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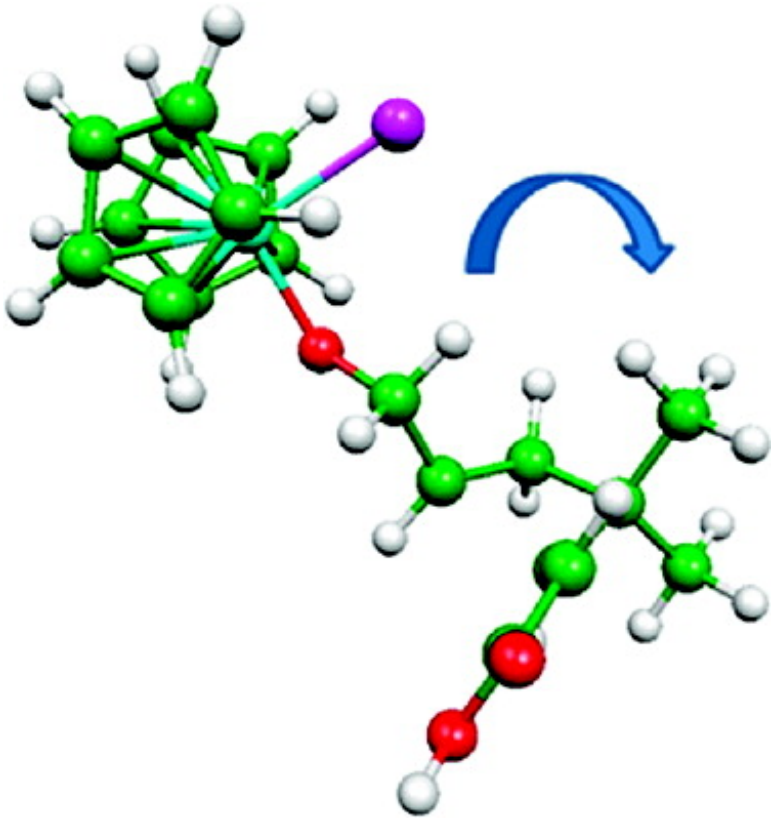

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Titanocene Catalyzed 4-*exo* Cyclizations: Mechanism, Experiment, Catalyst Design

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Abstract: A method for the preparation of a variety of cyclobutanes via 4-*exo* cyclization of radicals is presented. Radical generation is carried out by electron transfer from titanocene(III) chlorides to epoxides. The reaction relies on the acceleration of the cyclization through the use of α,β-unsaturated carbonyl compounds as radical traps and the thermodynamic stabilization of the cyclobutylcarbinyl radicals through conjugation. The mechanism of the transformation was investigated by a combined theoretical and experimental study. The computational results provide the crucial energetic and structural features of pertinent intermediates and transition structures. Moreover, the origins of the diastereoselectivity of the 4-*exo* cyclization are outlined for the first time. Catalysts for those cases where "Cp_2TiCl" did not perform in a satisfactory manner have been devised. Through the introduction of *tert*-butyl or *cyclo*-hexyl substituted cyclopentadienyl ligands the longevity of the pivotal β-titanoxy radicals is increased sufficiently enough to enable the slow but often surprisingly diastereoselective formation of the cyclobutylcarbinyl radical. The resulting transformation constitutes the first general approach to cyclobutanes using radical chemistry.

Introduction

Over the past decades the application of radical chemistry in the synthesis of complex molecules has developed at a breathtaking pace.[1] Noticeable limitations still exist, however. One of the relatively unexplored fields is constituted by the synthesis of small rings.[2] The substantial difficulties encountered in the preparation of four-membered rings are due to not only their inherent strain but also the ring-closure of the pentenyl radical being among the slowest radical reactions.[3] In many cases 4-*exo* cyclizations are therefore too slow to maintain an efficient chain propagation. A number of examples relying on the *gem*-dialkyl or *gem*-dialkoxyl substitution adjacent to the radical center have been reported.[4] However, the crucial issue of the stereoselectivity of the cyclization has to date not been addressed at all. In brief, no general method for the synthesis of cyclobutanes employing classical free radical chemistry is available. Additionally, it has even been challenged if the 4-*exo* cyclization is indeed kinetically favorable[5] as suggested by Baldwin' s rules.[6]

In the field of metal mediated radical chemistry the above-mentioned kinetic restrictions do not necessarily apply. Progress toward efficient 4-*exo* cyclizations has thus been more successful. With SmI_2, the currently most popular electron-transfer reagent,[7] cyclizations with ketyl radicals and acrylates or vinylsulphones as radical traps result in the formation of cyclobutanols.[8] However, the use of ketones as radical precursors may lead to undesired 5-*endo* cyclizations.[8c]

The application of titanocene(III) chloride in radical chemistry constitutes a rapidly expanding field of research.[9] This is especially so for the radical generation from epoxides introduced by Nugent and RajanBabu.[10] The structure of the reagent[11] and the mechanism of the ring opening[12] have been established. Recently, the catalytic variants of their reaction have become

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even more popular.[13] Important examples of rare reactions such as enantioselective radical generation[13d,h,p] or 3-*exo* cylizations[13m,n] controlled by polarity matching of radical reduction have been developed in this manner. Also, a number of pertinent applications in the synthesis of complex molecules have emerged such as titanocene-catalyzed epoxypolyene cyclizations.[13k,o] Epoxide opening has also been used with excellent success for the initiation of the polymerization of styrene.[14] Other metal complexes have been proven to be less general, even though interesting methodology has been developed.[15]

Stoichiometric and catalytic pinacol couplings have attracted less attention due to their restricted substrate scope, even though the first example of an enantioselective coupling has been reported.[16] Additionally, a number of other synthetic applications have been evolving recently.[17]

In the field of the 4-*exo* cyclization only two isolated examples have been reported to date. Fernández-Mateos and his group employed an aldehyde[18] and a nitrile[19] as a radical trap to yield a cyclobutanol and a cyclobutanone, respectively, with Nugent's and RajanBabu's original protocol. A general synthetic approach to cyclobutanes using titanocene based radical chemistry, however, has not been described. Such a method, which is disclosed here, is highly desirable not only for understanding the thermodynamic, kinetic and stereochemical aspects of the 4-*exo* cyclization in general but also for applications in the synthesis of complex molecules which are also quite attractive as cyclobutanes constitute important structural motifs in a number of natural products and biologically active substances.[20]

Results and Discussion

Our approach to developing titanocene catalyzed 4-*exo* cyclizations is firmly based on a close interaction between experimental and theoretical studies. The prime virtue of such combined investigations is that appropriate catalysts and reaction conditions can be designed with the knowledge of the mechanistic details outlined by computational chemistry. Hence, we present the methods and results of our computational approach first and thereafter discuss our synthetic investigations.

Computational Studies

Computational chemistry provides unique and highly useful tools for predicting reaction and activation energies and for delivering crucial information on the molecular structures of intermediates and transition states. However, the very accurate high level wavefunction-based *ab initio* methods are still restricted to relatively small molecules, and less rigorous approaches such as density functional theory (DFT) are used for the by far majority of investigations.

Benchmarking and the Accuracy of DFT Calculations for *4-exo* Cyclizations. Cyclization of the Parent Pentenyl Radical. In this study they were only applied for scrutinizing the cyclizations of the parent pentenyl radical **1** (Scheme 1) and a derivative containing an acrylate as an activated radical acceptor. In this manner high quality benchmarks for the density functional theory first principle methods[21] employed in the calculations of the titanocene containing systems are generated. Such quality benchmarking is critical for this study as no reliable experimental data are available for the reactions of both **1** and related systems.[4,5] The CCSD(T) method (coupled cluster ansatz with singles and doubles and perturbative triple substitutions) was employed

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Scheme 1. 4-*exo* and 5-*endo* Cyclization of **1**

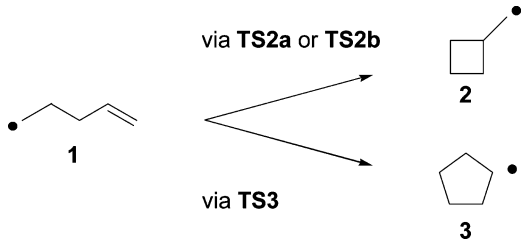

Table 1. Single-Point Energies of the 4-*exo* and 5-*endo* Cyclization of **1** by CC and DFT Methods in kcal mol^{-1} Including ZPE

	RCCSD cc-pVTZ	RCCSD E_{23}	RCCSD(T) cc-pVTZ	RCCSD(T) E_{23}	RI-BP86 TZVP	B3LYP TZVPP	B3LYP 6-31G*[a]
1	0	0	0	0	0	0	0
2	3.3	3.1	3.2	3.1	3.0	6.1	4.5
3	−17.6	−17.9	−17.4	−17.7	−17.5	−14.6	−19.0
TS2a	22.3	22.2	19.8	19.6	15.3	19.1	18.1
TS2b	20.3	20.3	17.8	17.6	13.5	17.3	-
TS3	19.8	19.7	17.3	17.0	13.5	17.2	16.3

[a] B3LYP/6-31G* energies of Chatgilialoglu et al.[5]

for this purpose, since it is one of today's most accurate quantum chemical methods applicable to systems of this size.[22]

The geometry optimizations were carried out within the framework of DFT with the BP86/TZVP method (Becke−Perdew gradient corrected exchange and correlation density functional[21] combined with a polarized split-valence basis set of triple-ζ quality) using the RI approximation (resolution of identity) within the TURBOMOLE[23] program package. The *ab initio* calculations of this work were performed with the MOLPRO[24] and TURBOMOLE[23] program packages at the RI-BP86/TZVP optimized structures. The zero-point energy (ZPE) was obtained from numerical force constants based on RI-BP86/TZVP calculations.

In order to obtain the required highly accurate reaction and activation energies for the reactions of **1** we performed CCSD(T)/cc-pVTZ calculations at the DFT geometries. These results together with the outcome of the computationally less demanding CCSD/cc-pVTZ calculations are summarized in Table 1.

It should be noted that the benchmarking was also carried out on a number of conformers of **1**, **2**, and **3** to obtain a broader set of data that are presented in the Supporting Information. In order to reduce the error in our reaction energies, we extrapolated the CCSD and CCSD(T) results obtained with the cc-pVXZ ($X = 2, 3$) basis set of Dunning[25] to the basis set limit. We used the two-point fit as introduced by Halkier and Helgaker et al.[26]

$$E_{23} = E_3^{HF} + \frac{8E_2^{corr} - 27E_3^{corr}}{-19}$$

Here, E_3^{HF} represents the Hartree−Fock energy in the cc-pVTZ basis set, whereas E_2^{corr} and E_3^{corr} stand for the correlation energies obtained with the cc-pVDZ and the cc-pVTZ basis set, respectively. Despite the fact that the basis set extrapolation using a double/triple-ζ basis set does not provide the absolute energies at the basis set limit very accurately, in this manner the error in the relative energies is reduced.[22]

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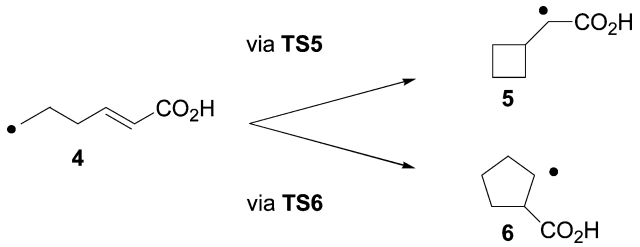
Scheme 2. 4-*exo* and 5-*endo* Cyclization of **4**



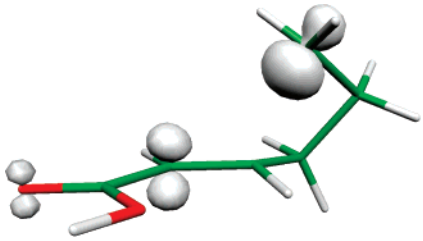
We point out that the basis set extrapolation has only a minor effect on the relative CCSD and CCSD(T) energies; i.e., the CC results are quite stable with respect to extensions of the one-particle basis set. From our results it is also clear that both CC methods give excellent agreement concerning the energies of the substrate and product radical and hence also of the reaction energy. The computationally less demanding RCCSD cc-pVTZ method overestimates the activation barriers by about 2.5 kcal mol^{-1}. However, the differences in the activation barriers of the different processes are the same for both methods. In accordance with experimental experience, our findings demonstrate that the 4-*exo* cyclization of the pentenyl radical is a thermodynamically disfavored process. The rather high activation energy for a radical reaction suggests that opening of cyclobutylcarbinyl radicals is irreversible in agreement with the experiments.[3] As a deviation from Baldwin's rules,[6] the competing 5-*endo* cyclization should proceed faster, despite being stereoelectronically disfavored. Moreover, due to the absence of ring strain, this cyclization proceeds with a substantially lower reaction energy.

When comparing B3LYP/TZVPP and the RI-BP86/TZVP energy with the CC results, it becomes clear that none of the two DFT methods is superior to the other in all respects. The RI-BP86/TZVP reaction energies are closer to the CCSD(T) results than the ones obtained by B3LYP/TZVPP. On the other hand the B3LYP/TZVPP activation barriers are somewhat more accurate than the RI-BP86/TZVP barriers. For both methods the differences in activation and reaction energies are essentially the same. Therefore, both DFT methods are suitable for studying the competition between these closely related 4-*exo* and 5-*endo* cyclizations.

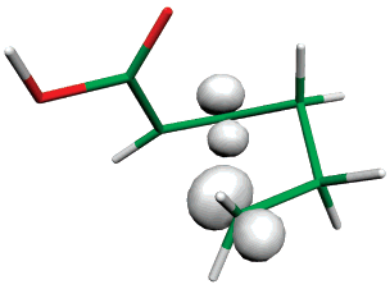
In 2002 Chatgilialoglu et al. studied the reactions of **1** applying the B3LYP/6-31G* functional.[5] Their results are included in the last column of Table 1. The agreement with our CC results is fair concerning the reaction energies and hence the thermodynamic features of the cyclization. However, in our study two possible transition states for the 4-*exo* cyclization that are characterized by angles of approach of the radical toward the olefin of 118° and 115° were identified. Surprisingly, the attack from the angle of 118° is more advantageous (by 2.0 kcal mol^{-1}) than the approach of 115°. In Chatgilialoglu's study only this latter and less favored transition state was identified. Hence, the activation energy of the 4-*exo* cyclization relative to the 5-*endo* cyclization was overestimated. Nevertheless, both Chatgilialoglu's and our study confirm the notion that the 5-*endo* cyclization is favored thermodynamically and kinetically, albeit to a noticeably lesser extent in our case.

4-*exo* Cyclization with an Activated Radical Acceptor. With these reliable results for the archetypal 4-*exo* cyclization in hand, we turned our attention to studying the cyclization reactions of **4** as shown in Scheme 2. In this manner the influence of activating the radical acceptor through conjugation on reaction and activation energies can be studied in detail. The results of these calculations are essential for the understanding of our titanocene catalyzed reactions and are summarized in Table 2.

Introduction of the acid group renders the 4-*exo* cyclization kinetically more favorable, while the 5-*endo* process remains thermodynamically preferred. It is quite remarkable that the electronic activation of the double bond compensates the developing strain of the cyclobutane



TS5



TS6

Figure 1. Spin densities of **TS5** and **TS6** at the RI-BP86/TZVP level of theory.

Table 2. Activation and Reaction Energies of the 4-*exo* and 5-*endo* Cyclization of **4** in kcal mol^{-1} Including ZPE

	4	5	6	TS 5	TS 6
RI-BP86 TZVP	0.0	−2.6	−14.2	9.9	14.9
RI-BP86 TZVPP	0.0	−2.6	−14.0	9.9	15.1
RCCSD cc-pVTZ	0.0	−1.1	−16.7	17.0	21.3

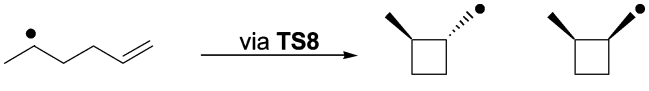
in the transition structure by more than 3 kcal mol^{-1} compared to **1** according to the CC results. This is, however, in line with the mechanistic analyses of the intermolecular addition reactions of radicals to activated olefins, such as acrylates.[27] The strong acceleration of the 4-*exo* cyclization can be rationalized by comparing the electronic structures of both transitions states as shown in Figure 1. The mesomeric stabilization of **TS5** is apparent from the delocalization of the evolving spin center. This is not possible for **TS6**, of course.

We note that **TS5** is more stable than the **TS6** state by about 5 kcal mol^{-1} at the DFT level and 4.3 kcal mol^{-1} in the CCSD case. As already observed for **1** (Table 1) the DFT calculations underestimate the absolute barriers compared to the CCSD. However, the differences between both pathways are essentially the same. Since we are mainly interested in the comparison of reactivities, this systematic error seems acceptable and does not affect the conclusions of our work.

A kinetically controlled reaction, i.e., an irreversible cyclization, will be observed if radical trapping is swift enough to prevent ring opening of the cyclobutylcarbinyl radical. Because the activation energy for ring opening is rather high for a radical reaction, cyclization is predicted to occur in the presence of a highly efficient reduction of the cyclobutylcarbinyl radical to an enolate with reagents such as SmI_2 or "Cp_2TiCl".

Performance of DFT Methods in Predicting the Diastereoselectivity of the 4-*exo* Cyclization. The quantities of main interest are the energy differences of two 4-*exo* products or their corresponding transition states. Therefore we benchmarked our DFT result of this difference with CCSD(T)/cc-pVTZ calculations for the formation of **8**. For these purposes the differences in the activation and reaction energies were calculated (Table 3).

Table 3. Results of the Calibration Studies of the 4-*exo* Cyclization of **7** in kcal mol^{-1}; the Coupled Cluster Energies Were Obtained at the RI-BP86 Geometry



7 *trans*-**8** *cis*-**8**

	CCSD(T)/ cc-pVTZ	CCSD/ cc-pVTZ	RI-BP86/ TZVP
E(*cis*-**8**)−E(*trans*-**8**)	1.5	1.6	2.0
E(*cis*-**TS8**)−E(*trans*-**TS8**)	0.1	0.2	0.7

The results of the RI-BP86/TZVP and the CC methods are in very good agreement. The discrepancies between the methods in the differences of both the reaction and activation energies are only in the range of 0.5 kcal mol^{-1}. This clearly demonstrates that in the comparison of electronically closely related structures, such as the competing 4-*exo* cyclization pathways here, the intrinsic errors of the DFT methods cancel each other efficiently. The computationally less lavish RI-BP86 method was therefore employed in the following investigations.

Effect of *gem*-Dimethyl and Dimethoxy Substitution on the Reaction and Activation Energy of the 4-*exo* Cyclization

"The *gem*-dialkyl effect is the name given to the acceleration of a cyclization due to the replacement of hydrogen atoms with alkylgroups tethering the two reaction centers" as pointed out by Jung.[4d] There have been two experimental[3c,4a] and one early computational[4b] report on the nature of this effect in 4-*exo* cyclizations. Here, we establish its kinetic and thermodynamic basis for the four exemplary cases shown in Figure 2 and summarized in Table 4 with the aid of more reliable state of the art calculations.

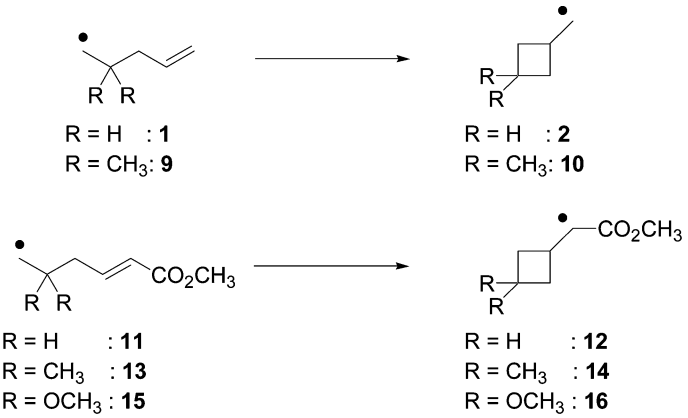
The RI-BP86/TZVP potential energy surface of these 4-*exo* cyclizations clearly demonstrates how the *gem*-dimethyl substitution affects the course of these reactions. For both sets of radicals the respective transition structures as well as the corresponding cyclobutylcarbinyl radicals are stabilized by 3−4 kcal mol^{-1}. This effect is additive and independent of the presence of an acrylate as a radical trap (entries 3 and 4). Also, the effect is both thermodynamic[28] and kinetic in nature. In the case of an irreversible cyclization only the stabilization of the transition structures will be relevant, of course.

Another intriguing aspect of 4-*exo* cyclizations has been described by the group of Jung.[4a,b] It was established that *gem*-dialkoxy substitution adjacent to the radial center promotes cyclobutane formation with substantially higher efficiency than *gem*-dialkyl substitution. To verify this effect with modern methods we have investigated the reaction of **15** (Table 5, entry 5).

We note that for the activation and reaction energy of the cyclization is lower for the *gem*-dimethoxy substituted radical than for the corresponding *gem*-dimethyl substituted radical. Thus, our calculations correctly reproduce the trend observed by Jung et al.[4a,b]

(27) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340−1371.

(28) Magers, D. H. *J. Org. Chem.* **2007**, *72*, 2533−2537.



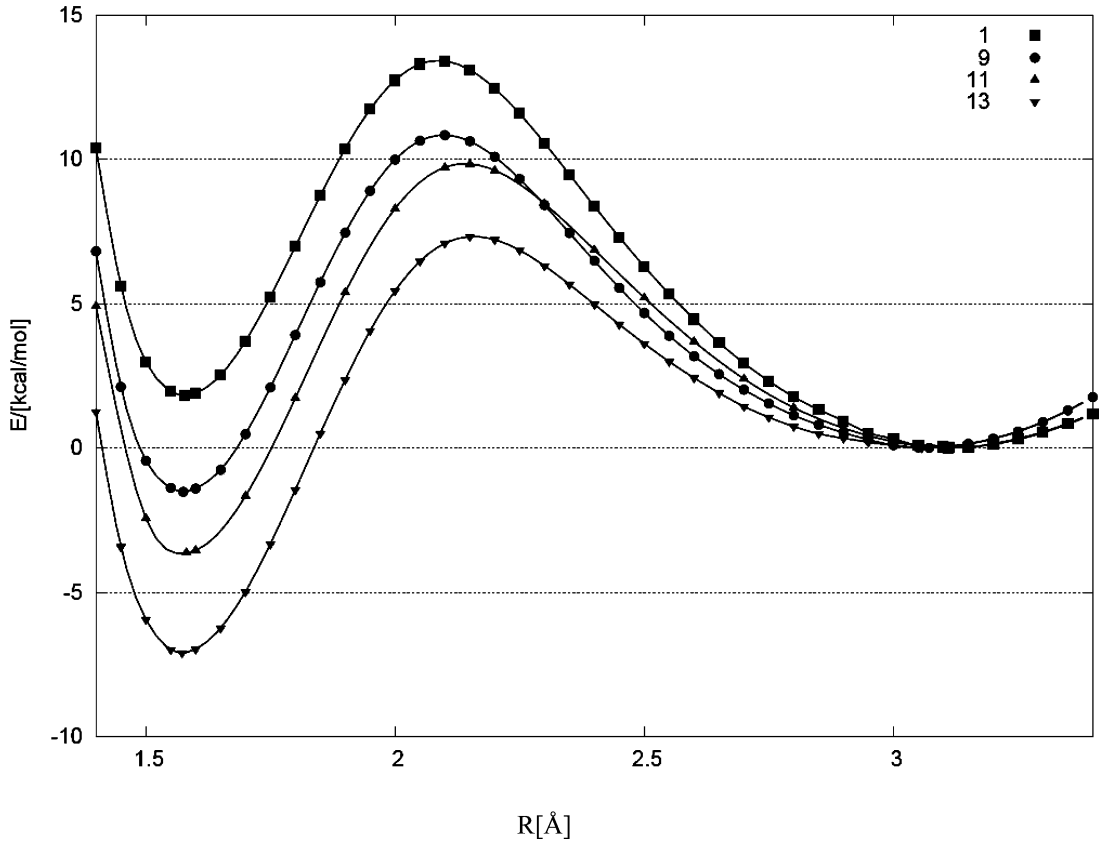


Figure 2. *gem*-Dimethyl effect in the cyclizations of **1** and **9** and of **11**, **13**, and **15**.

Table 4. Kinetic and Thermodynamic Aspects of the *gem*-Dimethyl Effect in kcal mol^{-1} at the RI-BP86/TZVP Level Including ZPE

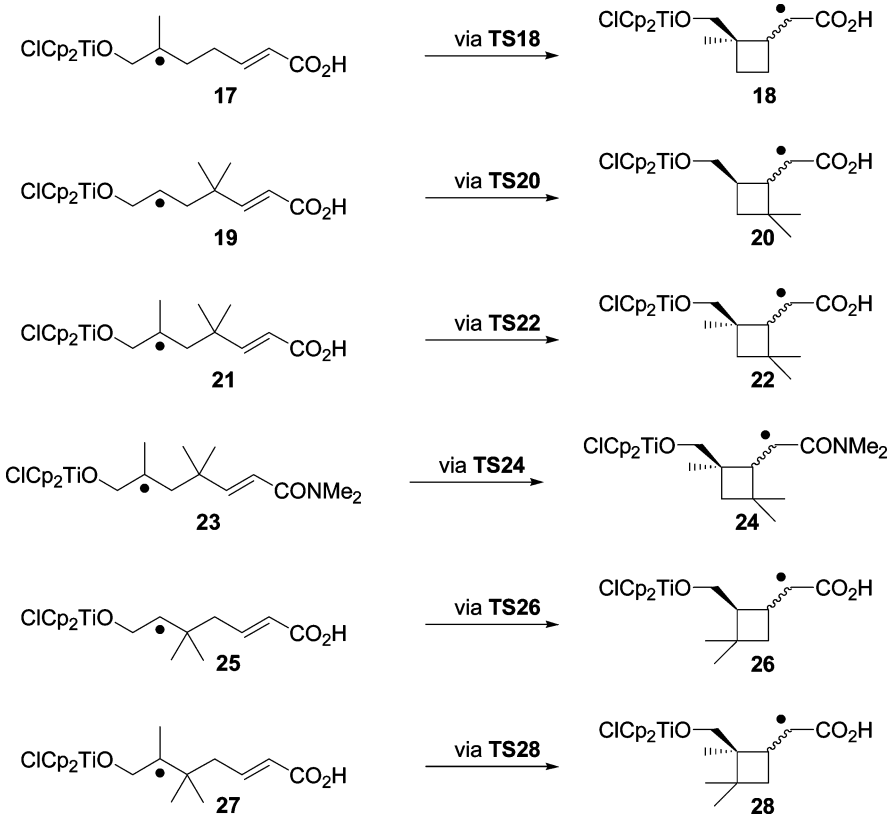
entry	substrate	product	ΔE	E_a
1	**1**	**2**	3.2	13.5
2	**9**	**10**	−0.3	10.6
3	**11**	**12**	−2.0	9.9
4	**13**	**14**	−5.9	7.2
5	**15**	**16**	−8.0	6.5

Table 5. RI-BP86/TZVP Reaction Energies for the Cyclizations Shown in Scheme 3 in kcal mol^{-1} Including the ZPE

entry	substrate	product	ΔE (*cis*)	ΔE (*trans*)	E_a (*cis*)	E_a (*trans*)
1	**17**	**18**	+1.7	+1.8	9.1	9.2
2	**19**	**20**	−1.1	−4.6	9.0	4.6
3	**21**	**22**	−0.2	−1.6	7.5	4.4
4	**23**	**24**	−1.0	−1.3	7.4	5.0
5	**25**	**26**	−2.4	−4.5	7.5	6.5
6	**27**	**28**	+0.1	+0.1	7.7	7.3

Computational Results of "Cp_2TiCl: Mediated 4-*exo* Cyclizations. For studying titanocene mediated cyclizations we chose the reactions depicted in Scheme 3 for the following reasons. First, the variation of radical substitution and the positioning of the *gem*-dimethyl group allow a systematic evaluation of the reaction and activation energies and hence the diastereoselectivity of the 4-*exo* cyclization that is essential for any preparative application. Second, the structural features of the pertinent titanocene containing radicals and transition structures provide essential information for the design of appropriate reaction conditions. Third, radicals containing an ester group instead of the carboxylic acid investigated here can be easily generated experimentally from readily accessible vinyl epoxides. The computational predictions can therefore be readily

Scheme 3. Computationally Investigated Titanocene Mediated 4-*exo* Cyclizations



verified. Finally, the *gem*-dimethyl substituted cyclobutanes generated by reduction of **20** and **26** constitute interesting intermediates for the synthesis of cyclobutane containing caryophyllane or caryophyllene natural products.[20]

The results of the calculations are summarized in Table 5. Only the substrate and product conformers with the lowest energy are included to obtain the reaction energies and the reaction barriers in order to reduce the complexity of the discussion. This simplification is appropriate as the different conformers, especially the cyclobutane conformers, are all thermally readily accessible (see Supporting Information for a complete listing of structural and energetic details).[29]

Discussion of the Energies of Activation

We will start our analysis with the activation energies and concentrate especially on their differences that are decisive for the stereoselectivity of the cyclobutane formation. When keeping in mind that the RI-BP86/TZVP method underestimates the barriers of the 4-*exo* cyclization (Table 2), the activation energies shown in Table 5 are rather high for radical reactions. Thus, in any synthetic study care will have to be taken to avoid competing pathways. This is particularly so for **17** (entry 1). The formation of both *cis*- and *trans*-**18** seems thus rather unlikely.

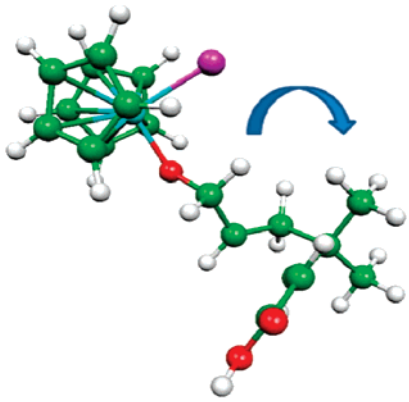
Because the cyclization of **19** (entry 2) is predicted to be most selective it is also suited best for a more detailed analysis of the factors affecting the relative stabilities of the transition structures. We suggest the 1,3-diaxial interaction between the CH_2OTiCp_2Cl and a CH_3 group (indicated by the arrow) in *cis*-**TS 20** that is absent in *trans*-**TS 20** as the most important reason for the high difference in the energy of activation (Figure 3).

Similar 1,3-diaxial interactions [between a CH_3 group of the *gem*-dimethyl group and either the CH_2OTiCp_2Cl group (***cis*-TS22**) or a CH_3 group (***trans*-TS22**)] are present in both **TS22** (entry 3), and hence the cyclization of **21** is distinctly less selective. The same reasoning applies for the reaction of **23** (entry 4). Thus, the *gem*-dimethyl effect provides a means for controlling the diastereoselectivity of the 4-*exo* cyclization in addition to promoting this reaction kinetically. As we postulate 1,3-diaxial interactions to be the major reason for the observed diastereoselectivity of the cyclization, it may be expected that the bulkiness of the cyclopentadienyl ligands could have some influence on the outcome of the reaction. This should be especially so for **19** (entry 2) and to a lesser extent for **21** and **23** (entries 3 and 4).

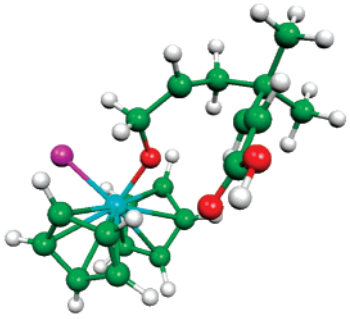
In the case of **25** (entry 5) and **27** (entry 6) the relative stabilities of the *cis*- and *trans*-**TS** are dominated by the interactions between the radical's substituents and the neighboring *gem*-dimethyl group. Because of the *pseudo*-equatorial positioning of the CH_2OTiCp_2Cl group *trans*-**TS26** is more stable than *cis*-**TS26** with the *pseudo*-axial CH_2OTiCp_2Cl group. This difference is only slight (1.0 kcal mol^{-1}) due to the relatively loose structures of *trans*-**TS26** and *cis*-**TS26**. The energetic difference between both **TS28** is even smaller. Both **26** and **28** should be formed with low diastereoselectivity

When comparing **26** and **28** quantitatively, we note that the difference between $\Delta(E_a(cis) - E_a(trans))$ of **26** and **28** is only 0.6 kcal mol^{-1}. This value is well within the limits of the accuracy of the RI-BP86/TZVP method. Thus, any prediction if **26** or **28** is formed with higher selectivity is not possible.

(29) Egawa, T.; Fukuyama, T.; Yamamoto, S.; Takabayashi, F.; Kambara, H.; Ueda, T.; Kuchitsu, K. *J. Chem. Phys*. **1987**, *86*, 6018−6026.



cis-TS20



trans-TS20

Figure 3. 1,3-Diaxial interaction as reason for the diastereoselectivity in the formation of **20**.

Thermodynamic Considerations. The reaction of **17** (entry 1) lacking the *gem*-dimethyl substitution is, as expected, both thermodynamically and kinetically the most unfavorable case. This is in agreement with the failure of such cyclizations in radical chain reactions. The reaction energies for the tertiary radicals are lower than those for the respective secondary radicals due to the difference in radical stabilities and the additional steric interactions in the cyclobutane.

This can be readily seen for the reactions of **25** (entry 5) and **27** (entry 6). The advantageous *trans*-diequatorial substitution by the CH_2OTiCp_2Cl and the $CHCO_2H$ groups in the thermodynamically favored cyclization of **25** results in a lower reaction energy for *trans*-**26**. However, the presence of the additional CH_3 group in **27** results in two adjacent quarternary carbons in the cyclobutylcarbinal radical **28**. The resulting disadvantageous interactions between vicinal equatorial and axial groups lead to a thermodynamically disfavored cyclization with equally stable *cis*- and *trans*-isomers of **28**.

Finally, the results suggest a kinetically controlled and thus irreversible titanocene catalyzed cyclization. An efficient polarity controlled trapping of the electron deficient cyclobutylcarbinyl radical by a second equivalent of the strongly reducing titanocene(III) reagents will occur before ring opening. This is because, as opposed to the titanocene catalyzed 3-*exo* cyclizations,[13n] the barriers for ring opening of the cyclobutylcarbinyl radical are too high.

Synthetic Investigations

Our theoretical study can only address the intrinsic features of the 4-*exo* cyclizations. Due to their relatively high activation energies, this is not sufficient for fully predicting the outcome of the reactions. The two intermolecular processes outlined below can in principle interfere with the cyclizations and have to be investigated experimentally.

First, termination of the cyclization occurs by reduction of the carbonyl substituted radical with a second equivalent of the titanocene. This reductive trapping must be sufficiently fast to warrant a high yield of the desired product. The rate of the reduction will be dependent on catalyst concentration and the steric bulk of its ligands. Second, the β-titanoxy radicals generated after epoxide opening can be reduced quite efficiently by titanocene(III) complexes if the desired radical processes, such as our 4-*exo* cyclization, are slow. This has been demonstrated to be especially critical with secondary radicals such as **19** that are not sterically shielded. Thus, these steps, which are critical for the performance of the overall process, can in principle be controlled by proper choice of the catalyst.

To understand and control their relative influence the catalysts shown in Scheme 4 were employed in our synthetic studies.[12,30] These complexes contain ligands of varying steric bulk and are known to reduce radicals with differing efficiency. In this manner, the important issue of catalyst design for the 4-*exo* cyclizations can be addressed in a rational manner.

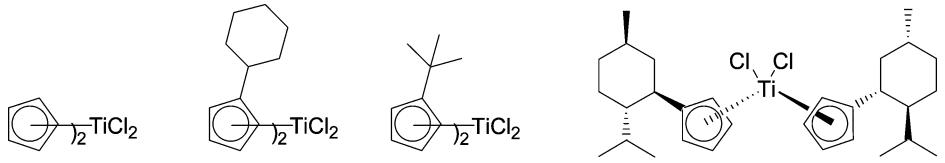
Our reactions summarized in Table 6 were selected for the experimental study for the following reasons. First, these radicals generated from the epoxides closely resemble the "computational substrates," and hence the quality of the calculations can be assessed in a straightforward way. Second, the influence of radical and catalyst substitution on the performance of the reaction can be studied in a clear-cut manner. Therefore, the mono- and 2,2-disubstituted epoxides with the *gem*-dimethyl group in either or both of the available positions and the catalysts shown in Scheme 4 were employed in our study. Also, the suitability of α,β-unsaturated amides as radical traps can be evaluated experimentally.

Because the diastereoselectivity of the reactions are dependent on the catalyst we propose that the cyclizations do indeed proceed via the β-titanoxy radicals. Moreover, this has been shown to be the case in the other titanocene catalyzed reactions, also.[9c] Therefore, the observed selectivities in the stoichiometric and catalytic reactions are identical. In these studies it has also been demonstrated that the reducing agents for the radicals generated by the cyclization are the titanocene(III) complexes.

Typical practical aspects of the titanocene catalyzed 4-*exo* cyclization become apparent from the comparison of the reactions of **33**, **35**, and **37**. With **29**, substrates **35** and **37** are readily transformed into the desired products **36** and **38**. Catalyst **30** gives a similar result, whereas **31** results in a low conversion and hence very low yield of **36**. It seems that **31** is too bulky to bind **35** and initiate epoxide opening. Thus, under the conditions employed here, the tertiary radicals, once generated, are fairly persistent toward reduction by the titanocene(III) complexes. The situation changes dramatically for the reaction of the monosubstitiuted epoxide **33**, which is completely consumed

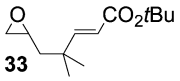
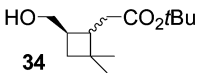
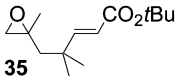
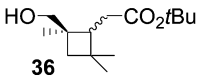
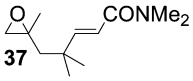
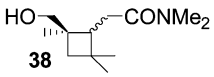
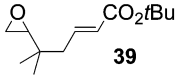
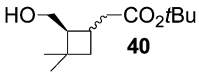
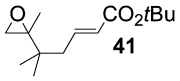
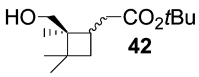
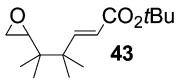
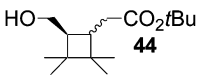
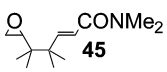
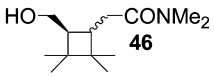
(30) (a) Gansäuer, A.; Bluhm, H.; Pierobon, M.; Keller, M. *Organometallics* **2001**, *20*, 914−919. (b) Gansäuer, A.; Rinker, B.; Barchuk, A.; Nieger, M. *Organometallics* **2004**, *23*, 1168−1171.

Scheme 4. Titanocenes Used as Catalysts for the 4-*exo* Cylization Investigated Experimentally



29 **30** **31** **32**

Table 6. Titanocene Catalyzed (10 mol %, 2 equiv of Mn, 2.5 equiv of Coll·HCl; See Supporting Information for Details) 4-*exo* Cylizations Investigated Experimentally

entry	substrate	product	cat.	yield	*trans*/*cis*
1	 **33**	 **34**	**31**	51	>95:5
2	 **35**	 **36**	**29**	82	67:33
3	**35**	**36**	**30**	84	69:31
4	**35**	**36**	**31**	21	77:23
5	 **37**	 **38**	**29**	92	83:17
6	 **39**	 **40**	**29**	53	56:44
7	**39**	**40**	**32**	54	67:33[a]
8	 **41**	 **42**	**29**	91	67:33
9	**41**	**42**	**30**	89	73:27
10	 **43**	 **44**	**29**	88	90:10
11	**43**	**44**	**30**	82	>95:5
12	 **45**	 **46**	**29**	81	89:11
13	**45**	**46**	**30**	72	91:9

[a] The product was obtained as a racemate according to the NMR analysis of the Mosher esters.

by all catalysts. Only **31** leads to the formation of the desired **34**. This suggests that only titanocenes with very bulky ligands can prevent the interfering preliminary reduction of the secondary radical formed. Hydroxyester **34** constitutes an interesting building block for the preparation of the caryophyllene and norcaryophyllene natural products.[20]

In agreement with the computational results, the formation of **34** is highly diastereoselective and much more selective than the reaction of **35**. This suggests that our interpretation of the diastereoselectivity of the 4-*exo* cyclization based on 1,3-diaxial interactions in the transition structures is correct and can thus be used as a rule of thumb for related cases.

The reactions of **39** and **41** further support the conclusions of the computational study. As predicted, the formation of both **40** and **42** are only slightly diastereoselective. Moreover, with the *gem*-dimethyl group neighboring the radical center, preliminary reduction of the β-titanoxy radicals is distinctly suppressed compared to **33**. Hence, even the use of **29** results in a reasonable yield of the desired **40**. With the bulky **31**, hardly any of the substrate reacts as already observed with **35**.

Finally, we addressed the relative importance of the positioning of the *gem*-dimethyl group with substrates **43** and **45** containing four methyl substituents. Gratifyingly, even the sterically least demanding complex **29** leads to a high yield and

satisfactory diastereoselectivity in the formation of **44**. The more bulky **30** results in the formation of **44** as essentially a single isomer. This supports our notion of the importance of the 1,3-diaxial interactions. Amide substitution results in a slightly reduced selectivity. Thus, in **43** and **45** the advantages of the positioning of both *gem*-dimethyl groups, the relatively high kinetic persistence of the β-titanoxy radical with an adjacent *gem*-dimethyl group, and the high diastereoselectivity of the cyclization with a *gem*-dimethyl group adjacent to the radical trap are combined to result in a high yielding and highly selective reaction.

Conclusion

In summary, by our combined computational and experimental studies we have outlined the basic features of 4-*exo* cyclizations that are pertinent to the development of the first general titanocene catalyzed synthesis of substituted cyclobutanes. The RI-BP86/TZVP method was established to be suitable for the description of the scrutinized systems by comparison with high level CC methods. The computational investigations have resulted in a number of novel insights into the reaction mechanism including the first understanding of the diastereoselectivity of the process.

By choice of the appropriate titanocene complexes, we have established efficient conditions for the catalytic preparation of a number of substituted cyclobutanes. It proved to be essential to properly adjust the steric demands of the catalysts in order to increase the diastereoselectivity of the cyclization and to suppress undesired side reactions such as premature radical reduction. As predicted by the calculations, the reactions can be highly diastereoselective.

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Supporting Information Available: The RI-BP86/TZVP optimized structures and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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