JACS ARTICLES

Published on Web 11/04/2009

Catalysis via Homolytic Substitutions with C−O and Ti−O Bonds: Oxidative Additions and Reductive Eliminations in Single Electron Steps

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Abstract: In a combined theoretical and experimental study, an efficient catalytic reaction featuring epoxide opening and tetrahydrofuran formation through homolytic substitution reactions at C−O and Ti−O bonds was devised. The performance of these two key steps of the catalytic cycle was studied and could be adjusted by modifying the electronic properties of the catalysts through introduction of electron-donating or -withdrawing substituents to the titanocene catalysts. By regarding both steps as single electron versions of oxidative addition and reductive elimination, a mechanism-based platform for the design of catalysts and reagents for electron transfer reactions evolved that opens broad perspectives for further investigations.

Introduction

C−O bonds can be formed or cleaved via homolytic substitutions of carbon spin centers (radicals) or metal spin centers with M-O or C−O bonds, respectively. These reactions are discussed as key steps in a number of topical transformations. Homolytic substitutions that lead to the formation of C−O bonds include the ring closing step of β-metaloxy radicals in olefin epoxidations mediated by chromium complexes[1] or catalyzed by manganese salen complexes,[2] the hydroxylation of radicals by organometallic complexes,[3] and the titanocene catalyzed or mediated tetrahydrofuran-synthesis via alkoxylation of carbon centered radicals.[4] Even the oxygen rebound step in the hydroxylation reactions of hydrocarbons by the P450 enzymes may be considered as another example of this type of transformation.[5] The formation of the C−O bonds in these reactions is accompanied by the cleavage of the M−O bond and a decrease in the oxidation state of the metal by one. Formally, these elementary steps therefore constitute single electron versions of reductive eliminations.

The microscopic reversal of these reactions, homolytic substitutions with C−O bond cleavage, has only recently attracted substantial synthetic interest.[6] They were first discussed in the context of epoxide deoxygenations through Cr(II) complexes by Kochi.[7] With the introduction of titanocene(III) complexes for epoxide opening by Nugent and RajanBabu,[8] the resulting β-titanoxy radicals could for the first time be reduced by hydrogen atom transfer[8c] and employed in cyclizations[8a,d] with carbonyl compounds and nitriles[9] or intermolecular addition reactions to α,β-unsaturated olefins.[8b] The recently developed

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10.1021/ja907817y CCC: $40.75 © 2009 American Chemical Society

catalytic conditions[10] have expanded the scope of this reaction even further and have resulted in a number of useful synthetic applications, such as the stereoselective generation of radicals,[11] unusual cyclizations,[12] epoxypolyene cyclizations via radicals,[13] radical tandem processes,[14] and polymerization reactions.[15] These C−O bond cleavages are accompanied by the formation of the M−O bond and an increase of the oxidation state of the metals by one and hence constitute single electron versions of oxidative additions.[16]

Due to its easy shuttling between the oxidation states three and four,[17] the Cp_2TiCl_2/Cp_2TiCl couple is to date unique in being able to efficiently induce both single electron oxidative addition and single electron reductive elimination. This particular characteristic is highly attractive for the development of catalytic reactions featuring both processes as key-steps. We have been able to realize exactly such a Cp_2TiCl (**1**) catalyzed process, shown in Scheme 1.[4]

While the reaction is potentially of high synthetic value, bi- and tricyclic tetrahydrofurans can be prepared atom-economically[18] from simple starting materials; the low 67% yield of **3** suggests that **1** is by no means the most suitable catalyst.

Here, we describe a combined experimental and theoretical approach to the development of much more efficient conditions for this transformation. It is based on controlling the performance of the single electron oxidative addition to the epoxide and the reductive elimination leading to tetrahydrofuran formation through carefully adjusting the electronic properties of the titanocene catalysts. This can be achieved in an experimentally straightforward manner by the introduction of electron-donating or -withdrawing substituents to one or both of the cyclopentadienyl ligands.

To the best of our knowledge, this concept has not been described in the literature for single electron transfer catalysis. Thus, our results will be of relevance for the design of other reagents or catalysts for reactions involving single electron transfer steps.[19] Potential applications include the highly important transformations of ketyl radicals,[20] anion radical [2 + 2] cycloadditions,[21] or reactions proceeding via SOMO catalysis.[22]

Results and Discussion

This investigation is firmly based on a close interaction between theoretical and experimental studies for the identification of an efficient catalyst for our reaction. The prime virtue of this combined study is that theory provides the knowledge of reaction and activation energies as well as the determination of the structures of pertinent intermediates of the oxidative addition and reductive elimination. In this manner, the crucial data for the evaluation of our concept will be provided. The synthetic study will establish which of the complexes are stable under the reaction conditions and which of these two elementary reactions is more critical for an efficient catalytic reaction. Moreover, only an experimental study can establish which titanocene(III) complexes can effectively suppress undesired intermolecular side-reactions, e.g., interception of the pivotal radical intermediates by a second equivalent of the titanoce-

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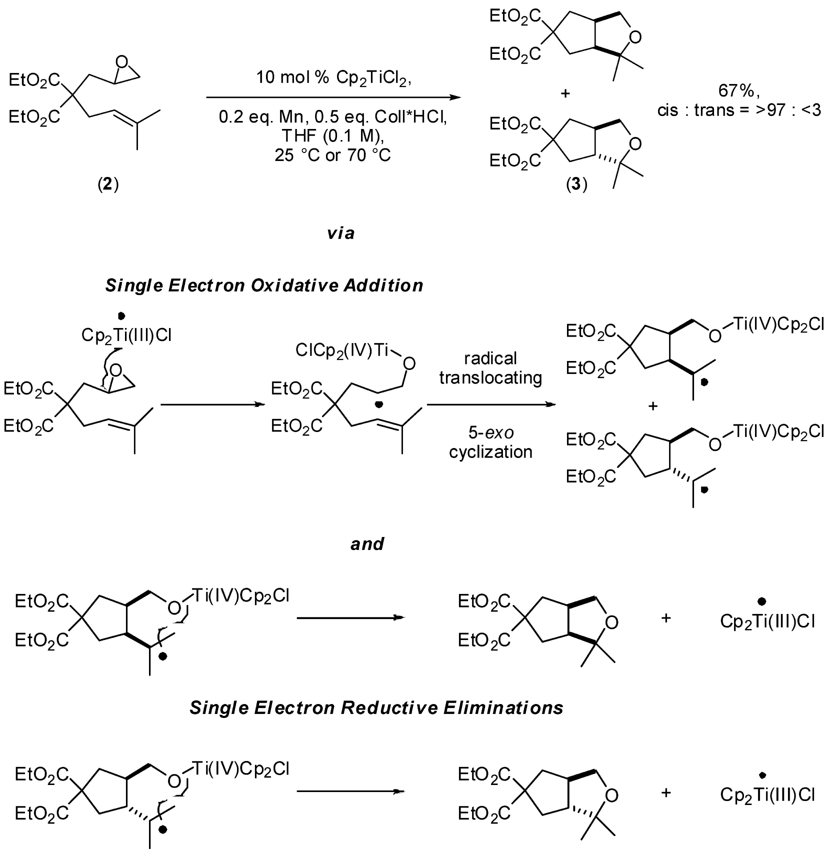
Scheme 1. Cp_2TiCl (**1**) Catalyzed Tandem Sequence Featuring Homolytic C−O Bond Cleavage and Formation (Coll = 2,4,6-Trimethyl Pyridine) and Its Mechanism



ne(III) reagent. Thus, the combination of these complementary methods is unique in providing a mechanism-based platform for efficient catalyst design.

Theoretical Studies

Methods. The ORCA[23] electronic structure program package was used for all calculations. Structures and transition states were optimized with the BP86 functional[24] and Ahlrichs' TZVP[25] basis set, making use of the resolution-of-the-identity RI approximation (in the Split-RI-J variant[26] with the appropriate Coulomb fitting sets).[27] The recently implemented transition state searcher of the ORCA package is based on eigenvector following and is very efficient due to the use of partial Hessians. Transition states were found by first performing a relaxed surface scan along the bonds to be broken. The maximum energy structures of these scans were taken as a guess for the transition state search. Transition states and minima were verified through frequency calculations that were performed by two-sided numerical differentiation of analytic gradients. Zero Point Vibrational Energy (ZPVE) corrections were computed from the calculated harmonic frequencies and are included in the reaction energies and activation energies throughout. All calculations on open-shell species employed the spin-unrestricted formalism.

In order to avoid a possible bias introduced into the modeling through a specific method, density functional as well as wave function-based correlation methods were investigated. The methods used include the "gold standard" B3LYP method,[28] the more efficient "pure" BP functional,[24] and the spin-component scaled second-order many body perturbation theory (SCS-MP2).[29]

The tetrahydrofuran solvent was simulated by a polarizable continuum model (COSMO).[30] Molecular dynamics runs were performed with the CAChe software[31] and the MM3 force field.[32] A few of the lowest energy structures (typically 3−5) from a 100-ps trajectory were further optimized using density functional theory (BP86/TZVP) and the lowest energy conformer was regarded as the most significant for this study.

Epoxide Complexation and Oxidative Addition. We chose the complexation of oxirane and oxidative addition to this

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(23) ORCA−an ab initio, density functional and semiempirical program package. Written by F. Neese with contributions from Ute Becker, Dmitry Ganyushin, Dimitrios Liakos, Simone Kossmann, Taras Petrenko, Christoph Riplinger, and Frank Wennmohs. Version 2.6, revision 71, Universität Bonn, 2008.

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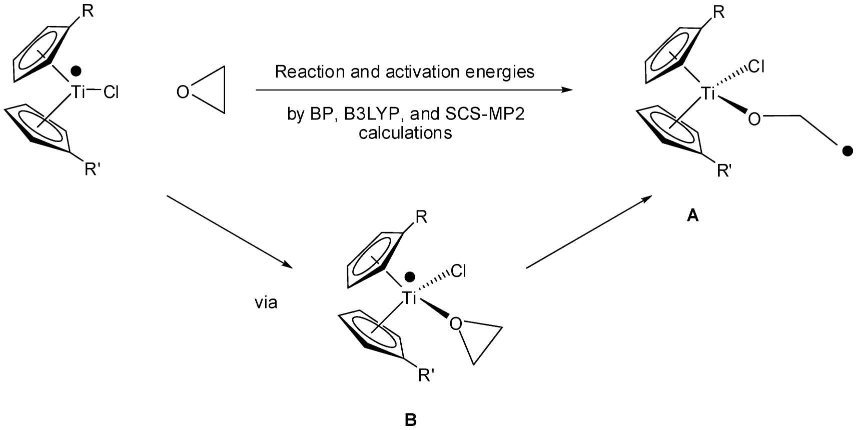
Scheme 2. Model System for the Study of the Complexation of and the Oxidative Addition to Epoxides



substrate as our model system for epoxide opening (Scheme 2). Since steric interactions between this epoxide and the ligands are minimal and the question of the regioselectivity of ring-opening does not arise, the electronic effects of the substituents can be studied with the smallest possible interference by other factors. The reaction proceeds in two discrete steps via complexation of the epoxide to yield **B** and inner-sphere electron transfer from titanium in **B** to yield the β-titanoxy radical **A**.

Table 1. Reaction Energies (ΔE) of the Formation of **B** in kcal mol^{-1} (def2-TZVPP basis set)[a]

cat	R, R′	BP	B3LYP	SCS-MP2
1	H, H	−1.2	−2.2	−10.9
4	H, Cl	−2.1	−3.0	−12.2
5	H, OMe	−0.8	−2.0	−11.5
6	H, CN	−2.3	−3.2	−12.3
7	H, CO_2Me	−3.9	−4.1	−13.3
8	CO_2Me, CO_2Me	−2.4	−2.8	−11.9
9	H, NO_2	−5.0	−4.5	−13.0
10	H, Me	0.3	−0.7	−9.9
11	H, *t*-Bu	1.0	0.2	−9.9

[a] ZPVE calculated by using BP86/TZVP is included.

The results for the formation of **B** are summarized in Table 1. Whereas both DFT methods give similar results for the complexation energies of ethylene oxide, the SCS-MP2 method predicts a substantially more exothermic reaction. However, the trends of the complexation energies are similar for all methods employed.

In agreement with intuition, epoxide binding is most favorable for the more Lewis-acidic titanocenes **9**, **7**, and **6** containing the electron withdrawing $-NO_2$, $-CO_2Me$, and $-CN$ group, respectively. Complex **8**, the only disubstituted titanocene investigated here, behaves differently for sterical reasons. The epoxide ligand is positioned parallel to the Ti−Cl bond and thus rotated by 90° compared to the other titanocenes where the epoxide is oriented perpendicular to the Ti−Cl bond, as shown in Figure 1. The *tert*-butyl substituted **11** displays the lowest binding energies due to the combination of the bulkiness of its ligand and its reduced Lewis-acidity.

Finally, we note that the Ti−O distances are shortest for the complexes with electron withdrawing groups due to their increased Lewis-acidity (233 pm for **1**, 228 pm for **7**, and 225 pm for **8**). This particular point is of prime importance for the design of novel catalysts for stereoselective ring-opening reactions[11] because the steric interactions between the complex and the substrates can be fine-tuned by electronically modulating the cyclopentadienyl ligands.

The inner sphere electron transfer in **B**, that yields the pivotal β-titanoxy radical **A**, constitutes the single electron oxidative addition and is the critical step of epoxide opening. The reaction energies of this reaction are summarized in Table 2.

As for the complexation, the absolute values of the reaction energies of the oxidative additions depend to some extent on the computational method employed. Interestingly, the SCS-MP2 values are quite similar to the B3LYP results and are uniformly about 6 kcal mol^{-1} less exothermic than those predicted with the BP functional. However, the trends along the series of catalysts obtained by each of the three methods are again quite similar. Since only these differences are essential for the discussion of the relative reactivity of the catalysts, our data provide a most satisfactory basis for further discussions.

For all methods, the oxidative addition to ethylene oxide is thermodynamically most favorable for the methyl substituted catalyst **10**. The importance of steric interactions is highlighted by the bulky *tert*-butyl substituent in **11** that renders the oxidative addition less exothermic for all methods by about 4 kcal mol^{-1}. Electron withdrawing substituents disfavor the oxidative addition. This is a reflection of their reduced electron transfer ability that seems to be more pertinent than the stronger Ti−O bonds formed with more Lewis acidic titanocenes. The ester-substituted complexes **7** and **8** are leading to the least exothermic reaction. It is surprising that complex **9**, containing a nitro group and the most powerful electron withdrawing substituent studied here, results in more exothermic oxidative additions than **7** and **8**.

Finally, we note that in solution, where a fast exchange between the solvent (usually THF) and the epoxide substrates at titanium is occurring,[17] the oxidative addition constitutes the decisive contribution in the generation of the pivotal β-titanoxy radicals. In the gas phase, however, the complexation is an essential step of the complete sequence because of the absence of solvation. These overall reaction energies that are obtained by addition of the energies of both steps are summarized in Table 3.

For all complexes, the overall gas phase reaction energies are exothermic. However, they follow no clear tendency. The trends for the reaction energies of the complexation and the oxidative addition are opposing and since neither of the steps is dominating, no clear-cut dependency of the overall gas phase reaction energy on the substitution pattern of the cyclopentadienyl ligand is observed.

Activation Energy. For an understanding of the reactivity of the titanocene complexes, knowledge of the activation energies

1*oxirane **7***oxirane **8***oxirane

Figure 1. Structures of the oxirane complexes of **1**, **7**, and **8**.

Table 2. Reaction Energies (ΔE) of the Ring-Opening of **B** in kcal mol^{-1} (def2-TZVPP basis set) via Oxidative Addition to Ethylene Oxide[a]

cat	R, R′	BP	B3LYP	SCS-MP2
1	H, H	−7.0	−1.1	−0.8
4	H, Cl	−6.7	−0.5	−0.4
5	H, OMe	−5.8	0.3	−1.2
6	H, CN	−6.5	−0.6	−0.3
7	H, CO_2Me	−4.7	0.7	1.1
8	CO_2Me, CO_2Me	−5.2	0.1	−0.5
9	H, NO_2	−6.2	−1.5	−0.6
10	H, Me	−10.5	−4.3	−4.3
11	H, *t*-Bu	−6.5	−0.3	0.0

[a] ZPVE calculated by using BP86/TZVP is included.

Table 3. Overall Reaction Energies (ΔE) of the Formation of **A** from the Titanocenes and Ethylene Oxide via **B** in kcal mol^{-1} (def2-TZVPP basis set) through Complexation and Oxidative Addition[a]

cat	R, R′	BP	B3LYP	SCS-MP2
1	H, H	−8.2	−3.3	−11.7
4	H, Cl	−8.8	−3.5	−12.6
5	H, OMe	−6.6	−1.7	−12.7
6	H, CN	−8.8	−3.8	−12.6
7	H, CO_2Me	−10.4	−3.4	−12.1
8	CO_2Me, CO_2Me	−7.6	−2.7	−12.4
9	H, NO_2	−11.2	−5.0	−13.6
10	H, Me	−10.2	−3.6	−14.2
11	H, *t*-Bu	−5.5	−0.1	−9.9

[a] ZPVE calculated by using BP86/TZVP is included.

Table 4. Activation Energies (E_a) in kcal mol^{-1} (def2-TZVPP basis set) of Oxidative Addition to Ethylene Oxide from **B**[a]

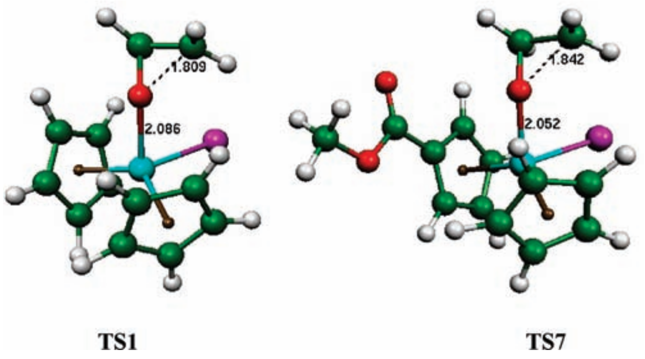
cat	R, R′	BP	B3LYP	SCS-MP2
1	H, H	7.4	14.3	20.6
4	H, Cl	5.3	12.9	19.0
5	H, OMe	7.9	14.7	21.5
6	H, CN	8.6	14.9	22.6
7	H, CO_2Me	8.4	14.4	22.9
8	CO_2Me, CO_2Me	9.4	15.9	24.6
9	H, NO_2	8.9	14.9	23.4
10	H, Me	7.5	14.4	19.6
11	H, *t*-Bu	7.2	13.5	19.7

[a] ZPVE calculated by using BP86/TZVP is included.

of the oxidative additions is essential. In this manner, relative rates can be predicted that are essential for issues of selectivity when undesired side-reactions are to be avoided.

The activation energies of the opening of ethylene oxide are summarized in Table 4. They were obtained by locating the transition states for each catalyst system. As observed for the reaction energies, the absolute values of the activation energies differ significantly depending on the method employed. Benchmark calculations on open-shell transition states indicate that the results obtained with the BP functional tend to be significantly too low, while those resulting from SCS-MP2 are mostly too high.[33] Hence, in absolute terms, preference should probably be given to the B3LYP values that are generally intermediate between BP and SCS-MP2. Gratifyingly, and similar to what was observed for the reaction energies, the trends of the activation energies are nearly identical for all methods.

For all methods, the oxidative addition is predicted to be slowest for the electron deficient complexes, especially **8**, and fastest for **4**, **10**, and **11**. The high E_a for **8** is most likely also due to the already observed steric effects in this complex. In the monosubstituted complexes, steric effects are less pertinent. This is because the presence of the *tert*-butyl group in **11** does not lead to a higher activation energy than for **1** or **10** for all methods employed.



TS1 **TS7**

Figure 2. Transition states of oxidative addition to ethylene oxide by **1** and **7**.

In the transition state, the epoxide is largely cleaved and hence product-like,[34] as indicated by the C−O bond lengths of 181 pm **TS1** and 184 pm for **TS7**, respectively (Figure 2). The C−O bond length in ethylene oxide is 143 pm. In accordance with the Hammond postulate[34] **TS7** is "later" than **TS1**. Because the transition structures are product-like, the same factors affecting the reaction energies should also dominate the activation energies although to a lesser extent. In general, this trend is indeed observed and **TS6**, **TS7**, **TS8**, and **TS9** with the electron deficient titanocenes are therefore less favorable than **TS1**, **TS10**, and **TS11** featuring the electron rich complexes, even though the differences are small.

The B3LYP values for E_a, that are most reliable in an absolute sense, are high compared to typical radical reactions, such as

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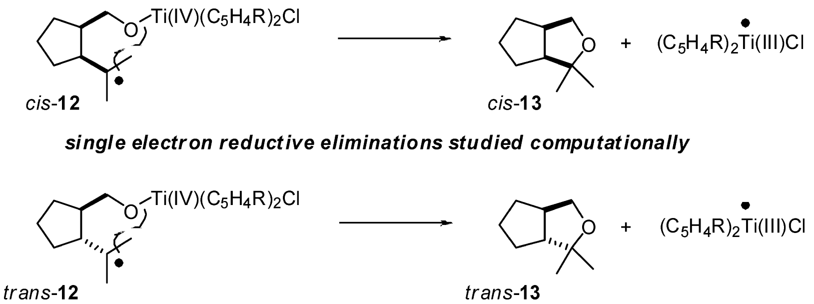
(33) Schwabe, T.; Grimme, S. *Acc. Chem. Res.* **2008**, *41*, 569–579.
(34) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

Scheme 3. Model System for the Study of the Tetrahydrofuran Forming Reductive Elimination



radical reduction by a second equivalent of the titanocene,[8,35] or the 5-*exo* cyclization.[36] However, in our tandem sequence, epoxide deoxygenation after the undesired trapping by a second equivalent of the titanocene(III) should not be critical, because the 5-*exo* cyclization ensuing oxidative addition is much faster than intermolecular radical trapping.

In summary, the computational study demonstrates that the oxidative addition to ethylene oxide is a thermodynamically possible process for all complexes investigated. However, the B3LYP and SCS-MP2 methods predict the reaction energy of ring-opening with the electron deficient **7** and **8** as well as the bulky **11** to be close to zero or even slightly endothermic. Also the oxidative addition is considerably slower for titanocenes with electron withdrawing substituents than for titanocenes with electron donating substituents. This is in line with the experience from oxidative additions proceeding in two electron steps that are generally faster for more electron rich complexes.

Reductive Elimination. In order to devise efficient catalysts for the reductive elimination leading to tetrahydrofuran formation, it is crucial to establish if this step is thermodynamically favorable. Moreover, it is essential to know the activation energies of the process in order to devise conditions suppressing undesired side-reactions. This may be especially critical for an intermolecular radical reduction by the titanocene (III) reagents before the single electron reductive elimination. We chose model system **12**, lacking only the ester groups of the synthetic substrate, for studying these issues (Scheme 3). The calculations were carried out with the BP and B3LYP methods because they had delivered results similar to the SCS-MP2 method in the study of the oxidative addition. After the reductive elimination, the titanocene complex is generated in an unsolvated form. Potentially interactions with the solvent could significantly influence the reaction energy. Therefore, COSMO-calculations mimicking the THF solvent of the reaction were also included. These values are summarized in Tables 5 and 6.

All methods employed predict the formation of the *cis*-**13** system to be thermodynamically highly favored over the generation of *trans*-fused **13** by about 10 kcal mol^{-1}. In agreement with chemical intuition, this reflects the higher strain of systems containing two *trans*-fused five-membered rings.[37] Surprisingly, the COSMO-calculations resulted in only small changes in reaction energies (1.7−4.2 kcal mol^{-1} more exothermically). Thus, the solvation of the respective substrates and products is almost equally favorable. We suggest that the more favorable interaction of THF with the more Lewis-acidic Ti(IV) in **12** compensates for the solvation of the two products of the reductive elimination to some extent because the Ti(III) center formed constitutes a weaker Lewis-acid. For the purposes of this study, solvation effects are therefore surprisingly small.

Table 5. Reaction Energies (ΔE) in kcal mol^{-1} (def2-TZVPP basis set) of the Reductive Elimination of **12** to **13**[a]

cat	R, R		BP	B3LYP	B3LYP (COSMO)
1	H, H	cis	−12.6	−18.9	−21.4
		trans	−1.4	−7.6	−9.3
6	H, CN	cis	−11.4	−18.1	−20.3
		trans	−0.3	−6.5	−8.8
7	H, CO_2Me	cis	−10.8	−17.7	−20.7
		trans	−0.3	−6.7	−9.8
8	CO_2Me, CO_2Me	cis	−12.5	−19.1	−22.6
		trans	−1.4	−7.5	−11.7
11	H, *t*-Bu	cis	−12.5	−19.5	−22.9
		trans	−3.9	−10.2	−13.6

[a] ZPVE calculated by using BP86/TZVP is included.

Table 6. Activation Energies (kcal mol^{-1}; def2-TZVPP basis set) of the Reductive Elimination of **12** to **13**[a]

cat	R, R		BP	B3LYP
1	H, H	cis	2.4	5.1
		trans	9.9	11.1
6	H, CN	cis	3.3	5.6
		trans	12.8	13.0
7	H, CO_2Me	cis	2.9	5.8
		trans	7.9	9.0
8	CO_2Me, CO_2Me	cis	3.0	5.6
		trans	8.1	9.0
11	H, *t*-Bu	cis	5.6	8.2
		trans	10.1	11.2

[a] ZPVE calculated by using BP86/TZVP is included.

It is nevertheless clear, that **7** constitutes a much stronger Lewis-acid than **1**, because the computational solvent exchange between **1***THF and **7** that leads to **1** and **7***THF is exothermic by 16.6 kcal mol^{-1} (Scheme 4).

For an understanding of the overall catalytic cycle, the activation energies (Table 6) and transition structures (Figure 3) of the reductive elimination, that are discussed next, are probably even more relevant than the reaction energies. This is because they give an indication of the relative rates of the elementary steps and provide the basis for a discussion of potential side-reactions and their prevention.

For all titanocenes and methods the activation energy leading to the formation of *cis*-**13** is substantially lower than that for the formation of *trans*-**13**. Thus, some of the strain of the product *trans*-bicyclo [3.3.0] system is already present in the transition state of the reductive elimination. However, the difference is

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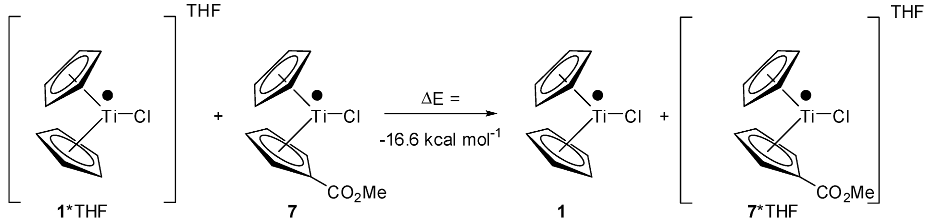
(35) (a) Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017–7026. (b) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041–2044. (c) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359–1371.

(36) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.

(37) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911–2914.

Scheme 4. Solvent Exchange between **1** and **7** by COSMO



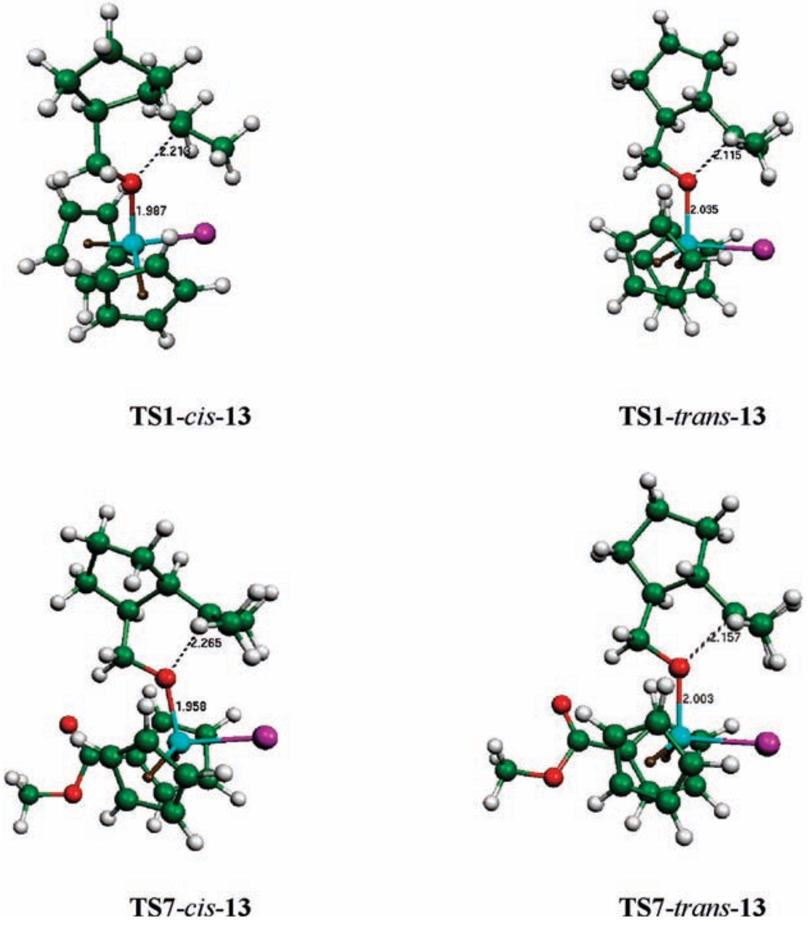
smaller than for the reaction energies, because in agreement with the Hammond postulate,[34] the transition states are "early".

Within the series leading to the formation of *cis*-**13**, the activation energies are lowest for **1** and highest for **11**. The introduction of the *tert*-butyl substitution leads to steric interactions that deteriorate the approach of the radical to the Ti−O bond. The electron deficient titanocenes **6**, **7**, and **8** result in somewhat higher activation energies for the formation of both *cis*- and *trans*-**13** than **1**. In the *cis*-transition states, the C−O distance is shortest for **TS1-*cis*-13** (221 pm) and slightly longer for **TS6-*cis*-13** and **TS7-*cis*-13** (226 and 227 pm, respectively) and longest for **TS8-*cis*-13** (233 pm). As expected from the Hammond postulate, the C−O distances in the *trans*-transition structures are substantially shorter. Two examples are shown in Figure 3.

Because of the high activation energies for the formation of *trans*-**13** the interception of *trans*-**12** by a second equivalent of the titanocene(III) complexes will most likely be the most efficient undesired side-reaction of the entire catalytic sequence. In agreement with the experiments, this should be less critical or even uncritical for the much faster formation of the *cis*-disubstituted tetrahydrofuran derivatives.[4]

In summary, the computational results are of prime importance for the development of an efficient overall catalytic cycle. Both the oxidative addition and the reductive elimination are predicted to be feasible for all titanocenes investigated. Of these complexes, the electron rich titanocenes should react fastest in the absence of competing radicals pathways. The most critical side-reaction is predicted to be the trapping of radical of the type *trans*-**12**. The rather complex interplay of the undesired side-reactions with the desired reductive elimination will depend on a number of parameters of the concrete practical setup and is beyond the scope of the theoretical study. It is therefore experimentally investigated.

Synthetic Investigations. Of course, the ultimate goal of any study aiming at the design of efficient catalysts must be the realization of the overall reaction and, if possible, an understanding of the experimental factors affecting the efficacy of

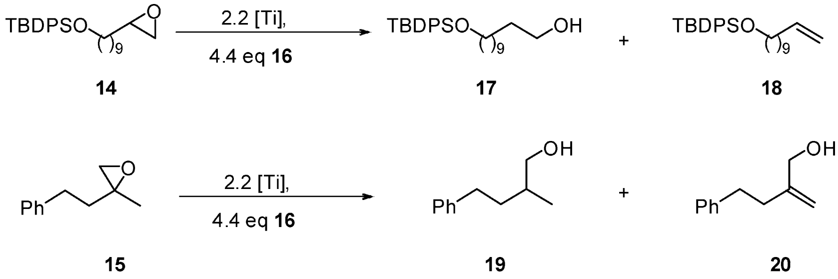


TS1-*cis*-13 **TS1-*trans*-13**

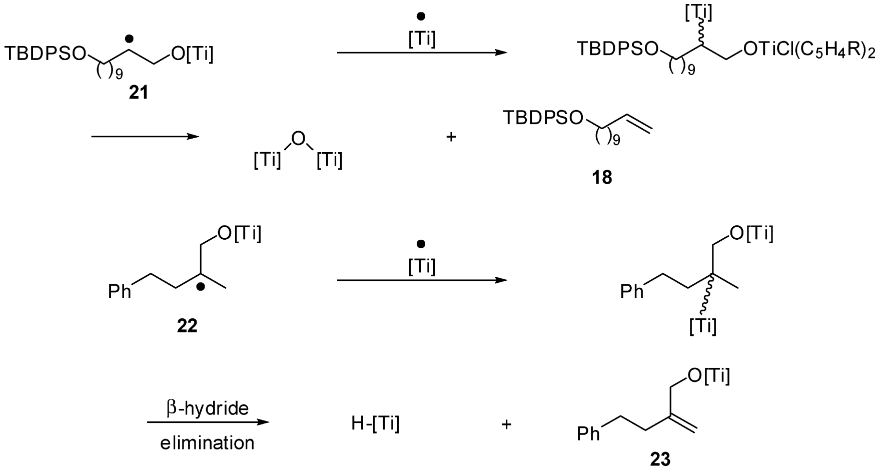
TS7-*cis*-13 **TS7-*trans*-13**

Figure 3. Transition states of the tetrahydrofuran forming reductive elimination of **12** to **13** by **1** and **7**.

Scheme 5. Test Reactions for the Oxidative Additions and Radical Trappings ([Ti] = $(RC_5H_4)(R'C_5H_4)TiCl$)



Scheme 6. Interception of β-Metaloxy Radicals by Titanocene(III) Reagents ([Ti] = (RC_5H_4) $(R'C_5H_4)TiCl$)



the pertinent steps. Also, only a synthetic study can establish the stability and thus the practical applicability of the computationally investigated complexes under the experimental conditions.

We have addressed these issues in a two step approach: First, the oxidative addition to epoxides was studied with a special emphasis on understanding the characteristics of undesired radical trapping. Second, the complete catalytic cycle was implemented. This was done with the aim of avoiding any undesired side reactions identified above.

Of the titanocenes computationally investigated, we have synthesized the titanocene(IV) dichlorides of **1**, **4**, **7**, **8**, **10**, and **11** according to known procedures.[38] The titanocene(IV) dichloride of **6** was prepared for the first time. For details of the preparation see Supporting Information. Complexes **5** and **9** were not employed. This is because the calculations did not suggest particular properties for **5** and under the experimental conditions, the $-NO_2$ group in **9** would most likely be reduced either by the metal powders employed or by the titanium(III) center. The titanocene(III) derivatives were prepared from their corresponding dichlorides by in situ reduction with Mn powder.[8,17]

Epoxide Opening. We examined the oxidative addition to epoxides **14** and **15** in order to establish the feasibility of this process. Our reaction conditions [2.2 equiv. of the titanocene(III) reagent, 4.5 equiv. γ-terpinene (**16**)] were chosen to ensure an efficient competition between oxidative addition followed by H-atom abstraction from **16** to yield **17** and **19**, respectively, and undesired radical trapping that yields **18** and **20**, respectively (Scheme 5). By using two substrates with different substitution patterns at the epoxide, radical trapping by the titanocenes can be examined as a function of radical substitution in a straightforward manner. The novel nitrile substituted **6** (for details of the preparation, see Supporting Information) could not be used due to its relatively low solubility that is about 0.01 M in THF. This renders a comparison of the results with the other complexes pointless.

The mechanisms of the formation of **18** and **20** are depicted in Schemes 6. Olefin **18** is formed via trapping of β-titanoxy radical **21** and elimination of an oxotitanium-species. Allylic alcohol **20** is generated from **22** by interception with a second equivalent of the titanocene(III) reagent, β-hydride elimination, and protic workup of **23** as shown in Scheme 6.

The results of the epoxide opening are summarized in Tables 7 and 8.

All of the titanocenes investigated oxidatively add to epoxide **14**. However, the substitution of the complexes has a significant influence on the fate of radical **21**. Complex **10** and especially **11** lead to high isolated yields of the deoxygenation product **18** and hardly any **17**. Hence, these complexes trap **21** much more efficiently than even γ-terpinene (**16**). The use of **1** and **4** does not alter the picture substantially. However, the situation changes significantly with the introduction of electron withdrawing groups. For **7**, hydrogen atom abstraction can already compete with radical trapping. Only the use of **8** leads to the preferred formation of **17** (**17**: **18** $\approx$ 4:1) in about 50% yield. Thus, **8** is rather inefficient in the reductive trapping of secondary radicals. However, **8** slowly decomposes under the reaction conditions and hence the conversion to the desired products is incomplete.

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[38] (a) Complex **4**: Conway, B.; Rausch, M. *Organometallics* **1985**, *4*, 688–693. (b) Complex **7**: Rausch, M. D.; Lewison, J. F.; Hart, W. P. *J. Organomet. Chem.* **1988**, *358*, 161–168. (c) Complex **8**: Bruce, M. R. M.; Sclafani, A.; Tyler, D. R. *Inorg. Chem.* **1986**, *25*, 2546–2549. (d) Complex **10**: Ott, K. C.; deBoer, E.; J, M.; Grubbs, R. H. *Organometallics.* **1984**, *3*, 223–230. (e) Complex **11**: Hart, S. L.; Duncalf, D. J.; Hastings, J. J.; McCamley, A.; Taylor, P. C. *J. Chem. Soc., Dalton Trans.* **1996**, *284*, 3–2849.

Scheme 7. Performance of the Titanocene (R, R′ = H) Catalyzed Tandem Sequence at 95 °C (Coll = 2,4,6-trimethyl pyridine)

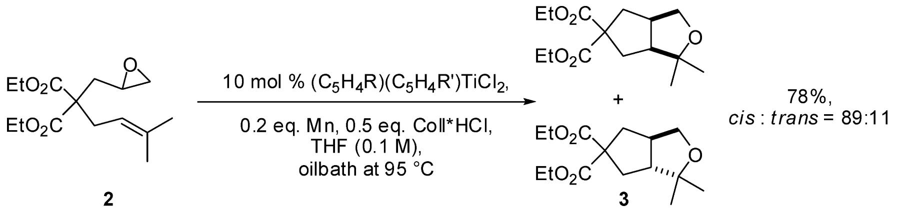


Table 7. Oxidative Addition Reactions to **14**

cat	R, R′	yield **17** + **18**/ %	**17**/ %	**18**/ %
1	H, H	97	19	78
4	H, Cl	84	20	64
7	H, CO_2Me	89	35	54
8	CO_2Me, CO_2Me	ca. 60	ca. 50	12
10	H, Me	87	13	74
11	H, *t*-Bu	86	5	81

Table 8. Oxidative Addition Reactions to **15**

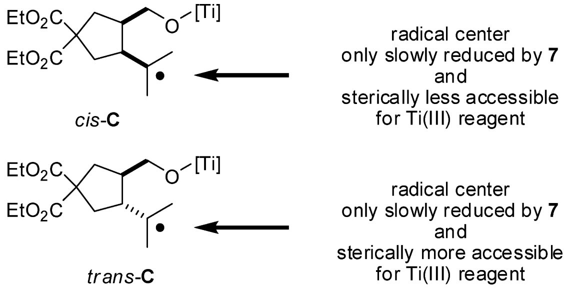
cat	R, R′	**19** + **20**/ %	**19**/ %	**20**/ %
1	H, H	52	45	7
4	H, Cl	67	56	11
7	H, CO_2Me	70	67	3
8	CO_2Me, CO_2Me	46	43	3
10	H, Me	66	51	15
11	H, *t*-Bu	61	31	30

Moreover, the dimer of the cyclopentadienyl ligand, that is formed via a Diels−Alder reaction, could not be completely removed from **17** via column chromatography. Therefore, only an approximate yield of **17** is indicated in Table 7. Nevertheless, these findings amply highlight the power of the electronic fine-tuning of the titanocene(III) properties in oxidative addition reactions to epoxides. To obtain a more general understanding of the interplay of this effect with substitution pattern of the epoxide we studied the reaction of **15** next (Table 8).

Gratifyingly, all complexes investigated also oxidatively add to **15**. As above, the substituents on the cyclopentadienyl ligand exert a large influence on the outcome of the reaction. With the ester-substituted complex **7**, **19** is obtained in 67% yield together with hardly any of the undesired **20** (3%) being formed. This constitutes the highest combined yield of products and suggests that **7** is the best titanocene(III) reagent for the opening of 1,1-disubstituted epoxides without interference of reductive radical trapping. The introduction of a second ester group in **8** results in a marked decline of the isolated yields due to the low stability of **8**. All other complexes also gave lower combined yields of **19** and **20** than **7**. Moreover, **20** was formed in higher relative amounts. The use of *tert*-butyl substituted **11** gave the worst result in this respect. Alcohols **19** and **20** were formed in almost equal proportions. Surprisingly, the undesired radical reduction is also most efficient for tertiary radicals with the bulkiest complex **11** even though titanocene mediated or catalyzed reactions are usually rather sensitive to steric effects.[39]

It has been reported that for the titanocene mediated reductions the inner sphere character of electron transfer decreases with decreasing complexation ability of the organic substrates.[17] The radical centers in **21** and **22** that possess no coordination site for titanium, should therefore be reduced in a process with relatively high outer sphere character. In this case, the redox-potential represents the crucial property of the reductant. It is well established that alkyl-substituted titanocenes constitute significantly more powerful electron transfer reagents.[40] In agreement with the experimental results, in the oxidative additions to both **14** and **15** the use of **11** should therefore lead to the highest amount of the undesired reductive trapping of the intermediate radicals **21** and **22**.

Scheme 8. Critical Issues for the Performance of Tetrahydrofuran Formation via Reductive Elimination ([Ti] = (RC_5H_4) ($R'C_5H_4$)TiCl)



Of the titanocenes studied here, **7** is best for mediating the epoxide opening because it is stable under the reaction conditions and does not promote undesired radical trapping, even though it is intrinsically not the most reactive complex for oxidative addition. In order to investigate the importance of these effects on the efficiency of the tetrahydrofuran forming reductive elimination, the performance of the overall catalytic sequence was studied next.

Implementation of the Complete Catalytic Sequence. To this end, we investigated the transformation of **2** to **3** in some detail. Before employing the substituted titanocenes, we focused on the identification of reactions conditions favoring the desired intramolecular course of the catalytic reaction over the undesired intermolecular reductive radical trapping (Scheme 7).

Table 9. Transformation of **2** to **3** by Substituted Titanocene(III) Complexes

cat	R, R′	**3**/ %	cis/trans
1	H, H	78	89/11
4	H, Cl	72	86/14
6	H, CN	80	78/22
7	H, CO_2Me	95	83/17
8	CO_2Me, CO_2Me	24	82/18
10	H, Me	69	90/10
11	H, *t*-Bu	61	94/6

Two essential parameters in this respect are the reaction temperature and the concentration of the substrates and catalysts. No significant difference in the isolated yield was observed when running the reaction at room temperature or 70 °C (67% yield at both temperatures). Quite surprisingly, we found that a further

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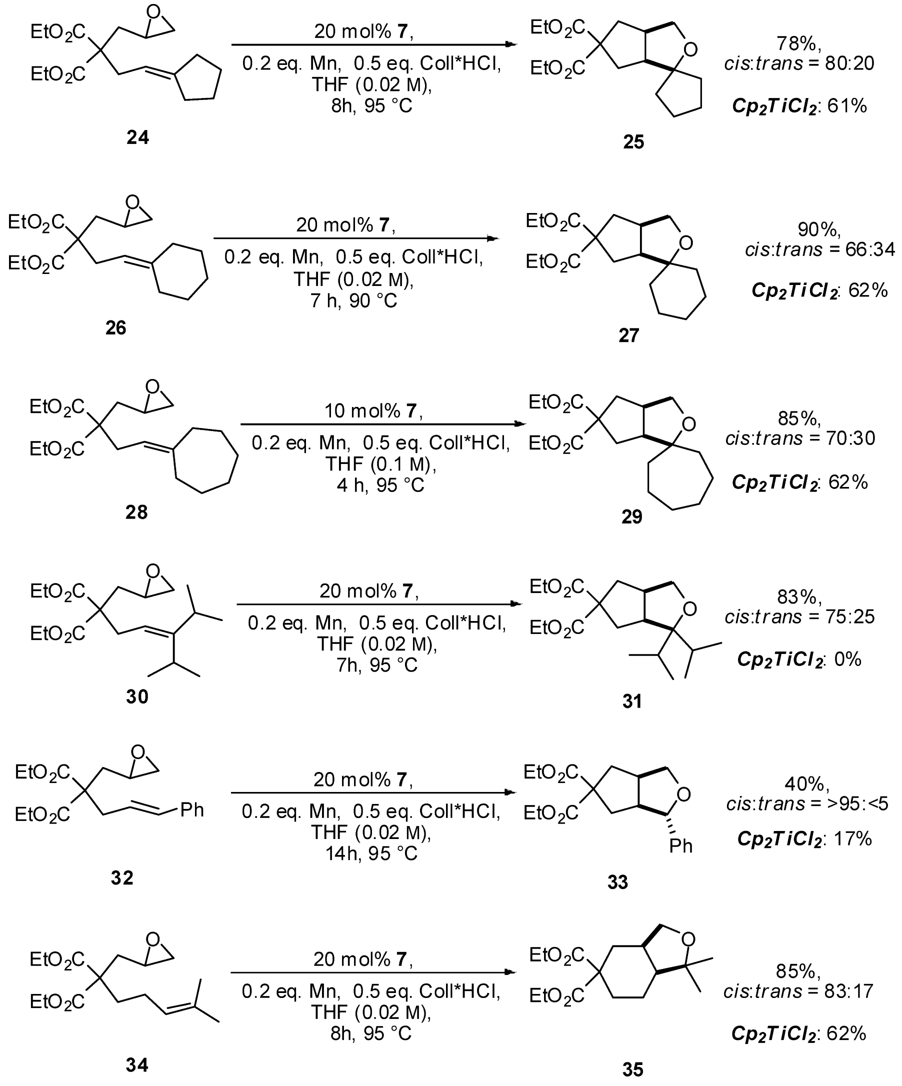
(39) Gansäuer, A.; Rinker, B.; Barchuk, A.; Nieger, M. *Organometallics* **2004**, *23*, 1168–1171.

(40) Johnston, R. F.; Borjas, R. E.; Furila, J. L. *Electrochim. Acta* **1995**, *40*, 473–477.

Scheme 9. Titanocene Catalyzed Tetrahydrofuran Synthesis (Coll = 2,4,6-trimethyl pyridine)



increase of the oil bath temperature to 95 °C increased the isolated yield of **3** to 78%. Moreover, *trans*-**3** was obtained for the first time (Scheme 7). The concentration (0.1 M in THF) was not decreased further in order to avoid the use of larger amounts of solvent and extended reaction times. It has been shown however, that this may be necessary in cases where sterically demanding radical substitution is encountered.[4a,d] Collidine hydrochloride was added to the reaction medium to enforce catalyst regeneration after undesired radical trapping.

The conditions shown were employed in the further catalyst screening experiments. The nitrile substituted **6** could be readily employed in these investigations, because the 10 mol % of **6** used were readily soluble under these conditions (Table 9).

The ester substituted complex **7** gave an almost quantitative yield of **3** and is therefore substantially superior to all other complexes. Introduction of the second ester group in **8** results in a much lower yield of **3**, which is due to the instability of this complex. Extensive decomposition of **2** was also observed in this particular case. Of the other complexes, the alkyl substituted titanocenes **10** and **11** gave the worst results, while **1** and the novel **6** gave almost identical yields of **3**.

The superiority of **7** over the alkyl substituted **10** and **11** implies that the relative performances of radical trapping leading to undesired side-products and reductive elimination leading to THF formation constitutes the critical aspect of the catalytic sequence. We suggest that the prevention of radical reduction is most relevant here, because the calculated activation energies for tetrahydrofuran formation are rather high for radical reactions. Thus, the decreased capability of **7** for radical reduction results in an increased lifetime of the pivotal radical intermediates *cis*- and *trans*-**C** (Scheme 8), that is essential for the occurrence of the reductive elimination. Radical trapping is not critical after the oxidative addition since the radical translocating 5-*exo* cyclization is a very fast reaction in both titanocene-mediated or -catalyzed radical reactions.

The quick interception of *trans*-**C** is also responsible for the apparently higher diastereoselectivity of the overall sequence in the presence of **10** and **11**. Both complexes are more potent SET reagents than **7** and hence reduce higher portions of *trans*-**A** before the reductive elimination takes place. This also accounts for the lower yields of **3** obtained with these catalysts. The alternative explanation, a radical translocating 5-*exo* cyclization proceeding with higher diastereoselectivity in the presence of **10** and **11** is less likely.[41] This is because it has been demonstrated that the influence of alkyl substitution on the diastereoselectivity of titanocene mediated or catalyzed cyclizations in such simple systems is rather low. Moreover, this simple analysis does not take the lower yields of **3** with **10** and **11** into account.

We investigated the performance of **7** for a number of other substrates that lead to relatively low yields of the desired products with **1**. In all cases, the reductive elimination is even more critical than for **2** because the radicals attacking the Ti−O bond are sterically either more demanding (from **24**, **26**, **28**, and **30**) or electronically stabilized (from **32**). These results are summarized in Scheme 9.

The concentration and catalyst loading for each substrate are identical to those that have turned out to be most suitable for **1**. With **1** it is often essential to employ high dilution (0.02 M in THF) or to use ethyl acetate (EtOAc) as solvent, because reduction of Cp_2TiCl_2 is slower in this solvent and hence reductive radical trapping is additionally disfavored. With **7**, the use of EtOAc as solvent is not necessary.

Most gratifyingly, catalyst **7** is superior to **1**[4a,d] in all examples investigated. This is most striking for the reaction of **30**, where no product **31** is formed at all in the presence of **1**. The effect is less pronounced but still highly important in the other cases, also. Even though for **32** the yield is clearly not ideal, it is still much higher than the 17% obtained for **1**. These relatively low yields with the highly stabilized benzylic radicals are most likely due to a substantially reduced exothermicity of tetrahydrofuran generation compared to the reactions of the alkyl substituted radicals. Thus, side reactions such as the formation of polymers were observed. Complex **7** is also markedly superior to Cp_2TiCl for the preparation of **35** featuring a 6-*exo* cyclization. In this case, the diastereoselectivity is only slightly reduced from 87:13 to 83:17.

These findings amply highlight the general significance of effectively suppressing reductive radical trapping in the case of sterically and electronically difficult reductive eliminations for an efficient overall catalytic sequence.

Conclusions

In summary, we have demonstrated by a combined theoretical and experimental study how the performance of the titanocene catalyzed homolytic C−O bond cleavage and homolytic C−O bond formation can be controlled by adjusting the electronic and steric properties of the cyclopentadienyl ligands. The knowledge of the activation and reaction energies and the structures of pertinent intermediates and transition states obtained as well as the ability to suppress undesired side reactions provides a mechanism-based platform for the development of efficient tandem sequences. This was demonstrated in the development of a much more efficient catalyst for a tandem sequence featuring a single electron oxidative addition and a single electron reductive elimination for the synthesis of bi- and polycyclic tetrahydrofurans.

In a broader perspective, our study highlights that the same concepts that have proven highly successful in the development of classical catalytic systems, featuring organometallic key reactions that proceed in two electron steps, can be applied to the development of metal-catalyzed reactions occurring in single electron steps. This should open broad perspectives for the design of novel reactions, such as tandem sequences featuring slow elementary steps, e.g., titanocene catalyzed epoxypolyene cyclizations, or transformations with the highly important ketyl radicals.

Acknowledgment. We are indebted to the *Deutsche Forschungsgemeinschaft* (SFB 813 “Chemistry at Spin Centers”) and the *Fonds der Chemischen Industrie* (Sachbeihilfen) for generous financial support.

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

JA907817Y

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