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Mechanism of Titanocene-Mediated Epoxide Opening through Homolytic Substitution

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Abstract: The mechanism of titanocene-mediated epoxide opening was studied by a combination of voltammetric, kinetic, computational, and synthetic methods. With the aid of electrochemical investigations the nature of a number of Ti(III) complexes in solution was established. In particular, the distribution of monomeric and dimeric Ti(III) species was found to be strongly affected by the exact steric conditions. The overall rate constants of the reductive epoxide opening were determined for the first time. These data were employed as the basis for computational studies of the structure and energies of the epoxide−titanocene complexes, the transition states of epoxide opening, and the β-titanoxy radicals formed. The results obtained provide a structural basis for the understanding of the factors determining the regioselectivity of ring opening and match the experimentally determined values. By employing substituted titanocenes even more selective epoxide openings could be realized. Moreover, by properly adjusting the steric demands of the catalysts and the substrates the first examples of reversible epoxide openings were designed.

Introduction

Over the last decades radical chemistry has been increasingly used in the synthesis of complex molecules. This is mainly due to the mildness of radical generation, the excellent tolerance of these reactive intermediates toward numerous functional groups, and the high predictability of a number of key radical reactions.[1] In the field of metal-induced radical chemistry titanocene-mediated[2] and titanocene-catalyzed[3] epoxide opening reactions have recently attracted considerable interest.[4] Important examples of rare reactions such as enantioselective radical generation[3d,i] or 3-exo- and 4-exo-cyclizations[3n,p] controlled by polarity matching of radical reduction have been developed. A number of pertinent applications in the synthesis of complex molecules have emerged, e.g., titanocene-catalyzed epoxypoly-

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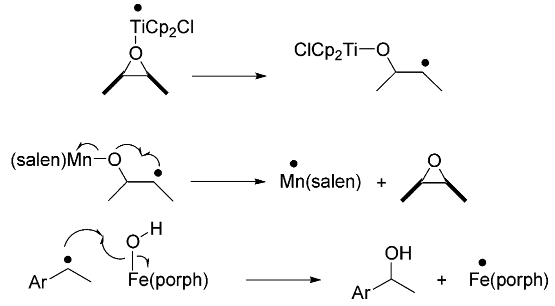
ene cyclizations.[3l,o,q] Moreover, the titanocene-mediated epoxide opening has been used with excellent success for the initiation of the polymerization of styrene.[5] Titanocene-mediated or titanocene-catalyzed pinacol couplings have attracted less attention due to their restricted substrate scope, even though the first example of an enantioselective coupling has been reported.[6]

An attractive feature of titanocene catalysis is that the regioselectivity of ring cleavage is opposite to S_N2 reactions,[7] such as Jacobsen's outstanding catalytic epoxide openings.[7d−g] Therefore, the preparative usefulness of epoxides,[8] in organic synthesis is increased even further. Despite this conceptual and preparative usefulness of the titanocene-mediated or titanocene-catalyzed transformations, to the best of our knowledge nothing is known about the exact mechanism of the titanocene-mediated epoxide opening. Here, we present a full account of the first study elucidating this mechanism by a combination of electrochemical, kinetic, computational, and synthetic methods.[9] The results are of fundamental interest due to the insights in the molecular details of the reaction and lead the way for the development of even more selective catalysts or processes.

Moreover, our investigation provides a unique link between the mechanism of reductive opening of epoxides, where a C−O bond is cleaved through a homolytic substitution reaction, and reactions where C−O bonds are formed through homolytic substitutions featuring metal oxygen bonds as radical traps. Examples for the latter transformations are alkoxylation reactions such as epoxidations via β-metaloxy radicals,[10] hydroxylations of hydrocarbons via C−H bond activation by organometallic complexes,[11] and our titanocene-catalyzed THF synthesis.[3k,m] Even the oxygen rebound step, that is intensely debated for the P450 enzymes, may be regarded as another case of this type of reaction.[12] These reactions are highlighted in Scheme 1.

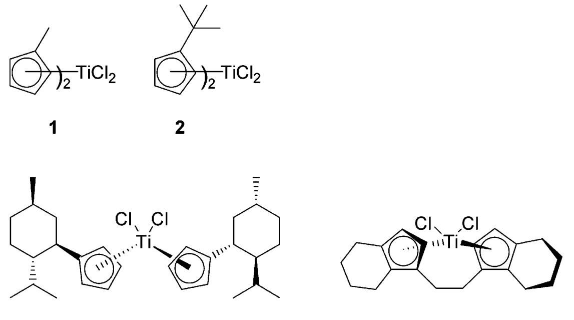
Scheme 1. Reactions Featuring Homolytic Substitution Reactions with Metal Oxygen Bonds (porph = Porphyrin)



Results and Discussion

We selected four alkyl-substituted titanocene dichlorides, $(RCp)_2TiCl_2$, with the aim of identifying the principal species formed in Zn-reduced solutions and their reactivity toward epoxides. The substituent at the cyclopentadienyl ring ranges from the relatively small Me over *tert*-butyl to the bulky menthyl[13] group along with an ethylene-bridged tetrahydroindenyl moiety (Chart 1).[14] These substituents are interesting not only with respect to their steric and electronic effects, in general, but also because of their potential synthetic applications in stereoselective epoxide openings.

Chart 1. Structures of the Substituted Titanocenes Used in This Study



1 **2**

3 **4**

For comparative purposes unsubstituted titanocene dichloride, Cp_2TiCl_2, was included in the study. In previous work we have succeeded in elucidating the composition of the electrochemically and metal-induced reductions of Cp_2TiCl_2 in THF by means of cyclic voltammetric and kinetic measurements.[15] We were able to demonstrate that the principal constituents of such solutions are monomeric and dimeric Ti(III) species. Trinuclear

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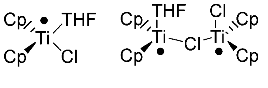
Chart 2. Proposed Structures of Solvated Cp_2TiCl (**5a**) and $(Cp_2TiCl)_2$ (**5b**)



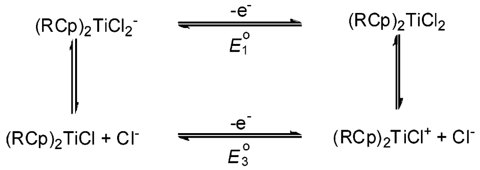
5a*THF **5b*THF**

complexes or ionic clusters were not present, despite their isolation and characterization in solid state.[16]

In Chart 2 the proposed structures of the two principal Ti(III) species Cp_2TiCl (**5a**) and $(Cp_2TiCl)_2$ (**5b**) are depicted assuming that any free coordination site would be occupied by solvent molecules, i.e., THF. An analysis of the solid-state structure of the dimeric species pointed to a symmetric arrangement.[17] However, since kinetic measurements involving electron acceptors such as benzyl chloride, benzaldehyde, and epoxides revealed that the dimer had a surprisingly high reactivity in solution, we suggested that the half-open arrangement shown in Chart 2 with an accessible coordination site actually might be the active reagent in solution.[15c,d] This interpretation was recently supported by computational studies.[9] A particular interesting aspect to consider herein is therefore the extent by which the presence of various substituents at the cyclopentadienyl ring may influence the monomer/dimer distribution. To obtain a picture as comprehensive as possible the present study was carried out employing a combination of cyclic voltammetric, kinetic, computational, and synthetic methods.

Electrochemical Reduction of $(RCp)_2TiCl_2$. First our focus will be on the electrochemical reduction of $(RCp)_2TiCl_2$ with the expectation that the mechanistic scheme can be described in terms of the square scheme already elucidated in the case of Cp_2TiCl_2 (Scheme 2).[15b]

Scheme 2. Square Scheme Describing the Electrochemical Reduction of $(RCp)_2TiCl_2$



The essential feature of this scheme is that the electrochemical reduction of $(RCp)_2TiCl_2$ to $(RCp)_2TiCl_2^-$ on the reductive sweep in cyclic voltammetry is followed by a reversible fragmentation reaction, in which the electroactive $(RCp)_2TiCl$ and Cl^- are generated. On the oxidative sweep, oxidation of $(RCp)_2TiCl_2^-$ and/or $(RCp)_2TiCl$ results in the direct or indirect regeneration of the parent $(RCp)_2TiCl_2$ compound. In the case of $(RCp)_2TiCl$ the conversion goes through the $(RCp)_2TiCl^+$ intermediate that is involved in a fast equilibrium reaction with Cl^-. Eventually, $(RCp)_2TiCl$ may dimerize to afford the electroactive dimer, $[(RCp)_2TiCl]_2$, although the inclusion of this reaction is of much less importance for substituted titanocene dichlorides as the analysis of the chemically reduced solutions will reveal.

Cyclic voltammograms recorded of the various solutions of $(RCp)_2TiCl_2$ are collected in Figure 1. In consistency with the detailed analysis provided elsewhere[15b] for Cp_2TiCl_2 the most profound feature is the appearance of the redox wave around −1.4 V vs Fc^+/Fc (abbreviation for ferrocenium/ferrocene) pertaining to the $(RCp)_2TiCl_2/(RCp)_2TiCl_2^-$ couple. The peak separation increases nonlinearly as a function of sweep rate as expected for a quasi-reversible charge-transfer process. At the same time a small wave positioned at less negative potentials originating from the oxidation process of $(RCp)_2TiCl$ tends to appear on the oxidative sweep, i.e., at high sweep rates the lower part of the square scheme comes into play. Upon addition of tetrabutylammonium chloride as a chloride source to the solution, enhancement of the rate of the reaction between $(RCp)_2TiCl$ and Cl^- induces a further shift of the equilibrium reaction toward $(RCp)_2TiCl_2^-$ to favor once again the upper part of the square scheme.

In our previous work the dissociation equilibrium constant for $Cp_2TiCl_2^-$ was estimated on the basis of such experiments and extensive simulations to a value of 10^{-4} M.[15b] Because essentially the same or a slightly larger amount of tetrabutylammonium chloride is required (>400 mol %) to deplete the small $(RCp)_2TiCl$ wave in the case of **1**−**4**, this study reveals that the equilibrium constant is essentially of the same magnitude for the substituted titanocene dichlorides. Thus, the overall effect of the bulkiness of the cyclopentadienyl ligands on this particular reaction is relatively small. In contrast, the substituent effect on the redox properties of the $(RCp)_2TiCl_2/(RCp)_2TiCl_2^-$ system is clearly detectable. While the standard potential was determined to be −1.27 V vs Fc^+/Fc for Cp_2TiCl_2,[15b] we find values of −1.40, −1.34, −1.37, and −1.48 V vs Fc^+/Fc for **1**, **2**, **3**, and **4**, respectively. A discussion of these data along with others obtained will be given below.

Chemical Reduction of $(RCp)_2TiCl_2$. The second part of the voltammetric analysis is concerned with the study of Zn-reduced solutions of $(RCp)_2TiCl_2$, denoted Zn−$(RCp)_2TiCl_2$. Such an investigation of Ti(III)-containing solutions is not only important because it complements the above study focusing on Ti(IV) as starting material but also because it may provide additional information pertinent to the many important synthetic applications using Zn−$(RCp)_2TiCl_2$. The present analysis is based on the reasonable assumption that the mechanistic scheme already resolved for Zn−Cp_2TiCl_2 can be applied for the four substituted cases **1**−**4** as well.[15c]

The general conclusion from our previous work[15c−e] is that the principal species formed in THF solutions of Zn−Cp_2TiX_2 (X = Cl, Br, and I) are a mixture of Cp_2TiX, $(Cp_2TiX)_2$, and Cp_2Ti^+, the distribution of which is dependent on the halogen considered.[15d] For example, Cp_2Ti^+ is present in quite substantial amounts only for X = Br and I, whereas it is completely absent for X = Cl. In all three solutions the amounts of Cp_2TiX and $(Cp_2TiX)_2$ are appreciable being formed in a mixture having a dimerization equilibrium constant of $(1-3) \times 10^3$ M^{-1}. The anion $Cp_2TiCl_2^-$ is of no importance, unless the reduction of Cp_2TiCl_2 is carried out electrochemically. This is due to the fact that the zinc chlorides present in the Zn-reduced solutions will be able to take up additional chlorides.

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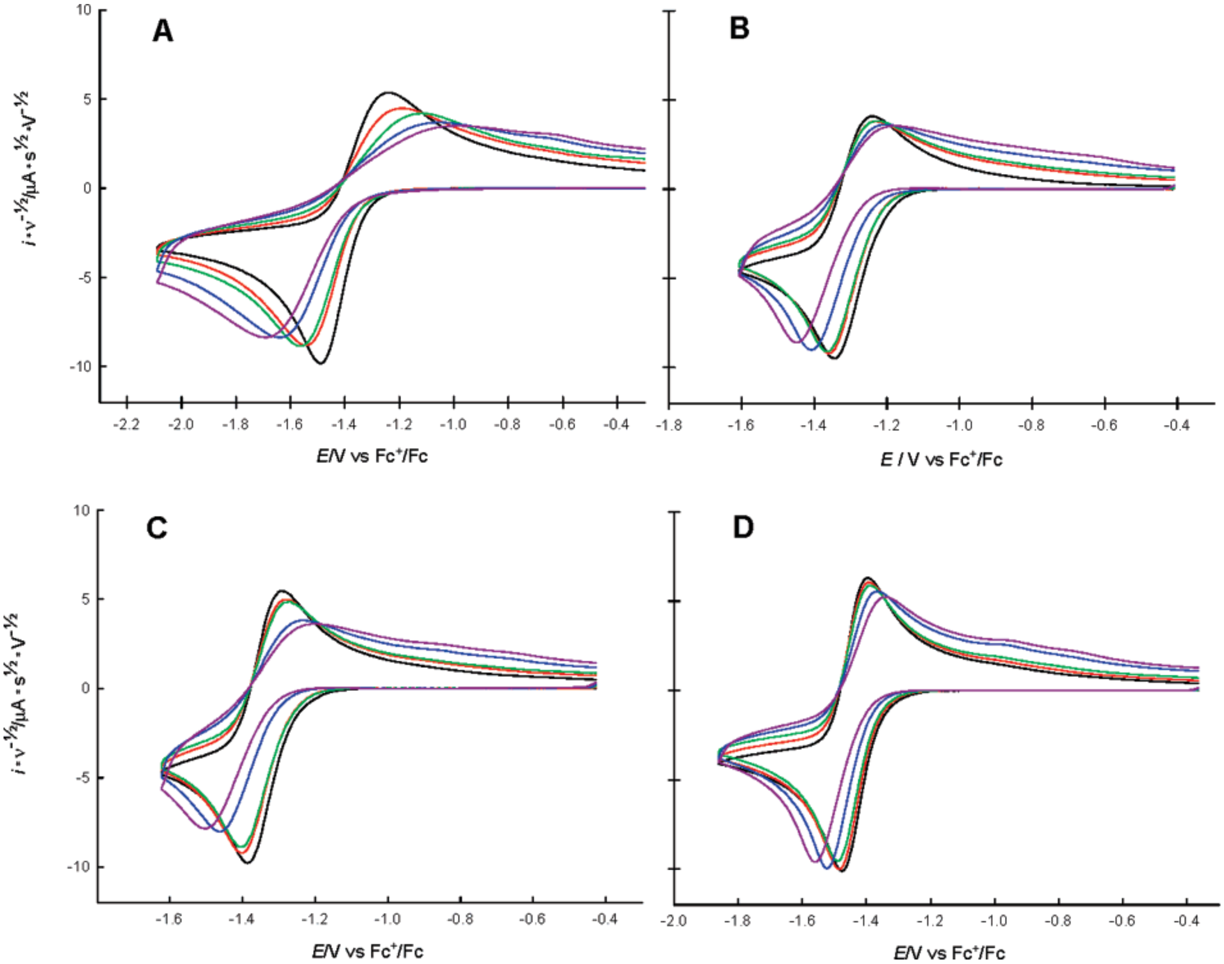


Figure 1. Cyclic voltammograms of 2 mM solutions of **1** (A), **2** (B), **3** (C), and **4** (D) recorded at sweep rates of 0.1 (black), 0.5 (red), 1 (green), 5 (blue), and 10 V s^{-1} (magenta) in 0.2 M Bu_4NPF_6/THF. Currents are normalized with respect to sweep rate.

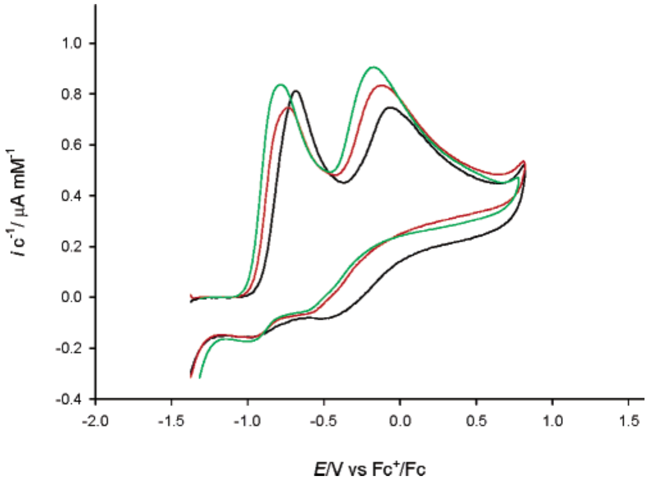


Figure 2. Cyclic voltammograms of solutions containing Zn−**1** in concentrations of 0.7 (black), 1.1 (red), and 1.8 mM (green) recorded at a sweep rate of 0.1 V s^{-1} in 0.2 M Bu_4NPF_6/THF. Currents are normalized with respect to concentration.

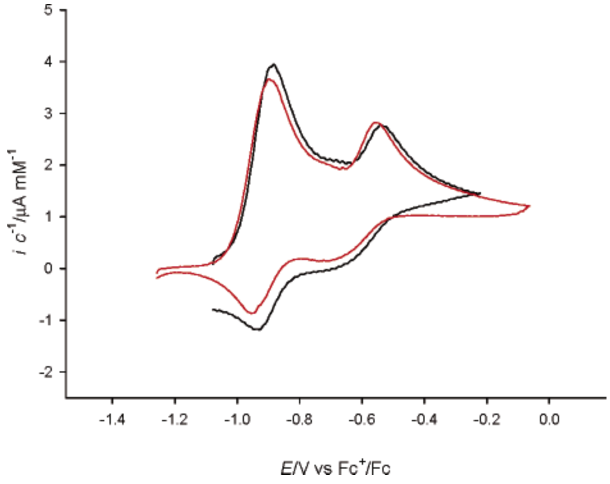
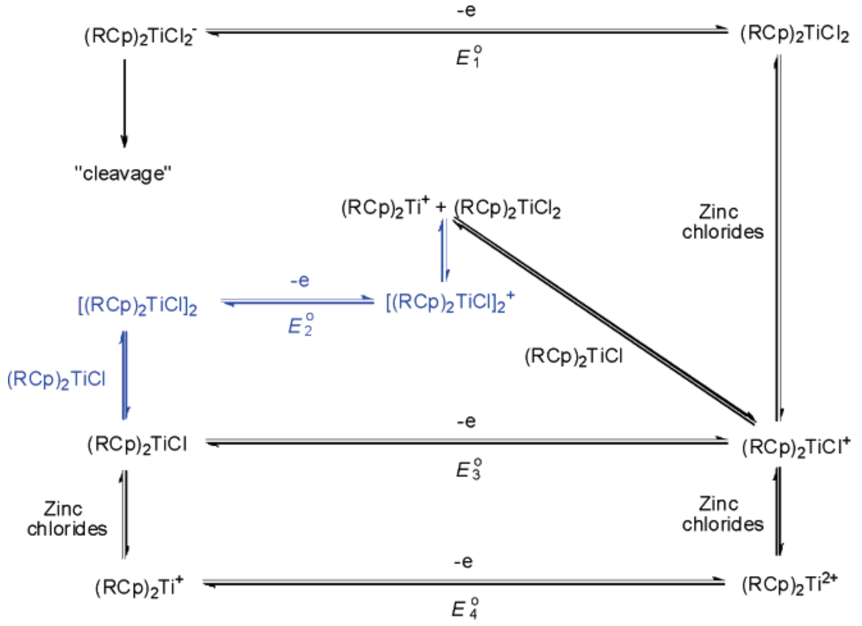


Figure 3. Cyclic voltammograms of solutions containing Zn−**4** in concentrations of 0.7 (black) and 1.5 mM (red) recorded at a sweep rate of 1 V s^{-1} in 0.2 M Bu_4NPF_6/THF. Currents are normalized with respect to concentration.

The earlier cyclic voltammetric studies also gave immediate access to a characterization of the oxidation processes pertaining to the electroactive species $Cp_2TiCl_2^-$, $(Cp_2TiCl)_2$, Cp_2TiCl, and Cp_2Ti^+. Although all of these four species are not present initially in the solution, they may be generated in followup reactions taking place at the electrode surface during the sweep in cyclic voltammetry. Such followup reactions include a father−son reaction between Cp_2TiCl and Cp_2TiCl^+, a direct fragmentation of the dimer cation $(Cp_2TiCl)_2^+$, and chloride transfer reactions between various titanium-based species and the zinc chlorides.

One of the essential questions raised by the present study is how the substituent on the cyclopentadienyl ring will affect the parameters associated with the reaction scheme. While the first

Scheme 3. Proposed Mechanistic Scheme for the Electrochemical Oxidation of Zn−$(RCp)_2TiCl_2$ (R = H, Me)



part of our study has revealed already a substituent effect on the redox properties of the $(RCp)_2TiCl_2/(RCp)_2TiCl_2^-$ couple, it is yet to be elucidated if this will apply also to the $[(RCp)_2TiCl]_2^+/[(RCp)_2TiCl]_2$, Cp_2TiCl^+/Cp_2TiCl, and Cp_2Ti^{2+}/Cp_2Ti^+ redox couples, not to mention the possible effect the substituent may exert on the chemical reactions.

In Figure 2 we have collected cyclic voltammograms recorded at three different concentrations of Zn−**1**. The oxidation wave appearing at −0.8 V vs Fc^+/Fc actually consists of two processes, with the first one becoming more dominant as the concentration increases. The two-component nature of the wave is particularly pronounced for the intermediate concentration. Thus, the first process is attributed to the oxidation of the $[(MeCp)_2TiCl]_2$ dimer and the second one to the oxidation of the $(MeCp)_2TiCl$ monomer. The oxidation peak at −0.2 vs Fc^+/Fc originates from the oxidation of $(MeCp)_2Ti^+$ generated in the chemical reactions occurring during the cyclic voltammetric sweep. Surprisingly, the peak potential of the $(MeCp)_2Ti^+$ wave varies appreciably as a function of concentration, but this may be related to the strong adsorption tendency of this species as revealed by the rather broad and almost bell-shaped feature of the wave. In any case this will introduce some additional uncertainty in the determination of the standard potential of the $(MeCp)_2Ti^{2+}/(MeCp)_2Ti^+$ redox couple. As seen in Scheme 3 the generation of $(MeCp)_2Ti^+$ is accompanied by the formation of $(MeCp)_2TiCl_2$, the presence of which is substantiated by the reduction wave that is about to appear at ca. −1.5 V vs Fc^+/Fc on the reverse sweep (compare with Figure 1).[18] At this point we may therefore state that introducing a methyl group at the cyclopentadienyl ring does not change the overall mechanistic scheme, although the exact values of the associated parameters of course may differ (see below).

With respect to the solution of Zn−**4**, voltammograms recorded at two different concentrations are shown in Figure 3. At first sight the overall appearance with the presence of two characteristic oxidation waves is the same as for Zn−Cp_2TiCl_2 and Zn−**1**, but there is a distinct difference in the sense that there is no splitting of the first wave. The same lack of a splitting is also seen for the Zn-reduced solutions of **2** and **3** (Supporting Information). This lends support to the hypothesis that the dimerization reaction for the more highly substituted titanocene chlorides is less favorable. In these cases the mechanism thus becomes somewhat simplified since the blue part involving the dimer in Scheme 3 can be omitted.

Discussion of Cyclic Voltammetric Data. In the further analysis of the cyclic voltammograms the goal was to obtain quantitative information about the composition of the solutions. In general, all relevant potentials, heterogeneous and homogeneous rate constants as well as equilibrium constants were extracted by digital simulations (using the program DigiSim 3.03)[19] of the experimentally obtained voltammograms recorded at different sweep rates and concentrations. A detailed description of the exact model parameters used as well as relevant fits can be found in the Supporting Information. Below the focus will be on the most important parameters extracted, i.e., the standard potentials and the dimerization equilibrium constant. The standard potentials are summarized in Table 1.

In general, for a given substituent the standard potentials determined for the redox couples $(RCp)_2TiCl_2/(RCp)_2TiCl_2^-$, $[(RCp)_2TiCl]_2^+/[(RCp)_2TiCl]_2$, $(RCp)_2TiCl^+/(RCp)_2TiCl$, and $(RCp)_2Ti^{2+}/(RCp)_2Ti^+$ increase (i.e., becomes less negative) in the order listed. This is in line with the results already obtained and discussed in the case of Cp_2TiCl_2.[15b−d] From a thermodynamic point of view the electron-donating ability of the Ti(III) species is thus $RCp_2TiCl_2^- \gg (RCp_2TiCl)_2 > RCp_2TiCl \gg RCp_2Ti^+$. However, as already shown by our earlier investigations[15b−d] this order does not hold from a kinetic point of view (see below).

A particularly interesting issue to discuss in this context is the influence of the substituent on the potentials. Considering only the inductive effect of electron-donating alkyl groups one would predict that the potentials should become more negative going from Cp_2TiCl_2 to **1**, **2**, or **3**, and further to **4**. Indeed this

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(18) In general, application of potentials below −1.4 V vs Fc^+/Fc had to be avoided because reduction of the zinc ions present could cause deleterious adsorption of metal on the electrode surface.

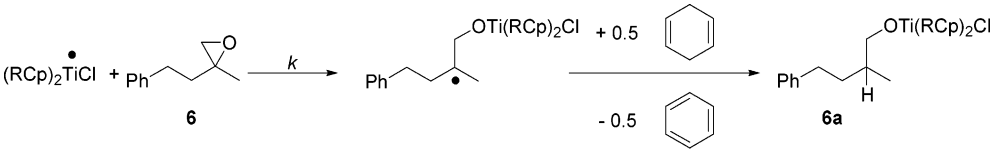
(19) Rudolph, M.; Feldberg, S. W. *DigiSim version 3.03*; Bioanalytical Systems, Inc.: West Lafayette, IN.

Table 1. Relevant Data Extracted from Cyclic Voltammograms Recorded on Zn-Reduced Solutions of **1**−**4**

	Zn–Cp_2TiCl_2	Zn–**1**	Zn–**2**	Zn–**3**	Zn–**4**
$E_1°$/V vs Fc^+/Fc^a	-1.27 ± 0.04^b	-1.40 ± 0.03^c	-1.34 ± 0.03^c	-1.37 ± 0.03^c	-1.48 ± 0.03^c
$E_2°$/V vs Fc^+/Fc^a	-0.81 ± 0.03^d	-0.91 ± 0.03			
$E_3°$/V vs Fc^+/Fc^a	-0.75 ± 0.03^d	-0.81 ± 0.03	-0.81 ± 0.03	-0.84 ± 0.03	-0.94 ± 0.03
$E_4°$/V vs Fc^+/Fc^a	-0.43 ± 0.03^d	-0.35 ± 0.08	-0.55 ± 0.03	-0.54 ± 0.03	-0.62 ± 0.03

[a] Potentials can be converted to SCE by adding 0.52 V. [b] From ref 15b. [c] Obtained from cyclic voltammograms recorded on solutions of **1**−**4** (see above). [d] From ref 15c.

Scheme 4. Mechanistic Scheme for the Reaction between Zn-Reduced Titanocene Dichlorides and **6**



expectation is met for the three series involving $[(RCp)_2TiCl]_2$, $(RCp)_2TiCl$, and $(RCp)_2Ti^+$. The only outlier pertains to the cation system for R = Me, but presumably this should be attributed to the adsorption problems encountered for this particular system. In contrast, unexpected results are obtained for the $(RCp)_2TiCl_2$ series, in that the *tert*-butyl- (**2**) and menthyl-substituted titanocene dichlorides (**3**) have redox potentials being intermediate to those of Cp_2TiCl_2 and $(MeCp)_2TiCl_2$. The bridged ansa-compound (**4**) with its fixed geometry gives rise to the most negative value as also seen for the other series.

The unusual order of potentials emphasizes the importance of effects other than purely inductive. The influence of substituents on the electrochemical reduction of titanocene dichlorides has been addressed already in other studies.[20] In general, a correlation is expected between the reduction potentials and the Hammett substituent coefficients, i.e., systems having electron-donating substituents are more difficult to reduce.[20b] However, in the series of methyl-substituted titanocene dichlorides exceptions pertaining to the sterically encumbered tetra- and pentamethylcyclopentadienyl ligands exist. In the latter case a positive shift in the reduction potential is even encountered.[20c] It has been suggested that such a behavior can be brought about by steric strain between the cyclopentadienyl ligands which will not only induce additional hindrance to rotation but also lower the dihedral angle between the cyclopentadienyl ring planes.[20c] Our results corroborate this interpretation in the sense that the potentials for the sterically encumbered **2** and **3** are less negative than that of **1**. The steric effects on the potentials are smaller for the series involving $[(RCp)_2TiCl]_2$, $(RCp)_2TiCl$, and $(RCp)_2Ti^+$, in which one or both chloride ligands are absent. The issue of solvent (i.e., THF) coordination and the possible lack of such a coordination for the sterically most hindered compounds seem to have only a minor effect on the standard potentials.[20c,21]

The substituents on the cyclopentadienyl ring also exert a strong effect on the equilibrium distribution of the Ti(III) species in the Zn-reduced solutions. While the simulations of the cyclic voltammograms reveal that neither $(RCp)_2TiCl_2^-$ nor $(RCp)_2Ti^+$ are present in any appreciable amount (although they may be generated at the electrode surface during the cyclic voltammetric sweep), independent of the substituent, the exact distribution of the monomer $(RCp)_2TiCl$ and the dimer $[(RCp)_2TiCl]_2$ is strongly affected. As previously determined for the solution derived from Zn−Cp_2TiCl_2 the two species are in rapid equilibrium with an equilibrium constant of 3×10^3 M^{-1}.[15b−d] For **1** the dimer still remains an important constituent having an equilibrium constant of 10^3 M^{-1}, but already to a lesser extent.[9] Furthermore, bulkier ligands as in **2**−**4** make the monomer the only detectable species in cyclic voltammetry; a dimerization equilibrium constant of 100 M^{-1} can be set as a limiting value as deduced from digital simulations. For a 2 mM Zn-reduced solution of either Cp_2TiCl_2, **1**, or **2**−**4**, this will imply that the dimer/monomer ratio will be 1.5, 0.8, and <0.15, respectively.

These results are reasonably in line with EPR studies on the series of $(C_5H_{5-n}Me_n)_2TiX$ ($n = 0-5$), in which it was found that compounds with $n = 3-5$ were monomeric, whereas those with $n = 0-2$ were dimers, at least in toluene. In 2-methyltetrahydrofuran, on the other hand, the latter compounds dissociated due to a solvent molecule coordination.[21] At this point we do not know to which extent the less favorable dissociation process we seem to observe for the Zn-reduced solutions of Cp_2TiCl_2 and **1** in THF should be attributed to the concentration ranges considered, the presence of supporting electrolyte in cyclic voltammetry, or other factors.

Kinetic Studies. Kinetic analysis of the epoxide opening with Zn-reduced solutions of **2**−**4** was carried out with the aim of characterizing in further details the reactive Ti(III) species. As model compound for the epoxide we selected 2-methyl-2-phenethyl-oxirane (**6**), because under the reaction conditions chosen, 1,1-disubstituted epoxides are converted into titanocene alkoxides, such as **6a**, in high yield. The kinetic analysis is therefore not complicated by interfering pathways. Epoxide **6** was also used in our previous kinetic analysis of Zn-reduced solutions of Cp_2TiCl_2 and **1**.[9] The relevant rate constant, *k*, was extracted by monitoring the disappearance of the Ti(III) species using absorption spectroscopy (Scheme 4).

While the kinetic analysis of the solutions involving Zn−Cp_2TiCl_2 and Zn−**1** was complicated by the fact that an equilibrium mixture of both the reactive monomer and dimer is present,[9,15c] the situation in the case of Zn−(**2**−**4**) is much simpler because of the absence of the dimer. Employment of **6** in an excess will confine the kinetics to simple pseudo-first-

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(20) (a) Mugnier, Y.; Fakhr, A.; Fauconet, M.; Moise, C.; Laviron, E. *Acta Chem. Scand.* **1983**, *B37*, 423−427. (b) Johnston, R. F.; Borjas, R. E.; Furilla, J. L. *Electrochim. Acta* **1995**, *40*, 473−477. (c) Langmaier, J.; Samec, Z.; Varga, V.; Horáček, M.; Mach, K. *J. Organomet. Chem.* **1999**, *579*, 348−355.

(21) (a) Mach, K.; Raynor, J. B. *J. Chem. Soc., Dalton Trans.* **1992**, 683−688. (b) Mach, K.; Varga, V.; Schmid, G.; Hiller, J.; Thewalt, U. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1285−1294.

Table 2. Rate Data Obtained in the Epoxide Opening of **6** with Zn-Reduced Solutions of Cp_2TiCl_2 and **1**−**4**

Ti(III) reagent	Zn–Cp_2TiCl_2 monomer	Zn–Cp_2TiCl_2 dimer	Zn–**1** monomer	Zn–**1** dimer	Zn–**2** monomer	Zn–**3** monomer	Zn–**4** monomer
$k/M^{-1}\ s^{-1}$	0.5[a]	1.4[a]	1.3[a]	3.9[a]	0.10	0.74	4.8

[a] From ref 9.

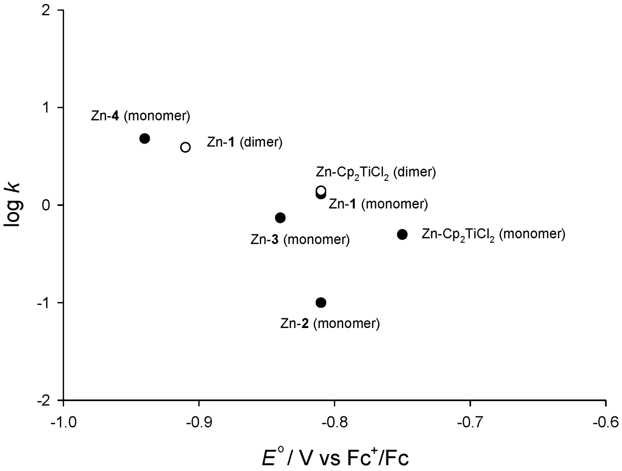

Figure 4. Logarithm of the observed rate constant, *k*, for the Ti(III)-mediated opening of **6** vs the standard potential *E*° for the relevant Ti(IV)/Ti(III) system.

order conditions. As in the synthetic work, 1,4-cyclohexadiene (CHD) was added to chemically reduce the tertiary radical intermediate formed upon the stereoselective electron-transfer-mediated epoxide opening,[22] thus precluding efficiently side reactions involving the radical and the Ti(III) species. This is in keeping with the 1:1 reaction stoichiometry observed for the Ti(III) and epoxide reagents. Note that the alternative formation of the primary radical intermediate is less favorable. The kinetics followed a simple exponential decay that was unaffected by the exact concentration of CHD employed. Thus, electron transfer constitutes the rate-controlling step of the overall reduction. This renders any mechanism with a quick and reversible epoxide opening before radical trapping unlikely.

We also note that in the previous synthetic work[22] the yield of the product 2-methyl-4-phenylbutan-1-ol was determined to be larger than or equal to 55% for all the systems studied herein, the exception being Zn−**4** with a disappointing 21% yield. Those reactions were carried out under catalytic conditions using collidine hydrochloride as proton source to liberate the Ti(IV) species from the alkoxides formed. Thus, it seems that for Zn−**4** another step in the catalytic cycle is too inefficient for a satisfying performance of the reaction. Most likely, this is the protonation with collidine hydrochloride for catalyst regeneration.

In Table 2 we have collected all relevant rate data obtained in the present and previous work.[9] In Figure 4 the data are plotted against the relevant standard potentials. The general expectation on thermodynamic grounds that the rate should diminish as the driving force of the reaction (expressed as $-FE°$) is decreased is by and large fulfilled. For instance, the fact that Zn−**1** constitutes a better electron-transfer agent than Zn−Cp_2TiCl_2 can be attributed to its higher reducing ability and that the steric demands of the $C_5H_4CH_3$ and C_5H_5 ligands are similar.

The low reactivity of the Zn−**2** monomer along with the high reactivity of the two dimeric systems of Zn−Cp_2TiCl_2 and Zn−**1** are interesting features. In the former case this may be attributed to the presence of the sterically demanding *tert*-butyl groups which apparently—and even to a larger extent than the menthyl groups in Zn−**3**—are able to prevent a close pairing up of the Ti(III) reagent with the epoxide **6**. The high reactivity of the Zn−Cp_2TiCl_2 and Zn−**1** dimers is surprising in the sense that an analysis of the solid-state structure has pointed to a symmetric structural arrangement with no vacant coordination site.[17] We therefore suggest that the actual solution structure is of the half-open type **5b** depicted in Chart 2.[9,15c,d] In fact, the availability of a coordination site would be a prerequisite for having a fast inner-sphere electron-transfer reaction. In this sense the dimer can be considered as a highly Lewis acidic intermediate formed from the monomer **5a** (Chart 2) according to the principle of activation of electrophiles through dimeric association.[23]

It is also noteworthy that previous investigations on $Cp_2TiCl_2^-$ have suggested[15b,c] that its lack of reactivity as an electron donor can be attributed to the fact that the coordination around the Ti core is that of a distorted tetrahedron.[24] Because a pentavalent arrangement in the transition state would appear highly unlikely, this would leave the outer-sphere electron-transfer reaction as the only viable pathway for this species. In keeping with this interpretation is the finding that the cation Cp_2Ti^+ with its easily accessible coordination site is a rather potent electron donor in spite of its relatively high oxidation potential (see Table 1).[15c,d]

Computational Studies. On the basis of the above experimental results, we turned our attention toward insights into the reaction mechanism on a molecular level. We studied the complexation of a number of epoxides by Cp_2TiCl (**5a**) and its dimer (**5b**), the activation and reaction energies of ring opening, and the structures of all pertinent intermediates, transition states, and products by density functional theory (DFT) calculations with the BP functional and a TZVP basis set.[25] This pure density functional is suited for the description of reactions of transition metal compounds and has been successfully used in the literature for chemically similar systems.[26] One must be aware, however, that the absolute barriers of radical reactions predicted by this method are usually too low.[27] Since we are mainly interested in the comparison of reactivities of various epoxides, this systematic error seems acceptable and does not affect the conclusions of our work.

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(22) Gansäuer, A.; Barchuk, A.; Fielenbach, D. *Synthesis* **2004**, *15*, 2567−2573.

(23) Negishi, E.-i. *Chem. Eur. J.* **1999**, *5*, 411−420.

(24) Clearfield, A.; Warner, D. K.; Saldarriaga-Molina, C. H.; Ropal, R. *Can. J. Chem.* **1975**, *53*, 1622−1629.

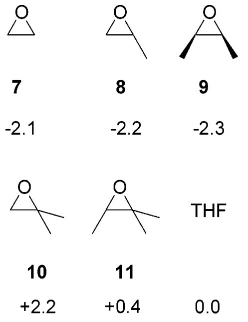
(25) Technical details of computation: All DFT calculations were performed with the TURBOMOLE program package (see 25a). The geometries and energies were obtained with the BP functional (see 25b,c) and a polarized valence triple-ζ basis set (TZVP) (see 25d) using unrestricted wavefunctions. Spin densities for the TS were calculated using the Mulliken population analysis scheme. (a) *TURBOMOLE 5.6*; Ahlrichs, R.; et al. Universität Karlsruhe, 2003. For the complete citation, see the Supporting Information. (b) Becke, A. D. *Phys. Rev. B* **1988**, *38*, 3098−3100. (c) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824. (d) Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829−5835.

(26) (a) Abashkin, Y. G.; Collins, J. R.; Burt, S. K. *Inorg. Chem.* **2001**, *40*, 4040−4048. (b) Jacobsen, H.; Cavallo, L. *Organometallics* **2006**, *25*, 177−183.

(27) For an example see: Hemelsoet, K.; Moran, D.; Van Speybroeck, V.; Waroquier, M.; Radom, L. *J. Phys. Chem. A* **2006**, *110*, 8942−8951.

Binding of the Epoxides by Titanocene(III) Complexes. Binding of the epoxides **7**−**11**, that serve as simplified surrogates for the preparatively employed substrates, to **5a** was studied first. These complexes are relatively easy to describe computationally, they are involved in epoxide opening, and they provide a valuable model for higher substituted titanocenes. The binding enthalpies of **7**−**11** relative to those of the **5a*THF** complex are summarized in Scheme 5.

Scheme 5. Epoxides Investigated Computationally and Their Complexation Energies by Cp_2TiCl (**5a**) Relative to Those of THF



Replacement of THF from **5a** by **7**−**9** is thermodynamically favorable. This is in line with the experimental observation that mono and cis-1,2-disubstituted epoxides react swiftly with titanocene complexes in THF. However, this situation changes markedly for **10** and **11**. In both cases THF replacement is thermodynamically disfavored. These epoxides are nevertheless rapidly opened by **5a**, and hence both epoxide and THF binding must be considered reversible and fast. The 1,1-disubstitution pattern of **10** and **11** constitutes the reason for this difference as can be inferred from the structures of their Cp_2TiCl complexes that are shown in Figure 5.

The hydrogen atom at the substituted carbon of the epoxide in **8** cannot be replaced with a methyl group without causing geometrical changes in the binding of the epoxide. A rotation by 90° is necessary to enable the less favorable binding. Interestingly, however, the Ti−O bond is slightly longer in **5a*8** than in **5a*10**.

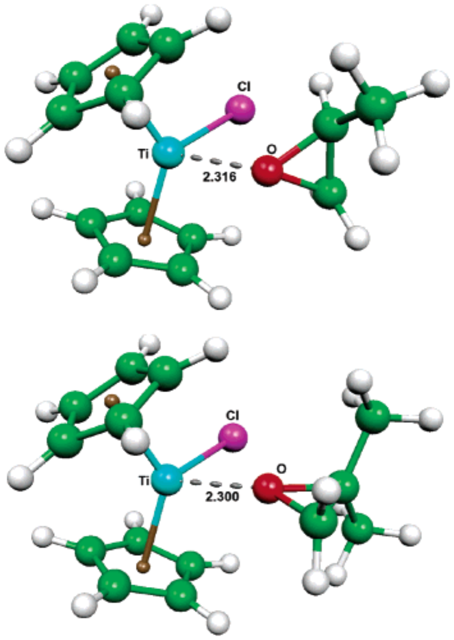
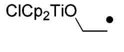
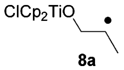
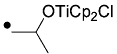
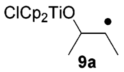
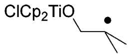
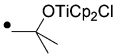
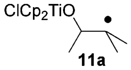
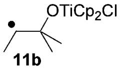


Figure 5. Structure (BP86/TZVP) of the **5a** complexes of **8** (top) and **10** (bottom). Distances in angstrom.

Table 3. Activation and Reaction Energies of the Epoxide Complexes **5a*7**−**5a*11** in kcal mol^{-1}

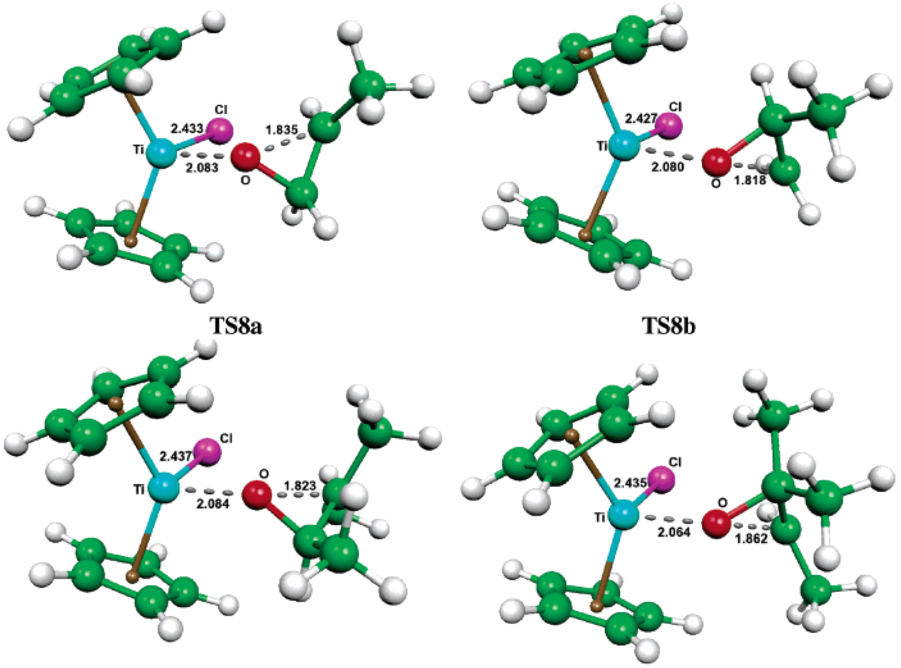
Product	ΔE	$\Delta E^{\ddagger}$	Substrate	$\Delta E^{\ddagger}$	ΔE	Product
 **7a**	-4.1	8.7	**5a*7**	-	-	-
 **8a**	-4.0	8.2	**5a*8**	9.4	-1.8	 **8b**
 **9a**	-1.8	8.8	**5a*9**	-	-	-
 **10a**	-8.5	7.0	**5a*10**	9.0	-1.3	 **10b**
 **11a**	-4.9	8.7	**5a*11**	10.3	+0.7	 **11b**

These differences in the geometry and energy of substrate binding are general. As for **5a**, binding of **10** by Zn−**3** is energetically disfavored compared to that of (*R*)-**8** or (*S*)-**8**. At the same time **10** is rotated by 90° compared to both enantiomers of **8**. These complexation studies provide important quantitative and qualitative insights into the initiation of epoxide opening mediated by Cp_2TiCl or substituted titanocenes. The properties of the other predominant species in solution $(Cp_2TiCl)_2$ are even more relevant to most synthetic applications.

As expected, the calculations with the closed structure of $(Cp_2TiCl)_2$, that possesses no vacant coordination site, did not provide a stable complex with **8**. However, the already mentioned half-open structure **5b** was found to readily form a complex with **8**. In this complex, the second Cp_2TiCl unit is pointing away from the other titanocene and the chlorine atom of the second Cp_2TiCl unit has no contact with the first Ti center. Thus, the complexes of **5a** and **5b** with **8** are structurally surprisingly similar in the vicinity of **8**. This is also the case for the complex of **10** with **5b**. The epoxide is rotated by 90° exactly as in the complex with **5a**.

Discussion of the Energies of Activation and the Transition Structures. We turned our attention to studying the key step of the overall reaction, the epoxide opening through the homolytic substitution reaction, next. For the same reasons as above, the reactions of the Cp_2TiCl complexes of **7**−**11** were studied first. The activation energies of ring opening, $\Delta E^{\ddagger}$, are summarized in Table 3. They are in the range of 7.0−10.3 kcal mol^{-1} and indicate that radical generation should be facile at room temperature, in agreement with the experimental results. Formation of the higher substituted radicals is kinetically favored.

In the transition structures the spin density on the evolving radical center is typically lower (approximately 0.3) than on titanium (approximately 0.7). Thus, radical stability is most likely not the only contribution to the control of regioselectivity of epoxide opening. As the other important factor, we suggest steric interactions between the epoxide and the cyclopentadienyl ligands. This will be especially relevant when two radicals with the same substitution pattern or radicals with relatively low



TS8a **TS8b**

TS11a **TS11b**

Figure 6. Transition structures of the opening of **8** and **11**.

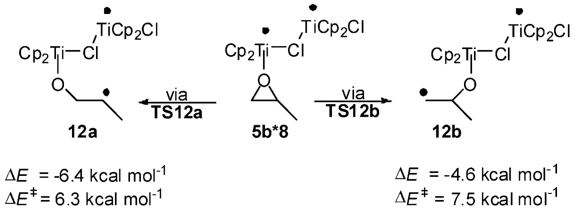
stability differences, such as primary and secondary radicals or secondary and tertiary radicals, are formed during ring opening.

Inspection of the transition structures of the opening of **5a*8**, **TS8a** and **TS8b**, that are shown in Figure 6 as representative examples, and of the opening of **5a*11**, **TS11a** and **TS11b** provides substantiation for this hypothesis. In **TS8a** relatively close contacts between the cyclopentadienyl ligands and **8** were observed. Both H_{cis} and H_{trans} are placed at a distance of 2.39 Å (and the CH_3 group at more than 2.9 Å) from the cyclopentadiene. In **TS8b** H_{cis} is placed at 2.40 Å from the ligand and the CH_3 group at only 2.30 Å. Thus, in addition to the stability difference of the forming radicals, the larger CH_3 group gets into closer contact with the ligand during the less favored opening to the primary radical.

A similar situation arises in the opening of **11**. In **TS11a** only the hydrogen atom and the methyl group attached to the secondary carbon are positioned at a close distance to the ligands (2.23 and 2.35 Å), whereas in **TS11b** all three methyl groups are in close contact to the cyclopentadienyl ligands. As in the case of **TS8a**, **TS11a** is therefore electronically and sterically favored. The stability difference of the transition structures due to the steric differentiation should be increased even further, when the cyclopentadienyl ligands contain properly positioned bulky alkyl substituents. Support for this hypothesis and its applications in stereoselective catalysis is presented in the context of the experimental results.

These findings are highly pertinent for the discussion of the reactions of substituted titanocenes. However, for **1** and the Cp_2TiCl_2-derived catalysts, that are most frequently used in synthetic applications reactions of epoxide, complexes of the highly Lewis acidic dimers may constitute the prevalent (depending on the exact concentrations employed) and more reactive species in solution. Our calculations for the complex **5b*8** are summarized in Scheme 6.

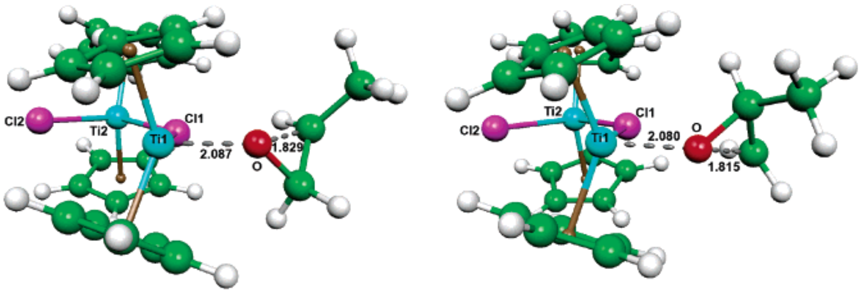
Scheme 6. Transition Structures, Activation, and Reaction Energies of the Opening of **8** by **5b**



The activation energies for the opening of **5b*8** were calculated to be 6.3 kcal mol^{-1} for the formation of **12a** and 7.5 kcal mol^{-1} for the formation of **12b**. Both values are about 2 kcal mol^{-1} lower than for the corresponding complex **5a*8**. Even though the calculations do not include solvent effects, they predict a substantially higher reactivity of the **5b**-derived epoxide complexes exactly as observed experimentally. This can be explained by a larger stabilization of the strongly Lewis acidic half-open dimer through the developing charge in the transition structure. In **TS12a** and **TS12b** the Cl of the second Cp_2TiCl group is pointing away from the epoxide that is being opened as shown in Figure 7. As a consequence the geometries of the transition structures' half-open epoxide complexes are very similar to **TS8a** and **TS8b**.

This is also reflected in identical stability differences between **TS12a** and **TS12b** and **TS8a** and **TS8b**, respectively. In the case of an irreversible epoxide opening identical regioselectivities are expected for **5a** and **5b**. Therefore, the Cp_2TiCl-derived transition structures, that are much easier to calculate, can be used as excellent models for the computationally more demanding $(Cp_2TiCl)_2$-derived structures.

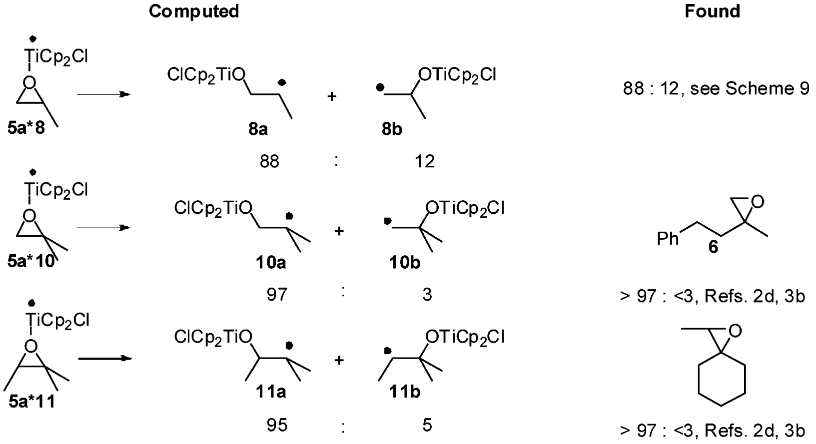
The reliability of the computational results can be qualitatively estimated by comparing predicted and experimentally deter-



TS12a **TS12b**

Figure 7. Transition structures (BP86/TZVP) of the opening of **8** with **5b**. Distances in angstrom. (Ti−Cl distances in angstrom are the following. **TS12a**: Ti1−Cl1 2.558, Ti2−Cl1 2.699, Ti2−Cl2 2.454, Ti1−Cl2 4.313. **TS12b**: Ti1−Cl1 2.553, Ti2−Cl1 2.687, Ti2−Cl2 2.454, Ti1−Cl2 4.317.)

Scheme 7. Computed and Observed Regioselectivity of an Irreversible Opening of Various Epoxides



mined relative values of the regioselectivity of epoxide opening. For an irreversible ring opening reaction the calculations predict ratios of 88:12 for **8a** and **8b**, 97:3 for **10a** and **10b**, and 95:5 for **11a** and **11b** at 25 °C as shown in Scheme 7. In the case of a swift radical trapping the same ratios are expected in the final products, also.

Discussion of the Reaction Energies of Ring Opening. Even though the kinetic measurements suggest that epoxide opening is kinetically controlled, analysis of the reaction energies of ring opening provides additional and essential insight into important features of this process. Epoxide opening is exothermic, and the formation of the higher substituted radicals is thermodynamically favored in all cases investigated as summarized above in Table 3.

Quite surprisingly, the differences in the reaction energies of a number of β-titanoxy radicals do not correlate with the stability differences of related free alkyl radicals based on bond dissociation energies (BDE).[28] For example, **7a** and **8a** are formed with about the same reaction energy ($\Delta E \approx -4.0$ kcal mol^{-1}) from their Cp_2TiCl complexes, even though secondary radicals are more stable than primary radicals by approximately 3 kcal mol^{-1} based on their BDE. This must be caused by steric interactions with the cyclopentadienyl ligand in **8a**, which fully counterbalances the radical's increased stability. A similar trend of product stability is observed in the generation of the radicals **10b** and **11b**.

The formation of **10a** is more favorable by 4.5 kcal mol^{-1} compared to **8a**. This is even higher than the typical stability difference between a tertiary and a secondary radical. Generation of the looser structure of **10a** releases some of the energy associated with the less favorable complexation in **5a*10**. Another strong indication of the pertinence of steric effects is obtained from the energy of ring opening of **9**. Even though a secondary radical is formed as in the case of **8**, the energy of ring opening is higher by about 2 kcal mol^{-1}. This is due to relatively strong interactions of the additional methyl group with the cyclopentadienyl ligands.

For the dimer **5b** the opening of **8** was investigated computationally (Scheme 6). The reaction energies of ring opening to **12a** and **12b** are −6.4 and −4.6 kcal mol^{-1}, respectively, and thus about 3 kcal mol^{-1} more favorable than for **5a*8**. This can be explained by a higher stabilization of the more Lewis acidic dimer through the negatively charged oxygen. The stability differences between **12a** and **12b** are only slightly lower than for **8a** and **8b**.

An important mechanistic perspective arises from the low energy of activation and low energy of formation of the primary radicals **8b** and **10b** and the secondary radicals **8a**, **9a**, and **11b**. The ring closure of these β-metaloxy radicals to the initial titanocene epoxide complexes should become possible in the

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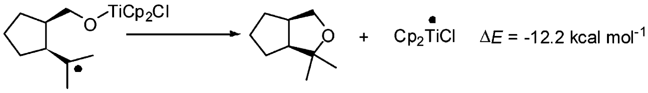
(28) See for example: (a) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *32*, 493−532. (b) Rüchardt, C.; Beckhaus, H.-D. *Top. Curr. Chem.* **1985**, *130*, 1−22. (c) Bordwell, F. G.; Zhang, X.-M. *Acc. Chem. Res.* **1993**, *26*, 510−517. (d) Brocks, J. J.; Beckhaus, H.-D.; Beckwith, A. L. J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935−1943. (e) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263. (f) Zipse, H. *Top. Curr. Chem.* **2006**, *263*, 163−189 and references therein. For an interesting discussion concerning radical stabilization, see: (g) Coote, M. L.; Pross, A.; Radom, L. *Org. Lett.* **2003**, *5*, 4689−4692. (h) Gronert, S. *J. Org. Chem.* **2006**, *71*, 1209−1219. (i) Gronert, S. *J. Org. Chem.* **2006**, *71*, 7045−7048.

absence of efficient radical traps. As demonstrated below, we have indeed been able to obtain the very first experimental evidence for this hypothesis of a reversible epoxide opening.

In general, the reaction energies of ring opening are surprisingly low when considering the release of the oxirane's ring strain and the formation of the strong titanium−oxygen bond. We suggest that the difference in stability between the titanium-centered and carbon-centered radical is responsible for these low values. Apparently, the high stability of the metal-centered radical almost compensates the loss of ring strain and the favorable formation of the titanium−oxygen bond.

This suggests that cleavage of aziridines or even oxetanes, that are less strained than epoxides, with Cp_2TiCl will be difficult, if not impossible. Moreover, it should be feasible to prepare relatively unstrained rings through a homolytic substitution reaction of titanium−oxygen bonds by radicals. This has indeed been observed by us for tetrahydrofurans,[3k,m] as shown in Scheme 8, and later by others, also.[2k,29] The energy of formation of the *cis*-bicyclo[3.3.0] system was calculated to be exothermic by about 12 kcal mol^{-1}.

Scheme 8. Tetrahydrofuran Formation via Homolytic Substitution

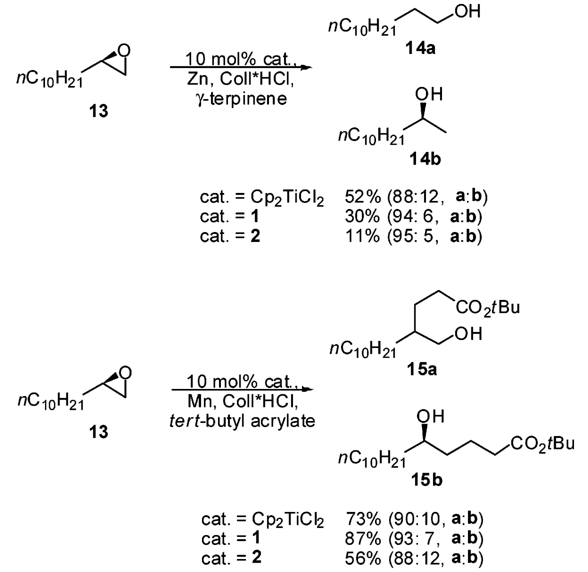


This ring closure is mechanistically related to the alkoxylation of Mn−O and Cr−O bonds via radicals that is discussed as one of the key steps of the Mn(salen) and Cr(salen)-catalyzed epoxidations.[10] It is even reminiscent of the postulated oxygen rebound step of the P450 enzymes for the hydroxylation of radicals.[12]

The titanocene-catalyzed reductive epoxide opening constitutes the microscopic reversal of the ring-forming step of the epoxidations. Thus, in homolytic substitution reactions involving metal−oxygen bonds a subtle interplay between the stability of the metal- and carbon-centered radicals, the metal−oxygen bond strength, and the size of the rings formed or broken is operating.

Synthetic Studies. The electrochemical, kinetic, and computational investigations have provided a wealth of useful mechanistic information and predictions about the outcome of epoxide opening. In the following sections we describe our efforts aimed at verifying these predictions, at understanding and designing stereoselective reactions of enantiomerically pure catalysts with enantiomerically pure substrates, and at the development of the first reversible epoxide openings. To confirm the predicted regioselectivities, the reactions of **13**, a nonvolatile substitute of **8**, were carried out with Cp_2TiCl_2, **1**, and **2**, using the hydrogen atom donor γ-terpinene as reducing agent or *tert*-butyl acrylate as radical trap as shown in Scheme 9.

Scheme 9. Selectivities in the Opening of **13** with the Catalysts Cp_2TiCl_2 and **1**−**2**



The regioselectivities observed with Cp_2TiCl_2 are in excellent agreement with the predicted values and independent of the reducing/trapping agent. Thus, our mechanistic proposal of an irreversible ring opening obtained from the kinetic studies is strongly supported for the Cp_2TiCl_2-derived catalysts. The observation that no substantial amounts of polymers were obtained from the reactions involving *tert*-butyl acrylate suggests that even under the catalytic conditions epoxide opening constitutes the slowest step of the overall reaction. Thus, reductive trapping of the enoyl radical generated through addition to the acrylate, that is favored by polar effects, seems to be substantially faster than the disfavored polymerization of the acrylate.[2b,3n] Note that collidine hydrochloride serves as proton donor to liberate the Ti(IV) species from the ionic products formed.

The substituted catalyst **1** resulted in a slightly but noticeably higher selectivity of ring opening as expected if selectivity is influenced by steric factors in the transition states. However, in the γ-terpinene case, the isolated yields are too low to be synthetically useful. Catalyst **2** performs distinctly worse as already suggested by the kinetic experiments. Clearly, tertiary alkyl substitution is not suitable for an improved performance of the catalytic reaction.

A more powerful approach to the understanding of the importance of steric effects in the ring opening of epoxides is constituted by the reaction of enantiomerically pure substrates and catalysts. In these cases, diastereomeric epoxide titanocene complexes are formed that may display differing reactivity profiles. In this respect, ring opening of (*R*)-**13** with both enantiomers of Zn−**3** in the presence of γ-terpinene or *tert*-butyl acrylate leads to instructive results. Matched and mismatched cases of regioselectivity were observed as expected for an irreversible course of the reactions as shown in Scheme 10. Gratifyingly, in the matched cases complete selectivity of epoxide opening was combined with higher yields of the products.

An interesting outcome was observed for the mismatched cases. The ratio of primary to secondary alcohols in the products depended noticeably and reproducibly on the radical trap employed. We suggest that a closure of the intermediate primary radical is faster than its trapping, and thus epoxide opening of **13** to the primary radical becomes reversible. The approach of trapping agents such as γ-terpinene is hindered as the radical center is positioned in the sterically blocked environment of the catalyst's pocket. Considering that the ring opening of

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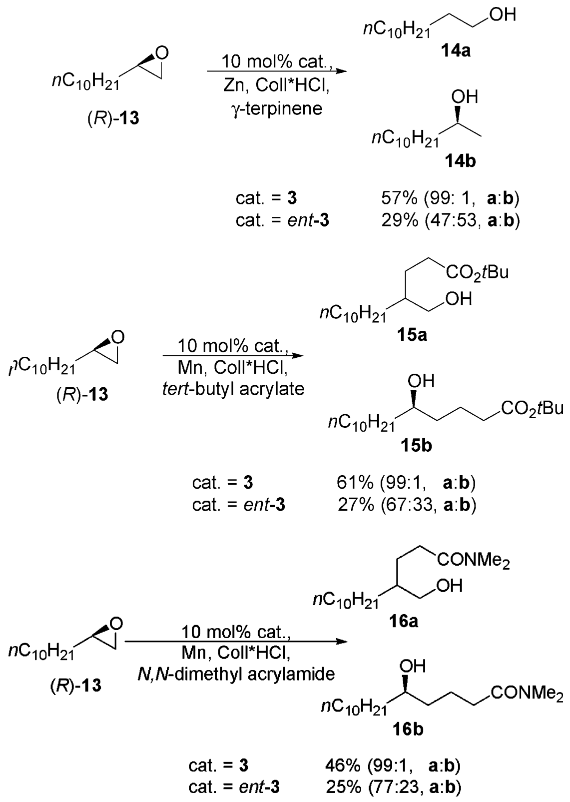
(29) (a) Trost, B. M.; Shen, H. C.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3943−3947. (b) Trost, B. M.; Shen, H. C.; Surivet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 12565−12579. (c) Leca, D.; Song, K.; Albert, M.; Goançalves, M. G.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Synthesis* **2005**, 1405−1420.

Scheme 10. Matched and Mismatched Selectivity in the Opening of (*R*)-**13** by **3** and *ent*-**3**



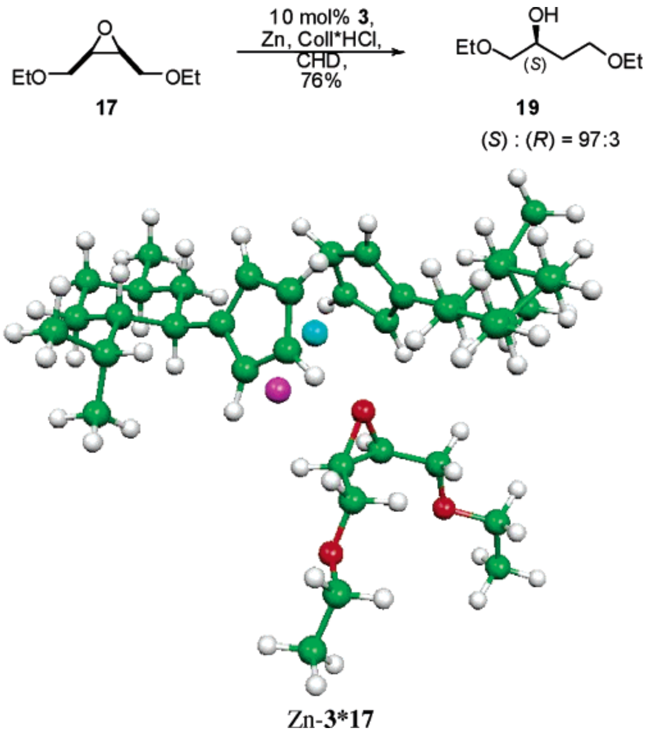
monosubstituted epoxides to primary radicals is only just thermodynamically favorable and the activation energies of ring opening are low (Table 3), this ring closure should not constitute a problem thermodynamically or kinetically.

While these mismatched cases of ring opening provide the first reliable hints for a reversible epoxide opening, the analysis of the results is somewhat complicated by the presence of both electronic and steric effects on the regioselectivity of the overall transformation. To exclude the influence of electronic contributions on the regioselectivity and reversibility of ring opening, we investigated the reactions of two cis-1,2-disubstituted epoxides, denoted meso-epoxide **17** and **18**, featuring a smaller and a large substituent.

Meso-epoxides constitute the easiest starting point for a study of the steric control of ring opening. Both substituents of the epoxide are identical, and the reactions are not complicated by kinetic resolutions. An example of our highly enantioselective opening of meso-epoxide **17** is shown in Scheme 11 together with the epoxide catalyst complex Zn−**3*17**.[3d,i]

The highly enantioselective preparation of **19** amply demonstrates the validity of our concept of steric control in the absence of an electronic preference for ring opening. A qualitative explanation for the high selectivity can be derived by a correlation between the substrate titanocene complex Zn−**3*17** and the transition structures as already carried out above for **TS8a** and **TS8b**. Breaking of the left-hand C−O bond in Zn−**3*17** results in an increased and energetically unfavorable interaction of the right-hand $CH_2OCH_2CH_3$ group with the ligand compared to the complex. In this manner (*R*)-**19** will be formed after reduction and protonation.

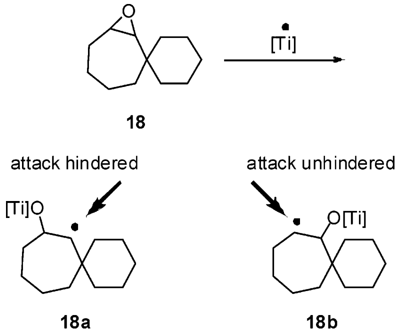
Scheme 11. Enantioselective Opening of meso-Epoxide **17** with **3** and Structure of Zn−**3*17**



Breaking of the right-hand C−O results in a diminishing of the steric interactions between the right-hand $CH_2OCH_2CH_3$ group and the ligand during the preferred formation of (*S*)-**19**. Thus, the experimentally observed formation of (*S*)-**19** is readily explained by our simple model of minimizing steric interactions.

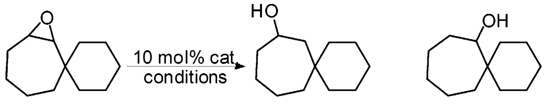
Finally, we investigated the cis-1,2-disubstituted epoxide **18** with two substituents displaying distinctly differing steric bulk. This was done primarily with the goal of understanding the interactions of the sterically demanding cyclohexyl group with the ligands of Zn−**3**. An additional point of interest, that is also shown in Scheme 12, arises from the bulky substituent of **18**. Due to this shielding reactions of the radical with sterically demanding radical traps may become particularly slow. Therefore epoxide opening could become reversible.

Scheme 12. Issues of Reactivity in the Opening of **18** ([Ti] = Cp_2TiCl or Zn−**3**)



The results of our investigations with Cp_2TiCl_2 and **3** as catalysts and CHD and the commercially available γ-terpinene as hydrogen atom donors are summarized in Scheme 13. With the combination of Cp_2TiCl_2 and CHD the observed regioselectivity (4.7:1 in favor of **20**) is in line with a minimization of the interactions of the cyclopentadienyl ligand with the cyclohexyl group. However, matters are more complicated as the regioselectivity markedly depends on the hydrogen atom donor

Scheme 13. Opening of **18** by Cp_2TiCl and **3**



	18	**20**	**21**
cat = Cp_2TiCl_2; Zn, 1.5 Coll*HCl, CHD		47	10
cat = Cp_2TiCl_2; Zn, 1.5 Coll*HCl, γ-terpinene		37	23
cat = **3**; Zn, 1.5 Coll*HCl, γ-terpinene		82 ee < 10	<1

employed. With the sterically more demanding γ-terpinene[22] the ratio of **20** to **21** was reduced to 1.6:1. The sterically hindered radical **18a** is reduced slower than **18b** by the latter H atom donor. These findings exclude an irreversible ring opening in this specific situation and strongly support a reversible epoxide opening.

However, this situation changes completely with catalyst **3**. Under all conditions **20** was obtained as the sole product of an irreversible epoxide opening. Alcohol **20** was obtained in almost racemic form (e.r. < 60:40). Thus, **3** does not constitute an efficient catalyst for the resolution of cis-1,2-disubstituted epoxides. Moreover, the steric interactions of either enantiomer of the bulky catalyst with the cyclohexyl group are by far more important than any other factor including the slow reduction of the sterically hindered radical **18a**. Epoxide opening appears to be irreversible. Thus, it is in principle possible to switch between an irreversible and reversible epoxide opening by properly adjusting the steric demand of the catalyst, the radical's substituents, and the trapping reagent.

Conclusion

In summary this study has established the structure of a number of Ti(III) catalysts in solution and the kinetics of the titanocene-mediated epoxide reduction. In particular, the distribution of monomeric and dimeric Ti(III) species was found to be strongly affected by the exact steric conditions. The kinetic measurements strongly suggest an irreversible epoxide opening in the presence of efficient radical traps. These results were used as the experimental basis for the calculation of the structure and energy of the titanocene(III)−epoxide complexes, the transition states of ring opening, and the product β-titanoxy radicals. For steric reasons 1,1-di- and higher substituted epoxides bind differently than mono- and 1,2-disubstituted epoxides. The transition structures and activation energies suggest that both the stability differences of the forming radicals and steric interactions between the catalysts' ligands and the substrate are essential in controlling the regioselectivity of ring opening. The relevance of the computational study is highlighted by the excellent agreement between the predicted and experimentally observed regioselectivities.

The use of Kagan's catalyst **3**[13] in the opening of monosubstituted and cis-1,2-disubstituted epoxides has led to highly selective and preparatively useful epoxide openings on several occasions that can be readily rationalized with our steric model of controlling the regioselectivity of ring opening. In the mismatched cases the first examples of reversible epoxide openings were observed. With cis-1,2-disubstituted epoxides containing one bulky and one small substituent the course of the epoxide opening depends on the catalyst employed. Our results provide a unique link between the mechanism of the titanocene-mediated epoxide opening and that of epoxidation reactions featuring β-metal oxy radicals,[10] and of hydroxylation reactions featuring C−H activation steps by organometallic reagents[11] or the P450 enzymes.[12]

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Supporting Information Available: Details of the cyclic voltammetric studies, atomic coordinates of all structures, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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