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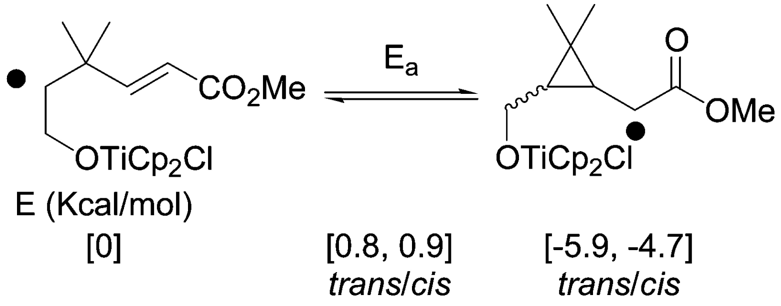

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A Combined Theoretical and Experimental Study of Efficient and Fast Titanocene-Catalyzed *3-exo* Cyclizations

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Abstract: The mechanism of titanocene mediated *3-exo* cyclizations was investigated by a combined theoretical and experimental study. A gradient corrected density functional theory (DFT) method has been scaled against titanocene dichloride, the parent butenyl radical, and in bond dissociation energy (BDE) calculations. The BP86 method using density fitting, and a basis set of triple-ζ quality emerged as a highly reliable tool for studying titanocene mediated radical reactions. The computational results revealed important kinetic and thermodynamic features of cyclopropane formation. Surprisingly, the β-titanoxy radicals, the first intermediates of our investigations, were demonstrated to possess essentially the same thermodynamic stabilization as the corresponding alkyl radicals by comparison of the calculated BDEs. In contrast to suggestions for samarium mediated reactions, the cyclization was shown to be thermodynamically favorable in agreement with earlier kinetic studies. It was established that stereoselectivity of the cyclization is governed by the stability of the intermediates and thus the trans disubstituted products are formed preferentially. The observed ratios of products are in good to excellent agreement with the DFT results. By a combination of computational and experimental results, it was also shown that for the completion of the overall cyclopropane formation the efficiency of the trapping of the cyclopropylcarbinyl radicals is decisive.

Introduction

Over the past decades, radical chemistry has been increasingly used in the synthesis of complex molecules.[1] Limitations also exist, however. One of the relatively unexplored but potentially very useful fields is constituted by the synthesis of small rings.[2] Difficulties encountered in the preparation of three- and four-membered rings are due to the strain of these compounds. Thus, ring opening proceeds usually much faster than ring closure. Strategies in classical free radical chemistry circumventing this problem have emerged recently. They include incorporation of some of the products' strain into the substrates, fast and irreversible fragmentation reactions following the initial cyclization, and stabilization of the cyclopropylcarbinyl radical through conjugation. However, selective trapping to yield the cyclopropane remains difficult and in sterically unbiased cases reactions in the presence of Bu_3SnH predominantly yielded the ring opened products.

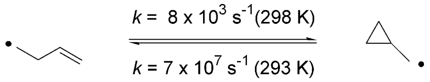

Figure 1. Typical kinetics of the *3-exo* cyclization.

The kinetics and thermodynamics of the *3-exo* cyclization, on the other hand, have been studied thoroughly.[3] As a consequence, the rate constants and activation energies have been determined with high accuracy. The ring opening of the parent system shown in Figure 1 is among the fastest radical reactions known ($k \approx 10^8$ s^{-1}). Nevertheless, the *3-exo* cyclization itself is also a relatively fast reaction ($k \approx 10^4$ s^{-1}) that is kinetically attractive if the reverse reaction can be retarded or the cyclopropyl carbinyl radical trapped selectively.[3a,c]

Because of the accurate and reliable kinetic studies, the depicted equilibrium has also attracted considerable interest in

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the field of theoretical chemistry.[4] A recent study by Radom assessed the quality of high level computational methods for the determination of activation energies and reaction enthalpies of the parent butenyl radical.[4b] More complex systems were not investigated, and thus issues of stereoselectivity cannot be addressed.

In the field of metal mediated radical chemistry, only very few examples of *3-exo* cyclizations have been observed.[5] As early as 1966, Barton described a single example of a chromium(II) mediated radical addition to an enone in a steroid derivative.[5a] Another isolated report by Lange concerned a low yielding samarium diiodide mediated fragmentation cyclization sequence involving an acrylate.[5b] Similar but general and high yielding methodology was explored by Guibé in the same year in samarium diiodide mediated cyclizations of δ-halo-α,β-unsaturated esters.[5c] A radical mechanism was postulated, and surprisingly it was proposed that opening of the intermediate ester substituted cyclopropylcarbinyl radical was thermodynamically favored. A *3-exo* cyclization of similar iodides mediated by zinc dust has been described very recently.[5d]

We have reported the first *3-exo* cyclization[6] catalytic[7] in titanocene(III) reagents based on the stoichiometric reductive epoxide opening introduced by Nugent and RajanBabu.[8] The efficiency of the *3-exo* cyclization is thought to be based on selective reductive trapping of cyclopropylcarbinyl radicals. Most recently, a single example of the stoichiometric version of this reaction has been reported independently by Fernández-Mateos.[8j]

Despite their preparative usefulness, the overall mechanistic picture of these reactions, including our own, has remained unclear, and the factors influencing chemo- and stereoselectivity are still unknown. The essential issue of catalyst control of selectivity could therefore not be rationally addressed so far.

Of course, computational chemistry has become a unique and highly useful tool for studying reaction mechanisms with the emergence of powerful computers and sophisticated ab initio methods. However, high level wave function-based ab initio methods are still restricted to relatively small molecules. The titanocene containing intermediates and transition structures are too complex to be studied by these procedures. We therefore decided to use density functional theory (DFT) first principle methods in this study. To establish their accuracy for the problems discussed here, they were scaled against the pertinent cases of titanocene dichloride, the parent butenyl radical cyclization, and the homolytic bond dissociation energies of the intermediates studied here. These calibration studies revealed that the DFT methods are highly reliable tools for our purposes.

The computational studies delivered the structures and energies of all relevant transition structures and intermediates composing a complete mechanistic picture. In particular, it was established in contradiction to the proposal by Guibé[5c] and in agreement with a study by Beckwith[3c] that the cyclization is thermodynamically favored. In combination with carefully designed experiments, it was further demonstrated that the equilibration of the cyclopropylcarbinyl radical is faster than its reduction by a second equivalent of Cp_2TiCl in the carbonyl substituted cases. Thus, the overall course of the reaction is determined by a unique combination of thermodynamic and kinetic factors.

Results and Discussion

Computational Studies. The geometry optimizations were carried out within the framework of density functional theory (DFT) with the BP86/TZVP method (Becke-Perdew gradient corrected exchange and correlation density functional[9] combined with a polarized split-valence basis set of triple-ζ quality) using the RI-approximation (resolution of identity) within the TURBOMOLE[10] program package (if not otherwise noted). For the DFT energy calculations of the optimized structures, the more extended TZVPP basis set was applied. The ab initio calculations of this work were performed with the GAUSSIAN,[11] MOLPRO,[12] and TURBOMOLE[10] program packages at the RI-BP86/TZVP optimized structures (if not otherwise noted). The zero point energy (ZPE) was obtained from numerical force constants based on RI-BP86/TZVP-calculations (if not otherwise noted). The error introduced by this approximation was checked and in the case of $TiCp_2Cl_2$ found to be smaller than 0.3 kcal/mol, which is probably negligible as compared to the density functional and basis set errors. The accuracy of the single point approximation was checked for the acid system of Tables 4 and

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Table 1. Stability of β-Titanoxy Radicals and Alkyl Radicals (BDE at 298.15 K in kcal/mol)

system/method	exp.[1a]	exp.[14]	B3LYP[15]	RI-BP86[a,b]
$H-C_2H_5$	98	101.1	100.0	99.4
$(CH_3)_2CH-H$	95	97.8		95.3
$(CH_3)_3C-H$	92	96.6		92.2
H−cyclopropyl	106	106.3		106.0
$Cp_2ClTiOCH_2CHCH_3-H$				96.6
$Cp_2ClTiOCH_2C(CH_3)_2-H$				92.2

[a] This work, RI-BP86/TZVPP//RI-BP86/TZVP including the ZPE obtained from numerical RI-BP86/TZVP frequencies, the hydrogen energies were obtained from Gaussian 03 calculations (see Table 1). [b] Includes a thermal correction to the BDE of 1.5 kcal/mol (2.5*RT*).

5 to be 0.03−0.08 kcal/mol. Therefore, the error introduced by the approximation is negligible, and the basis set error is reduced to a minimum.

Thermodynamic Considerations of Radical Stability: Calculation of Bond Dissociation Energies (BDE). To understand the effects of the Cp_2TiCl group on the thermodynamic stability of radicals, we calculated the BDEs of the corresponding titanocene alkoxides. This is of essential importance for understanding the reactivity of the β-titanoxy radicals because in reversible reactions the equilibria and in irreversible reactions the activation energies will be affected. To guarantee a correct quantitative description, we decided to calibrate the DFT methods against the experimentally determined values for typical hydrocarbons, for example, CH_3-H, $(CH_3)_2CH-H$, and $(CH_3)_3C-H$.

The Accuracy of the RI-BP86 Method for the Calculation of BDEs. To check the accuracy of our DFT-calculations, we compared the DFT-BDE of methane with experimental and high level ab initio values. The RI-BP86/TZVPP//RI-BP86/TZVP BDE of 104.8 kcal/mol agrees very well with the experimental BDE of 105[1a] kcal/mol and the CCSD(T)/cc-pVQZ//QCISD/cc-pVTZ value of 104.0 kcal/mol (coupled cluster singles and doubles with perturbative triples correction energy using Dunnings[13] correlation consistent basis set of polarized quadruple-ζ quality at the quadratic configuration interaction singles and doubles optimized geometry with Dunnings[13] correlation consistent basis set of polarized triple-ζ quality). More details of these benchmark calculations are given in the Supporting Information.

Scheme 1. *3-exo* Cyclization of the Butenyl Radical **2**

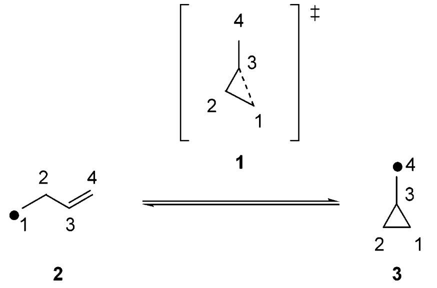

Table 2. Geometry Parameters of the *3-exo* Cyclization of **2** Calculated with Different Methods (Numbering from Scheme 1; Bond Lengths in angstroms, Angles in deg)

system	method	$C^1–C^2$	$C^2–C^3$	$C^3–C^4$	$C^1–C^3$	$\angle C^1C^2C^3C^4$
1	QCISD/6-31G*	1.484	1.494	1.388	1.915	
	B3-LYP/6-31G*	1.482	1.496	1.385	1.916	
	QCISD/cc-pVDZ	1.493	1.502	1.398	1.917	
	RI-BP86/TZVP[a]	1.484	1.498	1.385	1.920	
2	QCISD/6-31G*	1.500	1.510	1.336		−119.0[b]
	B3-LYP/6-31G*	1.497	1.510	1.333	2.509	119.4[b]
	QCISD/cc-pVDZ	1.508	1.520	1.346		116.7[b]
	RI-BP86/TZVP[a]	1.495	1.517	1.337	2.485	−114.5[b]
3	QCISD/6-31G*	1.498	1.524	1.466	1.524	
	B3-LYP/6-31G*	1.496	1.534	1.457	1.534	
	QCISD/cc-pVDZ	1.509	1.534	1.473	1.534	
	RI-BP86/TZVP[a]	1.496	1.538	1.452	1.542	

[a] Results of this work. [b] The variation of the angles can be explained by the symmetry. Two symmetry equivalent rotamers of the molecule exist. Additionally, the dihedral potential is very flat. The RI-BP86/TZVP energy varies by less than 0.1 kcal/mol for the $C^1C^2C^3C^4$-angle in the range from 110° to 120°.

Calculation of BDEs for *β*-Titanoxy Radicals. In Table 1, the relative stability of four alkyl radicals and two β-titanoxy radicals is shown on the basis of their BDEs. The RI-DFT values are in excellent agreement with the known experimental data.

Surprisingly, the inductive effect of the alkoxide is negligible thermodynamically. The computational results clearly demonstrate that no significant stabilization or destabilization of the radical center in β-titanoxy radicals is exerted by the $ClCp_2TiO$-group. Thus, as compared to alkyl radicals, no electronic effects have to be considered when employing the β-titanoxy radicals in retrosynthetic planning or in synthetic applications. Concerning the control of stereoselectivity of their reactions, the β-titanoxy radicals offer excellent prospects for a reagent controlled course due to the high steric bulk of the titanocene moiety. This feature will be relevant to both transition and product structures and must be carefully incorporated into any planning.

The Accuracy of the DFT Calculations for the *3-exo* Cyclization. With these encouraging results in hand, we next checked the accuracy of DFT calculations for the *3-exo* cyclization of the parent but-3-enyl radical **2** shown in Scheme 1.

The cyclization constitutes an ideal reaction for scaling of DFT-methods for three reasons. First, the system has been intensely studied experimentally. Second, it is small enough to be calculated with high accuracy even by the most advanced ab initio methods. Therefore, a number of computational results are available for comparison and identification of errors. Finally and most importantly, the cyclization proceeds through intermediates that, as already established by our BDE study, are thermodynamically closely related to those of our titanocene mediated reaction.

In Table 2, the accuracy of selected geometry parameters as compared to results from QCISD ab initio calculations with cc-

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Table 3. Selected Reaction and Activation Energies for the Ring Opening Reaction of the Cyclopropylcarbinyl Radical from Ref 4 and the Present Work (Reaction Energies and Activation Barriers in kcal/mol at 0 K without ZPE; the Experimental Values Are Corrected to 0 K, and the ZPE Was Subtracted by Smith;[4b] the Calculations with RI-Approximation Were Performed with TURBOMOLE 5.6[10])

method			
geometry	energy	$\Delta E^{\#}$	ΔE
B3LYP/6-31G*[4b]	B3LYP/6-31G*	8.4	−2.3
B3LYP/6-31G*[4b]	B3LYP/6-311+G(3df,2p)	7.3	−3.4
B3LYP/6-31G*[4b]	UMP2/6-311+G**	15.9	−0.1
QCISD/cc-pVDZ[4c]	QCISD/cc-pVDZ	10.4	−3.5
QCISD/cc-pVDZ[4c]	CCSD(T)cc-pVTZ	9.7[a]	−3.6[a]
RI-BP86/TZVP	RI-BP86/TZVP	6.7	−1.4
RI-BP86/TZVP	RI-BP86/TZVPP	6.9	−0.7
RI-BP86/TZVP	RI-MP2/TZVPP	16.5	+1.3
RI-BP86/TZVP	RI-CC2/TZVPP	12.4	+0.9
RI-BP86/TZVP	QCISD/cc-pVDZ[b]	10.3	−3.5
RI-BP86/TZVP	CCSD/cc-pVTZ[c]	12.0	−2.8
RI-BP86/TZVP	CCSD/cc-pVQZ[c]	12.0	−2.7
RI-BP86/TZVP	CCSD(T)/cc-pVTZ[c]	9.6	−2.7
exp.[4b]		7.46	−1.7, −1.9, −2.8, −3.7,[d] −4.6

[a] The most accurate ab initio calculation available so far. [b] Performed with Gaussian 03.[11] [c] Performed with MOLPRO 2002.1.[12] [d] Temperature and ZPE corrected experimental value of Halgren.[3h] For reasons of consistency, we used the B3LYP-based corrections of Smith.[4b]

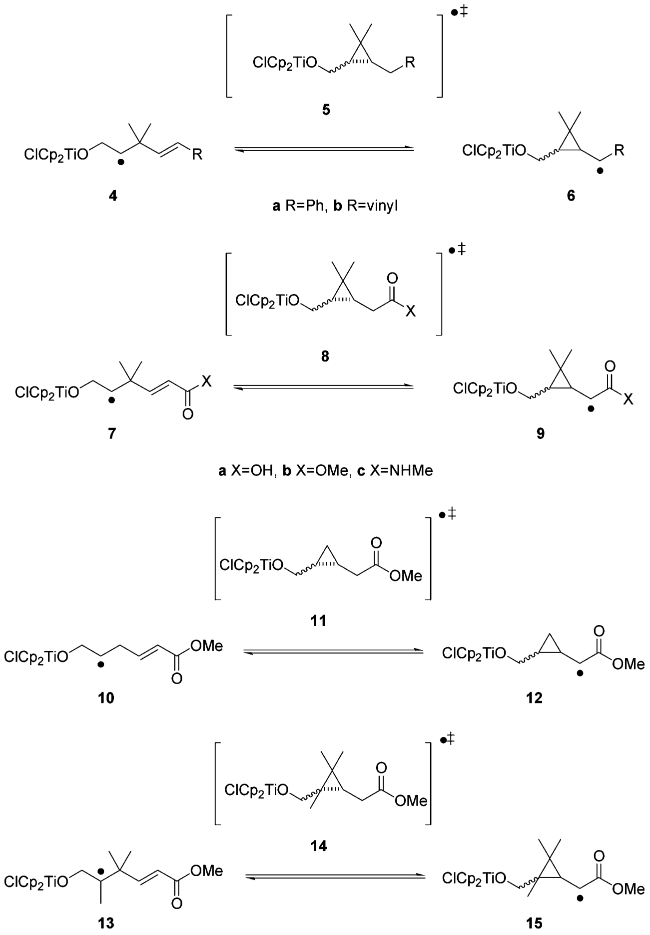

Figure 2. Reactions investigated in this computational study.

pVDZ[4c] and the 6-31G*[4a] basis sets of polarized valence double-ζ quality are shown. Additionally results of the standard DFT B3LYP/6-31G*[4b] approach are included for comparison. The RI-BP86/TZVP approach is found to generate structural parameters in excellent agreement with the computationally lavish wave function-based methods. Only in the case of the C^1-C^3-bond are the deviations larger than 0.02 Å. The reason for this exception can be found in the extremely flat potential between the two atoms in the course of the *3-exo* cyclization (vide infra).

Table 3 lists a summary of the theoretical results concerning the activation and reaction energies from refs 4 and of the DFT and ab initio calculations of the present work. The most reliable theoretical values obtained so far by the CCSD(T)/cc-pVTZ//QCISD/cc-pVDZ method are chosen as a benchmark. As compared to experimental energy barrier of 7.5 kcal/mol, the benchmark value of 9.7 kcal/mol overestimates the barrier by 2.2 kcal/mol. The RI-BP86/TZVPP//RI-BP86/TZVP approach yields an activation barrier of 6.9 kcal/mol, which is in excellent agreement with the experimental value.

Because of the substantial variation (−1.7 to −4.6 kcal/mol) and the large errors of the experimentally determined reaction energies, the situation is less clear-cut in this case. The ab initio benchmark calculations yield a calculated reaction energy of −3.6 kcal/mol close to the upper limit of the measured values. The DFT approaches RI-BP86/TZVPP/RI-BP86/TZVP yield energies (−1.4 and −0.7 kcal/mol) that are close to the lower limit.

To check the effect of the single point approximation of the ab initio calculations at the DFT structures on activation barriers and reaction energies, QCISD/cc-pVDZ//RI-BP86/TZVP and CCSD(T)/cc-pVTZ//RI-BP86/TZVP calculations were performed and compared to the ab initio results of Coosky.[4c] The QCISD case yields results nearly identical to the full ab initio values. In the CCSD(T) case, the reaction energy differs by only 1 kcal/mol, whereas again agreement is obtained for the activation energy. Considering the uncertainties associated with the experimental reaction energies, the DFT approximation must be considered as very satisfactory for our purposes.

These results clearly indicate that the RI-approximation in combination with DFT constitutes a powerful tool for the computational investigation of the titanocene mediated *3-exo* cyclizations. This is due to the excellent agreement between the calculated reaction energy, activation energy, and geometries of intermediates and transition structures with those of other more expensive computational approaches as well as the experimental values. We note that approaches applying computationally less demanding ab initio treatments such as MP2 or CC2 perform distinctly worse than the pure DFT approach and are therefore not recommended.

Computational Results of [Cp_2TiCl] Mediated *3-exo* Cyclizations. We decided to study the *3-exo* cyclizations of various radicals shown in Figure 2, to gain a comprehensive understanding of the potential energy hypersurface (PES), the geometries of intermediates, and the transition structures. Moreover, these computational results were compared to closely related experimental studies to obtain a clear picture of the overall reaction including the final radical reduction that is also relevant for related cyclizations.

Thermodynamic Considerations. The reaction energies are summarized in Table 4. The addition of radical stabilizing groups renders the cyclization slightly exothermic.

This is in agreement with two kinetic studies of free radicals by Ingold (stabilization by a phenyl group)[3a] and Beckwith

Table 4. RI-BP86/TZVPP//RI-BP86/TZVP Reaction Energies for the Reactions of **4**, **7**, **10**, and **13** in kcal/mol Including the ZPE

entry	substrate	product	ΔE (*trans*, *cis*)
1	**4a**	**6a**	−8.1, −6.8
2	**4b**	**6b**	−9.3, −8.2
3	**7a**	**9a**	−6.0, −4.9
4	**7b**	**9b**	−5.9, −4.7
5	**7c**	**9c**	−3.8, −3.1
6	**10**	**12**	−3.5, −2.1
7	**13**	**15**	−1.7, −1.4

(stabilization by an ester group)[3c] that suggest a thermodynamically favored cyclization but do not provide reaction energies.

Our results also indicate that Guibé's mechanistic proposal implying an endothermic ring closure in the samarium mediated cyclization of δ-halo-α,β-unsaturated esters is incorrect.[5c]

An interesting observation was made for the ester substituted radical lacking the geminal dimethyl group (entry 6). In this case, the exothermicity of the reaction was reduced by about 3 kcal/mol for both *cis* and *trans* cases. It should be noted that for the substrate radicals a stability difference of only 0.7 kcal/mol in favor of **7b** was observed. The stabilization in the case of **9b** must therefore be due to an effect of the cyclopropane, most likely the increased electronegativity of the ring carbons.[16] Thus, methyl substitution will result in additional stabilization of **10** versus **7** as indeed observed in the larger reaction energy.

Because the reaction energy is only slightly negative, we also investigated the effect of stabilizing the substrate radical by an additional methyl group for the ester substituted olefin (entry 7). It was found that the exothermicity of cyclization is reduced to just about 1.4 (*cis*) and 1.7 (*trans*) kcal/mol as compared to entry 4 [4.7 (*cis*) and 5.9 (*trans*) kcal/mol]. This result is again in good agreement with the stability difference of secondary and tertiary radicals according to their BDEs (ca. 4 kcal/mol).

The computational results suggest another experimental means for probing the mechanism of the reaction. In case of a reversible *3-exo* cyclization, the more stable *trans* isomer is predicted to be formed, except for **15** where the additional methyl substituent should result in an unselective cyclization.

Discussion of the Energies of Activation. The activation energies shown in Table 5 are among the lowest in radical chemistry and suggest that our *3-exo* cyclizations are extremely fast.

In agreement with chemical intuition for radicals **7a**−**7c**, the barrier is highest for **7c** that possesses the largest mesomeric stabilization of the carbonyl group. The course of the cyclization and evolution of spin density is shown in Figure 3 for **7b**.

With radical **10** lacking the geminal methyl groups, the activation energy is higher by ca. 2.5 kcal/mol as compared to **7b**. As no substantial destabilization of the substrate (0.7 kcal/mol) is observed, no reactive rotamer effect seems to be operating.[18] Also, no angle compressions were observed in the calculated structures of **7b** and **10**. Thus, the effect of the two methyl groups discussed above is already stabilizing transition structure **8b** and results in an acceleration of the cyclization, too.

Table 5. RI-BP86/TZVPP//RI-BP86/TZVP Activation Energies (kcal/mol) for the Reactions of **4**, **7**, **10**, and **13** Including ZPE (Barriers for the Opening of **6**, **9**, **12**, and **15** in Brackets)

entry	substrate	product	E_{act} *trans*, *cis*
1	**4a**	**6a**	1.3, 1.2 (9.4, 8.1)
2	**4b**	**6b**	1.0, 0.9 (10.3, 9.1)
3	**7a**	**9a**	1.9, 0.7 (7.8, 5.6)
4	**7b**	**9b**	0.8, 0.9 (6.7, 5.6)
5	**7c**	**9c**	3.0, 2.6 (6.9, 5.7)
6	**10**	**12**	3.3, 3.5 (6.8, 5.6)
7	**13**	**15**	2.2, 3.0 (3.8, 4.4)

The barriers of ring opening are relatively small, and thus ring opening is fast. Within the series of substrates where substitution of both radicals involved in the cyclization differs only in the carbonyl substituent, that is, **7a**, **7b**, **7c**, and **10**, the barriers for ring opening are very similar within the respective *cis* and *trans* series. Because the activation energies are of the same magnitude as for the cyclopropylcarbinyl radical (**3**) (*trans* series) or slightly lower (*cis* series), ring opening of **9a**, **9b**, **9c**, and **12** will have a rate constant of more than 7×10^7 s^{-1}, the value measured for **3**.

A readily reversible *3-exo* cyclization will occur in the absence of efficient trapping reagents. The differences in activation energies for the formation of the *cis* and *trans* disubstituted cyclopropanes are too small to be discussed quantitatively. Qualitatively, it is clear, however, that these differences will be smaller than the corresponding ΔE as the forming bonds between C1 and C3 are much longer than in the products.

Summary of the Computational Results. The computational results demonstrate that the *3-exo* cyclizations investigated here are very fast and thermodynamically favored reactions. The thermodynamic stabilization as compared to the parent butenyl radical (**2**) is due to a delocalization of the enoyl radical formed, as shown above in Figure 3.

However, ring opening is also predicted to be swift and comparable to the parent butenyl radical. Thus, in the absence of efficient trapping reagents, the stereoselectivity of the overall process is expected to be under thermodynamic control favoring the trans disubstituted cyclopropylcarbinyl radicals. To demonstrate the effects of the carbonyl groups on both reaction and activation energy, the PES of the reactions of **2** and **7b** are compared in Figure 4.

Inspection of PES demonstrates that the transition structure and product radical from **7b** are stabilized by about the same energy, presumably by mesomeric effects of the ester group, as compared to **2**.

The question of the speed of reduction of the cyclopropylcarbinyl radicals is too complex to be studied even for the DFT

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(18) For two reviews, see: (a) Jung, M. E. *Synlett* **1999**, 843−846. (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, in press.

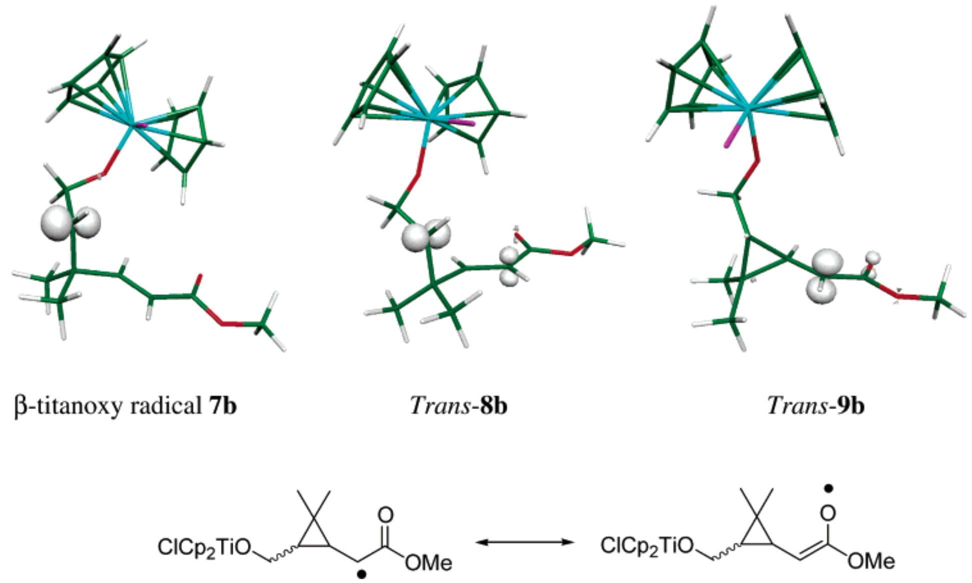


Figure 3. Evolution of spin density during the cyclization of **7b** and mesomeric stabilization of **9b**. The spin density was calculated and visualized with MOLEKEL.[17] The isovalue of the surface was set to 0.025.

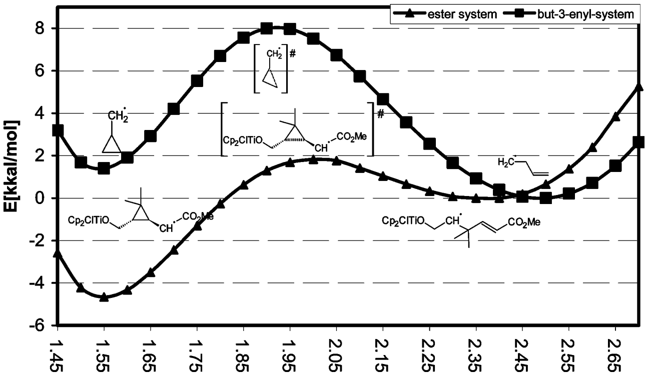


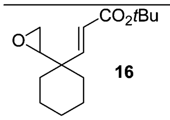
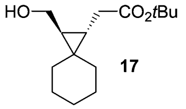
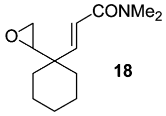
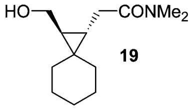
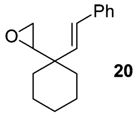
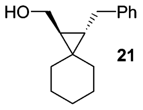
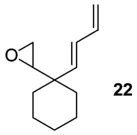
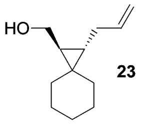
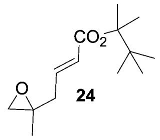
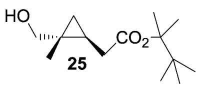
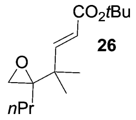
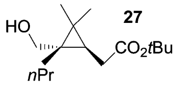
Figure 4. Comparison of the RI-BP86/TZVP PES of the reactions of **7b** and **2** (without ZPE).

methods and is therefore addressed experimentally as described in the following sections.

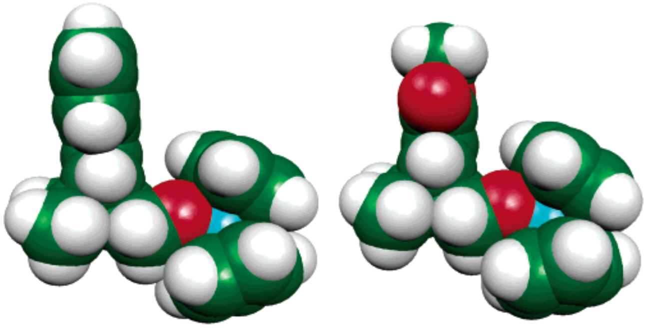
Experimental Results. We examined epoxyolefins **16**, **18**, **20**, **22**, **24**, and **26**, as substrates for comparison with the "computational" substrates. We have established before that changing a geminal dimethyl group by a cyclohexyl group and a methyl ester by the computationally lavish *tert*-butyl ester does not alter the outcome of such reactions substantially while volatile intermediates were avoided.

The results summarized in Table 6 demonstrate that the carbonyl substituted epoxides **16**, **18**, **24**, and **26** give the desired cyclopropanes in reasonable to high yields. The observed diastereoselectivities are in good to excellent agreement with the values expected for a reversible cyclization (Table 4). This implies that trapping of the cyclopropylcarbinyl radical by a second equivalent of Cp_2TiCl is slower than ring opening. A comparison of the experimental product ratios with the calculated ratios based on ΔE is possible because an advantageous cancellation of thermodynamic corrections in the *cis* and *trans* isomers can be expected. It is also reasonable to assume a similarly advantageous cancellation of the preexponential factors of the Arrhenius equation for the *cis* and *trans* reaction pathways, because the intermediates and transition structures involved are quite similar.

Table 6. Titanocene-Catalyzed Cyclopropane Formation (for Details of Reaction Conditions and Compound Characterization, See Supporting Information; for Reasons of Clarity, Only the Major Isomer Is Shown)

Substrate	Product	Yield (%)	dr
 **16**	 **17**	80	79:21
 **18**	 **19**	88	80:20
 **20**	 **21**	0	-
 **22**	 **23**	0	-
 **24**	 **25**	64	57:43
 **26**	 **27**	88	55:45

In the case of the phenyl and vinyl substituted epoxides **20** and **22**, none of the desired cyclopropane was observed in the crude reaction mixture or could be isolated. Instead, complex mixtures of polymeric materials were obtained. Here, trapping



6a **9b**

Figure 5. RI-BP86/TZVP optimized structures of cyclopropylcarbinyl radicals **6a** and **9b**.

of the cyclopropylcarbinyl radicals is too slow to be preparatively useful.

The structures of the cyclopropylcarbinyl radicals **6a** and **9b** shown in Figure 5 give an indication why trapping is fast in the enol radical case and slow in the benzyl radical case.

In the former case, the approach of the second equivalent of Cp_2TiCl is sterically difficult as the radical bearing carbon is "buried" within **6a**. Trapping of **6a** to yield a benzylic organotitanium compound must be considered as more difficult and thus slower as in **9b** where the more exothermic formation of an enolate takes place additionally.

Considering the relative magnitude of these thermodynamic and kinetic aspects, we suggest that thermodynamic considerations are not necessarily decisive. This is because from the termination of titanocene-catalyzed *5-exo* cyclizations it is known that alkyl radicals are reduced faster than benzylic radicals even though the less stable organometallic intermediates are formed.

In the case of the reduction of vinyl substituted **6b** where steric hindrance will be less relevant, the thermodynamic factors may be more important, however.

While the observed diastereoselectivity constitutes a strong hint for a reversible cyclization, we sought further evidence to support our hypothesis. In case of a reversible reaction, diastereoselectivity should be independent of the substrate's olefin geometry, diastereomeric composition at the epoxide, and its concentration in the reaction medium.

It is well documented for irreversible radical cyclizations, for example, in the *5-exo* case,[19] that diastereoselectivity is strongly dependent on olefin geometry in the preparation of bicyclic systems. We therefore examined epoxides **28** as substrates as demonstrated in Figure 6.

The results amply demonstrate that stereoselectivity of the cyclization is independent of substrate concentration and of olefin geometry. Bicyclic product **29** was obtained in essentially the same diastereomeric ratio in all three reactions. This is readily explained by a trapping of the enol radical that is slower than ring opening.

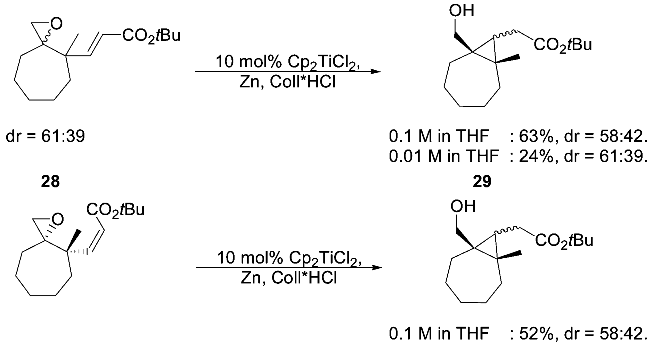


Figure 6. Effects of olefin geometry and concentration on the diastereoselectivity of the *3-exo* cyclization.

Thus, all experimental and computational evidence is in support of a reversible *3-exo* cyclization and a slower and irreversible trapping of the cyclopropylcarbinyl radicals. If this trapping is too slow, no cyclopropanes can be isolated and polymerization occurs instead as observed for **20** and **22**.

Conclusion

In summary, we have described a complete mechanistic scheme of titanocene mediated *3-exo* cyclization of vinyl epoxides containing carbonyl, phenyl, and vinyl groups and determined the structures of relevant intermediates and transition structures by DFT calculations. The RI-BP86/TZVP method used was scaled against the parent butenyl radical, the BDE of pertinent alkyl radicals, and Cp_2TiCl. It emerged as a highly reliable tool for describing and predicting metal mediated and free radical reactions.

The titanocene mediated *3-exo* cyclizations were investigated by a combination of experimental and computational studies. They turned out to be exothermic and reversible in contradiction to an earlier mechanistic proposal.[5c] The energies of activation for ring closure are among the lowest known for radical reactions. The crucial step for a successful completion of the reaction is constituted by a swift trapping of the cyclopropylcarbinyl radicals that is possible only for carbonyl substituted electrophilic radicals irrespective of the exothermicity of the cyclization.

Because our study provides a complete picture of the complex mechanism of the titanocene mediated *3-exo* cyclization, the results and methods applied also should be of distinct relevance for the successful design and understanding of other unusual radical cyclizations.

Acknowledgment. We are indebted to the Deutsche Forschungsgemeinschaft (SFB 624 "Template-Vom Design chemischer Schablonen zur Reaktionssteuerung") and the Fonds der Chemischen Industrie (Dozentenstipendium and Sachbeihilfen to A.G.) for generous financial support.

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.

JA050268W

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