Atroposelectivity

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Biocatalytic Desymmetrization of an Atropisomer with both an Enantioselective Oxidase and Ketoreductases**

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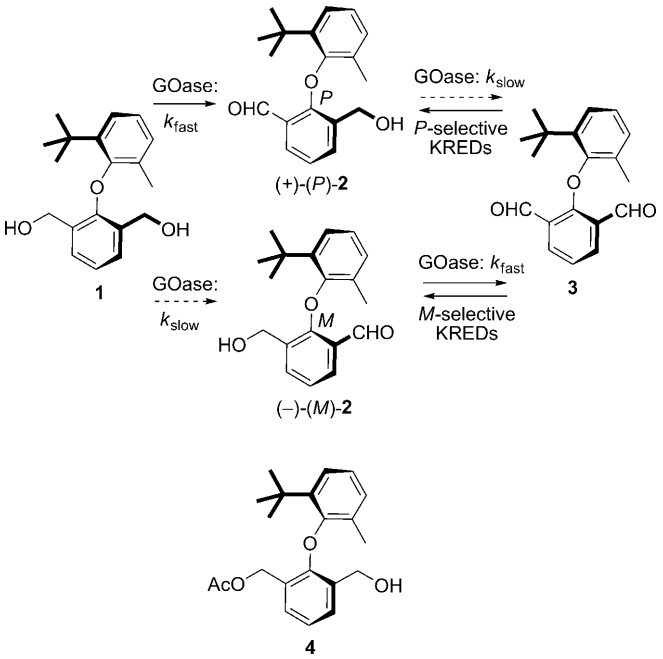
Atropisomeric ligands have found numerous powerful applications in catalysis,[1] and the atropisomeric biaryl bisphosphine binap played an important role in the award of a Nobel Prize to Noyori in 2001.[2] Enantiomerically pure atropisomers commonly employed as chiral ligands are generally made by resolution: there are still relatively few effective methods for direct asymmetric coupling to form single enantiomers.[3] Kinetic resolution[4] and dynamic resolution[5] under kinetic[5a] or thermodynamic[5b] control are particularly appealing given the possibility offered by atropisomerism for thermal racemization of the less reactive enantiomer. The use of desymmetrization for the synthesis of single atropisomers is rare.[6] Following the early example of enantioselective lithiation reported by Raston and co-workers,[6b] the research groups of Hayashi[6c] and Harada[6d] also reported chemical methods for desymmetrizing biphenyl compounds. A single example of the enzymatic desymmetrization of a biaryl compound with a lipase was reported by Matsumoto et al.[6e]

Herein, we report two novel and complementary biocatalytic approaches to the enantioselective synthesis of atropisomers by the desymmetrization of appropriate achiral substrates containing a pair of enantiotopic functional groups. The atropisomer in question is the diaryl ether **2**, which may be formed either by enantioselective oxidation of the symmetrical diol **1** or by the corresponding reduction of the symmetrical dialdehyde **3** (Scheme 1). The enzymes we employed for these transformations were 1) a variant of galactose oxidase (GOase) which had been previously evolved to accept chiral benzylic alcohols as substrates with high enantioselectivity (**1**→**2**)[7] and 2) a family of ketoreductases that are known to possess good activity and enantioselectivity for the asymmetric reduction of benzylic ketones (**3**→**2**).[8]



Scheme 1. Enantioselective transformations of atropisomeric and pro-atropisomeric diaryl ethers. GOase = galactose oxidase. KRED = ketoreductase.

Atropisomeric diaryl ethers[9] form part of the structure of vancomycin[10] and are promising scaffolds for the construction for new chiral ligands.[11] Dialdehyde **3** and diol **1** were made by our published route.[9] In an initial screen, we attempted enantioselective acetylation by incubating diol **1** with *Candida antarctica* lipase B and vinyl acetate. Slow acylation of **1** was observed with approximately 50% conversion after 24 h to the monoacetate **4** and modest enantioselectivity (60% *ee*). In contrast, when diol **1** was incubated with the previously reported M_{3-5} variant of GOase,[7] rapid oxidation to the monoaldehyde (*P*)-**2** resulted in 80% conversion after 24 h to material with 94% *ee*.

During the oxidation of **1** to **2**, rapid formation of the product (*P*)-**2** with approximately 88% *ee* (see below for assignment of the absolute configuration) was observed after 1 h, followed by a slower increase in enantiomeric purity to a maximum *ee* value of 94% (Figure 1). This increase in the *ee* value, along with the formation of the dialdehyde **3** (14% after 24 h), suggested that the minor enantiomer (*M*)-**2** produced in the enantioselective oxidation of **1** was removed preferentially by a secondary oxidation process to the dialdehyde **3**. Thus, the final enantiomeric purity of (*P*)-**2** resulted from a combination of enantioselective desymmet-

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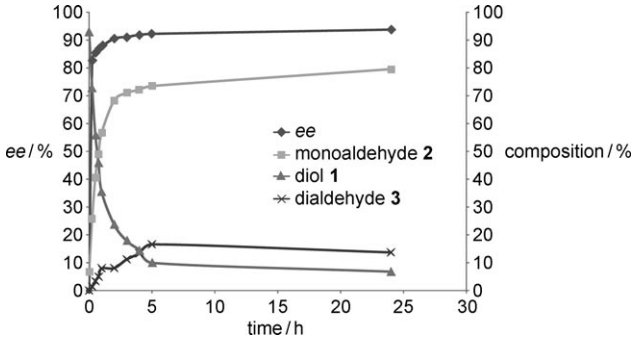

Figure 1. Enantioselective desymmetrization of diol **1** with the GOase M_{3-5} variant. Composition: ▲ diol **1**, ■ monoaldehyde **2**, × dialdehyde **3**; ◆ *ee* value of **2**.

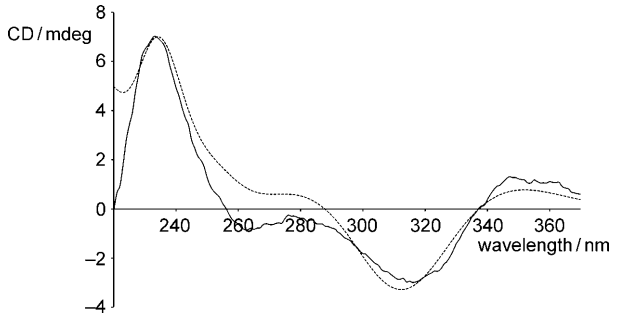

Figure 3. CD spectra of **2**. Solid line: spectrum observed for the less reactive enantiomer of **2**; dashed line: spectrum modeled for the lowest-energy conformer of (*P*)-**2**.

rization and kinetic resolution, as has been noted before for other systems.[6a]

To investigate the enantioselectivity of the kinetic resolution process, we incubated racemic (±)-**2** with the GOase M_{3-5} variant. We observed 89% conversion after 24 h (Figure 2). As expected, the remaining atropisomer was of

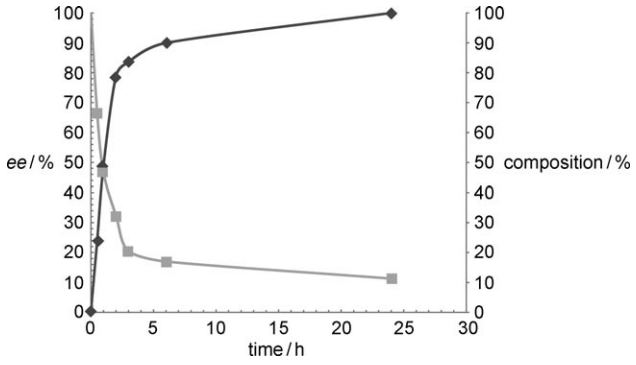

Figure 2. Kinetic resolution of (±)-**2** with the GOase M_{3-5} variant. Composition: ■ monoaldehyde **2**; ◆ *ee* value of **2**.

P configuration with an *ee* value of 99%. The resolution process proceeds more slowly than the desymmetrization reaction. The kinetic resolution under these conditions had a selectivity (*E*) value of approximately 4.[12,13]

The configurational stability of the sample of enantiomerically enriched **2** obtained by kinetic resolution was established by incubation in heptane at 90 °C. A slow first-order decay in the *ee* value from 62 to 34% was observed over a period of several days (see the Supporting Information). From this result, we deduced the half-life for racemization at this temperature to be 120 h, and estimated the barrier to enantiomerization to be greater than 130 kJ mol^{-1} at 90 °C.[14]

The absolute sense of the enantioselective oxidation was established by comparison of experimental and modeled circular dichroism spectra of the starting material remaining after kinetic resolution, (+)-(*P*)-**2** (see the Supporting Information). The modeled spectrum (Figure 3, dotted line) matches closely the experimental CD spectrum (Figure 3, continuous line), with positive maxima aligning at 234 (observed) and 235 nm (modeled) and at 348 (observed) and 353 nm (modeled), a negative maximum at 316 (observed) and 313 nm (modeled), and a shoulder in both observed and modeled spectra at 280 nm. The match confirms that the slower-reacting enantiomer of **2**, and hence also the product of the desymmetrization of **1**, has the *P* configuration (Scheme 1).

The active site of GOase is characterized by a bowl-shaped cleft near the surface of the protein.[15] Modeling of the two enantiomers of **2** into the binding site of GOase revealed that the bulky *tert*-butyl group of the substrate is forced to occupy a position in which it is pointing away from the cleft and towards the surface of the protein. In such a binding mode, the hydroxymethyl group of (*M*)-**2** is placed close to the copper-containing reactive center and poised for oxidation to the aldehyde (Figure 4). This model therefore

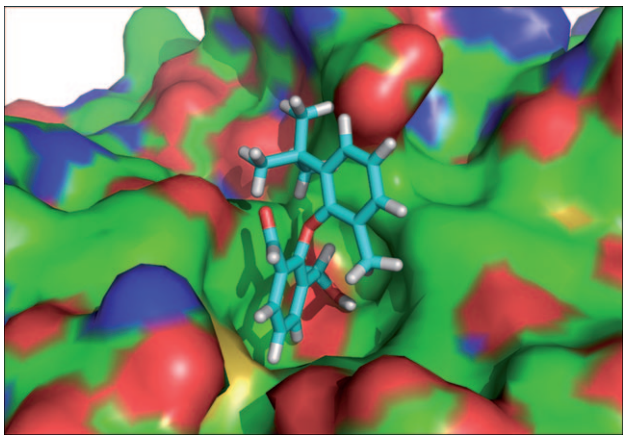

Figure 4. Model of the more reactive enantiomer (*M*)-**2** in the active site of galactose oxidase.

predicts that (*M*)-**2** is the faster-reacting enantiomer in the kinetic resolution process, an observation which is in agreement with the assignment of absolute configuration on the basis of circular dichroism.

We also examined an alternative approach for the synthesis of enantiomerically enriched monoaldehyde **2**: asymmetric reduction of the symmetrical dialdehyde **3** with ketoreductases (KREDs). KREDs have been widely applied to the asymmetric reduction of ketones, particularly benzylic

ketones,[16] but to our knowledge have not previously been used for the desymmetrization of pro-atropisomeric substrates. We screened 17 different KREDs[17] and determined the conversion and *ee* value of the product after 24 h (Table 1). All enzymes were active, and many showed high

Table 1: Reduction of **3** with ketoreductases (KREDs).

Entry	Enzyme[a]	Conversion[b] [%]	*ee* [%]	Configuration[c]
1	KRED101 (*R*)	53	24	*P*
2	KRED103	6	22	*P*
3	KRED104	3	75	*M*
4	KRED105	2	99	*M*
5	KRED106	3	11	*P*
6	KRED108 (*S*)	39	78	*M*
7	KRED109	3	54	*M*
8	KRED110	1	99	*M*
9	KRED114	95	40	*M*
10	KRED115 (*R*)	33	9	*M*
11	KRED116	23	79	*M*
12	KRED117	7	79	*M*
13	**KRED118 (*S*)**	**91**	**77**	***P***
14	KRED119 (*S*)	99	71	*P*
15	KRED120 (*S*)	22	87	*M*
16	**KRED121 (*R*)**	**84**	**61**	***M***
17	KRED124 (*R*)	3	99	*M*

[a] The typical selectivity of the KRED in the reduction of nonsymmetrical diaryl ketones is shown in parentheses (when known).[16] [b] Conversion after 24 h. [c] Major enantiomer produced by reduction.

enantioselectivity (Table 1, entries 4, 8, and 17); however, conversion was often low. Notable success was achieved with KRED118 (91% conversion, 77% *ee* (*P* enantiomer)) and KRED121 (84% conversion, 61% *ee* (*M* enantiomer); Table 1, entries 13 and 16). These KREDs were previously classified as either *S*- or *R*-selective on the basis of their stereoselectivity in the reduction of nonsymmetrical diaryl ketones.[16] Interestingly, this trend was not always followed for the reduction of **3**; that is, enantiomerically enriched (*P*)-**2** was obtained from both *R*-selective KRED101 and *S*-selective KRED118 (Table 1, entries 1 and 13). Similarly, (*M*)-**2** was obtained from both *R*- (KRED121) and *S*-selective (KRED108) enzymes (Table 1, entries 16 and 6). These results suggest that dialdehyde **3** binds at the active site of the ketoreductases in a different mode to that adopted by more conventional benzylic ketones.

Our results suggest that biocatalytic redox reactions may be more widely applicable to the asymmetric synthesis of atropisomers by desymmetrization. We are currently exploring further opportunities in this area.

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