JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

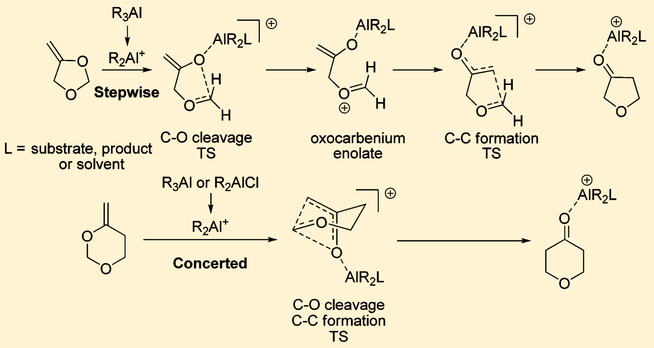
DFT Study on the Mechanism and Stereochemistry of the Petasis–Ferrier Rearrangements

Guo-Jie Jiang, Yi Wang, and Zhi-Xiang Yu*

College of Chemistry, Peking University, Beijing 100871, People's Republic of China

S Supporting Information

ABSTRACT: The Petasis–Ferrier rearrangement is a very important and useful reaction for the synthesis of multifunctional tetrahydrofurans and tetrahydropyrans from easily synthesized enol acetals. Here we report our DFT investigation of the detailed reaction mechanism of the Petasis–Ferrier rearrangement, proposing that the active promoting species in this reaction is the cationic aluminum species, instead of the usually considered neutral Lewis acid (this will give very high activation energies and cannot explain why the Petasis–Ferrier rearrangements usually take place at low temperature or under mild conditions). Calculations indicated that the mechanisms of the Petasis–Ferrier rearrangements for the formations of five- and six-membered rings are different. Formation of five-membered tetrahydrofuranone is stepwise with C–O bond cleavage to generate an oxocarbenium enolate intermediate, which then undergoes an aldol-type reaction to give the desired cyclized oxacycle. In contrast, the formation of six-membered tetrahydropyranone is a concerted and asynchronous process with the C–O bond breakage and aldol-type C–C bond formation occurring simultaneously. A DFT understanding of why the catalytic versions of the Petasis–Ferrier rearrangements cannot be realized when using R_2Al^+ as the active promoting species has also been discussed. In addition, DFT calculations were used to reveal the origins of the stereochemistry observed in the Petasis–Ferrier rearrangements.



■ INTRODUCTION

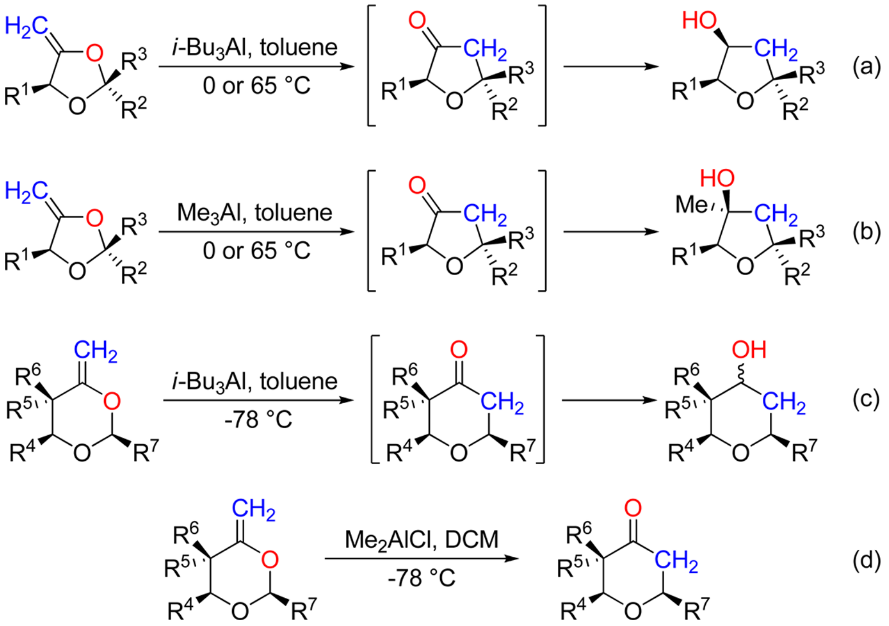
The Petasis–Ferrier rearrangement, discovered by Petasis and co-workers, is a very important and useful reaction for the synthesis of multifunctional tetrahydrofurans and tetrahydropyrans from easily synthesized enol acetals (Scheme 1).[1−3] The Petasis–Ferrier rearrangement reactions are usually promoted by stoichiometric amount of Lewis acids such as i-Bu_3Al, Me_3Al, and Me_2AlCl. Using Me_2AlCl as the promoter, tetrahydropyranones are generated as the final products (reaction d, Scheme 1),[3] while alcohols are obtained finally when i-Bu_3Al or Me_3Al is the used promoter (reactions a–c, Scheme 1).[2] The generation of alcohols using i-Bu_3Al as the promoter is due to the reduction of the generated ketones (reactions a and c, Scheme 1), which does not take place when Me_2AlCl is the promoter (reaction d, Scheme 1). When Me_3Al is the promoter, methyl transfer is observed and this also gives the alcohol product (reaction b, Scheme 1).

It was also found that the Petasis–Ferrier rearrangement is highly stereospecific. For example, Petasis and co-workers found that both ***anti*-1** and ***syn*-1**, which differ from each other by one stereocenter, give the same *syn* product **2** (reaction a, Scheme 2).[2a] Smith and co-workers also observed a similar phenomenon, showing that both ***Z*-3** and ***E*-3**, which have different external olefin configurations, afford the same *anti* product **4** (reaction b, Scheme 2).[3b] In addition, the Petasis–Ferrier reaction has been successfully applied by Smith and co-workers in the total synthesis of many complex natural products,[3,4] such as (+)-phorboxazole A and (−)-okilactomycin, further demonstrating the impact of this reaction in synthesis.

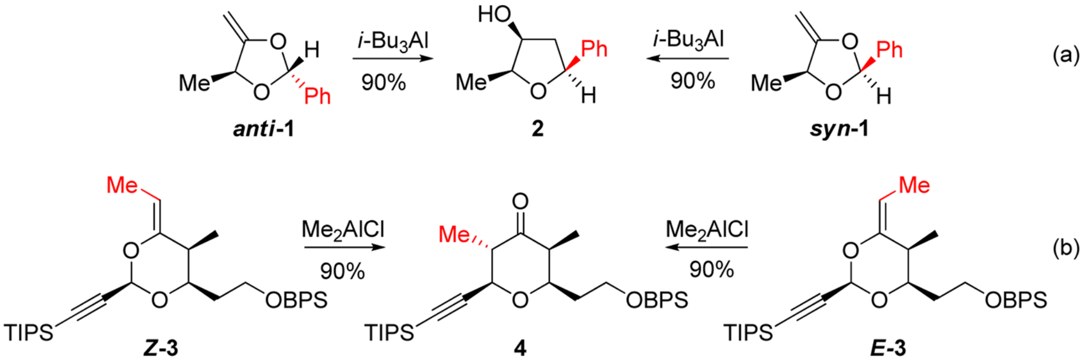
Despite the great success of Petasis–Ferrier rearrangements in synthesis,[5,6] their mechanisms have not been investigated. Scheme 3 depicts the widely accepted mechanisms.[1,2] It was proposed that the reaction starts from coordination of the Lewis acid to the enolic O atom of the substrate, followed by cleavage of the adjacent C–O bond to generate oxocarbenium enolate, which could be assisted by the antiperiplanar lone pair of the ethereal O atom. Finally an aldol-type reaction gives the product in a fashion of 5- or 6-(enolendo)-endo-trig cyclization. For the reaction of a six-membered enol acetal, the first step was also proposed to be C–O cleavage to generate an oxocarbenium enolate intermediate. This oxocarbenium enolate intermediate could undergo an oxonia-Cope rearrangement to give another oxocarbenium enolate in the reaction system. Finally, both oxocarbenium enolate intermediates undergo an aldol-type reaction, furnishing the same final Lewis acid coordinated tetrahydropyranone product (Scheme 3b).

Received: April 3, 2013
Published: June 14, 2013

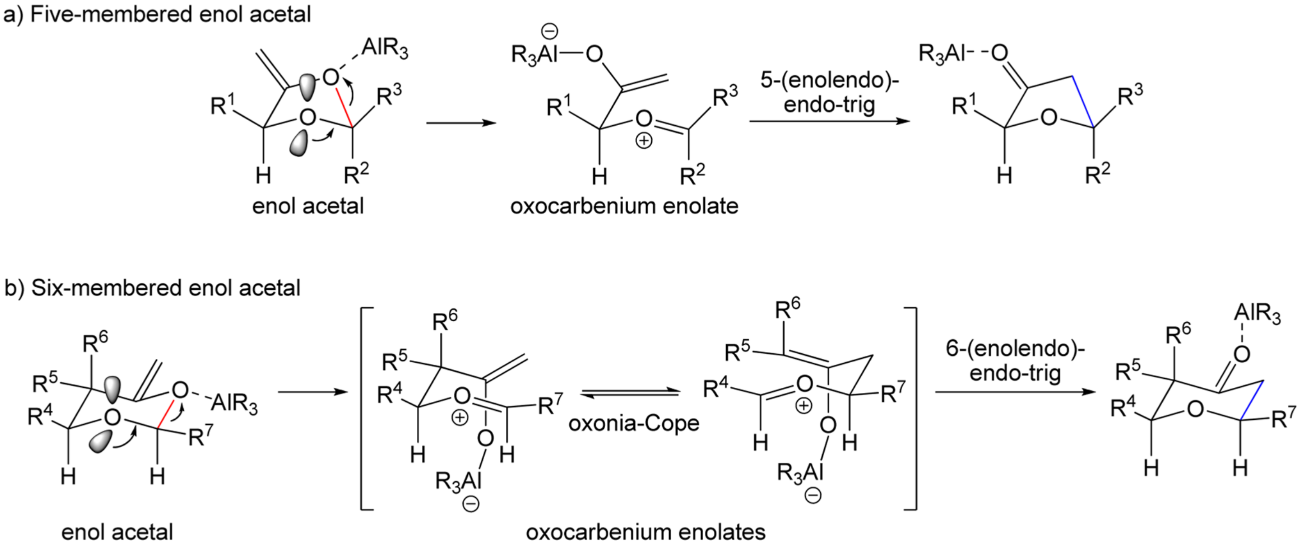
Scheme 1. Petasis−Ferrier Rearrangements Reported by Petasis and Smith, Respectively



Scheme 2. Stereochemistry of the Petasis−Ferrier Rearrangements

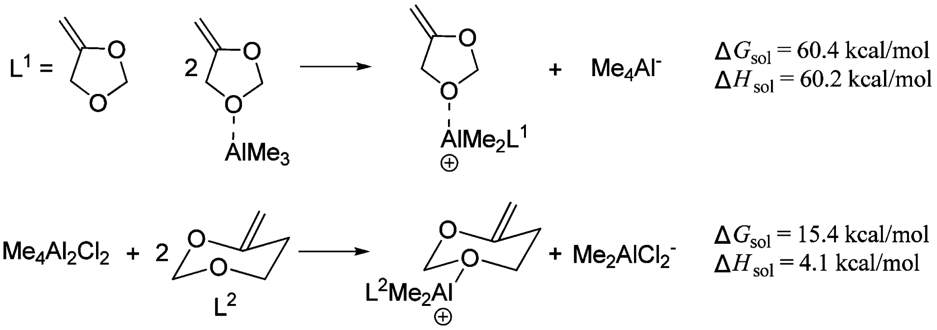


Scheme 3. Commonly Accepted Mechanisms of the Petasis−Ferrier Rearrangements



However, no experimental or computational studies have been carried out to support or disapprove these proposed mechanisms, nor has a computational rationalization of the stereochemistry been given. In addition, what are the real active promoting species to promote these transformations?[7] We believe that the mechanistic information is important not only

Scheme 4. Computed Energies of the Dissociation Reactions



for understanding the reaction and its stereochemistry but also for guiding the design and development of new reactions and catalysts.

One drawback of the Petasis–Ferrier reaction is that stoichiometric Lewis acids must be used. The catalytic version of the Petasis–Ferrier rearrangement is highly desired but not available at present. We believe that an in-depth understanding of the mechanism of the Petasis–Ferrier reaction will be helpful to synthetic chemists for designing and developing catalytic variants of the Petasis–Ferrier rearrangements.

Here we report our DFT investigation of the detailed reaction mechanism, proposing that the active promoting species in the Petasis–Ferrier reactions are the cationic aluminum species, instead of the usually considered neutral Lewis acids. We found that the mechanisms of the Petasis–Ferrier reactions for the formations of tetrahydrofuranone and tetrahydropyranone are different. Understanding the factors affecting the stereochemistry in the Petasis–Ferrier reactions is also the subject of the present computational investigation.

■ COMPUTATIONAL METHODS

All DFT calculations were carried out with the Gaussian 03 program package.[8] The geometry optimizations of all the minima and transition states were performed at the B3LYP[9] level of theory with the 6-31G(d)[10] basis set. The vibrational frequencies were computed at the same level of theory to check whether every optimized structure is an energy minimum or a transition state and to evaluate its zero-point vibration energy (ZPE). IRC calculations[11] were carried out to confirm that each transition state is connected with its corresponding reactant and product. Solvent effects were computed with the CPCM[12] model and UAHF radii in toluene for five-membered substrates and in dichloromethane (DCM) for six-membered substrates using the gas-phase optimized structures. ΔG_{sol} and ΔG_{gas} reported in this paper are relative Gibbs free energies calculated at 298 K in solution and in the gas phase, respectively. ΔE_0 is the zero-point vibration energy (ZPE) corrected electronic energy in the gas phase. All discussed energies in the paper and the Supporting Information are Gibbs free energies in solution (ΔG_{sol}) unless specified. Computed structures are illustrated using CYLVIEW drawings.[13] We point out here that, using the larger basis set of 6-311+G(d,p) at the B3LYP level gave activation energies very close to those computed by the B3LYP/6-31G(d) method, suggesting that the computed relative energies in the present system are not sensitive to the basis sets of DFT calculations (see the Supporting Information for details).

■ RESULTS AND DISCUSSION

In the original proposed reaction mechanisms of Petasis–Ferrier rearrangements, the Lewis acids (LA) are in their neutral states as the promoters. However, DFT calculations at the B3LYP/6-31G(d) level found that the activation energies for the formations of tetrahydrofuranone and tetrahydropyranone in these cases are very high (41.9 kcal/mol when LA is Me_3Al for the model substrate 4-methylene-1,3-dioxolane and 28.5 kcal/mol when LA is Me_2AlCl for the model substrate 4-methylene-1,3-dioxane; see the Supporting Information for details). We can rule out these mechanisms from a kinetic point of view, since the Petasis–Ferrier reactions usually take place at either 0–65 °C for five-membered series[2a] or −78 °C for six-membered series.[2b,3] Similar conclusions can be reached when using other computational methods such as MP2, CCSD(T), and M06, due to the obviously high activation energies computed by these high-level calculations.[14] We proposed that the active promoting species for the Petasis–Ferrier reactions could be a cationic species, R_2Al^+, generated through the dissociation reaction of $2R_3Al = R_2Al^+ + R_4Al^-$ when R_3Al is used as the Lewis acid (unfortunately, at this moment, details of this process is not known) or by the reaction of $R_4Al_2Cl_2 = R_2Al^+ + R_2AlCl_2^-$ when R_2AlCl is the Lewis acid used. Certainly the generated R_2Al^+ could be further stabilized by coordinating to the substrate, the product, or the solvent in the reaction system.[15] We have computed the energies of the dissociation reactions (Scheme 4). Since it is not correct to assume a complete separation of the ion pairs, the energy required for the formation of the ions is difficult to compute accurately. The computed energies in solution here were used to approximate the upper limits of the energies needed for the formations of the ions. Similar reports about generating cationic aluminum species from R_2AlCl have been given by Evans[16] and Castellino[17] experimentally as well as by Houk[18] and Tietze[19] computationally. In addition, experimental support for the existence of R_2Al^+ can be found in many systems (even though these observations were from very special cases, we proposed that a trace amount of R_2Al^+ could be generated in the Petasis–Ferrier reaction system and then this cationic species was used in the followed rearrangement reactions).[20] Recently, it was found that $InCl_3$-catalyzed cycloisomerization reactions of 1,6-enynes also have $InCl_2^+$ as the real catalytic species, giving more support that the cationic form of the Lewis acid could be the real catalyst or promoter.[7] Therefore, in parts 1 and 2, we detail how the Petasis–Ferrier rearrangements for the formations of tetrahydrofuranone and tetrahydropyranone take place using R_2Al^+ as the active promoting species, respectively. We then explain why the catalytic versions of the Petasis–Ferrier rearrangements are difficult in part 3. Finally we discuss the factors affecting the stereochemistry in the Petasis–Ferrier reactions (part 4).

1. Mechanism of the Petasis–Ferrier Rearrangement for the Formation of Tetrahydrofuranone from 4-Methylene-1,3-dioxolane. Figure 1 depicts the energy surface for the model substrate 4-methylene-1,3-dioxolane

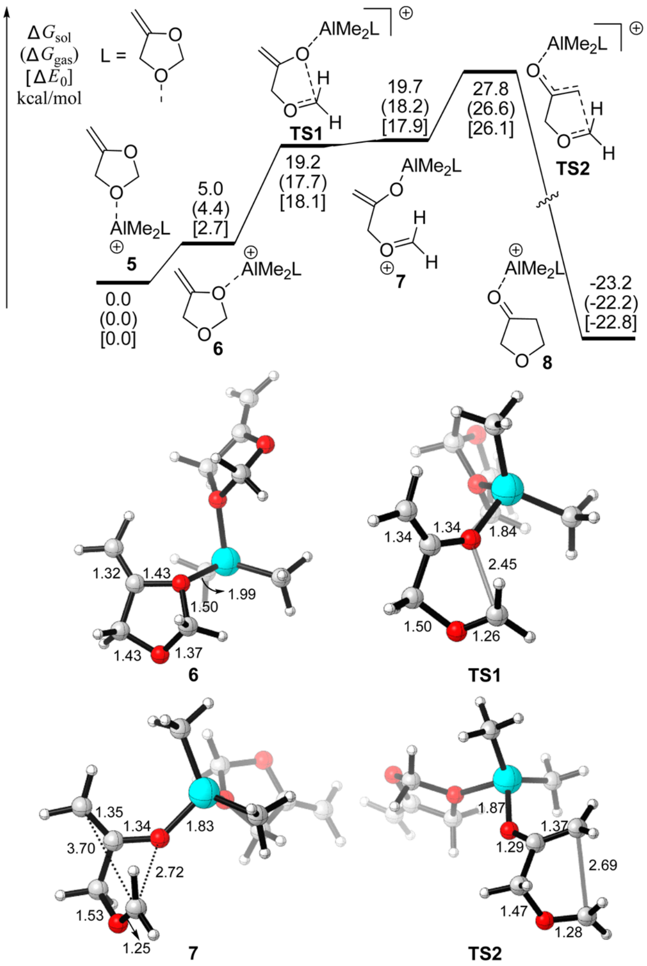


Figure 1. Energy surface for the model substrate 4-methylene-1,3-dioxolane with Me$_2$Al$^+$ as the active promoting species in the gas phase and toluene solution, together with the DFT computed structures of the key stationary points (distances in Å).

with Me$_2$Al$^+$ as the active promoting species in toluene solution. DFT calculations showed that the formation of tetrahydrofuranone starts from Me$_2$Al$^+$ coordination to the ethereal O atoms of two substrates in order to stabilize the cationic species, giving complex **5** (Figure 1). Here one substrate acts as a reactant in the followed transformations to give the final product while the other substrate is considered as a ligand, which meets the need for tetracoordination of the aluminum center. We must point out here that the proposed coordinating ligand could also be the ketone (or alcohol) product of the studied rearrangement or a solvent molecule. These possibilities will not change the cationic nature of the active promoting species and the reaction mechanism. Therefore, our discussion here focuses on using one substrate as a ligand coordinating to Me$_2$Al$^+$.

Complex **5** is in equilibrium with complex **6**, in which the enolic O atom of one substrate is coordinated by the Al atom. Complex **6**, which is higher in energy (5.0 kcal/mol) than complex **5**, is the reacting species for a sequence of reactions followed. Calculations found that the cleavage of the adjacent C−O bond in **6** via **TS1** is easy, with an activation free energy of 14.2 kcal/mol in solution. In **TS1**, the breaking C−O bond distance is 2.45 Å. In the formed oxocarbenium enolate **7**, this C−O bond distance is elongated to 2.72 Å. We found that **TS1** and **7** are very close in energy, due to their similar structures. Therefore, the C−O cleavage step is endergonic and is not favored. However, once intermediate **7** is generated, it can readily undergo an aldol-type reaction, involving the nucleophilic attack of the enolate moiety at the oxocarbenium group via **TS2**. This step gives the final Me$_2$Al$^+$ coordinated product **8**, requiring an activation free energy of 8.1 kcal/mol and being exergonic by 42.9 kcal/mol. Apparently, the second cyclization step is the rate-determining step, and the activation free energy of the overall process for the Me$_2$Al$^+$-promoted Petasis−Ferrier reaction of the model substrate of 4-methylene-1,3-dioxolane is 27.8 kcal/mol (from **5** to **TS2**). This activation free energy very reasonably explains why the Petasis−Ferrier reaction of five-membered enol acetals is usually carried out at 0−65 °C (reactions a and b, Scheme 1).[2a]

2. Mechanism of the Petasis−Ferrier Rearrangement for the Formation of Tetrahydropyranone from 4-Methylene-1,3-dioxane. In contrast to the stepwise rearrangement process for the five-membered enol acetal, formation of tetrahydropyranone from the model six-membered substrate 4-methylene-1,3-dioxane is a concerted and asynchronous process (Figure 2). The rearrangement also

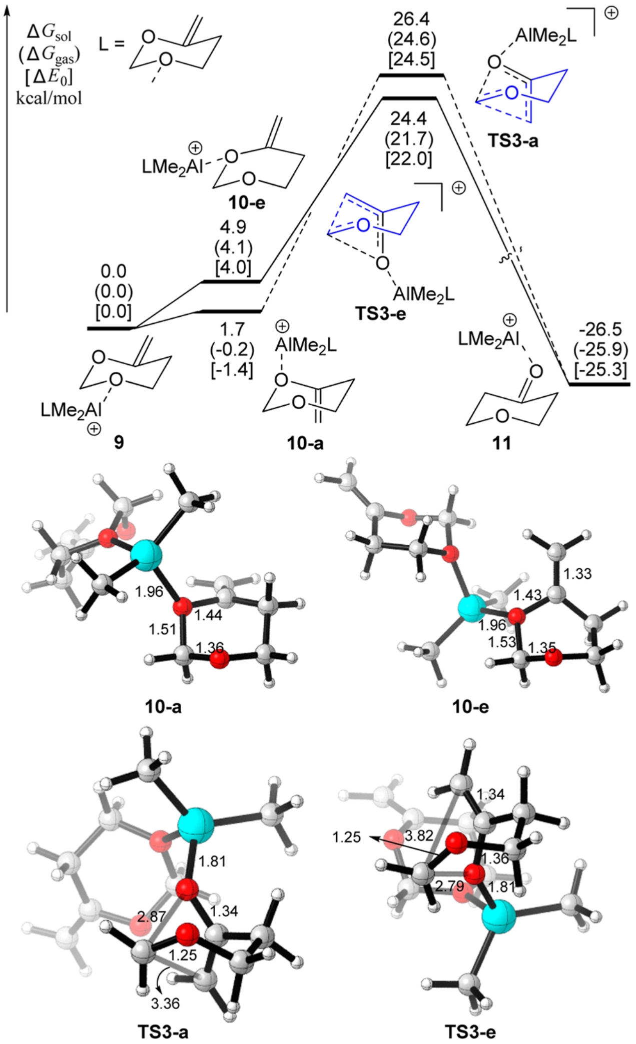
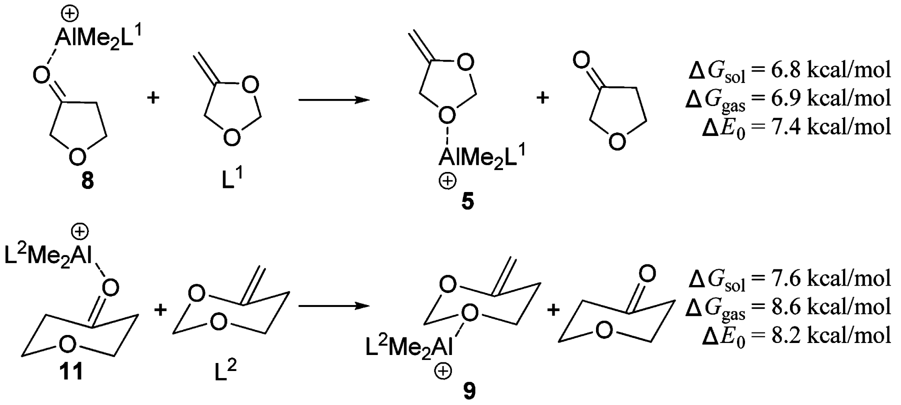


Figure 2. Energy surface for the model substrate 4-methylene-1,3-dioxane with Me$_2$Al$^+$ as the active promoting species in the gas phase and DCM solution, together with the DFT computed structures of the key stationary points (distances in Å).

Scheme 5. Computed Energies of the Ligand-Exchange Reactions between the Me_2Al^+ Coordinated Products and Enol Acetals



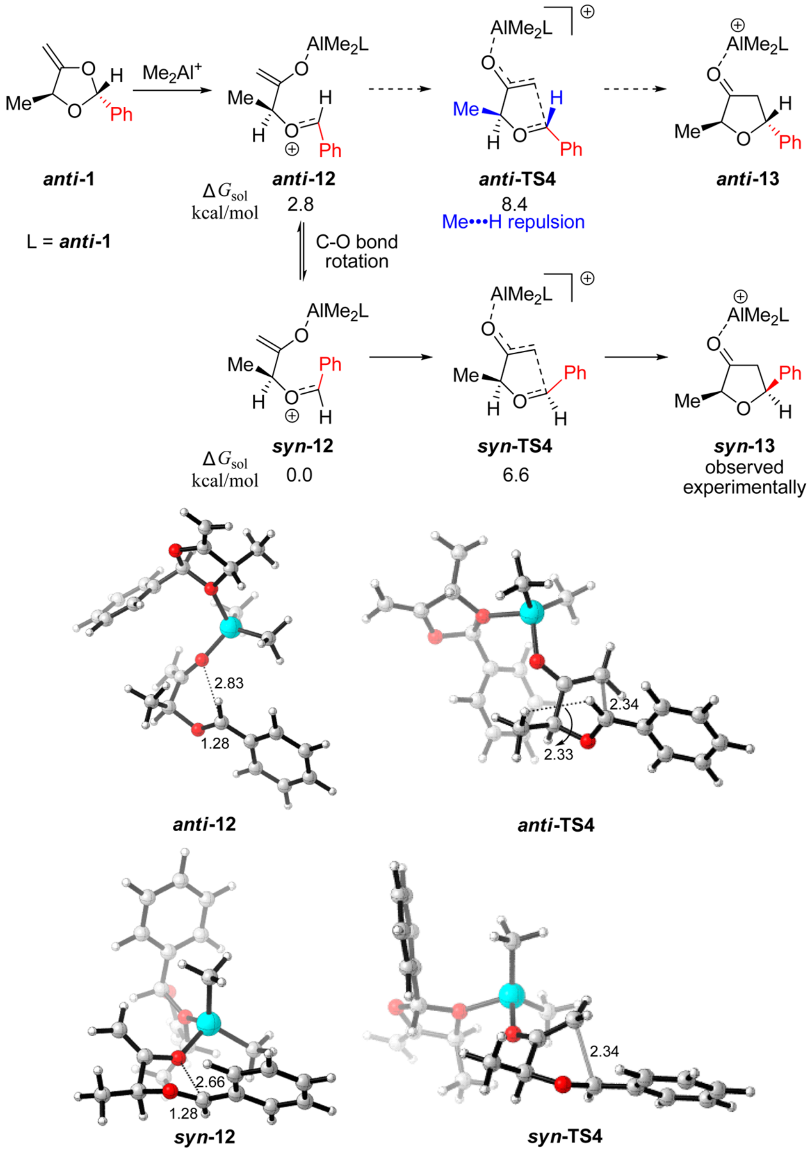


Figure 3. Rationalization of the stereochemistry for ***anti*-1** giving ***syn*-13** product (distances in Å).

starts from Me_2Al^+ coordination to the ethereal O atoms of two substrates, giving complex **9**. This complex is in equilibrium with complexes **10-a** and **10-e**. In complex **10-a**, Me_2Al^+ coordinates to the enolic O atom in the axial position, whereas in **10-e**, Me_2Al^+ coordinates to the same O atom in the equatorial position. Both **10-a** and **10-e** undergo concerted [1,3]-sigmatropic processes to give the final Me_2Al^+ coordinated product **11** via **TS3-a** and **TS3-e**, respectively. **TS3-e** is lower than **TS3-a** by 2.0 kcal/mol in energy, due to different conformations of the forming six-membered tetrahydropyran

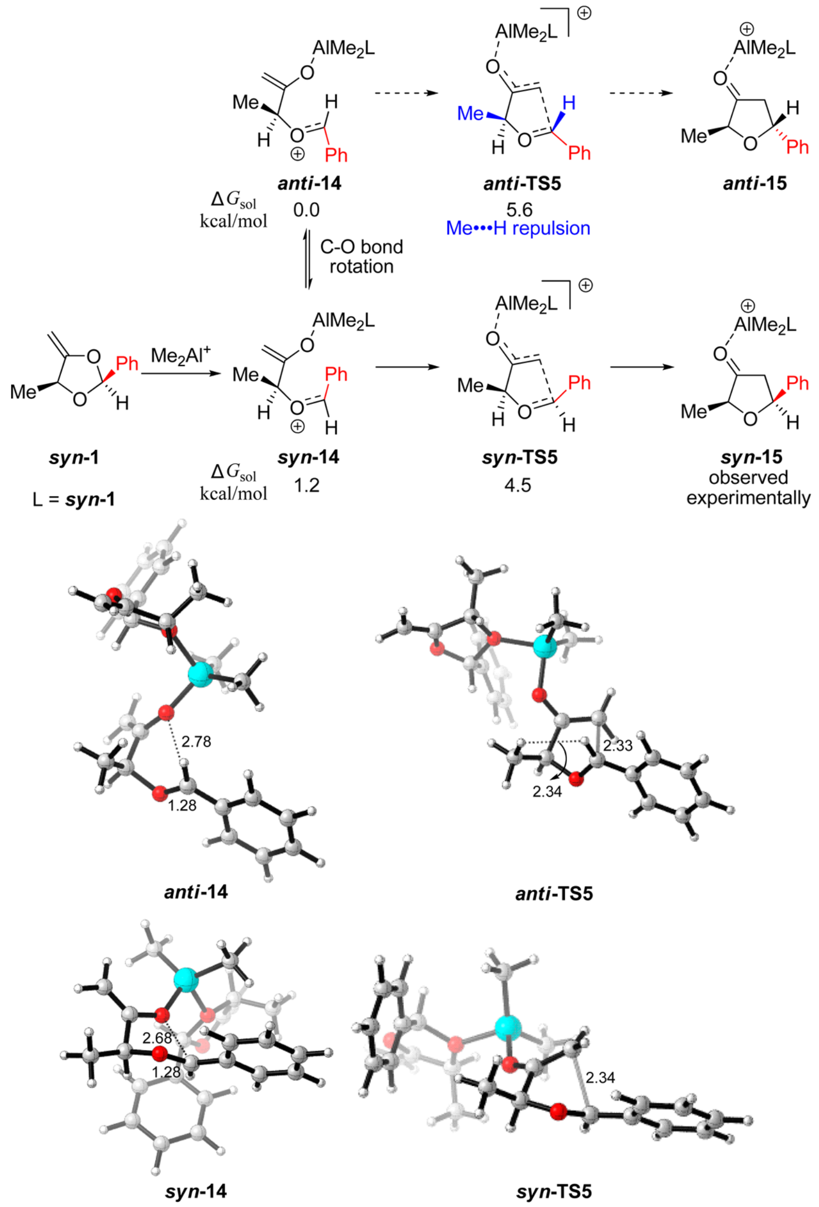


Figure 4. Rationalization of the stereochemistry for ***syn*-1** giving ***syn*-15** product (distances in Å).

frameworks: i.e., a chair conformation in **TS3-e** vs a boat conformation in **TS3-a**. In **TS3-a**, the breaking C—O bond distance is 2.87 Å and the forming C—C bond distance is 3.36 Å, while in **TS3-e**, these two distances are 2.79 and 3.82 Å, respectively. In both **TS3-a** and **TS3-e**, the distances of the breaking C—O bond and the forming C—C bond differ greatly, indicating that the concerted [1,3]-sigmatropic processes are asynchronous.

The overall activation free energy in solution for the rearrangement of the model substrate of 4-methylene-1,3-dioxane is 24.4 kcal/mol (from **9** to **TS3-e**), about 3.4 kcal/mol lower than that for the model substrate 4-methylene-1,3-dioxolane. This is in agreement with the experimental observations, where the formation of six-membered tetrahydropyran is much easier than that of five-membered tetrahydrofuran, evidenced by the different reaction temperatures used for the Petasis—Ferrier reactions of six- and five-membered enol acetals (−78 and 0−65 °C, respectively).[2,3] The higher activation free energy for the latter is due to the fact that this stepwise reaction requires an endergonic C—O bond cleavage. In contrast, the C—O cleavage and C—C bond formation occur simultaneously in the tetrahydropyran case, due to the fact that such a structure is allowed for the six-membered-ring system. Therefore, the energy-demanding bond-breaking process is partially compensated by the aldol-type bond-forming process and, consequently, less activation free energy is required for the generation of tetrahydropyran with respect to the generation of tetrahydrofuran.

We must stress that the previously proposed oxonia-Cope rearrangement transition state (Scheme 3b)[1,2b] cannot be located in the formation of tetrahydropyranone. This can be understood by the fact that the concerted transition state can exist for the substrate 4-methylene-1,3-dioxane, while the proposed intermediate precursors required for the oxonia-Cope rearrangement are not favored energetically due to the endergonic cleavage of the C—O bond from the substrate—Al complex **9**.

3. Explanation of Why Catalytic Versions of Petasis–Ferrier Rearrangements Are Difficult Using Me_2Al^+ as the Active Promoting Species. One drawback of the Petasis–Ferrier reaction is that stoichiometric amounts of Lewis acids must be used as promoters. Catalytic versions of the Petasis–Ferrier rearrangements have not been realized so far. In the above discussions, we only computed the energy surfaces of the stoichiometric Petasis–Ferrier reactions. To make these reactions reach their catalytic variants, regenerations of the catalytic species are required. We computed the ligand-exchange reactions between the Me_2Al^+ coordinated products and enol acetals (Scheme 5). Both processes are endergonic (6.8 kcal/mol for five-membered enol acetal and 7.6 kcal/mol for the six-membered enol acetal). This suggests that, for the catalytic Petasis–Ferrier rearrangement of the five-membered enol acetal substrate, the activation free energy would be 34.6 kcal/mol, while this would be 32.0 kcal/mol for a six-membered enol acetal substrate rearrangement. These activation energies are very high, indicating that catalytic versions of Petasis–Ferrier reactions using Me_2Al^+ as the active promoting species cannot be reached.

4. Rationalization of the Stereochemistry. Stereochemistry is also found in the Petasis–Ferrier reaction. Petasis and co-workers found that the rearrangements of both *anti*- and *syn*-5-methyl-4-methylene-2-phenyl-1,3-dioxolane (***anti*-1** and ***syn*-1**; Scheme 2) give only the *syn* product (reaction a, Scheme 2).[2a] Here we provide our rationalization of these results by taking advantage of the mechanistic insights given in parts 1 and 2.

For the *anti* substrate ***anti*-1**, DFT calculations found that Me_2Al^+ coordination to the enolic O atom of the substrate generates the oxocarbenium enolate ***anti*-12** (Figure 3). However, ***anti*-12** is in equilibrium with ***syn*-12** in the reaction system via the C–O bond rotation. Calculations found that ***anti*-12** is 2.8 kcal/mol higher than ***syn*-12** in terms of Gibbs free energy in solution. However, the activation free energy of the rate-determining cyclization step from ***syn*-12** is 1.8 kcal/mol lower than that from ***anti*-12**. This indicates that the cyclization step of ***anti*-1** will pass through the transition state ***syn*-TS4** instead of ***anti*-TS4**, producing exclusively the Me_2Al^+ coordinated *syn* product ***syn*-13**.

A similar computational result was also found for the *syn* substrate ***syn*-1** (Figure 4). Me_2Al^+ coordination to the enolic O atom of the *syn* substrate gives two oxocarbenium enolates, ***syn*-14** and ***anti*-14**, which are in equilibrium in the reaction system. Even though ***syn*-14** is 1.2 kcal/mol higher than ***anti*-14** in terms of Gibbs free energy in solution, the activation free energy of the rate-determining cyclization step from ***syn*-14** is 1.1 kcal/mol lower than that from ***anti*-14**. This suggests that the rearrangement reaction overcomes transition state ***syn*-TS5** instead of ***anti*-TS5**, also leading dominantly to the Me_2Al^+ coordinated *syn* product ***syn*-15**.

The above calculations agree with the experiments. The higher energy of the *anti* transition state with respect to the *syn* state is due to a disfavored allylic 1,3-strain: i.e., the steric repulsion of the methyl group and the benzyl hydrogen atom in the former transition state.[21] This is demonstrated by the short distances between the benzyl hydrogen atom and the adjacent hydrogen atom in the methyl group in ***anti*-TS4** (2.33 Å, Figure 3) and ***anti*-TS5** (2.34 Å, Figure 4). The phenyl groups in all transition states, either *anti* or *syn*, point away from the forming five-membered rings and experience no steric repulsions.

Smith and co-workers revealed that trisubstituted enol acetals, no matter whether the external alkenes in the substrates are in a *Z* or *E* configuration, undergo the Petasis–Ferrier rearrangements to give the same *anti* product (reaction b, Scheme 2).[3b] To rationalize this, DFT calculations of the rearrangements of model reactions of ***Z*-16** and ***E*-16** to generate the fully substituted tetrahydropyranones were performed (Figure 5).

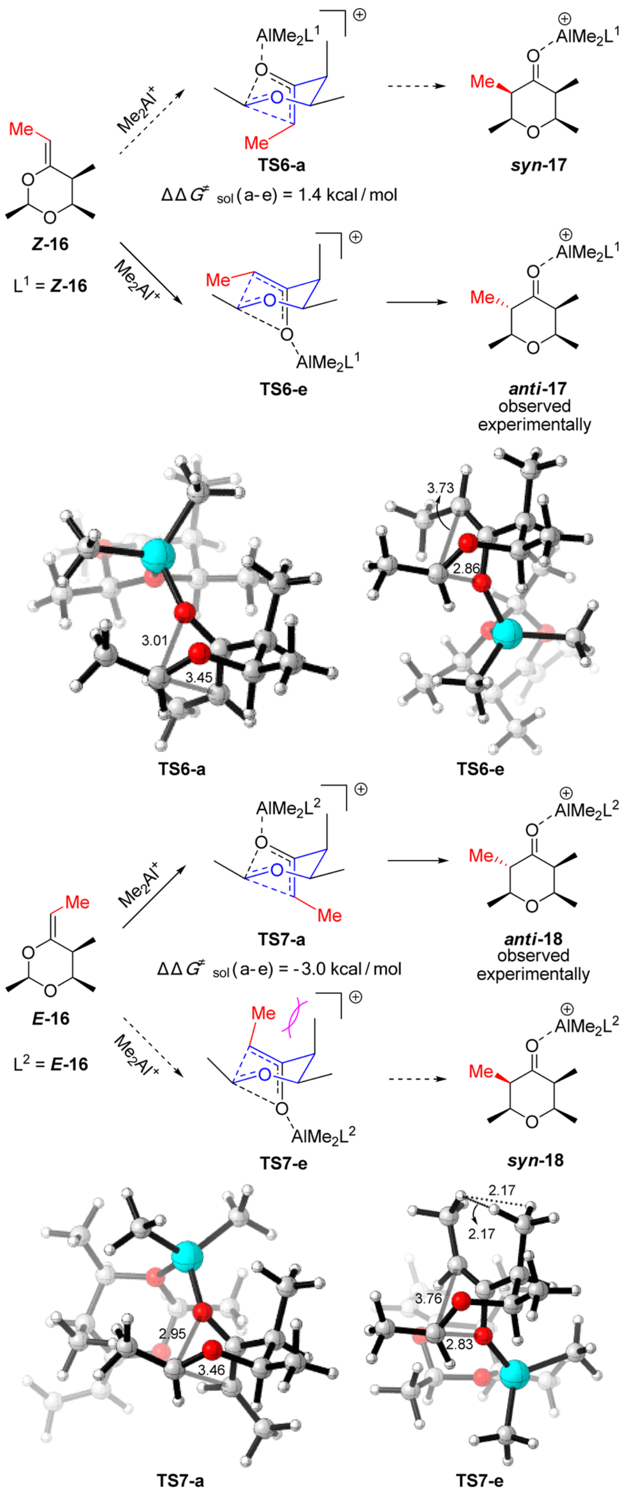


Figure 5. Rationalization of the stereochemistry for ***Z*-16** and ***E*-16** giving the same *anti* product (distances in Å).

Substrate **Z-16** has two competing reaction pathways: one pathway gives Me_2Al^+ coordinated *anti* product ***anti*-17** via transition state **TS6-e**, in which the forming tetrahydropyran framework has a chair conformation, and the other pathway gives ***syn*-17** via transition state **TS6-a**, in which the forming tetrahydropyran framework has a boat conformation. Calculations found that **TS6-e** is 1.4 kcal/mol lower than **TS6-a**, suggesting that ***anti*-17** is obtained dominantly. This agrees with Smith's experiment. The preference of **TS6-e** over **TS6-a** in terms of energy can be appreciated by the favored chair conformation of the forming tetrahydropyran framework in the former in comparison with the boat conformation of the forming tetrahydropyran framework in the latter.

For substrate **E-16**, transition state **TS7-a** (leading to ***anti*-18**) is favored over **TS7-e** (leading to ***syn*-18**) by 3.0 kcal/mol in terms of Gibbs free energy. Therefore, the Me_2Al^+ coordinated *anti* product ***anti*-18** is expected to be obtained exclusively. This also agrees with Smith's experiment. Even though **TS7-e**, which has a chair conformation of the forming tetrahydropyran framework, is expected to be favored over **TS7-a**, which has a boat conformation of the forming tetrahydropyran framework, **TS7-e** has an unfavorable 1,3-diaxial repulsion between the two methyl groups (an H···H distance of 2.17 Å is found in **TS7-e**). This 1,3-diaxial repulsion here overrides the conformation preference of a chair transition state over a boat transition state, making **TS7-e** disfavored with respect to **TS7-a**. For substrate **Z-16**, the methyl group of the *Z*-alkene in **TS6-e** is in the equatorial position of the chair transition state and does not experience steric repulsion from the methyl group in the axial position, while for substrate ***E*-16**, the methyl group of the *E*-alkene in **TS7-e** is in the axial position of the chair transition state and experiences steric repulsion from the methyl group in the axial position.

■ CONCLUSION

In summary, DFT calculations suggest that the active promoting species in the Petasis–Ferrier rearrangement is the cationic aluminum species (R_2Al^+), instead of the usually considered neutral Lewis acid (R_3Al or R_2AlCl), and the mechanisms of the Petasis–Ferrier rearrangements for the formations of five- and six-membered rings are different. Formation of tetrahydrofuranone is stepwise with C–O bond cleavage first to generate an oxocarbenium enolate intermediate, which then undergoes an aldol-type reaction to give the desired cyclized oxacycle. In contrast, the formation of tetrahydropyranone is a concerted and asynchronous process with the C–O bond breakage and aldol-type C–C bond formation occuring simultaneously. We have also explained why the catalytic versions of the Petasis–Ferrier rearrangements are difficult using R_2Al^+ as the active promoting species. In addition, the stereochemistry observed in experiments can be readily rationalized by these mechanisms and DFT calculations. It was found that the exclusive formation of *syn* product from the rearrangements of both *anti*- and *syn*-5-methyl-4-methylene-2-phenyl-1,3-dioxolane (***anti*-1** and ***syn*-1**) is due to a disfavored allylic 1,3-strain in the rate-determining cyclization transition states, leading to the *anti* product. Experimentally, the rearrangements of trisubstituted enol acetals, in which the external alkenes can be in a *Z* or *E* configuration, give only *anti* product. DFT calculations found that, for the *Z*-enol acetal, the rearrangement transition state leading to the *anti* product has a favored chair conformation of the forming tetrahydropyran framework, while the transition state leading to *syn* product has a disfavored boat conformation of the forming tetrahydropyran framework. However, for the *E*-enol acetal, the methyl group from the original *E*-alkene of the substrate occupies the axial position in the chair transition state and experiences an additional 1,3-diaxial repulsion with a methyl group, which is also in an axial position. This 1,3-diaxial repulsion overrides the conformation preference of a chair transition state over a boat transition state; thus, the reaction of the *E*-substrate favors a boat transition state and gives the *anti* product. The present study is important for understanding not only the Petasis–Ferrier reactions but also other Lewis acid promoted or catalyzed reactions. This will also help chemists to design new catalysts and reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving computational details and computed Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for Z.-X.Y.: yuzx@pku.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are indebted to the generous financial support from the Natural Science Foundation of China (21232001) and the National Basic Research Program of China-973 Program (2011CB808600).

■ REFERENCES

(1) *Strategic Applications of Named Reactions in Organic Synthesis*; Kürti, L., Czakó, B., Eds.; Elsevier Academic Press: Burlington, VT, 2005; pp 342–343.

(2) (a) Petasis, N. A.; Lu, S.-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394. (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.

(3) (a) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913.

(4) For a review, see: (a) Smith, A. B., III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675. For selected reports, see: (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (c) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426. (d) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (e) Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637. (f) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948. (g) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *7*, 4399. (h) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292. (i) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (j) Smith, A. B., III; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872. (k) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T.; Meis, R. M. *J. Org. Chem.* **2008**, *73*, 1192. (l) Smith, A. B., III; Bosanac, T.; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348. (m) Smith, A. B., III; Sfouggatakis, C.; Risatti, C. A.; Sperry, J. B.; Zhu, W. Y; Doughty, V. A.; Tomioka, T.; Gotchev, D. B.; Bennett, C. S.; Sakamoto, S.; Atasoylu, O.; Shirakami, S.; Bauer, D.; Takeuchi, M.; Koyanagi, J.; Sakamoto, Y. *Tetrahedron* **2009**, *65*, 6489.

(5) For selected recent reports involving Petasis–Ferrier rearrangements, see: (a) Bae, H. J.; Jeong, W.; Lee, J. H.; Rhee, Y. H. *Chem. Eur. J.* **2011**, *17*, 1433. (b) Sze, E. M. L.; Rao, W.; Koh, M. J.; Chan, P. W. H. *Chem. Eur. J.* **2011**, *17*, 1437.

(6) For selected recent reports involving aza-Petasis−Ferrier rearrangements, see: (a) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354. (b) Cui, L.; Li, C.; Zhang, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9178. (c) Liu, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 7301. (d) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011.

(7) For a recent report discussing the real catalytic species in $InCl_3$-catalyzed cycloisomerization reactions of 1,6-enynes, see: Zhuo, L.-G.; Zhang, J.-J.; Yu, Z.-X. *J. Org. Chem.* **2012**, *77*, 8527.

(8) Frisch, M. J., et al. *Gaussian 03, revision D.02*; Gaussian, Inc., Wallingford, CT, 2004.

(9) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(10) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(11) (a) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161. (b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (c) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

(12) (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669. (c) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70.

(13) Legault, C. Y. *CYLView, version 1.0b*; Université de Sherbrooke, Sherbrooke, Québec, Canada, 2009; http://www.cylview.org.

(14) The activation energies for the formation of tetrahydrofuranone using a neutral Lewis acid are 48.8 kcal/mol by the MP2/6-311+G(d,p) method, 50.4 kcal/mol by the CCSD(T)/6-31G(d) method, and 45.8 kcal/mol by the M06/6-31G(d) method, respectively, while those for the formation of tetrahydropyranone using a neutral Lewis acid are 40.7 kcal/mol by the MP2/6-311+G(d,p) method, 40.3 kcal/mol by the CCSD(T)/6-31G(d) method, and 37.7 kcal/mol by the M06/6-31G(d) method, respectively. See the Supporting Information for details.

(15) Townsend, N. S.; Shadbolt, S. R.; Green, M.; Russell, C. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3481 and references within.

(16) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (c) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884. (d) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

(17) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

(18) Lam, Y.-h.; Cheong, P. H.-Y.; Mata, J. M. B.; Stanway, S. J.; Gouverneur, V.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 1947.

(19) Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952.

(20) For a review, see: (a) Dagorne, S.; Atwood, D. A. *Chem. Rev.* **2008**, *108*, 4037. For selected reports, see: (b) Bott, S. G.; Alvanipour, A.; Morley, S. D.; Atwood, D. A.; Means, C. M.; Coleman, A. W.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1987**, *26*, 485. (c) Means, N. C.; Means, C. M.; Bott, S. G.; Atwood, J. L. *Inorg. Chem.* **1987**, *26*, 1466. (d) Atwood, D. A.; Jegier, J. A.; Rutherford, D. *J. Am. Chem. Soc.* **1995**, *117*, 6779. (e) Muñoz-Hernández, M.-Á.; Sannigrahi, B.; Atwood, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 6747. (f) Kim, K.-C.; Reed, C. A.; Long, G. S.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 7662. (g) Lichtenberg, C.; Robert, D.; Spaniol, T. P.; Okuda, J. *Organometallics* **2010**, *29*, 5714. (h) Khandelwal, M.; Wehmschulte, R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7323.

(21) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.