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Titanocene-Catalyzed Regiodivergent Epoxide Openings

Andreas Gansäuer,* Chun-An Fan, Florian Keller, and Jutta Keil
Kekulé-Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard Domagk Strasse 1, 53121 Bonn, Germany

Received December 1, 2006; E-mail: andreas.gansaeuer@uni-bonn.de

In the field of stereoselective epoxide opening a number of impressive reactions largely dominated by S_N2-type transformations have been reported.[1] The reductive epoxide opening via electron transfer from titanocenes[2,3] has emerged as an attractive alternative to these classical strategies. It combines the traditional advantages of radical chemistry with a regioselectivity of ring opening opposite to the nucleophilic substitutions and the possibility to control the course of ring opening by the catalyst.[4] We have demonstrated the relevance of the last point in our enantioselective opening of *meso*-epoxides.[5]

Here, the first example of a regiodivergent opening of sterically and electronically unbiased epoxides is described. We employ this terminology because nonracemic substrates were used, too. With racemic substrates such reactions have also been termed "parallel resolutions" or "divergent reactions of racemic mixtures".[6] A mathematical treatment of these processes has been provided.[6c] The mechanistically complementary reaction of vinyloxiranes with dialkylzinc reagents has been reported.[7] In our case the regioselectivity of ring opening is decisive. This concept could not be realized even with Jacobsen's exceptional system.[1d]

We chose epoxides **1** and **2** as substrates for our initial investigation with Kagan's complex **3** [8] (Scheme 1, Table 1). Both **3** and *ent*-**3** gave higher yields of readily separated **4** and **5** (84%−95%) than Cp_2TiCl_2 (77%, **4**/**5** = 63:37).

Our results amply demonstrate that both **3** and *ent*-**3** constitute suitable catalysts for the desired regiodivergent opening of **1** and **2**. In the case of **1**, the minor isomers **5** are obtained in high enantiomeric ratios (5:95 and 96.5:3.5). As expected, the major isomers are formed with slightly reduced selectivity. Our reaction proceeds under reagent control. Thus, **3** and *ent*-**3** provide **4** and **5** with reversed enantioselectivity.

The use of enantiomerically enriched substrates in regiodivergent epoxide openings can result in an extremely attractive double asymmetric process not possible with *meso*-epoxides. The major product should be produced in much higher enantiomeric purity than the substrate in a yield higher than the theoretical 50% for racemic substrates. Gratifyingly, this was indeed observed when employing **2** as substrate. With catalyst *ent*-**3**, **4** was obtained in 76% yield and an er of 97:3. The minor product **5** was obtained in only 10% yield and with low enantioselectivity. With **3**, the opposite regioisomer of epoxide opening **5** 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 low enantioselectivity.

Scheme 2 provides a mechanistic rationale for the outcome of the reaction of **1** and **2**. In the case of identical substituents R and R′ our analysis is reduced to only one complex. Therefore, the extremely popular opening of *meso*-epoxides (R = R′) constitutes a subclass of the more general regiodivergent ring-opening presented here.

The regioselectivity of radical generation is explained by our recently established model of steric control of epoxide opening.[9]

Scheme 1. Regiodivergent Epoxide Opening of **1** and **2**.

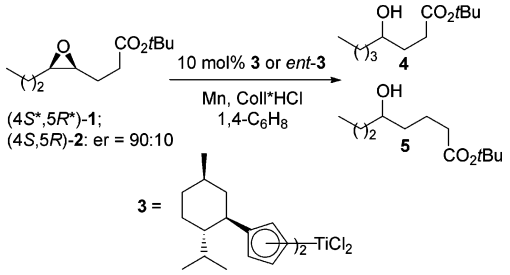
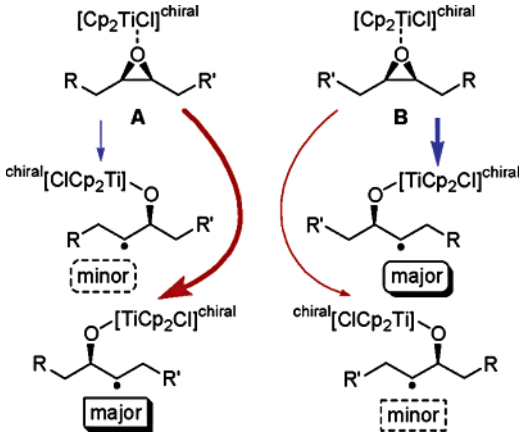


Table 1. Regiodivergent Epoxide Opening of **1** and **2** (See Supporting Information for Details)

entry	sub	cat	**4**/%	er[a]	**5**/%	er[a]
1	**1**	**3**	51	88.5:11.5	44	5:95
2	**1**	*ent*-**3**	45	9.5:90.5	42	96.5:3.5
3	**2**	**3**	13	46:54	71	99.5:0.5
4	**2**	*ent*-**3**	76	97:3	10	25:75

[a] (*R*)/(*S*) by comparison to authentic samples and from substrates.

Scheme 2. Mechanism of the Regiodivergent Epoxide Opening.



Accordingly, the diastereomeric epoxide titanocene complexes **A** and **B** constitute the first intermediates of ring opening. In the case of electronically and sterically similar substituents R and R′ as in **1** and **2**, **A** and **B** are formed and opened with similar efficacy. Otherwise a classical kinetic resolution would have been observed. The stereodifferentiating event of the overall process is constituted by epoxide opening in **A** and **B**. We have demonstrated this step to be highly enantioselective in the reactions of *meso*-epoxides.[5] For a regiodivergent opening circumstances are more complicated. Each of the two products is formed through the dominant pathway of ring opening of one complex and the minor pathway of the other complex. The minor product will be obtained in higher enantioselectivity, as indeed observed for **1**.

With enantiomerically enriched substrates the major product is obtained through the dominant pathway of the prevalent complex

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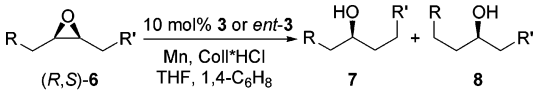
Table 2. Regiodivergent Epoxide Opening of Unbiased Substrates (See Supporting Information for Details)

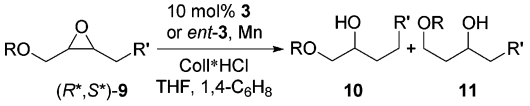


6a: R = nC_4H_9, R' = CH_2CO_2tBu, (5*R*,4*S*):(5*S*,4*R*) = 94:6
6b: R = nC_6H_{13}, R' = CH_2CO_2tBu, (5*R*,4*S*):(5*S*,4*R*) = 94:6
6c: R = nC_4H_9, R' = CH_3, (4*R*,3*S*):(4*S*,3*R*) = 94:6
6d: R = nC_5H_{11}, R' = CH_3, (4*R*,3*S*):(4*S*,3*R*) = 87:13

entry	substrate	catalyst	product	yield/%	**7**/**8**[a]	**7**/er[b]	**8**/er[b]
1	**6a**	**3**	**7a/8a**	77	86:14	99:1	66:34
2	**6a**	*ent*-**3**	**7a/8a**	88	18:82	35:65	99:1
3	**6b**	3	**7b/8b**	73	82:18	99:1	53:47
4	**6b**	*ent*-**3**	**7b/8b**	76	12:88	45:55	99:1
5	**6c**	3	**7c/8c**[c]	82	84:16	0.5:99.5	34:66
6	**6c**	*ent*-**3**	**7c/8c**[c]	86	4:96	40:60	0.5:99.5
7	**6d**	3	**7d/8d**[c]	89	83:17	0.5:99.5	70:30
8	**6d**	*ent*-**3**	**7d/8d**[c]	88	12:88	50:50	0.5:99.5

[a] Determined by ^{1}H NMR analysis of the crude mixture; **7**/**8** with Cp_2TiCl_2 was about 40:60 in all cases (see Supporting Information). [b] (*R*)/(*S*) from configuration of substrates. [c] Zn used instead of Mn; **7** and **8** not separated.

Scheme 3. Regiodivergent Epoxide Opening for the Synthesis of Derivatives of 1,2- and 1,3-Diols



9a: R = nC_4H_9, R' = CH_2CO_2tBu; **9b**: R = CH_2CO_2tBu, R' = C_2H_5

and the minor pathway of the minor complex. This double asymmetric process results in major products with much higher enantiomeric purity than the substrate, exactly as found for **2**. Table 2 summarizes further examples of the reaction.

Our reaction is general and ester substitution is not necessary (entries 5−8). The hydroxyesters (entries 1−4) are important intermediates for the synthesis of γ- and δ-lactones.[10] By treatment of **8b** with TsOH, (*R*)-4-dodecanolide,[11] a defensive secretion of beetles, was obtained (92%) with the highest enantiomeric purity reported. From **7b** (*R*)-5-dodecanolide, a component of the odor of cheddar,[12] was obtained (96%). Reactions with glycidol ethers were also carried out (Scheme 3).

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 in the reactions of the "Sharpless" epoxides.[2b] 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.

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 **1**. 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).

Table 3. Regiodivergent Epoxide Opening for the Synthesis of Derivatives of 1,2- and 1,3-Diols (See Supporting Information)

entry	substrate	catalyst	product	yield/%	**10**/**11**[a]	**10**/er[b]	**11**/er[b]
1	**9a**	**3**	**10a/11a**	85	54:46	10:90	96:4
2	**9a**	*ent*-**3**	**10a/11a**	81	52:48	91:9	3:97
3	**9b**	**3**	**10b/11b**	77	66:34	19:81	99:1
4	**9b**	*ent*-**3**	**10b/11b**	74	80:20	65:35	10:90

[a] Determined by ^{1}H NMR analysis of the purified products. For Cp_2TiCl_2: **9a**, 72:28; **9b**, 90:10. [b] Absolute configuration not determined. Measured from products and separated lactones.

In summary, we have devised the first regiodivergent opening of unbiased epoxides that provides the ring-opened products in high enantiomeric excess from racemic and exceptionally high enantiomeric purity from enantioenriched substrates in a double asymmetric process. It constitutes a more general case of the very important enantioselective openings of *meso*-epoxides.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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