

Enantioselective Synthesis

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General, Highly Selective Synthesis of 1,3- and 1,4-Difunctionalized Building Blocks by Regiodivergent Epoxide Opening

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Dedicated to Professor Johannes Beck on the occasion of his 60th birthday

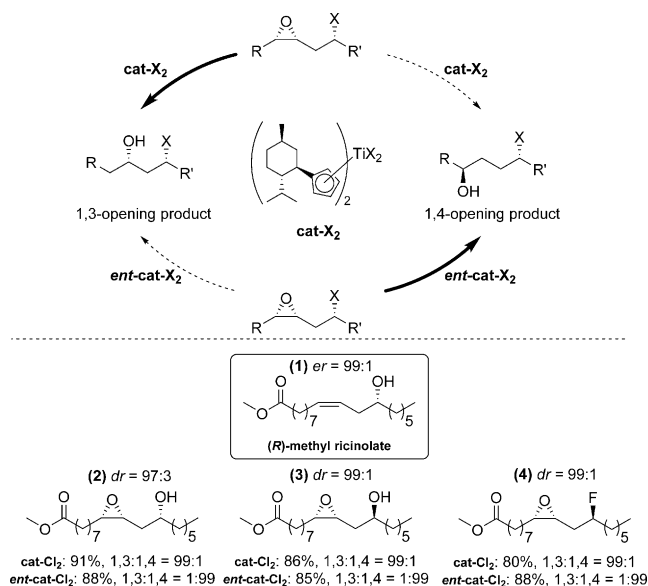
Abstract: We describe a regiodivergent epoxide opening (REO) featuring a catalyst-controlled synthesis of enantiomerically and diastereomerically highly enriched or pure syn- and anti- 1,3- and 1,4-difunctionalized building blocks from a common epoxide precursor. The REO is attractive for natural product synthesis and as a branching reaction for diversity-oriented synthesis with epoxides.

Reaction sequences that result in the generation of functional and structural diversity are highly attractive for the synthesis of specific molecules, such as natural products, or for the preparation of entire classes of substances.^[1] To this end, meeting of a number of requirements is mandatory. First, the sequence must contain a step that provides a branching point in an ideally highly selective catalyst-controlled step. Second, the preparation of the synthetic intermediates and the catalyst-controlled step must tolerate a variety of functional groups.

Here, we report a general synthetic approach to the synthesis of 1,3- and 1,4-difunctionalized molecules. These compounds are of high interest in many respects.^[2] Polyol fragments or polyol-containing building blocks are important for the synthesis of biologically active substances or natural products.^[2] Alcohols with an additional 1,3- or 1,4-halide functionality are of high potential importance for pharmaceutical applications. In this respect, it should be noted that over 20% of the approved pharmaceutical agents and more than 30% of the commercial agrochemicals contain fluorine.^[3]

Our key reaction for generating structural diversity is a regiodivergent epoxide opening (REO)^[4] of suitably functionalized epoxides, that constitutes the more general case of the desymmetrization of *meso*-epoxides.^[5] We chose epoxide (**2**) which is readily obtained from methyl (*R*)-ricinoleate (**1**) by VO(acac)₂-catalyzed epoxidation^[6] as scaffold for investigating functional group manipulation at the epoxide stage and for establishing efficient reaction conditions for the REO (Scheme 1).

Gratifyingly, the REO with Kagan's complex (**cat-Cl₂**)^[7] and its enantiomer (**ent-cat-Cl₂**) allows excellent reagent



Scheme 1. REO as key step for the generation of 1,3- and 1,4-difunctionalized molecules as exemplified for **2** and its derivatives (7 mol % **cat-Cl₂**, 1.5 equiv Lut-HCl, 1.5 equiv Mn, 2.2 equiv Bu₃SnH, 0.3 M in THF, 3 days, 25 °C).

control resulting in a regiospecific opening of **2–4** (7 mol % **cat-Cl₂**, 1.5 equiv Lut-HCl, 1.5 equiv Mn, 2.2 equiv Bu₃SnH, 0.3 M in THF, 3 days, 25 °C). Unless stated otherwise, the diastereomeric and regioisomeric ratio of the products, if applicable, were determined by ¹³C-NMR spectroscopy of crude mixture after removal of Sn-containing compounds or from the isolated products due to overlapping signals in the ¹H-NMR spectra. It has been demonstrated^[8] that the NMR techniques used here are accurate for the determination of diastereomeric and regioisomeric ratios. Compared to ¹H-NMR spectroscopy, the errors of the ratios are typically < 2–5%^[8] and, therefore, within experimental error.

Our reaction is thus almost ideal for generating structural diversity from a single precursor. Coll-HCl, the typically employed acid for mediating titanocene(III) catalysis^[9] leads to a noticeably slower reaction. The use of Lut-HCl with Kagan's complex still requires a relatively high catalyst loading of 7 mol % to achieve high yields after 72 h (Table 1, entry 1). We were interested in exploiting halide effects^[9] to lower catalyst loading and reaction time. The use of **ent-cat-Br₂** in combination with Lut-HBr resulted in a more active but distinctly less selective system for the opening of **2** (entry 2).

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Table 1: Anion effect on catalyst performance in the REO of **2** (1.5 equiv Lut-HX, 1.5 equiv Mn, 2.2 equiv Bu₃SnH, 0.3 M in THF, 25 °C).

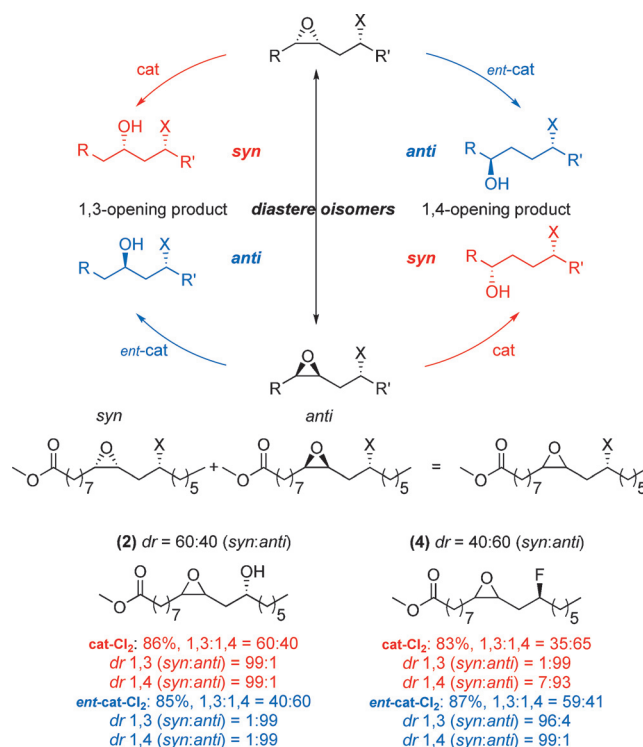
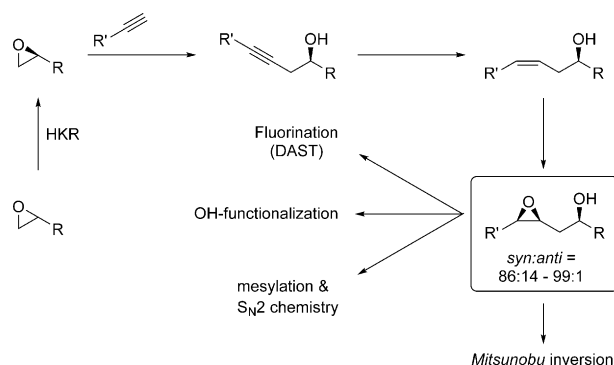
Entry	Cat. (mol%)	X in Lut-HX	t [h]	Yield [%]	rr (1,3:1,4)
1	ent-cat-Cl₂ (7)	Cl	72	91	1:99
2	ent-cat-Br₂ (7)	Br	1	98	9:91
3	ent-cat-Cl₂ (7)	Br	2	92	2:98
4	ent-cat-Cl₂ (5)	Br	12	90	1:99
5	ent-cat-Cl₂ (2)	Br	10	27	1:99
6	ent-cat-Cl₂ (2)	Br	72	87	2:98

Gratifyingly, the use of **cat-Cl₂** in combination with Lut-HBr resulted in a much faster reaction with a selectivity comparable to the system **cat-Cl₂**/Lut-HCl (Table 1).

The higher reactivity of the **cat-Br₂**/Lut-HBr system can be explained by the observation that **cat-Br₂** is reduced by Mn much faster than **cat-Cl₂**. This is due to the weaker Ti–Br bond. Unexpectedly, however, ring-opening by **cat-Br**, the active Ti^{III} catalyst of the **cat-Br₂**/Lut-HBr system, is distinctly less selective than by the corresponding **cat-Cl**. Gratifyingly, the reaction of **cat-Cl₂**/Lut-HBr (entry 3) combines the advantages of the high regioselectivity observed with **cat-Cl₂**/Lut-HCl and the higher reactivity obtained with **cat-Br₂**/Lut-HBr. This is due to the formation of **cat-Cl,Br** under the reaction conditions. This “mixed” complex is reduced quickly by cleavage of the weaker Ti–Br bond to yield **cat-Cl** that induces ring-opening with high selectivity. Our system can either be used to reduce the reaction time at higher catalyst loading (entries 3 and 4) or to reduce catalyst loading at longer reaction time (entry 6).

An important aspect of the REO is the use of mixtures of substrates (Scheme 2). We investigated this issue by employing epoxides *syn*- and *anti*-**2** as well as *syn*- and *anti*-**4** as mixtures of substrates. From a 60:40 mixture *syn*- and *anti*-**2**, we obtained a separable 60:40 mixture of 1,3- and 1,4-diol diastereomerically and enantiomerically pure in a combined yield of 86 %. A similar result was obtained with a mixture of *syn*- and *anti*-**4**. The regioselectivity in the opening of *syn*-**4** is not perfect. With **cat-Cl₂** the 1,4-fluoro alcohol is obtained in 7:93 d.r. and with **ent-cat-Cl₂** the 1,3-fluoro alcohol is obtained in 96:4 d.r. With a 56:44 mixture of *syn*- and *anti*-**2** the **ent-cat-Cl₂**/Lut-HBr system resulted in slightly lower selectivities (77 %, 1,3:1,4 = 39:61, 1,3: *syn:anti* = 3:97; 1,4: *syn:anti* = 8:92) than **ent-cat-Cl₂**/Lut-HCl, but in a strongly accelerated reaction (2 h). Therefore, our REO is attractive for the generation of *syn*- and *anti*- 1,3- and 1,4-difunctionalized compounds.

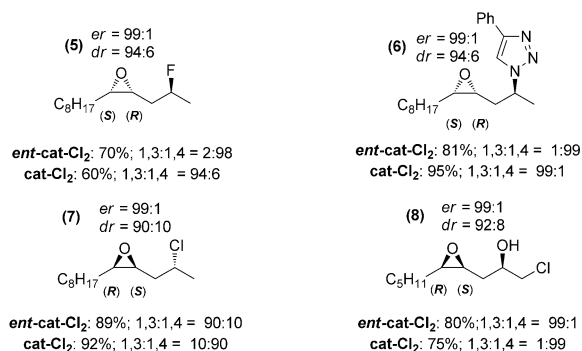
With these results in hands, we turned our attention to the scope of the REO. In order to be able to generate structural and functional diversity, it is mandatory to develop a general synthesis of the REO substrates. Our approach for the synthesis of enantiomerically pure *syn*-β-hydroxy epoxides is shown in Scheme 3. It features highly reliable key reactions that tolerate a variety of functional groups. The required enantiomerically pure epoxides are prepared by Jacobsen's hydrolytic kinetic resolution (HKR).^[10] The (*Z*)-homoallylic alcohol obtained by alkyne addition to the epoxide and P2-Ni-catalyzed hydrogenation^[11] is transformed to the desired *syn*-β-epoxy alcohol by a diastereoselective VO(acac)₂-cata-

**Scheme 2.** Performance of the REO in the reaction of ricinolate-derived diastereomeric mixtures of epoxides. Regioisomeric ratios: from isolated yields.**Scheme 3.** Synthetic approach to the REO substrates.

lyzed epoxidation with diastereoselectivities of 86:14–99:1.^[6] The β-hydroxy group can be further functionalized by the methods indicated to provide a large array of structurally and functionally diverse substrates for the REO.

Some of our results obtained from the REO of the substrates prepared according to Scheme 3 are summarized in Scheme 4. The synthesis of the substrates (described in detail in the Supporting Information) is broadly applicable and allows the incorporation of halides and of azides. Moreover, we were able to carry out a Cu-catalyzed 1,3-dipolar cycloaddition^[12] to further functionalize the epoxide.

The REO of the substrates generally provides the desired products in good to high yields. The regioselectivity of the reagent-controlled ring-opening is excellent with the fluoride and the triazole as the β-substituent. With a β-chloro and β-



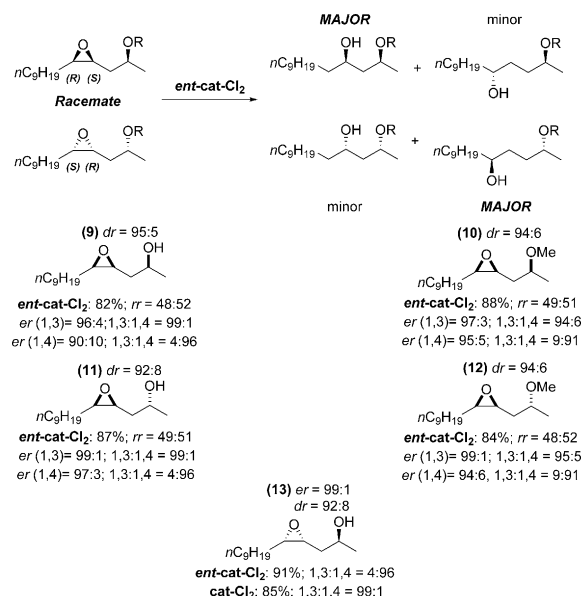
Scheme 4. REOs of various β -epoxy functionalized substrates (7 mol % cat., 1.5 equiv Lut-HCl, 1.5 equiv Mn, 2.2 equiv Bu₃SnH, 0.3 M in THF, 3 days, 25 °C).

hydroxy substituent a slight decrease of catalyst control (regioselectivity 92:8–89:11) was observed in the case of epoxides with the (S,R) configuration (Scheme 4) and **cat-Cl₂** as well as (R,S) configuration at the epoxide and **ent-cat-Cl₂**. The minor product is in all cases easily removed by chromatography.

Arguably, the most common and therefore most relevant building blocks that can be prepared via the REO described here are 1,3- and 1,4-diols and their derivatives.^[2] These functional units are ubiquitous in biologically active substances, especially antibiotics, and have therefore been in the focus of synthetic studies for many years. We studied the performance of the reaction in the opening of racemic β -hydroxy and β -alkoxy substituted epoxides (Scheme 5) in parallel resolution reactions first. In this manner, the performance of the REO with both enantiomers of the substrate can be evaluated in a single experiment. We chose methyl substitution at the β -substituent in the second set of substrates because in many 1,3-diols (part of) the polyol framework is O-methylated.^[13]

The results demonstrate that for the “anti-substrates” almost perfect parallel resolutions take place [for **11** (OH): the following numbers reproduce the experimental results well: (R,S) epoxide to 1,3-diol: $rr = 97:3$ and (S,R) epoxide to 1,4-diol: $rr = 99:1$]. Therefore, the “anti-epoxides” seem to be highly attractive substrates for the synthesis of anti-1,3-diols and their O-methylated derivatives. For the “syn-substrates” the resolution is very efficient [for **10** (OMe): (R,S) epoxide to 1,3-diol: $rr =$ about 95:5 and (S,R) epoxide to 1,4-diol: $rr =$ about 99:1] but not quite as excellent as for the “anti-substrates”. For **9** and **10**, the **ent-cat-Cl₂**/Lut-HBr system resulted in high yields and almost identical selectivities (**9**: 90 %, 1,3:1,4-diol = 48:52, 1,4-diol: e.r. of 94:6, 1,3-diol: e.r. of 91:9, **10**: 92 %, 1,3:1,4-product = 48:52, 1,4-diol: e.r. of 94:6, 1,3-diol: e.r. of 97:3) but with a much shorter reaction time (3 h).

The opening of enantiomerically pure substrate **13** proceeds with high regioselectivity for both enantiomers of the catalyst. The reaction to the 1,4-diol is more selective and higher yielding than the opening to the 1,3-diol. The minor isomer is easily removed. As expected, the combination (weighted by yield) of both reactions of the enantiomerically pure substrate **13** (88 % yield, 1,3:1,4-diol = 47:53, 1,4-diol:



Scheme 5. Performance of the REO in the synthesis of 1,3- and 1,4-diols (7 mol % cat., 1.5 equiv Lut-HCl, 1.5 equiv Mn, 2.2 equiv Bu₃SnH, 0.3 M in THF, 3 days, 25 °C). Yield = combined yield of separated opening products. Regioisomeric ratios (rr): from isolated yields.

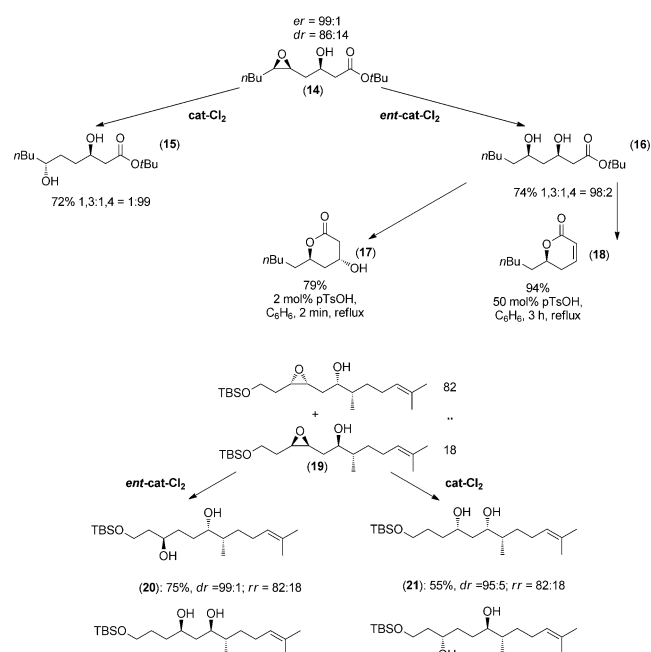
e.r. of 95:5, 1,3-diol: e.r. of 100:0) reproduces the parallel resolution of the racemic substrate **11** (87 %, 1,3:1,4-diol = 49:51; 1,4-diol: e.r. = 97:3; 1,3-diol: 99:1) reasonably well. The slight discrepancy is due to the error of ¹³C-NMR spectroscopy used for the determination of the regioselectivity of the REOs of **13**.

The 1,3-diols shown in Scheme 5 can also be prepared by an aldol reaction of acetone with *n*-undecanal and further manipulation. Aldol reactions with acetone and unbranched aldehydes result in relatively low enantioselectivities.^[14] Thus, our method is an attractive alternative to this classical approach.

To demonstrate the usefulness of the REO in the synthesis of diol-containing compounds we prepared two natural products [(–)-massioalactone (**18**) and (+)-3-hydroxy-5-decanolide (**17**)]^[15] and employed a functionalized building block derived from citrolleol (Scheme 6).^[16] Epoxyester (**14**) is opened to the desired enantiomerically pure 1,3-diol (**16**) by **ent-cat-Cl₂** with excellent selectivity and with **cat-Cl₂** to the enantiomerically pure 1,4-diol (**15**) in equally high selectivity. From **16** both natural products **17** and **18** can be prepared in high yield by pTsOH-mediated lactonization under the appropriate conditions.

The citrolleol-derived epoxides (**19**) are opened to the corresponding 1,3- or 1,4-diols with excellent reagent control according to Scheme 2. These reactions amply highlight the power of combining our modular substrate synthesis with the REO in the preparation of functionalized 1,3- and 1,4-diols.

In summary, the regiodivergent epoxide opening is an excellent and the only method to transform β -functionalized *cis*-2,3-difunctionalized epoxides into 1,3- or 1,4-difunctionalized building blocks containing at least one hydroxy group. Both the REO and the modular substrate synthesis tolerate



Scheme 6. REO for natural product synthesis and preparation of building blocks derived from citronellol.

a number of functional groups. Therefore, our method is not only attractive for natural products synthesis, and a general access to building blocks of important classes of compounds, such as 1,3- and 1,4-diols, but also as a new branching reaction for efficient diversity-oriented synthesis with epoxides.

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