Catalytic Asymmetric β-Oxygen Elimination

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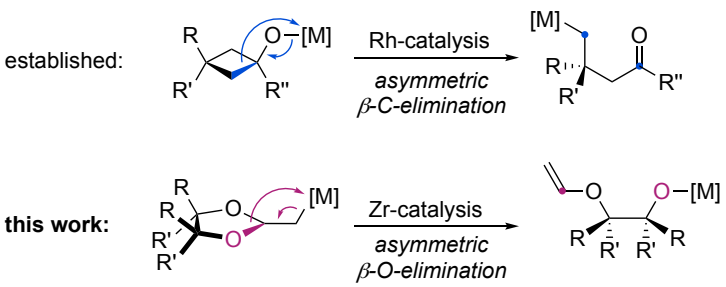
Abstract: A catalytic enantioselective β-O-elimination reaction is reported in the form of a zirconium-catalyzed asymmetric opening of *meso*-ketene acetals. Furthermore, a regiodivergent β-O-elimination is demonstrated. The reaction proceeds under mild conditions, at low catalyst loadings, and produces chiral monoprotected 1,2-diol building blocks in good yield and enantiomeric excess. The combination with a Mitsunobu reaction then gives access to all 1,2-diol stereoisomers and *trans*-1,2-aminoalcohols in high enantiomeric purity. A stereochemical analysis supported by DFT calculations reveals that a high selectivity in the hydrozirconation step is also important for achieving high enantioselectivity, although it does not constitute the asymmetric step. This insight is crucial for the future development of related asymmetric β-elimination reactions.

The development of new types of catalytic asymmetric bond formations and activations is at the heart of modern stereoselective synthesis.[1] One particularly intriguing case are β-elimination reactions that occur as a mechanistic key step in numerous important transition metal catalyzed processes.[2,3] In the recent years, catalytic enantioselective β-carbon eliminations have been developed and applied as an exquisite tool for the construction of quaternary stereocenters (Scheme 1).[2c,d,4] In contrast, catalytic enantioselective reactions involving a β-heteroatom elimination event usually have a preceding asymmetric hydro-, carbo-, or nucleometalation step.[2b,5] A direct enantioselective β-heteroatom elimination reaction in which the β-Het cleavage itself is stereodiscriminating has remained elusive with exception of an asymmetric β-F-elimination that was published very recently.[6] In this work, we now report a zirconium-catalyzed enantioselective β-oxygen elimination reaction in the form of an opening of cyclic ketene acetals.

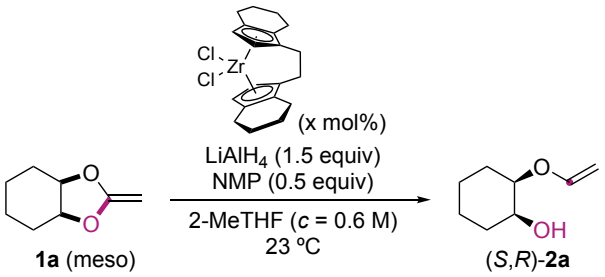
The reaction gives access to enantioenriched mono-vinylated diols that are versatile precursors of numerous chiral building blocks but difficult to prepare by other means.[7]



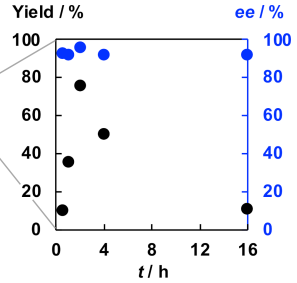
Scheme 1. Concept of a catalytic asymmetric β-O-elimination.

Our group has been exploring zirconium-catalyzed β-elimination reactions as a tool for the selective cleavage of unreactive carbon-heteroatom bonds.[8,9] The challenging nature of the targeted bonds, the highly abundant and non-toxic nature of zirconium and the fact that catalytic β-Het-elimination has mostly been reported with late transition metals render this approach attractive.[3] We reasoned that an asymmetric β-O-elimination could be realized with substrates having two enantiotopic C-O bonds and, therefore, *meso*-ketene acetals were chosen as precursors. After an initial hydrozirconation with an in situ generated chiral zirconium hydride catalyst, the following ring opening by β-elimination would be the desymmetrizing step. The asymmetric opening would lead to selectively monoprotected enantioenriched 1,2-diols, rendering the reaction a counterpart to common *meso*-diol-desymmetrizing acylation and sulfonylation reactions.[10]

Starting with *meso*-compound **1a** as substrate, it was quickly discovered that a highly enantioselective ring-opening to **2a** could be achieved in presence of 5 mol% (*R*,*R*)-(ebthi)$ZrCl_2$ as precatalyst (Scheme 2, entry 1). A combination of $LiAlH_4$ and *N*-methylpyrrolidine (NMP) as previously established by us for Zr-catalyzed β-eliminations was found ideal for achieving turnover.[8] Additional experiments showed that the yield in β-vinyloxy alcohol **2a** varied over time, reaching a maximum after 2 h. At this point, a precipitate had formed which was concluded to be a weakly soluble aluminium alkoxide of **2a**, hampering the hydrozirconation and cleavage of the vinyl group.[8] Extending the reaction time or switching the solvent to the more polar THF led to overreduction, giving significant amounts of achiral *cis*-cyclohexanediol. The enantioselectivity remained high, regardless of the reaction time (92–96% ee). Our investigations revealed that even a higher 82% yield could be achieved at a lower catalyst loading of 2.5 mol% if the reaction time was extended to 4 h (entry 2). A further reduction in catalyst amount and the absence of NMP reduced the yield, but the stereoselectivity remained unaffected (entries 3, 4). The absolute configuration of **2a** was established by X-ray analysis of a *para*-bromobenzoate derivative as (*S*,*R*).[11,12]



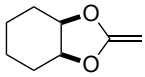
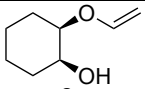
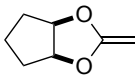
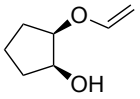
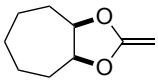
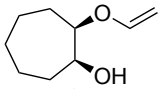
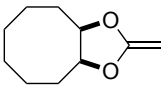
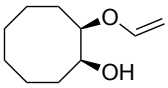
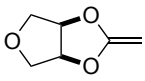
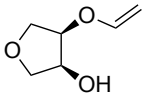
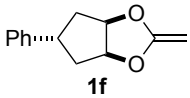
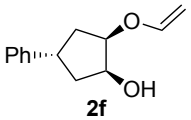
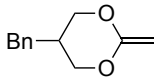
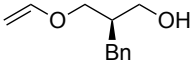
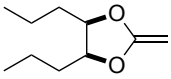
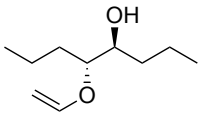
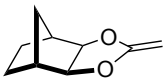
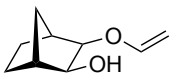
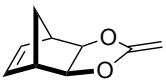
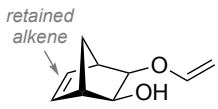
Entry	x / mol%	*t* / h	Yield / %	*ee* / %
1	5.0	0.5–16	12–76	92–96
2	**2.5**	**4**	**82**	**92**
3	1.0	4	12	92
4[a]	2.5	4	68	92
5[b]	2.5	4	12	92



Scheme 2. Reaction optimization. [a] Reaction without NMP. [b] Reaction in THF.

We were delighted to find that the reaction could be carried out on larger scale (2.6 mmol) with similar yield and enantioselectivity (Table 1, entry 1b). A reaction with the (*S*,*S*)-catalyst gave (*R*,*S*)-**2a** in 80% yield and 92% *ee*. Using the optimized conditions, we then submitted a number of structurally modified ketene acetals that could be readily accessed from the corresponding diols to the asymmetric β-elimination reaction. Ketene acetals with annulated five- and seven-membered rings worked well (entries 2 and 3) giving 90% and 86% *ee* and very high yields (99% and 96%, respectively). An eight-membered ring, showing higher conformational flexibility, still led to a good stereodiscrimination (83% *ee*, entry 4). A monovinylated dihydroxytetrahydrofuran was produced in 85% yield and 90% *ee* (entry 5). Exchanging the THF oxygen by a *trans*-configured phenyl-substituted carbon center led to 67% yield and 78% *ee* (entry 6). A ketene acetal derived from 2-benzyl-propane-1,3-diol, having only a remotely located prochiral center, led to a significantly diminished yield and enantioselectivity.[13] This could be rationalized by a reduced facial preference for the hydrozirconation of the ketene acetal double bond, which in turn was essential for achieving an asymmetric C-O bond cleavage (*vide infra*). Substrates that were derived from secondary alcohols and featured distinct concave and convex faces, on the other hand, gave excellent results. This was also true for substrate **1h** derived from a linear *meso*-diol, which afforded the ring-opening product **2h** in 71% yield and 84% *ee* (entry 8). Norbornene- and norbornadiene-based tricyclic ketene acetals gave good yields and high enantiomeric excess as well (entries 9, 10). Importantly, the internal alkene function of **1j** was retained and only traces of **2i** were observed (19:1 ratio).

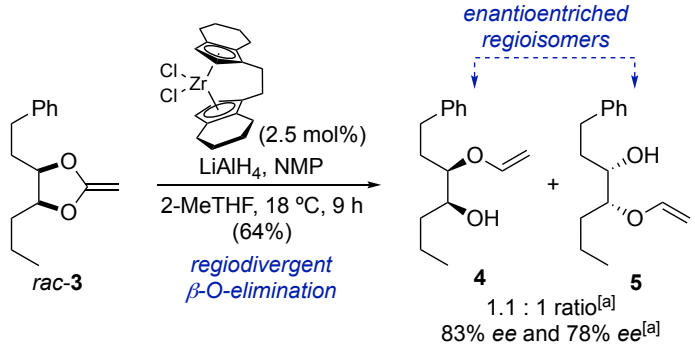
Table 1. Scope of the enantioselective β-O-elimination reaction.[a]

Entry	Substrate	Product	Yield / %	*ee* /%
1a 1b[b] 1c[c]	 **1a**	 **2a**	82 79 80	92 93 –92
2	 **1b**	 **2b**	99	90
3	 **1c**	 **2c**	96	86
4[d]	 **1d**	 **2d**	88	83
5	 **1e**	 **2e**	85	90
6	 **1f**	 **2f**	67	78
7	 **1g**	 **2g**	25	33[e]
8	 **1h**	 **2h**	71	84[f]
9	 **1i**	 **2i**	78	94
10	 **1j**	 **2j**	70[g]	86

[a] Reactions on the 0.2 mmol scale. Conditions: Table 1, entry 2. [b] 2.6 mmol scale reaction. [c] Reaction with 2.5 mol% (*S*,*S*)-(ebthi)$ZrCl_2$, giving (*R*,*S*)-**2a** as product. [d] Reaction with 5 mol% of catalyst. [e] The absolute configuration of **2g** was not determined. [f] Reaction run at 18 ºC for 9 h. [g] Contained 5% of **2i** as determined by GC-MS.

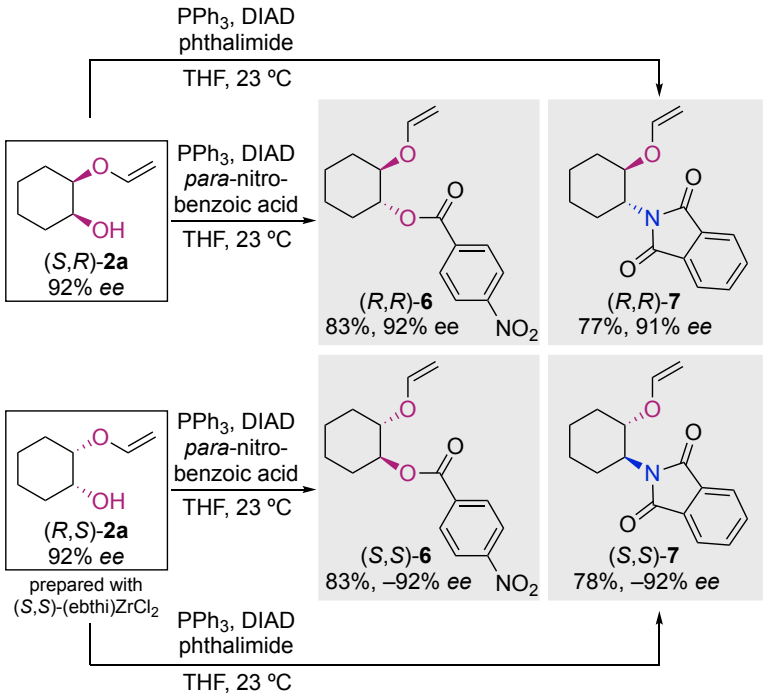
The concept of asymmetric β-elimination was then taken to the next level by attempting the regiodivergent opening of pseudo-*meso* substrate *rac*-**3** (Scheme 3),[14] which was prepared from *cis*-1-phenylhex-3-ene by dihydroxylation.[11] Ideally, the remote structural divergence between the phenyl group and methyl termination of the backbone would not influence the catalyst selectivity. The two substrate enantiomers would then lead to one enantioenriched regioisomer

each (**4** and **5**) in a ratio of 1:1. We were pleased to find that the reaction gave the desired regioisomers in 82% and 79% *ee* in a 1.1:1.0 mixture and 64% combined yield. The products were further oxidized and hydrolyzed to the free regioisomeric α-hydroxyketones in 91% overall yield and without significant loss (3–4%) in *ee*.[11]



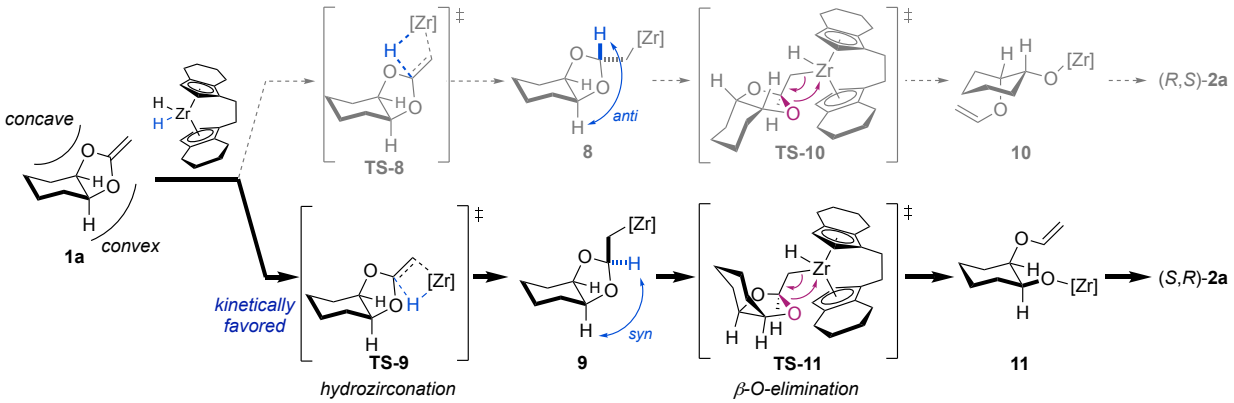
Scheme 3. Regiodivergent β-O-elimination. [a] Determined by chiral HPLC.

To show a potential application of the asymmetric β-O-elimination approach in the stereoselective synthesis of enantioenriched 1,2-diols and -aminoalcohols, the asymmetric ketene acetal opening was combined with a Mitsunobu reaction (Scheme 4). Using *para*-nitrobenzoic acid as nucleophile and conditions optimized for Mitsunobu inversions of cyclohexanols,[15] the *cis*-diol (*S*,*R*)-**2a** as well as its (*R*,*S*)-enantiomer were converted into the orthogonally protected *trans*-diols (*R*,*R*)-**6** and (*S*,*S*)-**6**, respectively, each in 83% yield and with full conservation of enantiopurity (92% *ee*). The enantioenriched *trans*-aminoalcohols (*R*,*R*)-**7** and (*S*,*S*)-**7**, could be independently accessed in 77–78% yield and 92% *ee* by an analogous reaction with phthalimide. Overall, all four 1,2-diol diastereo- and enantiomers as well as the two *trans*-1,2-aminoalcohol enantiomers were prepared in good yield and high enantiomeric excess.



Scheme 4. Accessing enantioenriched, orthogonally protected diols and aminoalcohols.

A stereochemical analysis of the reaction course was carried out that provided a rationale for the observed stereoselectivity (Scheme 5). The reaction involved two potentially stereoselectivity-determining events: first, the hydrozirconation that either occurred from the concave or the less hindered convex side of the molecule. The two corresponding transition states would then give the *anti*-intermediate **8** and kinetically favored *syn*-intermediate **9**, respectively. Secondly, the β-elimination step followed, which could occur from two rotational conformers of the individual intermediates, one of which would lead to a significantly lower transition state due to minimization of steric repulsion. In the case of **8**, the favored transition state was **TS-10** showing minimal steric interactions between the substrate and the ebthi ligand. It transitioned into **10** and ultimately gave (*R*,*S*)-**2a**. The bowl-shaped *syn*-intermediate **9**, on the other hand, led to transition state **TS-11**, with the two sterocenters at the ring junction being inverted, allowing the cyclohexyl ring to point away from the tetrahydroindenyl group of the ligand. The favored product **11** was the direct precursor to (*S*,*R*)-**2a**. As a direct consequence of this scenario, the enantioselectivity of the reaction was dependent on the selectivity of the hydrozirconation step. This rationale was confirmed by a computational analysis of the reaction paths (Figure 1). The calculations were performed on the PW6B95-D4-CPCM(2-MeTHF)/def2-QZVP//PBEh-3c level,[16–18] using the ORCA 4.2.1[19] program package. Several transition states including coordination isomers, conformers and rotamers were computed for the hydrozirconation and β-O-elimination steps each. In detail, it was found that the hydrozirconation from the convex side (leading to **9**) was favored by 2.6 kcal mol^{-1}. The corresponding transition states **TS-8** and **TS-9** were at 20.1 and 17.5 kcal mol^{-1}, which were in agreement with the rapid reaction at room temperature. The barriers for the β-O-elimination (**TS-10** and **TS-11**) were significantly lower (10.6 and 12.1 kcal mol^{-1}, respectively). For comparison, the lowest β-O-elimination transition states leading to the respective opposite enantiomers (**TS-10'** and **TS-11'**) were calculated and added to Figure 1. However, these were significantly higher in energy ($\Delta\Delta G^{\ddagger}$ = 4.4 and 6.0 kcal mol^{-1}, respectively). Hence, the favored convex pathway would exclusively give (*S*,*R*)-**2a** and the disfavored concave pathway only (*R*,*S*)-**2a**. Overall, this showed that the hydrozirconation was selectivity-determining and the rate-limiting step. The enantiomeric excess calculated from the difference transition state energies corresponded to 97.5% *ee*, which was in good agreement with the experimentally observed range of 92–96% *ee*. For completion, we calculated the reaction pathways starting from (*R*,*R*)-(ebthi)Zr(H)Cl as alternative hydrozirconation precursor, but this led to significantly higher activation barriers.[11,20] Moreover, the reaction of a zirconocene dichloride with an excess of $LiAlH_4$ or a similar hydride reagent is known to give the corresponding zirconocene dihydride,[21] which further supports the proposed dihydride mechanism.



Scheme 5. Stereochemical analysis for the observed selectivity.

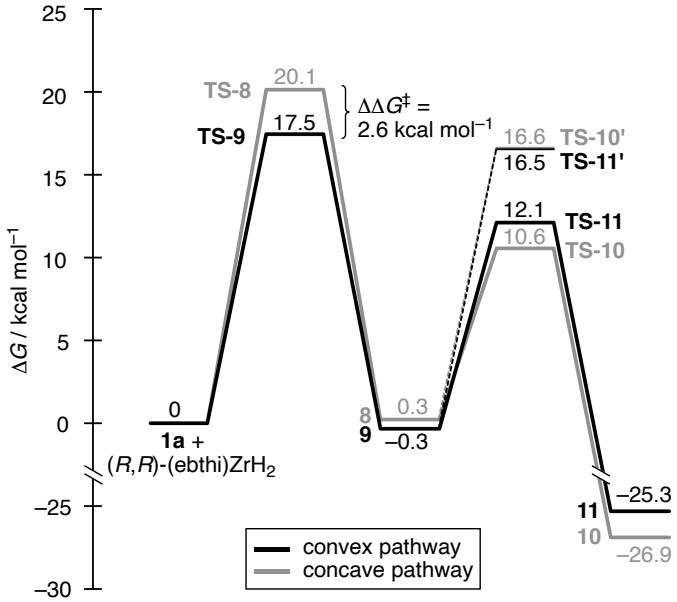


Figure 1. Calculation of the paths in Scheme 5 (PW6B95-D4-CPCM(2-MeTHF)/def2-QZVP//PBEh-3c). Values are the Gibbs free Energy in kcal mol^{-1}.

In conclusion, a catalytic asymmetric β-O-elimination has been developed on the example of an enantioselective opening of *meso*-ketene acetals. The reaction proceeds in presence of an in situ generated chiral zirconocene hydride catalyst at mild temperatures and it gives enantioenriched, monoprotected diols in high yield and *ee*. As a proof-of-principle, a regiodivergent β-O-elimination has been demonstrated as well. If desired, the usually obtained *cis*-diol products can be converted into enantioenriched *trans*-diols and -aminoalcohols without loss in enantiopurity. A stereochemical analysis supported by DFT calculations revealed that the hydrozirconation step leads to two diastereomeric intermediates, which are then converted into the opposing product enantiomers in the following asymmetric β-O-elimination. An efficient site differentiation in the hydrozirconation step is therefore important for achieving high enantioselectivity. This insight will greatly facilitate the development of other asymmetric β-elimination reactions using chiral zirconocene-based catalysts. Since chiral diols and vinyl ethers are frequently employed as

precursors in organic synthesis and polymer chemistry, the enantioselective β-O-elimination presented herein could be of broader relevance to these areas.[22,23]

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Keywords: asymmetric catalysis • β-elimination • reduction • regiodivergent • zirconium

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