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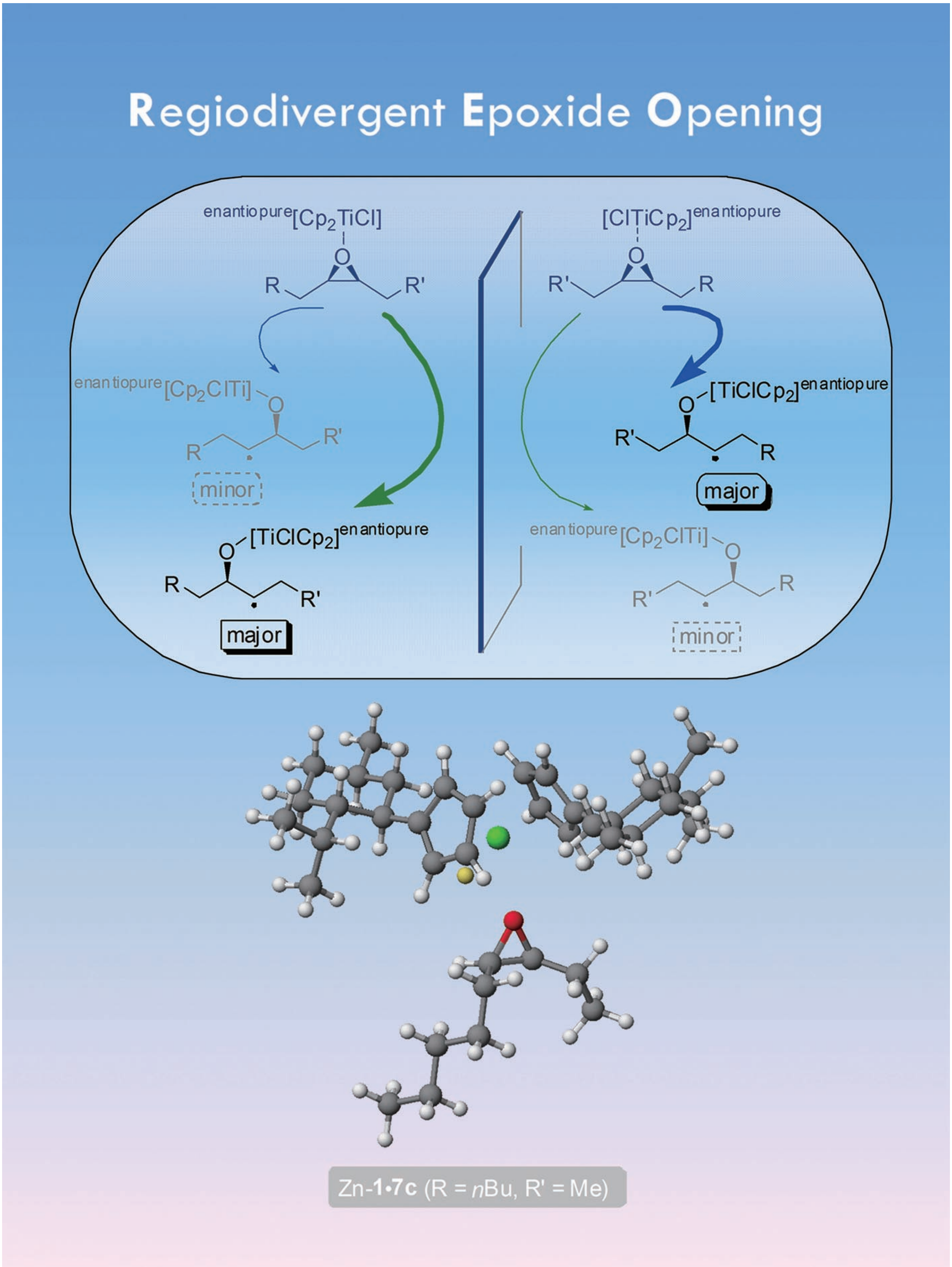

Regiodivergent Epoxide Opening: A Concept in Stereoselective Catalysis beyond Classical Kinetic Resolutions and Desymmetrizations

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Abstract: An approach to highly regiodivergent epoxide openings (REOs) is presented. The very popular kinetic resolutions of epoxides and openings of *meso*-epoxides constitute subclasses of such REOs. REOs are attractive for parallel resolutions, double asymmetric reactions of enantiomerically enriched epoxides, and for semisynthetic applications in the functionalization of natural products. They have been notoriously difficult to realize by means of S_N2 mechanisms. Our titanocene-catalyzed radical REO addresses this issue by decoupling epoxide opening and radical trapping and is firmly based on a mechanistic study of the reductive epoxide opening.

Keywords: catalysis · enantioselectivity · epoxides · radical reactions · regioselectivity

Epoxide Opening by Nucleophilic Substitution: Limitations Arising from the S_N2 Mechanism

Epoxides are amongst the most versatile compounds in organic chemistry. This is because they are not only important synthetic endpoints,[1] but also key intermediates for further manipulations.[2] Due to the high ring strain of oxiranes (about 27 kcal mol^{-1}) they are "spring loaded" for a number of interesting ring-opening reactions. In the past, this field has been heavily dominated by nucleophilic substitution reactions.[3] The usefulness of epoxides in S_N2 reactions has been expanded even further by the development of transition-metal-catalyzed desymmetrizations of *meso*-epoxides[3] and kinetic resolutions[3] mainly of monosubstituted and 1,1-disubstituted epoxides. In this manner a wide range of important 1,2-difunctionalized compounds have been obtained with high enantio- and complete diastereoselectivity through the back-side approach of the nucleophile. Two of the many excellent examples of catalytic epoxide openings are shown in Scheme 1.[3f,g]

Despite the resounding success especially of these catalytic processes, important limitations are caused precisely by the mechanistic key aspect of all S_N2 reactions. The displacement of the leaving group is sensitive to both the substitution pattern of the involved carbon atom and the bulk of the nucleophile employed. Hence a number of potentially useful reactions are kinetically hindered or even outright impossible.

Two simple examples underline these restrictions: First, intermolecular epoxide openings by means of S_N2 reactions usually do not occur at the higher-substituted carbon atom. Second, reactions of epoxides with sterically demanding substituents are frequently too slow to be preparatively useful.

Another more subtle limitation has emerged more recently. It has, to date, not been possible to observe the high regioselectivities obtained in the enantioselective opening of *meso*-epoxides in reactions of other epoxides. Surprisingly, this is even so for the most similar case, *cis*-1,2-disubstituted epoxides with two sterically and electronically unbiased groups.[4] The two examples shown in Scheme 2 highlight the problems. It seems hard to combine a high regioselectivity of epoxide opening with a high reactivity of both enantiomers of the substrate even with today's most successful catalysts. Hence, either rather unselective reactions or kinetic resolutions are observed.

Nevertheless, such reactions are, in principle, extremely attractive for applications in the synthesis of complex molecules and also very interesting conceptually. Here, we outline these synthetic perspectives and propose the title "regiodivergent epoxide opening" (REO) for such transformations if ring-opening constitutes the stereodifferentiating event. In a more general context, for racemic substrates such processes have been termed "parallel resolutions" or "divergent reactions of racemic mixtures".[5] A mathematical treatment has been provided.[5c] A complementary reaction

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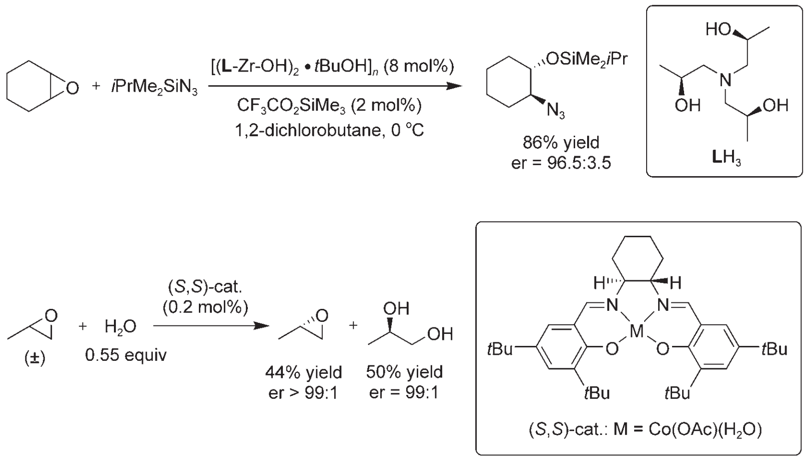
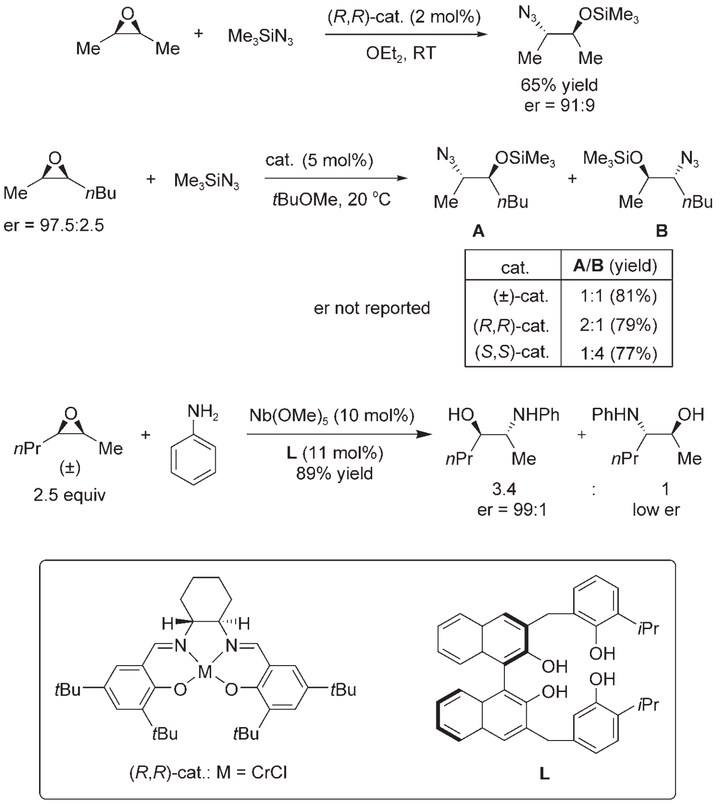


Scheme 1. Catalyzed epoxide openings by means of S_N2 reactions.[3f,g]

of vinyloxiranes with dialkylzinc reagents has been reported by Pineschi and Feringa.[6] Reductive elimination from an allylcopper complex constitutes the stereodifferentiating step and not the ring opening that we concentrate on here.

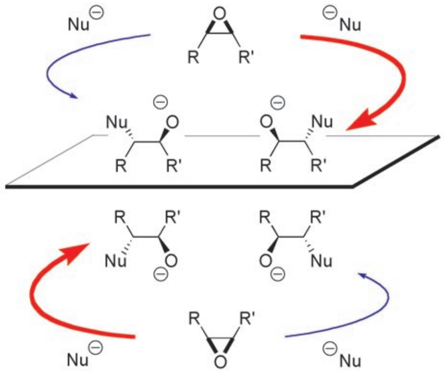


Scheme 2. Catalytic regioselective epoxide opening of an enantiomerically enriched substrate versus *meso*-epoxide opening.[4]

Regiodivergent Epoxide Opening (REO): Mechanistic Implications, Synthetic Potential, and Aspects of Catalyst Design

The analysis of a typical REO proceeding by means of a classical S_N2 mechanism is depicted in Scheme 3. REOs are, however, by no means confined to nucleophilic substitutions. In principle, any method for ring opening can be applied.[2]

Before entering the mechanistic discussion, we note that kinetic resolutions and openings of *meso*-epoxides constitute subclasses of the REO. In the former case, only one of the substrates reacts and in the latter case, the identity of the substituents (R′=R) reduces the analysis to the reaction of only one substrate. For the reaction of a racemic substrate, efficient REOs result in parallel resolutions. Both enantiomers are turned over, preferentially with similar rates. The products are formed by the major pathway of one substrate and the minor pathway of the other substrate and, therefore, with high enantiomeric purity.



Scheme 3. Concept of the catalytic regiodivergent epoxide opening (REO) for S_N2 reactions.

The use of enantiomerically enriched substrates in REOs leads to extremely attractive double asymmetric processes not possible with *meso*-epoxides. The major product is obtained through the dominant opening of the major enantiomer and the minor pathway of the minor enantiomer and hence with much higher optical purity than the substrate. This scenario is especially appealing when the synthesis of compounds with very high enantiomeric excess is required. The minor products are formed with low enantioselectivity.

Even in the case of enantiomerically pure substrates, the method is quite valuable. Semisynthetic modifications of epoxide-containing natural products seem especially well suited in this respect. By employing either enantiomer of the catalyst it should be possible to obtain two regioisomeric functionalized derivatives of the natural products with high selectivity, respectively.

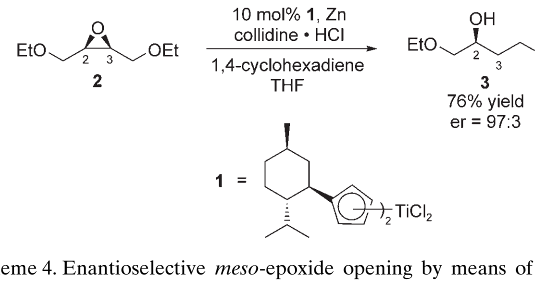
In contrast to the opening of *meso*-epoxides, the design of efficient REO catalysts must address two issues and is thus more complex. Both enantiomers of the substrate have to bind with similar efficiency to the catalyst and must then be opened with high and opposite regioselectivity. To serve this dual purpose, an efficient means for the differentiation of the heterotopic C–O bonds has to be provided that is at the same time relatively insensitive to the steric demand of the nucleophile and of the epoxide substituents. As already shown in Scheme 2, this seems hard to realize in S_N2 reactions. We, therefore, decided to initiate a program towards the development of efficient REOs that does not rely on nucleophilic substitution reactions but rather on reductive epoxide opening by means of electron transfer from titanocene(III) complexes.[7] The mechanistic key features of this reaction will be described briefly in order to be able to develop our concept of catalyst design.

Reductive Epoxide Opening by Electron Transfer from Titanocene(III) Reagents

The catalytic reductive epoxide opening by electron transfer from titanocenes has emerged as an attractive alternative to the classical nucleophilic substitution strategies.[8] It combines the well-established advantages of radical chemistry[9] with a regioselectivity of ring opening opposite to the nucleophilic substitutions. This has lead to a number of interesting and unusual applications in the synthesis of complex molecules.[10] To date, other low valent metal complexes have performed less satisfactory.[11]

Mechanism of the Reductive Epoxide Opening: Predetermined for the REO!

Based on synthetic experience, the reductive epoxide opening suggests itself as highly attractive for the development of REOs for three major reasons. First, the course of ring opening can be controlled by the catalyst as we have demonstrated in our enantioselective opening of *meso*-epoxides with Kagan's Zn-reduced **1**[12] to yield **3** from **2**, as shown in Scheme 4.[13] Second, the ring-opening event, that is, the electron transfer from the titanocene catalyst, is decoupled from the trapping of the generated radical. Thus, the problems encountered through the limitations of the S_N2 reactions do not necessarily apply for the reductive epoxide opening. Third, **1**, to date, the most efficient catalyst in our enantioselective opening of *meso*-epoxides does not induce kinetic resolutions.[14]



Scheme 4. Enantioselective *meso*-epoxide opening by means of electron transfer (ET).

A study of the mechanism of the reductive epoxide opening that we carried out in cooperation with the groups of Kim Daasbjerg in Aarhus (Denmark) and Stefan Grimme in Münster (Germany) provided the detailed insights that convinced us to pursue the titanocene-catalyzed REO.[15]

The electrochemical studies from Aarhus established that for Zn-reduced solutions of titanocenes with sterically demanding substituents, monomeric Ti^{III} complexes are predominant in solution. These species also constitute the active species for epoxide opening and not dimers as in the case of Zn–Cp_2TiCl_2. The rate of the overall reduction is independent of the presence of a radical trap, such as 1,4-cyclohexadiene. Thus, ring opening constitutes the rate-controlling step of the overall process and is under kinetic control exactly as desired for our REO.

On the basis of these results, the reaction mechanism was investigated on a molecular level by computational chemistry in Münster. For [Cp_2TiCl] and its dimer, the activation and reaction energies of ring opening and the structures of all pertinent intermediates, transition states, and products were determined by DFT calculations. Moreover, the complexation mode of a number of epoxides by various titanocenes including Kagan's Zn-reduced **1** was established.

A combination of two points suggests that Zn–**1** fulfills the requirements for an efficient REO catalyst in a rather promising manner and certainly in a much better way than the above-mentioned catalysts for the S_N2 reactions. First, for a number of epoxides, Zn–**1** binds both enantiomers equally well. Second, even though the catalyst's reactive site is rather loose, steric interactions between the ligands and the epoxide substituents constitute the main reason for the regioselectivity of ring opening. Surprisingly, this is not only the case for the generation of radicals from substrates with identical substitution patterns, such as *cis*-1,2-disubstituted epoxides including *meso*-epoxides, but also for the reactions of mono-, 1,1- and trisubstituted oxiranes.

These steric interactions are most easily understood when analyzing the opening of *meso*-epoxide **2** by Zn–**1** in Figure 1 first. From, the discussion it will become clear, that the same arguments apply for the REOs.

Breaking of the left-hand C2–O bond in Zn–**1·2**, the first intermediate of ring opening, results in an increased and energetically unfavorable interaction of the right-hand $CH_2OCH_2CH_3$ group with the ligand in the transition state. In this manner (*R*)-**3** would be formed after reduction.

Breaking of the right-hand C3–O bond leads to a reduction of these steric interactions. As a result, formation of (*S*)-**3** is preferred, exactly as observed experimentally. Clearly, this mechanism for controlling the regioselectivity of ring opening should also be operating with *cis*-1,2-disubstituted epoxides containing nonidentical, but sterically and electronically unbiased substituents. Combined with the fact that Zn–**1** does not induce kinetic resolutions, this strongly

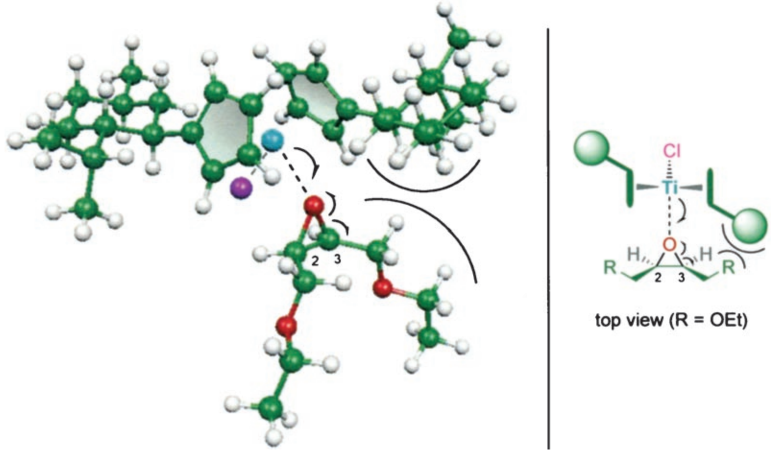
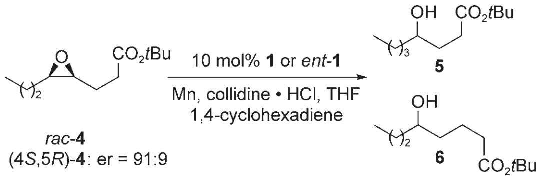


Figure 1. Structure of Zn–**1**·**2** as determined by DFT calculations with the BP functional and a TZVP basis set.

suggests that REOs with such substrates proceed efficiently. The experimental proof for this assumption will be presented next.

Synthetic Realization of the Titanocene-Catalyzed REO

We chose epoxides *rac*-**4** and (4*S*,5*R*)-**4** as substrates for our initial investigation with **1**. Both **1** and *ent*-**1** gave higher yields of readily separated **5** and **6** (84–95 %) than [Cp_2TiCl_2] (77 %, **5**/**6** 63:37) as shown in Scheme 5.[16] All results are summarized in Table 1.



Scheme 5. The first efficient titanocene-catalyzed REO.

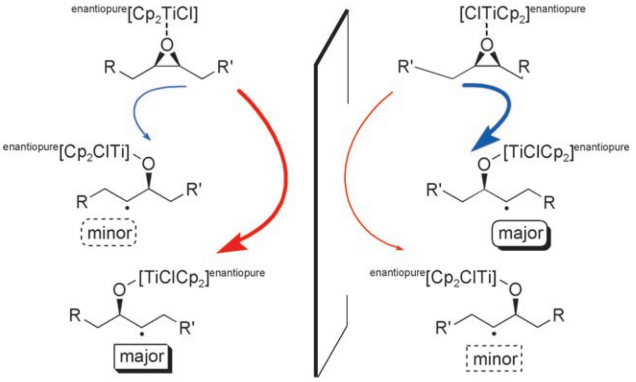
As hoped for, a rather effective parallel resolution was observed with *rac*-**4**. It should be noted that both enantiomers of **1** give similar ratios of **5** to **6**. Hence, no chelation by the ester is involved and both substituents must indeed be considered unbiased. This is, of course, important for the generality of our process. As expected, the minor isomers are formed with higher selectivity than the major products.

Table 1. REO of *rac*-**4** and (4*S*,5*R*)-**4**.

Entry	Substrate	Cat.	Yield of **5** [%]	er[a]	Yield of **6** [%]	er[a]
1	*rac*-**4**	**1**	51	88.5:11.5	44	5:95
2	*rac*-**4**	*ent*-**1**	45	9.5:90.5	42	96.5:3.5
3	(4*S*,5*R*)-**4**	**1**	13	46:54	71	99.5:0.5
4	(4*S*,5*R*)-**4**	*ent*-**1**	76	97:3	10	25:75

[a] *R*/*S* determined by comparison with authentic samples and from substrates.

Gratifyingly, the desired double asymmetric process with the enantiomerically enriched substrate (4*S*,5*R*)-**4** was also realized. With catalyst *ent*-**1**, **5** was obtained in 76 % yield with an er value of 97:3. The minor product **6** was obtained in only 10 % yield and with low enantioselectivity. With **1**, the opposite regioisomer of epoxide opening **6** was obtained as the major product in 71 % yield and, as above, with exceptionally high enantiomeric purity (99.5:0.5). Again, the minor product was formed in low yield and with low enantioselectivity. Scheme 6 provides a mechanistic rationale for the outcome of the REOs of *rac*-**4** and (4*S*,5*R*)-**4**.



Scheme 6. Mechanistic analysis of the titanocene-catalyzed REO.

According to our mechanistic study, the depicted titanocene epoxide complexes constitute the first intermediate of ring opening. The selectivity of the parallel resolution in the case of *rac*-**4** and the double asymmetric reactions with (4*S*,5*R*)-**4** is imposed by the high regioselectivity of ring opening in the complexes of both enantiomers of the epoxide with the enantiomerically pure titanocene. In this manner (4*S*,5*R*)-**4** is opened via the dominant opening of the major enantiomer and the minor pathway of the minor enantiomer. As a result, the main product is formed with much higher selectivity than the substrate.

The key difference relative to the openings by means of S_N2 reactions is constituted by the decoupling of ring opening and radical trapping. At first glance, the resulting loss of the diastereospecificity of the ring opening may be regarded as a severe disadvantage. However, we have already demonstrated that radical trapping can be highly diastereoselective with properly adjusted titanocene complexes.[13c,17] Our recently introduced modular titanocene synthesis[18] should increase the potential of this approach even further, as the catalysts can be tailored according to the specific demands of the situation.

Table 2. REO of **7**.

Entry	Substrate	Cat.	Product	Yield [%]	**8/9**[a]	er **8**[b]	er **9**[b]
1	**7a**	**1**	**8a/9a**	77	86:14	99:1	66:34
2	**7a**	*ent*-**1**	**8a/9a**	88	18:82	35:65	99:1
3	**7b**	**1**	**8b/9b**	73	82:18	99:1	43:47
4	**7b**	*ent*-**1**	**8b/9b**	76	12:88	45:55	99:1
5	**7c**	**1**	**8c/9c**[c]	82	84:16	0.5:99.5	34:66
6	**7c**	*ent*-**1**	**8c/9c**[c]	86	4:96	40:60	0.5:99.5
7	**7d**	**1**	**8d/9d**[c]	89	83:17	0.5:99.5	70:30
8	**7d**	*ent*-**1**	**8d/9d**[c]	88	12:88	50:50	0.5:99.5

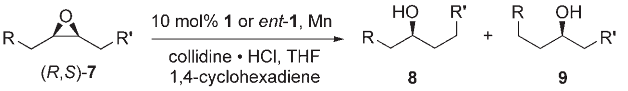
[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture; **8/9** with [Cp_2TiCl_2] was about 40:60 in all cases. [b] *R*/*S* determined from the configuration of substrates. [c] Zn was used instead of Mn; **8/9** not separated.

Table 3. REO of **10a** and **10b**.

Entry	Substrate	Catalyst	Product	Yield [%]	**11/12**[a]	er of **11**[b]	er of **12**[b]
1	**10a**	**1**	**11a/12a**	85	54:46	10:90	96:4
2	**10a**	*ent*-**1**	**11a/12a**	81	52:48	91:9	3:97
3	**10b**	**1**	**11b/12b**	77	66:34	19:81	99:1
4	**10b**	*ent*-**1**	**11b/12b**	74	80:20	65:35	10:90

[a] Determined by ^{1}H NMR spectroscopic analysis of the purified products. For [Cp_2TiCl_2]: **10a**: 72:28, **10b**: 90:10. [b] Absolute configuration not determined. Measured from products and separated lactones.

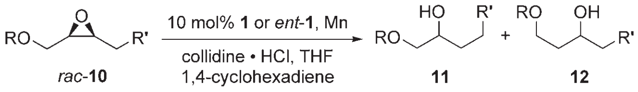
Our reaction is general and ester substitution is not necessary as summarized in Scheme 7 and Table 2 (entries 5–8). The hydroxyesters (entries 1–4) are important intermediates for the synthesis of γ- and δ-lactones.[19] By treatment of **9b** with TsOH (*R*)-4-dodecanolide,[20] a defensive secretion of beetles, was obtained (92 %) with the highest enantiomeric purity reported. From **8b** (*R*)-5-dodecanolide, a component of the odor of cheddar,[21] was obtained (96 % yield). Hence, both natural products were prepared by the action of *ent*-**1** or **1** on the same precursor, **7b**!



7a: R = *n*Bu, R' = CH_2CO_2tBu, (5*R*,4*S*):(5*S*,4*R*) = 94:6
7b: R = *n*Hexyl, R' = CH_2CO_2tBu, (5*R*,4*S*):(5*S*,4*R*) = 94:6
7c: R = *n*Bu, R' = Me, (4*R*,3*S*):(4*S*,3*R*) = 94:6
7d: R = *n*Pentyl, R' = Me, (4*R*,3*S*):(4*S*,3*R*) = 87:13

Scheme 7. REO for the synthesis of chiral alcohols.

Reactions with glycidol ethers were also carried out (Scheme 8). In these substrates, chelation of titanium constitutes an additional potential control element for the regioselectivity of ring opening. This has been demonstrated to be very important[7b] in the reactions of the Sharpless epoxides.[1a] The products of ring opening, derivatives of 1,2- and 1,3-diols are important intermediates for the synthesis of complex molecules. Our results are summarized in Table 3.



10a: R = *n*Bu, R' = CH_2CO_2tBu
10b: R = CH_2CO_2tBu, R' = Et

Scheme 8. REO for the synthesis of derivatives of 1,2- and 1,3-diols.

For simple alkylethers (entries 1–2), the possible chelation does not affect the reagent controlled course of the reaction. Thus derivatives of both 1,2- and 1,3-diols become available in high enantiomeric purity from racemic substrates similar to the reactions of *rac*-**4**. However, with two chelating groups in one substituent, a partially substrate-controlled reaction results, displaying matched and mismatched cases of selectivity of ring opening (entries 3–4).

Conclusion

We have devised the first efficient REO through our titanocene-catalyzed reductive epoxide opening. By decoupling ring opening from radical trapping, the typical disadvantages of S_N2 reactions are avoided. Our method combines a high regioselectivity of ring opening with the well established advantages of radical chemistry and should hence be of interest for many applications in the synthesis of complex molecules.

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