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Chemoenzymatic Synthesis of *O*-Containing Heterocycles from α-Diazo Esters

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The synergy of biocatalysis and transition metal catalysis is rapidly moving forward, providing increasingly effective workflows in chemical synthesis. Here we present a facile way to prepare synthetically challenging *O*-containing heterocycles bearing disubstituted stereogenic centers via catalytic chemoenzymatic transformation of α-diazo carbonyl compounds. We demonstrate that keto-α-diazoesters can be enzymatically reduced to the corresponding alcohols with exquisite enantioselectivity and under retention of the diazo group using the ketoreductases LbADH and Gre2p. To further functionalize the resulting enantiopure (*R*)- and (*S*)-hydroxyl α-diazo esters, a variety of Cu and Rh catalysts were screened for intramolecular ring closure. Six- and seven-membered rings with both, aliphatic and ester substituents, were obtained with up to 93:7 diastereomeric ratio and 81% yield. Up to 98% enantiomeric excess was obtained for both diastereomers, yielding the thermodynamically less favored α,ω-trans-oxepanes as the main products.

Chiral oxygen-containing heterocycles are commonly found motifs in various natural products and many biologically active molecules.[1] Prominent examples include Maoecrystal V[2], Heliannuol C[3] and the structural more complex Brevetoxins.[4] In recent years, several strategies for the diastereoselective and enantioselective construction of these important heterocycles have been developed. However, despite the known biological activity of this motif against multiple targets, only few synthetic methods have been reported to provide α,ω-disubstituted heterocyclic analogues with two stereogenic centers, especially in the case of medium-sized cyclic ethers. The synthetic challenges can be attributed to entropic restrictions as well as transannular and torsional strains during the formation of seven-membered cycles from acyclic precursors.[5]

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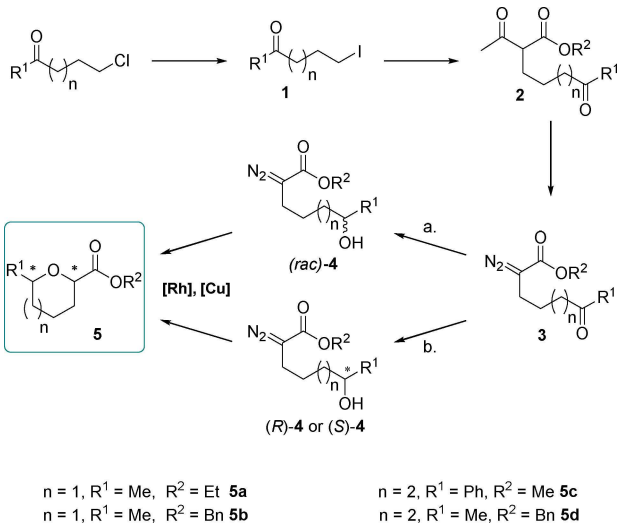
The methods to obtain *O*-containing heterocycles are literally based on two main strategies, namely the formation of a C–C or C–O bond.[6–9] The formation of a C–O bond has proven to be efficient and reliable. The most important methods used to form C–O bonds are S_N1 and S_N2 nucleophilic substitution, 1,4-conjugate addition, nucleophilic ring-opening of epoxides, metal-promoted cyclization, or hemiketalization/dehydration and hemiketalization/nucleophilic addition sequences.[6,8,9,10]

Here we describe a new approach to α,ω-disubstituted oxepanes, which provides these compounds in a stepwise approach where α-diazocarbonyl compounds (**3**, in Scheme 1) are reduced to the corresponding alcohols **4** in a stereoselective manner and then subjected to intramolecular cyclization by aid of a metal catalyst to yield the desired end products **5**. However, since the stereoselective reduction of diazoketones, such as **3** remains a synthetic challenge for conventional organometallic chemistry,[11] it was necessary to initially address the enantioselective reduction of ketone **3**.

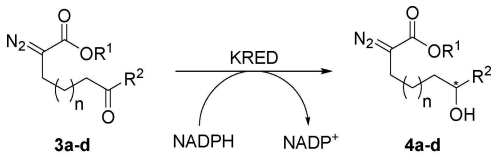
While it is well known that the reduction of carbonyl compounds with enzymes usually occurs with high chemo- and stereoselectivity,[12,13] to the best of our knowledge, no enzymatic reduction of keto-α-diazoesters has been reported yet. Such a biocatalytic approach would also have the advantage of meeting the growing interest in the development of cost-effective and environmentally friendly chemical processes.[14,15–20] In fact, biocatalytic reactions have already been reported in order to obtain oxygen-containing heterocycles.[21] Furthermore, examples of the combination of enzymatic reduction of ketones and (metal)organic catalysts clearly show that the two complementary systems can be advantageously used for the synthesis of valuable chiral components.[22]

Since only few methods for the stereoselective synthesis of oxepane derivatives have been described, despite their pharmacological relevance, and to investigate of whether the proposed



Scheme 1. Reaction sequence applied for the generation of *O*-containing heterocycles **5**. The starting material is converted into the corresponding iodoalkane **1** *via* a Finkelstein reaction followed by a nucleophilic substitution to yield **2**. Subsequent diazo transfer yields in keto-α-diazo ester compounds **3** which are reduced chemically with $NaBH_4$ (a) or enzymatically by using ketoreductases (KREDs) (b) to yield the enantiopure α-diazocarbonyl alcohols **4**. Various rhodium or copper catalysts were tested for the subsequent intramolecular cyclization to obtain the target compounds **5**.

Table 1. Turnover rates (TON) of various ketoreductases for the reduction of substrates **3a–d** by means of a NADPH consumption assay. Data were normalized to protein subunits and represent the mean of at least two independent experiments with duplicate analyses.



Entry	Enzyme	TON [μmol/(μmol*min)] 3a	3b	3c	3d	Expected selectivity[a]
1	LbADH	270.0	308.0	–[b]	140.4	(*R*)[13]
2	LkADH	88.5	50.0	–[b]	91.4	(*R*)[28]
3	Gre2p	23.3	22.5	–[b]	21.3	(*S*)[29]
4	Gre3p	0.2	0.3	–[b]	0.3	(*S*)[30]
5	GCY1	0.3	0.4	–[b]	0.3	(*S*)[31]

[a] The expected stereoselectivity is based on literature data for the reduction of methyl ketones. [b] No enzyme activity was detected.

chemoenzymatic route in Scheme 1 is feasible, we chose the synthesis of **5d** as a reference.[7] The ketone-containing α-diazocarbonyl compounds **3** were synthesized in three steps *via* a Finkelstein reaction and a subsequent nucleophilic substitution followed by a classical diazo transfer reaction. These α-diazocarbonyl compounds can undergo a wide range of chemical transformation reactions.[23] Among these, the transition-metal catalyzed insertion of an X–H bond (X = C, N, O, S, B and Si) represents one of the most efficient approaches to form C–C and C-heteroatom bonds *via* carbene-mediated intra- or intermolecular X–H insertion into α-diazocarbonyl compounds.[24,25] To enable the envisioned synthesis, we reasoned that the enantioselective reduction of **3** to the corresponding alcohol **4** should allow for ring closure with a transition metal catalyst to facilitate a highly stereoselective intramolecular insertion of the hydroxyl group into the *in situ* formed metal-carbenoid. Hence, screening of rhodium and copper catalysts, which are known for effective conversion of diazo compounds, should open the door to the ring-closing reaction of bifunctional diazo-compounds to give access to pyrans and oxepanes with a high degree of sp^3 carbon atoms in the ring structure.[26]

To further explore the strategy of metal carbenoid mediated cyclizations[25,27] for installment of the ω-stereocenter of **5a–d**, and to establish the novel chemoenzymatic route to these compounds (Scheme 1), we initially searched for suitable biocatalysts for the enantioselective reduction of the α-diazocarbonyl compounds **1**. To this end, several NADPH-dependent ketoreductases with known enantioselectivities towards methylketones were screened by means of a fluorescence-based NADPH consumption assay as shown in Table 1, allowing the direct comparison of the capability of the different enzymes to convert the substrates used in this study.

The *(R)*-selective bacterial enzymes LbADH and LkADH showed comparably high activities (Table 1, entry 1 and 2). LbADH showed by far the highest rate of conversion in the reduction of **3a**, **3b** and **3d**. Likewise, The *(S)*-selective Gre2p revealed acceptable conversion rates for these substrates. The phenyl-substituted ketone **3c** could not be reduced by any of the enzymes. Given the broad spectrum of substrates accepted by the enzymes,[12,13] we reason that the lack of reactivity observed presumably stems from limitations in substrate solubility. To scale-up the initial assessment for preparative synthesis, the two most promising enzymes, the *(R)*-selective LbADH and the *(S)*-selective (Gre2p), were then examined in more detail for their activity and enantioselectivity in the reduction of **3d** by using chiral HPLC analysis (Figure 1; see also Figure S1 in the Supporting Information). While the activity of LbADH was about 10-fold higher than that of Gre2p, both enzymes showed exquisite enantioselectivity, resulting in full conversion of **4d**. Using the two enzymes in a preparative scale reaction (140 mg of **3d**), the respective stereoisomers of enantiopure **4d** were obtained with isolated yields of up to 89%.

Of note, we also explored the use of whole cell biocatalysis for the stereoselective reduction of **3d** because this format is generally considered as economically efficient for cofactor-dependent processes.[32] Indeed, we found that live *E. coli* cells expressing the recombinant LbADH were capable of fully converting **3d** with an excellent enantioselectivity of >98% (Figure S2; for the cofactor regeneration systems used in this work, see Figure S3). Furthermore, we found that the use of *E. coli* extracts, so called crude extract cell-free systems (CECFs), which often reveal enhanced enzyme stability,[33] also led to similar excellent enantioselectivity (Figure S2) albeit with decreased conversion rates of about 57%. In summary, these results are remarkable as they represent the first biocatalytic

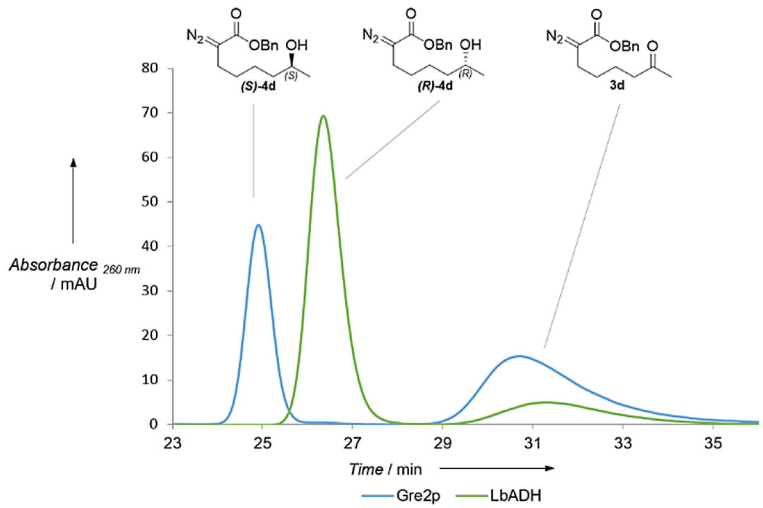
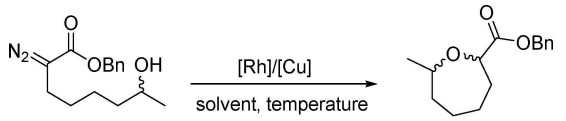


Figure 1. Representative chiral HPLC chromatograms of the enzymatic reduction of **3d**. Reductions were carried out with the *(R)*-selective LbADH (green) or the *(S)*-selective Gre2p (blue). Note that the presence of **3d** indicates an incomplete conversion in the given reaction time of 30 min. HPLC conditions: Phenomenex Amylose-2 column; 2% 2-propanol in *n*-heptane; 1.5 mL/min; 30 °C.

reduction of ω-keto substituted α-diazocarbonyl compounds and occur without damage to the diazocarbonyl group.

To further evaluate our proposed synthetic route, the metal catalyzed ring closure was initially optimized with the racemic alcohol *rac*-**4**, produced by a chemical reduction with $NaBH_4$ (Scheme 1). To this end, a range of rhodium and copper catalysts was tested under variable reaction conditions for cyclization of *rac*-**4d** (Table 2). We found that the reactions resulted in product yields of up to 81% (Table 2, entry 6) with diastereomeric ratios (d.r.) of up to 82:18 when rhodium catalysts were used (Table 2, entries 1–7). In comparison with $Rh_2(OAc)_4$ as catalyst, $Rh_2(cap)_4$ resulted in higher yields, but lower diastereoselectivity (Table 2, entries 6–10). In contrast, the copper-catalyzed O–H insertion led to even higher selectivity (93:7 d.r.) but substantially lower yields (Table 2, entry 12). Hence, $Rh_2(OAc)_4$ was used for further investigations as it offers an optimal compromise between yield and selectivity. We also tested the metal-catalyzed cyclization of 6-membered rings. For example, **4b** was subjected to cyclization, yielding the corresponding tetrahydropyrane derivative **5b**.

Table 2. Catalyst screening for the transition metal-catalyzed intramolecular O–H insertion reaction of **4d** to form **5d**.[a]



***rac*-4d** **5d**

Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b]	d.r. [%][c]
1	$Rh_2(OAc)_4$	Toluene	110	58	82:18
2	$Rh_2(OAc)_4$	Toluene	80	53	82:18
3	$Rh_2(OAc)_4$	Benzene	80	53	82:18
4	$Rh_2(OAc)_4$	DCE	83	50	76:24
5	$Rh_2(OAc)_4$	DCM	40	44	60:40
6	$Rh_2(cap)_4$	Toluene	110	81	75:25
7	$Rh_2(cap)_4$	Toluene	80	75	77:23
8	$Rh_2(cap)_4$	Benzene	80	55	75:25
9	$Rh_2(cap)_4$	DCM	40	76	60:40
10	$[Rh(cod)Cl]_2$	Toluene	110	51	75:25
11	$Cu(OTf)_2$·Tol	Toluene	110	19	97:03
12	$Cu(MeCN)_4$	Toluene	110	trace	–[d]
13[e]	$Rh_2(OAc)_4$	Toluene	80	50	73:27

[a] Reaction conditions: Catalyst (1.0 mol%), *rac*-**4d** (1.0 equiv.), solvent (2.0 mL). [b] Isolated yields. [c] The diasteremoetric ratio (d.r.) values were determined by HPLC. [d] d.r. could not be determined because only trace amounts of product were formed. [e] Enantiopure (*R*)-**4d**, obtained by enzymatic reduction was used. Reaction at 80 °C led to partial racemization ($ee \geq 92$), which was not evident at room temperature ($ee \geq 98$). Cod: 1,5-cyclooctadiene; Cap: tetracaprolactamate; Tf: trifluormethansulfonyl; DCE: dichloroethane; DCM: dichloromethane.

Next, preparative stereoselective reduction of **3d** was followed by the metal-catalyzed cyclisation of enantiopure **4d**, using optimized reaction conditions ($Rh_2(OAc)_4$, toluene, r.t.). Chiral HPLC analysis revealed the formation of only two diastereomers when enantiopure (*R*)-**4d** was subjected to cyclization, whereas four diastereomers were formed from (*rac*)-**4d** (orange and blue chromatograms, respectively, in Figure 2).

Assignment of the configurations was achieved by 2D-NOESY NMR analysis. We found that the main product of the reaction was the thermodynamically less-favored *trans*-configured oxepane derivative, as determined by NOE experiments. This is remarkable because the substituents in the *cis*-isomer are pseudo-equatorial to each other, which makes the *cis*-isomer thermodynamically more stable. Importantly, diastereomeric ratios of products obtained from **4d** (73:27, Figure 2) and **rac-4d** (82:18, Table 2) were approximately equal, thus indicating that the metal-catalyzed cyclization is not substantially affected by the configuration of the hydroxyl group. Furthermore, all tested conditions evaluated for (*rac*)-**4d** also resulted in a rather unselective conversion of the initial compounds. It can thus be assumed that the configuration of the newly formed stereogenic center is mainly determined by the O–H insertion reaction.

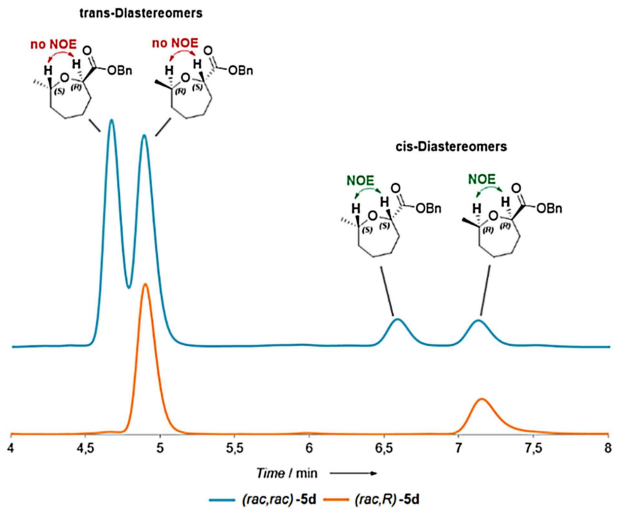


Figure 2. Chiral HPLC analysis of the ring closure reaction. The metal-catalyzed reaction of (*rac*)-**4 d** (blue) or (*R*)-**4 d** (orange) yields four or two stereoisomers, respectively. NOE-correlation between the α-H signal and the ω-H signal is indicative for the *cis*-isomer. Enantiomeric excess was determined *via* chiral HPLC analysis of **5 d**, obtained by subjecting (*R*)-**4 d** (orange) to the ring closure reaction. Cyclization of (*rac*)-**4 d** yielded four different stereoisomers with a d.r. value of 82:18, whereas *(R)*-**4 d** generated two diastereomers with a d.r. value of 73:27, and *ee* > 98%. Reaction conditions: 5 mol% $Rh(OAc)_4$, toluene, r.t.

In conclusion, herein we describe a novel chemoenzymatic route to the synthesis of oxepanes and tetrahydropyrans, both of which have a high potential for the synthesis of fine chemicals and pharmaceuticals. To this end, we demonstrated for the first time, that keto-α-diazoester compounds can be enzymatically reduced to the corresponding alcohols with exquisite chemo and enantioselectivity. The effectiveness of the reduction was demonstrated for isolated enzymes as well as whole cell biocatalysts. Furthermore, screening of various rhodium and copper catalysts with respect to turnover and stereoselectivity led to identification of suitable reaction conditions for the intramolecular cyclization of the enzymatically-produced hydroxy-α-diazoester compounds. This enables the synthesis of the trans-configured oxepanes with high diastereomeric excess and good yields, even in the not yet optimized process.

Since comparable state-of-the-art reactions require the use of toxic transition metal catalysts or stoichiometric use of reductants,[34] our reaction strategy employing a highly regio- and stereospecific enzymatic reduction paves the way to the establishment of 'greener' synthetic processes that are more cost efficient and environmentally friendly. Furthermore, given that numerous ketoreductases are known with which a wide variety of differently substituted carbonyl compounds can be reduced with high enantioselectivity,[20,21] the here presented strategy opens the door to novel α,ω-substituted *O*-containing heterocycles, whose potential for applications in pharmacy and technology can then be further investigated. On a broader perspective, our study also supports the concept of integrated production systems, wherein biocatalysts are combined with conventional metal and/or organocatalysts to enable the synthesis of complex molecules in sustainable processes.[15–20]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Keywords: Biocatalysis, Chemoenzymatic Cascades, Diazo compounds, Enantioselectivity, Heterocycles

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