.016 and 0.006, respectively, supporting the agostic interaction in the former pair. As will be discussed later, this feature might be important to the diastereoselectivity of the Kulinkovich reaction.

The cyclopropane-forming step is the rate-determining step due to its activation free energy of 17.2 kcal/mol, being slightly higher than that of the migration step (16.7 kcal/mol). This step is also exothermic by about 12.0 kcal/mol in terms of ΔE_0 .

After analysis of each step of reaction I, a conclusion reached here is that the reaction mechanism shown in Figure 1 is very feasible for the transformation of ester and titanacyclopropane to cyclopropanol due to the low activation free energy of 17.2 kcal/mol as well as the high exothermicity (ca. -54.1 kcal/mol of reaction I in terms of ΔE_0). Meanwhile, the downhill potential energy surface discloses that the cycloinsertion, migration, and cyclopropane-forming steps are all irreversible. The irreversibility of the cycloinsertion step implies that the regiochemistry encountered here is under kinetic control when $R^2 \neq H$. As will be discussed in the next section, the irreversible cycloinsertion step prefers the α -addition manifold, in which the cyclopropane-forming reaction is both the rate-determining and stereo-determining step possessing the experimentally observed diastereoselectivity.

Reaction II ($R^1 = R^2 = \text{Me}$). Origin of the Preference for the α -Addition Manifold. For reaction II, both α -addition and β -addition manifolds are possible. In addition, the $R^1(\text{Me})$ and $R^2(\text{Me})$ groups can be either cis or trans to each other. Therefore, there are four possible pathways (α -cis, α -trans, β -cis, and β -trans). As shown in Figure 4, our calculations indicate that the overall reaction potential energy surface is similar to that of reaction I with irreversible cycloinsertion, migration, and cyclopropane-forming reactions. Therefore, the regiochemistry for this reaction is determined by the relative stabilities of the cycloinsertion TS1s in the four competitive paths.

In contrast to the commonly accepted β -addition manifold, the potential energy surface in Figure 4 shows that the reaction favors the α -addition manifold over the β -addition manifold: In terms of electronic energy (ΔE_{ele}), both TS1 **11c** and **11t** in the α -addition manifold are lower than TS1 **18t** in the β -trans path, the lowest TS1 in the β -addition manifold, by about 1.5 kcal/mol (Figure 4). In terms of ΔG_{298} , this difference is increased to 2.8 kcal/mol (Figure 5), which corresponds to a selectivity ratio of 106:1, implying that the β -addition manifold can be ruled out.

The higher energies of the two cycloinsertion TS1s in the β -addition manifold relative to those in the α -addition manifold are obviously attributed to the steric repulsions: R^1 and R^2 in TS1 **18c** are eclipsed to each other with a $C_{R1} \cdots C_{R2}$ distance of 3.062 Å (This is referred to as $R^1 \cdots R^2$ repulsion); R^2 is also eclipsed to methoxyl group attached to the carbonyl carbon in TS1 **18t** with $C_{R2} \cdots O_5$ of 2.903 Å (This interaction is denoted as $R^2 \cdots O$ repulsion) (see Figure 5 and Supporting Information). Due to the same reason, the complexes **10c** and **10t** formed in the α -addition manifold are more stable than complexes **17c** and **17t** in the β -addition manifold.

The preference of the α -addition manifold should not be limited to the present case. It should be extended to almost all cases with R^1 and R^2 as alkyl groups since TS1 in the β -addition manifold suffers from $R^2 \cdots \text{ester}$ steric repulsion. One exception would be the case when R^1 is hydrogen atom. In this case, the $R^1 \cdots R^2$ repulsion in the β -cis TS1 becomes a $H \cdots R^2$ repulsion, which should be small enough so that the β -addition could compete with the α -addition. This will be examined with the reaction IV.

A recent experiment supporting this α -addition manifold comes from an analogue reaction between ketone and diisopropoxy(η^2 -propene)titanium generated by Sato's reagent ($\text{Ti}(\text{O}-i\text{-Pr})_4 + 2 i\text{-Pr-MgBr}$), where the cycloinsertion product is from

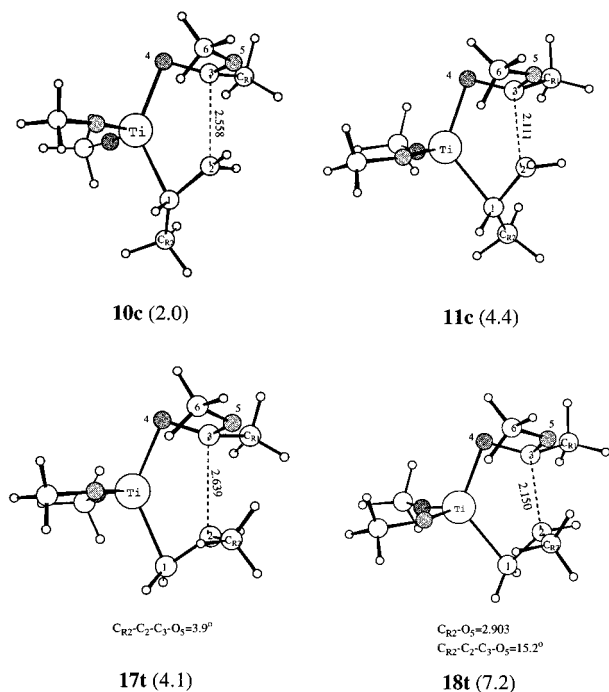
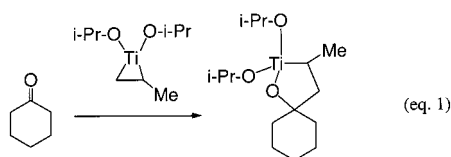


Figure 5. Calculated structures of complex and transition state for the cycloinsertion step in the α -cis and β -trans paths of reaction II. The values in parentheses are calculated relative free energies (ΔG_{298} , kcal/mol) of these structures with respect to the reactants.

α -addition (eq 1).^{15h} A similar α -addition mechanism was also observed in the polar addition reactions of aldehydes to alkene–zirconocenes, which were supposed to be kinetically controlled.^{12h,32}



Our calculations also indicate that the β -addition manifold leads to more stable IN1s than the α -addition. For example, IN1 **19c** is more stable than IN1 **12t** by about 1.0 kcal/mol in terms of ΔE_{ele} . As displayed by reaction I, although the C_2-C_3 bond in cycloinsertion TS1 **3** is eclipsed, it becomes staggered in the IN1 **4** (Figure 2). Due to the same reason, $R^1\cdots R^2$ or $R^2\cdots O_5$ repulsion in IN1 **19c** is reduced. IN1 **12t** in the α -trans path, on the contrary, would suffer from some steric interaction involving R^2 and the metal center (for structures of these IN1s, see the Supporting Information). Thus, if the cycloinsertion reaction were reversible, the β -addition would be the favored pathway. This might be the situation for some ring-expansion reactions of alkene–zirconocenes with olefins, which favor the β -addition fashion.^{12h,16}

Origin of the cis- R^1/R^2 Diastereoselectivity. The potential energy surface of reaction II indicates that the rate-determining step in the α -addition manifold is still the cyclopropane-forming step, which can transform **14** to cis- R^1/R^2 TCP **16c** or trans- R^1/R^2 TCP **16t**, depending on the relative energies of their corresponding TS3s, **15c** and **15t**.

In accordance with experimental observations, the preferred α -addition manifold is predicted to have an exclusive cis- R^1/R^2

R^2 diastereoselectivity, as indicated by a 2.9 kcal/mol stability of TS3 **15c** relative to TS3 **15t** in terms of ΔG_{298} . An inspection of the geometries of the two TS3s depicted in Figure 6 indicates that there is considerable steric interaction between the two cis methyl groups ($R^1\cdots R^2$ repulsion) in TS3 **15c**, which has a (R^1)H \cdots H(R^2) distance of only 2.25 Å. On the other hand, the $R^1\cdots R^2$ repulsion is absent in TS3 **15t**. Consequently, what is the origin of the preference for the cis- R^1/R^2 TS3 **15c**?

As pointed out earlier, due to a pentacoordination of C_1 in TS3 **7** of reaction I, the H_{11} involves an agostic interaction with Ti. In TS3 **15c**, the Ti- C_1 - H_1 angle is only 83° , with a Ti \cdots H $_1$ distance of 2.440 Å. Thus, TS3 **15c** benefits from an agostic interaction (denoted as (C_1)H \cdots Ti). On the other hand, in TS3 **15t**, the Ti- C_1 - C_{R2} and the Ti- C_1 - H_1 angles are 96° and 112° , respectively. Therefore, the agostic interaction in TS3 **15t** is absent, as indicated by the distance of its $H_1\cdots Ti$ of 2.961 Å. In addition, the R^2 methyl group in **15t** suffers from steric interactions with the metal center. Due to the small Ti- C_1 - C_{R2} angle, two of the R^2 methyl hydrogens are only about 3.0 Å away from Ti (this steric interaction is denoted as $R^2\cdots Ti$ repulsion).³³ On the contrary, the $R^2\cdots Ti$ repulsion in TS3 **15c** is absent because all its (R^2)H $\cdots Ti$ distances are over 3.3 Å (its $C_{R2}-C_1$ -Ti angle is about 118° , 22° larger than that in TS3 **15t**).

In contrast, our calculations reveal that the β -addition manifold has trans- R^1/R^2 diastereoselectivity instead. As shown in Figure 6B, the C_2-C_3 bond becomes nearly eclipsed in TS3 **22c**, which has the two methyl groups cis to each other. It is about 1.3 kcal/mol less stable than TS3 **22t**, which has two methyl groups trans to each other. The preference for the latter transition state is obviously due to its smaller steric repulsion involving $R^2\cdots O$ than the $R^1\cdots R^2$ repulsion in the former. This is parallel to the stabilities of the two products: TCP **16t** is more stable than TCP **16c** by 0.6 kcal/mol in terms of ΔE_{ele} . The two cycloinsertion TS1s **18t** and **18c** in the β -addition manifold also reflect this trend with TS1 **18t** being more stable than TS1 **18c** by about 1.3 kcal/mol in terms of ΔE_{ele} .

Thus, if β -addition manifold were the favored pathway, trans- R^1/R^2 cyclopropanol would be the major product. This is in contradiction to experimental observations, further supporting the conclusion that the α -addition manifold is the favored pathway.

To summarize, the α -addition manifold is generally favored. The cis- R^1/R^2 cyclopropane-forming transition state is stabilized by the (C_1)H \cdots Ti agostic interaction but destabilized by the $R^1\cdots R^2$ repulsion. The trans- R^1/R^2 cyclopropane-forming transition state is destabilized by the $R^2\cdots Ti$ repulsion. When R^2 increases its size, both $R^1\cdots R^2$ and $R^2\cdots Ti$ repulsions increase. As a result, the cis- R^1/R^2 cyclopropane-forming transition state is still favored over the trans- R^1/R^2 cyclopropane-forming transition state due to the existence of additional agostic interaction in the former. However, when R^1 becomes larger while R^2 is still the methyl group, only the adverse $R^1\cdots R^2$ repulsion in the cis- R^1/R^2 cyclopropane-forming transition state increases while the other interactions in both cis and trans TS3 remain almost unchanged, leading to a decrease in the stability of the cis- R^1/R^2 TS3 with respect to the trans- R^1/R^2 TS3. Therefore, the preference for the cis- R^1/R^2 cyclopropanol is reduced; the trans- R^1/R^2 cyclopropanol might even become the dominant product (Scheme 1c). This is tested with the reaction III, which is presented in the next section.

(32) Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y. Aoyagi, K.; Saburi, M. *Chem. Lett.* **1992**, 331.

(33) The (R^2)H \cdots Ti interaction in **15t** is ascribed as steric repulsion instead of α -agostic interaction due to the long distance of (R^2)H \cdots Ti (3.0 Å)^{31c,h} (the bond orders of two (R^2)H \cdots Ti are only 0.004 and 0.006, respectively).

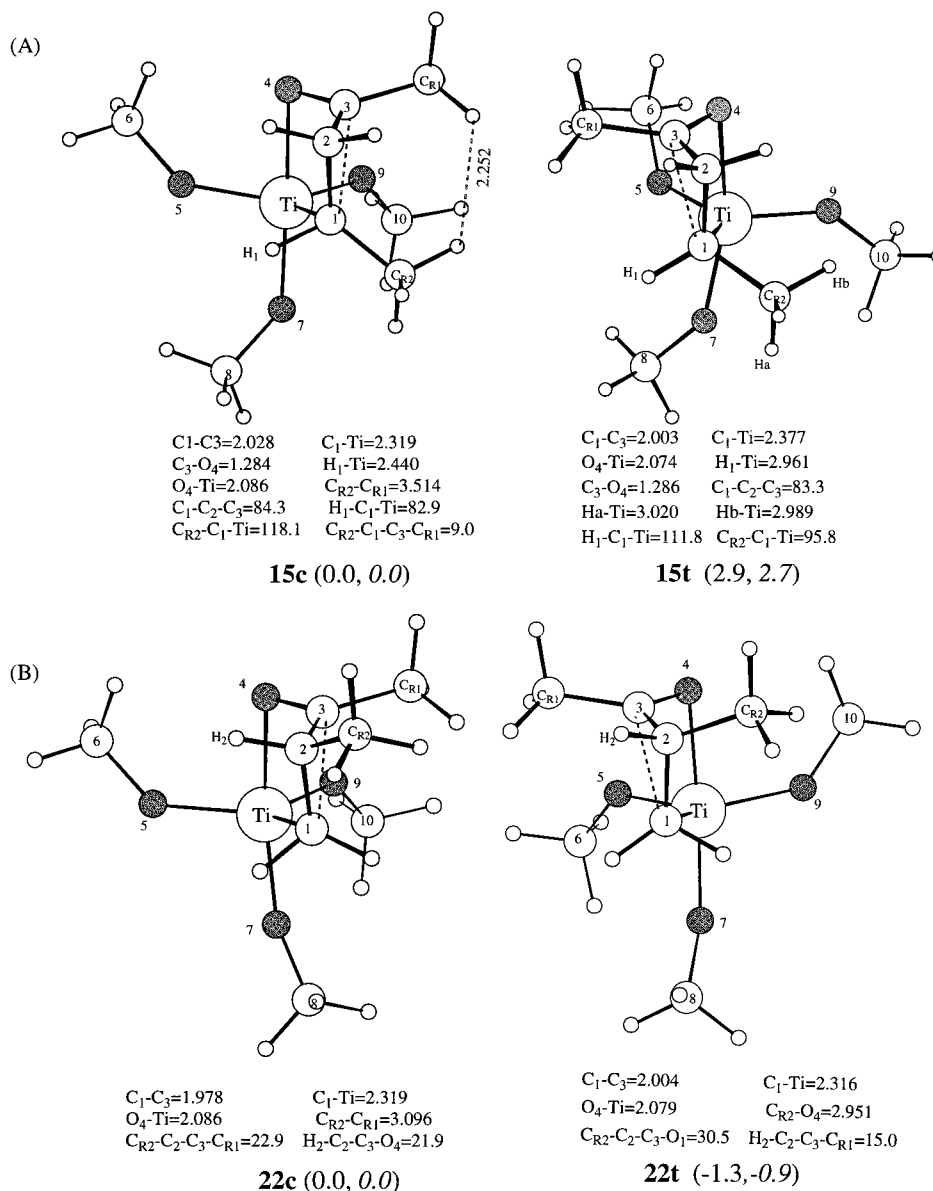


Figure 6. Calculated cyclopropane-forming transition states TS3s for the reaction II. (A) **15c** and **15t** in the α -addition manifold. (B) **22c** and **22t** in the β -addition manifold. The Roman and italic values in parentheses are relative free energies (ΔG_{298}) and ZPE corrected electronic energies (ΔE_0), respectively. Distances and angles are in Å and degrees, respectively.

Reaction III ($R^1 = t\text{-Bu}$, $R^2 = \text{Me}$). Since the study of reaction III is aimed at understanding the diastereoselectivity, we only concentrated on the stereo-determining cyclopropane-forming step in the α -addition manifold (the β -addition should be excluded due to $R^2 \cdots$ ester repulsion in its cycloinsertion TS1, larger than that displayed in reaction II). In agreement with our analysis of the origin of the diastereoselectivity, the preference for the cis- R^1/R^2 TS3 **24c** over the trans- R^1/R^2 TS3 **24t** almost disappears due to the increased $R^1 \cdots R^2$ repulsion in the former, which has two close (R^1)H \cdots H(R^2) contacts (the two close H \cdots H distances are 2.129 and 2.392 Å, respectively, see Figure 7).³⁴

In addition, it is found that the activation free energy from IN2 **23** to TS3 **24t** is 23.7 kcal/mol, 6 kcal/mol larger than that in reaction II (17.8 kcal/mol). The higher activation energy of reaction III compared to reaction II is likely the main reason the standard reaction conditions (20° in THF) are not suitable for the Kulinkovich reactions when R^1 is secondary and tertiary alkyl groups.¹⁰

Reaction IV ($R^1 = \text{H}$, $R^2 = \text{Me}$). We reasoned that the possible β -addition manifold could be fulfilled in a special case of $R^1 = \text{H}$ in that the $R^1 \cdots R^2$ repulsion in its β -cis path TS1 would become a negligible H \cdots R² interaction, making this path very competitive (on the contrary, the β -trans path can still be ruled out due to the $R^2 \cdots \text{O}$ repulsion in its TS1). Within our expectation, the β -cis TS1 **26c** is more stable than the α -cis TS1 **25c** and α -trans TS1 **25t** by about 0.2 kcal/mol (For structures, see Supporting Information). This suggests that both α - and β -addition manifolds can occur in this special case.

(34) The experimental results (Scheme 1c) gave a ratio of trans to cis product of 2.5:1, which corresponds to an estimated stability of trans- R^1/R^2 TS3 over cis- R^1/R^2 TS3 by about 0.6 kcal/mol in terms of free energy. Calculations in the gas phase give a preference to cis- over trans- R^1/R^2 TS3 by about 0.1 kcal/mol. This discrepancy can be reconciled by taking into account the solvent effect: Structure **24t** is more polar than **24c** (2.72 to 2.17 D), suggesting that polar solvent can stabilize **24t** more effectively than **24c**. Within our expectation, **24t** is calculated to be more stable than **24c** by about 0.7 kcal/mol in terms of free energy in THF ($\epsilon = 7.58$) utilizing the PCM³⁵ solvation model on the gas-phase geometries. It should be noted that the discrepancy might simply caused by the uncertainty of calculations.

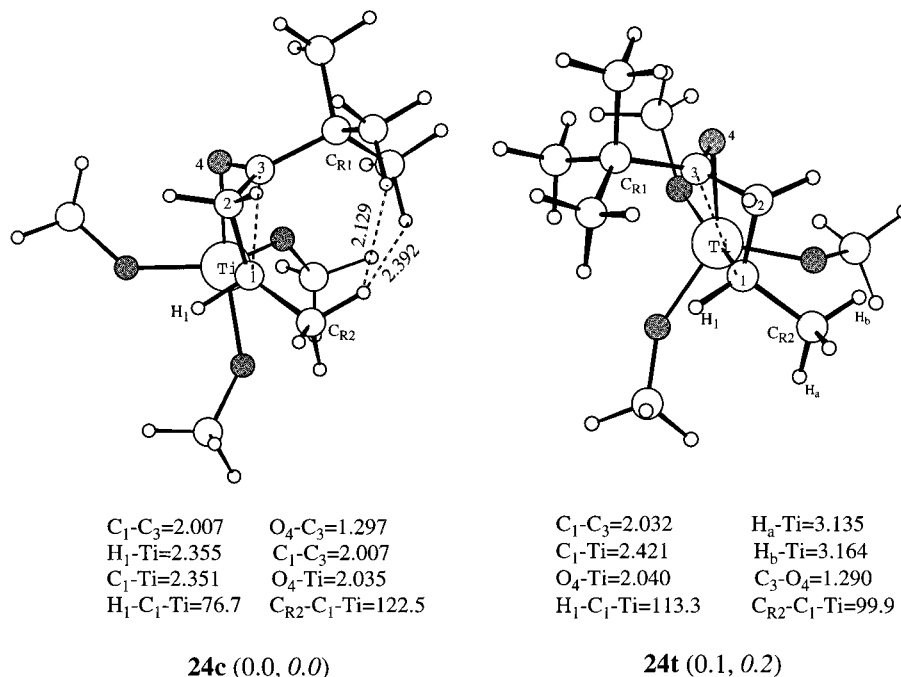


Figure 7. Calculated cyclopropane-forming transition states TS3s in the α -addition manifold for the reaction III. The Roman and italic values in parentheses are relative free energies (ΔG_{298}) and ZPE corrected electronic energies (ΔE_0), respectively.

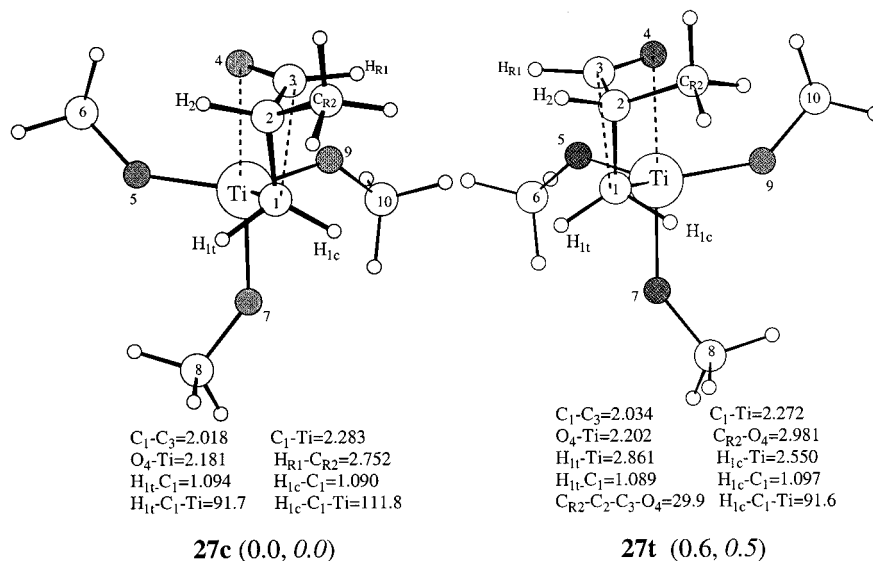


Figure 8. Calculated cyclopropane-forming transition states TS3s **27t** and **27c** in the β -addition manifold for the reaction IV. The Roman and italic values in parentheses are relative free energies (ΔG_{298}) and ZPE corrected electronic energies (ΔE_0), respectively.

For the α -addition, the $R^1 \cdots R^2$ interaction in the cis- R^1/R^2 TS3, which still benefits from an agostic interaction, is almost negligible. Therefore, the cis- R^1/R^2 cyclopropanol product in this manifold is expected to be exclusive.

Figure 8 shows the cis- and trans- R^1/R^2 TS3s of the β -addition manifold. These structures are geometrically similar. The cis- R^1/R^2 TS3 **27c** is calculated to be about 0.5 kcal/mol more stable than the trans- R^1/R^2 TS3 **27t**, apparently due to the steric interaction between the R^2 and the O_4 in the latter structure. It is expected that this preference would be increased when R^2 becomes larger. Thus, the cis- R^1/R^2 cyclopropanol is expected to be the major product.

Therefore, the calculations indicate that even when both α - and β -addition manifolds can take place when $R^1 = H$, these reactions still afford the cis- R^1/R^2 cyclopropanol. This is in agreement with the experimental observations that when $R^1 =$

H and $R^2 = n\text{-Bu}$, $n\text{-C}_6\text{H}_{13}$, Ph,³⁶ only cis- R^1/R^2 cyclopropanols are obtained (Scheme 1b).

Conclusions

The density functional theory studies of the reactions between ester $R^1\text{COOMe}$ and titanacyclopropane $\text{Ti}(\text{OMe})_2(\text{CH}_2\text{CH}_2\text{R}^2)$ reveal that the following mechanism is quite plausible for the Kulinkovich reaction: It starts with the formation of a complex

(35) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(36) When $R^1 = H$ and $R^2 = \text{Ph}$, it is expected that only the α -addition occurs due to the electronic stabilization caused by the Ph group that can lower energy of the TS1 when it is in the α position. See the reactions of (alkene)zirconocenes with different alkenes: (a) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266. (b) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (c) Coperet, C.; Negishi, E. Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695 and see also ref 12h.

between the ester and titanacyclopropane, followed by an irreversible cycloinsertion reaction to generate an intermediate of oxatitanapentane, which then undergoes intramolecular methoxy migration from the formal carbonyl carbon atom of the ester to titanium to afford the second intermediate.³⁷ The last step corresponds to the cyclopropane-forming reaction, which is the rate-determining step, to yield titaniumcyclopropanolate complex. Each step of this process is predicted to be facile with exothermicity.

When R¹ and R² are alkyl groups, the Kulinkovich reaction favors the α -addition manifold over the β -addition manifold since the cycloinsertion transition states of the latter involves R²...ester repulsion. The rate-determining cyclopropane-forming step is also the stereo-determining step, which prefers to give cis-R¹/R² 1,2-disubstituted cyclopropanols exclusively when R¹ is primary alkyl groups. The complete cis-R¹/R² diastereoselectivity is due to the existence of an agostic interaction in the cis-R¹/R² cyclopropane-forming transition state (TS3) and the R²...Ti repulsion in the trans-R¹/R² TS3. Only when R¹ becomes secondary and tertiary alkyl groups and R² = Me, the increased R¹...R² repulsion will decrease the stability of the cis-R¹/R² TS3 relative to that of the trans-R¹/R² TS3, leading to a lower

(37) We do not rule out the alternative mechanism of nucleophile (RMgBr, ⁱPrO-, R'O-) first attacking on titanium to yield a complex which would deliver methoxide to a Lewis acid (refs 2b, c)

diastereoselectivity. The favorable α -addition is further supported by the calculation result that the β -addition leads to the formation of trans-R¹/R² product, which is opposite to the experimental observations.

Only in a special case with R¹ = H and R² = alkyl groups can the β -addition manifold compete with the α -addition manifold. The cis-R¹/R² diastereoselectivity is still expected for this case.

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Note Added after ASAP: Several α -addition and β -addition designations were reversed throughout the paper in the version posted ASAP May 23, 2001; the corrected version was posted June 6, 2001.

Supporting Information Available: Tables of absolute energies and other thermodynamic parameters, Cartesian coordinates together with the figures of all species discussed in the text (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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