

Article

Stereoselective Enzymatic Reduction of 1,4-Diaryl-1,4-Diones to the Corresponding Diols Employing Alcohol Dehydrogenases

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Abstract: Due to the steric hindrance of the starting prochiral ketones, the preparation of chiral 1,4-diaryl-1,4-diols through the asymmetric hydrogen transfer reaction has been mainly restricted to the use of metal-based catalysts, oxazaborolidines, or organocatalysts. Herein, we demonstrated the versatility of oxidoreductases, finding overexpressed alcohol dehydrogenase from *Ralstonia* sp. (*E. coli*/RasADH) as the most active and stereoselective biocatalyst. Thus, the preparation of a set of 1,4-diaryl-1,4-diols bearing different pattern substitutions in the aromatic ring was achieved with complete diastereo- and enantioselectivity under mild reaction conditions.

Keywords: alcohol dehydrogenases; asymmetric synthesis; bioreduction; 1,4-diols; diketones

1. Introduction

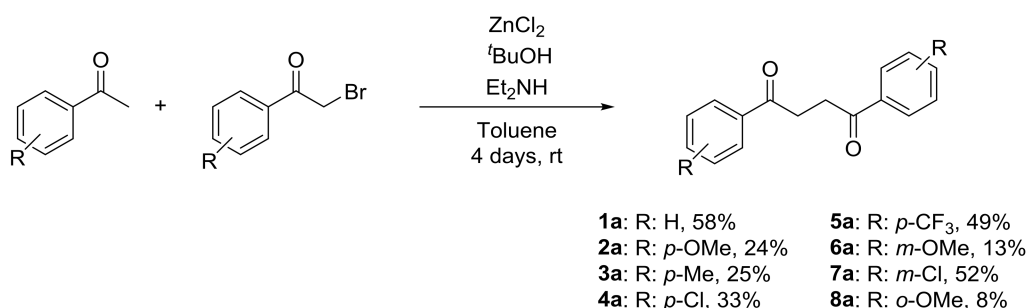
Optically active 1,4-diols can be found as structural motifs in a huge number of biologically active compounds as pharmaceuticals, flavors, and fragrances, but also in chiral ligands and auxiliaries for asymmetric synthesis purposes [1,2]. Their synthetic versatility has also been utilized as precursors of valuable compounds such as 2,5-disubstituted pyrrolidines and phosphine derivatives used as ligands in asymmetric hydrogenations [3–5]. In this context, 1,4-butanediol plays a key role due its applications in the food and cosmetic industry, but also as precursor of plastics, pharmaceuticals, fibers, solvents, and biologically active lactones, among others. For these reasons, the preparation of enantioenriched 1,4-diols using efficient and selective methodologies is a field of interest in organic chemistry. Different asymmetric strategies have been reported for their synthesis, the catalytic asymmetric transfer hydrogenation (CATH) of prochiral 1,4-dicarbonylic compounds being one of the most recurrent methods [6,7]. CATH is the most straightforward approach for obtaining the optically pure diols in quantitative yield, but presents difficulty in that the hydroxy ketone intermediate can also be attained and that (up to) four possible diastereoisomers can be formed. Therefore, several selective chiral catalysts and reducing reagents have been developed for the stereoselective asymmetric reduction of these prochiral diketones, including rhodium or iridium complexes [8], different borane complexes such as oxazaborolidines [9,10], or proline-type derivatives as catalysts in combination with the appropriate reducing agents [11,12].

Biocatalysis has emerged in the last decades as a mature technology for the production of optically active (poly)alcohols by means of the stereoselection displayed by different enzymes [13–17].

Among the wide set of (poly)alcohol structures that can be obtained using biocatalysts, the production of optically active 1,4-dialkyl-1,4-diols and their corresponding acetates has been described mainly by the action of lipases through resolution procedures involving acylation and transesterification processes [18–25], and only the resolution of the bulkier 1-phenylpentane-1,4-diol or its acetate has been successfully achieved [26,27]. Alcohol dehydrogenases (ADHs) are valuable biocatalysts that have been widely employed for the synthesis of chiral alcohols due to their usually excellent selectivity [28–31], including dicarbonyl bioreduction processes [32,33]. Among the wide set of alcohol structures that can be obtained with these enzymes, optically active 1,4-dialkyl-1,4-diols have been described. Efforts have been especially focused on the preparation of chiral 2,5-hexanediol, a key starting material for the preparation of several catalysts and drugs [34–37]. However, until now there are no examples about the enzymatic reduction of 1,4-diaryl-1,4-diketones to obtain the corresponding chiral 1,4-diaryl-1,4-diols, as these substrates are probably too bulky for ADH recognition. In the present paper, we describe for the first time the use of ADHs for the stereoselective preparation under mild reaction conditions (aqueous buffer and 30 °C) of a representative panel of 1,4-diaryl-1,4-diols bearing different pattern substitutions in the aromatic ring.

2. Results and Discussion

As a first step, the chemical synthesis of prochiral 1,4-diketones **1–8a** was developed to later study the biocatalyzed stereoselective synthesis of the optically active 1,4-diols **1–8b**. Different methods have been described for the preparation of these substrates [38,39]. Among them, we have carried out the synthesis of these compounds through the cross aldol condensation of 4'-substituted acetophenones with α -bromo-4'-substituted acetophenones, followed by 1,3-dehydrobromination of these products, and cleavage of the corresponding activated cyclopropyl intermediates in the presence of ZnCl_2 , $t\text{BuOH}$, and Et_2NH (Scheme 1) [40]. Thus, 1,4-diketones **1–8a** were obtained in yields varying from 8% for the *o*-methoxy derivative (**8a**) to 58% for 1,4-diphenylbutane-1,4-dione (**1a**).



Scheme 1. Synthesis of diketones **1–8a** from the corresponding 4'-substituted acetophenones and the α -bromo-4'-substituted acetophenones.

Once synthesized, the obtained diketones were tested in the bioreduction processes catalyzed by a set of commercially available and “made in house” alcohol dehydrogenases. As model substrate 1,4-diphenylbutane-1,4-dione (**1a**) was chosen. Thus, lyophilized cells of *E. coli* overexpressing alcohol dehydrogenases from *Ralstonia* sp. (*E. coli*/RasADH) [41], *Lactobacillus brevis* (*E. coli*/LBADH) [42], *Sphingobium yanoikuyae* (*E. coli*/SyADH) [43], *Thermoanaerobacter ethanolicus* (*E. coli*/TeSADH) [44] and *Rhodococcus ruber* (*E. coli*/ADH-A) [45] were tested. From previous studies, 25 mM substrate concentration was initially considered and 2.5% *v/v* of dimethylsulfoxide (DMSO) was used as cosolvent due to the low solubility of the ketones in the aqueous media, using Tris·HCl buffer 50 mM pH 7.5, and isopropanol (IPA) or glucose dehydrogenase (GDH) with glucose as reducing agents to recycle the nicotinamide cofactor [46]. The reactions were incubated for 24 h at 30 °C, observing only activity when *E. coli*/RasADH was utilized (Table 1). This result is not entirely surprising, as this NADP-dependent enzyme has been previously described as a valuable biocatalyst for the reduction

of sterically hindered substrates [47]. Hence, a conversion of 56% was reached by using this enzyme, leading to the formation of diol (1*S*,4*S*)-**1b** in a highly selective manner (98% *de*, >99% *ee*), not observing the hydroxy ketone intermediate (Table 1, entry 1). Remarkably, 82% conversion was obtained after 48 h maintaining the excellent selectivity (Table 1, entry 2).

In order to optimize the bioreduction using this enzymatic preparation, different conditions were studied (Table 1, entries 3–17). Firstly, in similar conditions the absence of cosolvent led to a decrease in the conversion (72%–82% conversion, entries 2–3). When the usual regeneration system (glucose/GDH) was changed to IPA (entry 4), the diastereoselectivity of the process dropped from 98% *de* to 78% *de*.

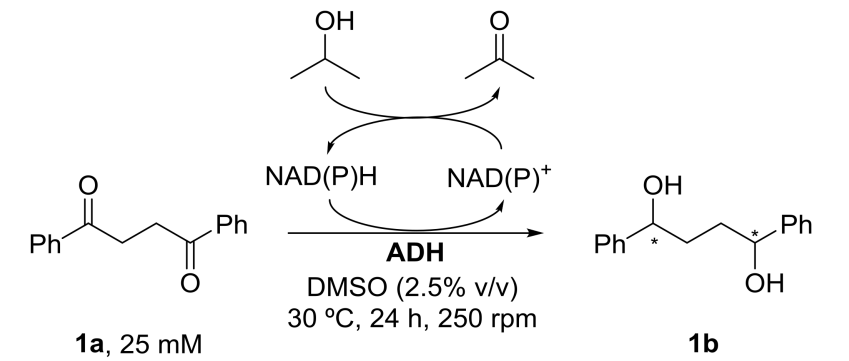
Table 1. Bioreduction of 1,4-diphenylbutane-1,4-dione (**1a**) using *E. coli*/RasADH ^a.

Entry	Regeneration System	Cosolvent	% (v/v)	t (h)	Conversion (%) ^b	<i>de</i> ^{b,c}	<i>ee</i> (%) ^{b,d}
1	Glucose/GDH	DMSO	2.5	24	56	99:1	>99
2	Glucose/GDH	DMSO	2.5	48	82	99:1	>99
3	Glucose/GDH	-	-	48	72	99:1	>99
4	IPA	-	-	48	72	89:11	>99
5	Glucose/GDH	EtOH	2.5	24	57	99:1	>99
6	Glucose/GDH	1,4-dioxane	2.5	24	72	99:1	>99
7	Glucose/GDH	1,4-dioxane	5	24	78	>99	>99
8	Glucose/GDH	1,4-dioxane	10	24	79	99:1	>99
9	Glucose/GDH	1,4-dioxane	10	48	80	99:1	>99
10	Glucose/GDH	MTBE	2.5	24	70	>99	>99
11	Glucose/GDH	MTBE	5	24	83	>99	>99
12	Glucose/GDH	MTBE	10	24	77	>99	>99
13	Glucose/GDH	MTBE	10	48	77	>99	>99
14	Glucose/GDH	THF	2.5	24	72	99:1	>99
15	Glucose/GDH	THF	5	24	88	>99	>99
16	Glucose/GDH	THF	10	24	80	99:1	>99
17	Glucose/GDH	THF	10	48	82	99:1	>99

^a For reaction details, see Materials and methods section; ^b Measured by High Performance Liquid Chromatography (HPLC); ^c Ratio of (1*S*,4*S*) and (1*R*,4*R*) to *meso*-diol; ^d Enantiomeric excess of (1*S*,4*S*)-**1b**.

Taking all these data into account, an exhaustive cosolvent screening was performed (entries 5–17). Ethanol (EtOH), 1,4-dioxane, methyl *tert*-butyl ether (MTBE), and tetrahydrofuran (THF) were chosen as suitable cosolvents for the biotransformation and employed in different quantities. When using 2.5% *v/v* of the organic solvent, for instance 1,4-dioxane, MTBE, and THF (entries 6, 10, and 14), better conversions than DMSO (entry 1) and EtOH (entry 5) were achieved, also affording excellent selectivities. An increase in the amount of these cosolvents from 2.5% to 5% *v/v* revealed even better conversions (entries 7, 11 and 15) and perfect diastereoselectivities (>99% *de*). Finally, the amount of cosolvent was increased up to 10% *v/v* (entries 8, 12, and 16), but unfortunately this did not lead to any improvement. Moreover, higher reaction times (from 24 h to 48 h, entries 9, 13, and 17) did not show better results. It must be pointed out that the hydroxy ketone intermediate was not observed in any case.

Commercial ADHs purchased from Codexis were also tested, as these enzymes have recently demonstrated interesting applications [48]. In this case, IPA was utilized as hydrogen source and phosphate buffer 125 mM pH 7.0 as suitable reaction medium. DMSO (2.5% *v/v*) was added again to solubilize the ketone. Thus, diketone **1a** was a suitable substrate for five of them (69–89% conversion, 74–99% *de*, Table 2). ADH-P2-D03 led to the formation of the opposite enantiomer (1*R*,4*R*)-**1b** (entry 4) with excellent enantioselectivity and 74% *de*. Thus, by modifying the biocatalyst, both enantiomers of diol **1b** could be achieved. Again, the hydroxy ketone intermediate was not detected.

Table 2. Bioreduction of 1,4-diphenylbutane-1,4-dione (**1a**) using commercially available alcohol dehydrogenases (ADHs) ^a.


Entry	ADH	Conversion (%) ^b	<i>de</i> ^{b,c}	<i>ee</i> (%) ^{b,d}
1	P1-B02	85	>99	>99
2	P1-B10	79	>99	>99
3	P1-B12	75	99:1	>99
4	P2-D03	89	87:13	>99 ^e
5	P2-D11	69	98:2	>99

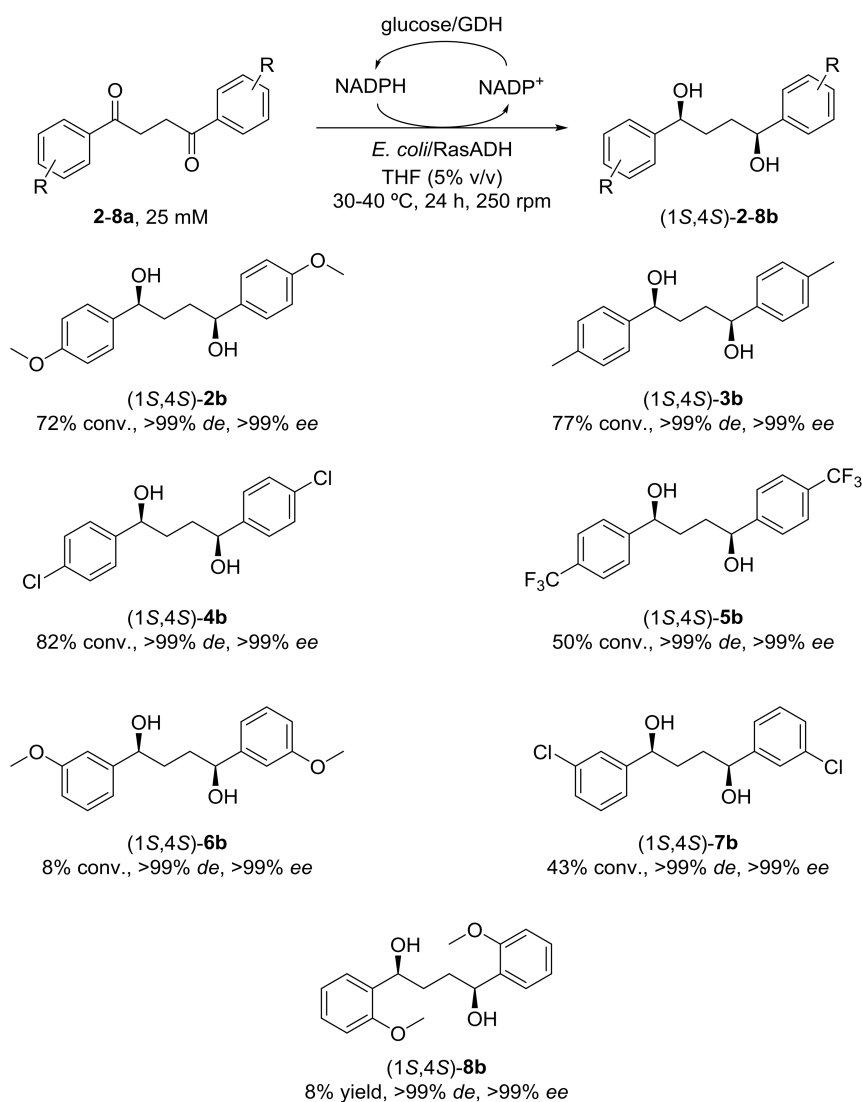
^a For reaction conditions, see Materials and methods section; ^b Measured by HPLC; ^c Ratio of (1*S*,4*S*) and (1*R*,4*R*) to *meso*-(1*R*,4*S*); ^d Enantiomeric excess of (1*S*,4*S*)-**1b**; ^e Enantiomeric excess of (1*R*,4*R*)-**1b**.

Seeking further exploitation of the synthetic approach, first we considered the study of similar substrates that differed at the *para* substitution of the aromatic ring. For this purpose, biotransformations with *E. coli*/RasADH and substrates **2–5a** were set up using the best conditions found in the reduction of diketone **1a** (Table 1, entry 15, 5% *v/v* THF, 30 °C, 24 h). The results are summarized in Scheme 2. In all cases, sole formation of (1*S*,4*S*)-diols **2–5b** was observed (>99% *de* and >99% *ee*), with no detection of the corresponding hydroxy ketone intermediates in any case. For chlorinated substrate **4a** (82% conversion), the results were comparable to those obtained with the model substrate (88% conversion). A small drop in the conversion was observed for methoxylated (**2a**) and methylated (**3a**) compounds (72% and 77%, respectively), while bulkier trifluoromethylated diketone **5a** showed a significant loss of activity (50% conversion).

Then, the study was also performed on substrates bearing *meta* or *ortho* substitution at the phenyl ring. Hence, diketones **6–8a** were used as substrates for RasADH. However, very low yields (8%) were observed for the corresponding enantiopure methoxylated derivatives (1*S*,4*S*)-**6b** and **8b**. A special mention is deserved for *ortho*-substituted diketone **8a**, that provided hydroxy ketone **8c** at higher extent (36%) than the corresponding diol **8b**. Regarding the *m*-chloro derivative **7a**, that showed higher enzymatic conversion (22%), two different experiments were also carried out. On the one hand, the amount of enzyme was doubled leading to the formation of (1*S*,4*S*)-**7b** in 34% conversion after 24 h. On the other hand, the temperature was raised up to 40 °C, obtaining (1*S*,4*S*)-**7b** in 43% conversion after 24 h. These results showed that the substitution pattern had an effect on the enzymatic activity, achieving the most valuable results for the *para*-substituted diketones.

Next, the bioreductions of diketones **2–5a** were also attempted with the commercially available ADHs reported in Table 2. Unfortunately, no conversion was observed in any case, demonstrating the difficulty of these bioconversions, only achieved with RasADH.

Finally, preparative biotransformations up to 100-mg scale were carried out using *E. coli*/RasADH under the optimized reaction conditions (Figure 1), using THF (5% *v/v*) as cosolvent at 30 °C and glucose/GDH as NADPH regeneration system. After 24 h, the conversions obtained were between 40% and 90%, isolating the corresponding diastereo- and enantiopure diols (1*S*,4*S*)-**1–5,7b** in moderate to high yields. The highest yield was obtained for the unsubstituted diol (1*S*,4*S*)-**1b**, which was recovered in 73% yield, while the *m*-chloro compound (**7b**) led to the lowest yield (10%).



Scheme 2. Selective bioreduction of diketones **2–8a** using *E. coli*/RasADH and tetrahydrofuran (THF) as cosolvent.

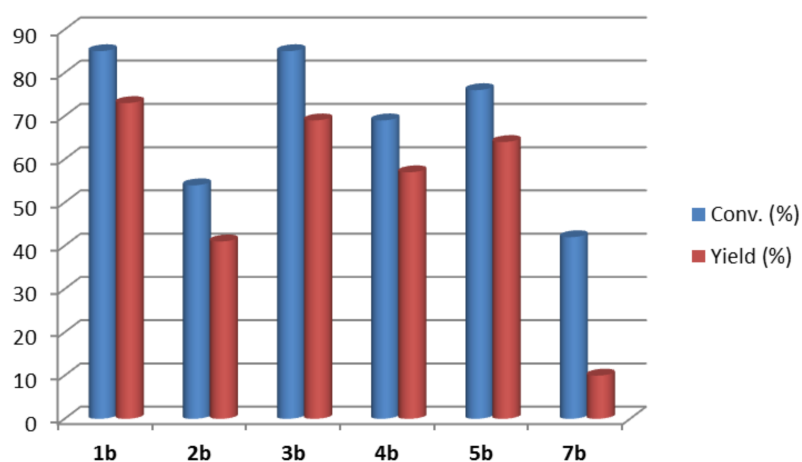


Figure 1. Conversions and isolated yields for the RasADH-catalyzed preparative biotransformations to obtain the optically active diols **(1S,4S)-1–5,7b**.

3. Conclusions

A series of 1,4-diaryl-1,4-diols were synthesized via ADH-catalyzed bioreduction from the corresponding bulky 1,4-diaryl-1,4-diketones. Among the different enzymatic preparations used, ADH from *Ralstonia* sp. (RasADH) overexpressed in *E. coli* afforded the best results in terms of conversions and diastereo- and enantiomeric excess, usually obtaining the (1*S*,4*S*)-diols, and only observing the formation of the hydroxy ketone intermediate in the case of the *o*-methoxylated derivative. The cofactor regeneration system and the addition of an organic cosolvent were studied, showing that glucose/GDH and THF were the best options. Herein we have shown that the bioreduction can be a useful alternative under mild conditions to obtain these appealing chiral compounds, which can be further employed as synthons for the preparation of other valuable derivatives.

4. Materials and Methods

As for the substrates and products studied in this contribution, HPLC separations, HPLC chromatograms of optically active 1,4-diaryl-1,4-diols and NMR spectra, please see the Supplementary Materials.

4.1. General Materials and Methods

The 4'-Substituted acetophenones and α -bromo-4'-substituted acetophenones were purchased from TCI Europe (Zwijndrecht, Belgium). NADPH as enzyme cofactor and all the other chemical reagents were obtained with the highest quality available from Sigma-Aldrich-Fluka (Steinheim, Germany). Alcohol dehydrogenases and GDH were obtained from Codexis Inc., (Redwood City, CA, USA). The production of *E. coli* overexpressed ADHs has been previously reported and these enzymatic preparations have been provided by Prof. Wolfgang Kroutil (University of Graz) [35,41,43].

NMR spectra were recorded on a Bruker AV300 MHz spectrometer (Bruker Co., Faellanden, Switzerland). All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. Measurement of the optical rotation values was carried out at 590 nm on a Autopol IV Automatic polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA). High performance liquid chromatography (HPLC) analyses were performed for conversion, enantiomeric excess, and diastereomeric excess value measurements using a Hewlett Packard 1100 chromatograph UV detector at 210 nm (Agilent Technologies, Inc., Wilmington, DE, USA). As chiral columns, Chiralpak AD-H (25 cm \times 4.6 mM) and Chiralpak IA (25 cm \times 4.6 mM) were used (Chiral Technologies, Mainz, Germany). Thin-layer chromatography (TLC) analyses were conducted with Merck Silica Gel 60 F254 precoated plates (Merck KGaA, Darmstadt, Germany) and visualized with UV and potassium permanganate stain. Column chromatography purifications were performed using Merck Silica Gel 60 (230–400 mesh, Merck KGaA, Darmstadt, Germany).

4.2. General Procedure for the Synthesis of 1,4-Diaryl-1,4-Diketones 1–8a

For the preparation of diketones 1–8a we followed a similar methodology to the one described in the literature [40]. Commercial anhydrous ZnCl₂ (2.72 g, 20 mMol) was placed into a one-neck 250-mL round-bottom flask and dried by melting under vacuum (1 torr) at 250–350 °C for 15–20 min. After cooling under vacuum to room temperature, toluene (10 mL), diethylamine (1.03 mL, 10 mmol) and ^tBuOH (0.95 mL, 10 mmol) were successively added. The mixture was stirred until zinc chloride was fully dissolved (approx. 2 h), and then the corresponding acetophenone (8.0 mMol) and α -bromoacetophenone (5.0 mMol) were successively added. The mixture was stirred at room temperature for 4 days. After this, CH₂Cl₂ (300 mL) was added and the resulting organic phase was successively washed with an aqueous H₂SO₄ 2.0 M solution (2 \times 120 mL), water (1 \times 150 mL) and brine (1 \times 150 mL). The organic phase was dried over Na₂SO₄, filtered, and the solvents were evaporated under reduced pressure. Crude solids, except compounds 6a and 8a that were purified by column chromatography (Hexane/EtOAc 4:1), were purified by crystallization in absolute EtOH in

order to yield the corresponding 1,4-diaryl-1,4-diketones (see Supplementary Materials) **1a** (0.69 g, 58% yield), **2a** (0.36 g, 24%), **3a** (0.33 g, 25%), **4a** (0.51 g, 33%), **5a** (0.91 g, 49%), **6a** (0.19 g, 13%), **7a** (0.79 g, 52%) and **8a** (0.11 g, 8%) [38–40,49–51].

4.3. General Procedure for the Synthesis of Racemic 1,4-Diaryl-1,4-Diols **1–8b**

Diketones **1–8a** (0.3 mMol) were dissolved in THF (2.0 mL) and NaBH₄ (90.8 mg, 2.4 mMol, 8.0 equiv.) was slowly added at room temperature. Reactions were stirred for 2–4 h until completion. After this, an aqueous HCl 1.0 M solution (2.0 mL) was added and the mixtures were extracted with CH₂Cl₂ (2 × 5 mL). The organic phases were dried over Na₂SO₄, filtered and the solvents were evaporated under reduced pressure. The reaction crudes were purified by column chromatography (EtOAc/hexane mixtures), isolating the racemic 1,4-diaryl-1,4-diols (±)-**1b** (61.7 mg, 85% yield), (±)-**2b** (65.2 mg, 72%), (±)-**3b** (65.6 mg, 81%), (±)-**4b** (71.9 mg, 77%), (±)-**5b** (102.1 mg, 90%), (±)-**6b** (30.0 mg, 52%), (±)-**7b** (58.3 mg, 62%) and (±)-**8b** (33.0 mg, 66%).

4.4. General Procedure for the Synthesis of Racemic 4-Hydroxy-1,4-Bis(2-methoxyphenyl)butan-1-one **8c**

Diketone **8a** (0.13 mMol) was dissolved in THF (0.9 mL) and NaBH₄ (21 mg, 0.54 mMol, 4.0 equiv.) was added at room temperature. The reaction was stirred for 30 min until the formation of the hydroxy ketone was observed by TLC analysis. After this, an aqueous HCl 1.0 M solution (2.0 mL) was added and the mixture was extracted with CH₂Cl₂ (2 × 5 mL). The organic layers were dried over Na₂SO₄, filtered and the solvents were evaporated under reduced pressure. The reaction crude was purified by column chromatography (EtOAc/hexane mixtures), isolating the racemic hydroxy ketone (±)-**8c** (2 mg, 5% yield).

4.5. General Procedure for the Enzymatic Conversion of 1,4-Diaryl-1,4-Diols **1–8b** Using Overexpressed *E. coli/RasADH*

Lyophilized *E. coli/RasADH* cells (15–30 mg), the cosolvent (2.5%–10% *v/v*), 1 mM NADP⁺ (60 μL of a 10 mM stock solution), 50 mM glucose (60 μL of a 500 mM stock solution) and glucose dehydrogenase (5 U) were added into an Eppendorf tube containing 1,4-diaryl-1,4-diketones (**1–8a**, 25 mM) in Tris·HCl buffer 50 mM pH 7.5 (420 μL). The reaction was shaken at 30–40 °C and 250 rpm for 24–48 h. After this time, the mixture was extracted with ethyl acetate (2 × 500 μL), the organic layers separated by centrifugation (2 min, 5700 × *g*), combined and finally dried over Na₂SO₄. Conversion, diastereomeric excess and enantiomeric excess values of 1,4-diaryl-1,4-diols **1–8b** were determined by HPLC (see Supplementary Materials).

4.6. General Procedure for the Bioreduction of 1,4-Diphenylbutane-1,4-Dione **1a** Using Commercial Alcohol Dehydrogenases

In a 2.0 mL Eppendorf tube, KRED (2 mg) was added to 900 μL phosphate buffer 125 mM pH 7.0 (1.25 mM MgSO₄, 1 mM NADP⁺) containing 1,4-diphenylbutane-1,4-dione (**1a**, 25 mM), DMSO (25 μL) and ⁱPrOH (100 μL). The reaction was incubated at 250 rpm and 30 °C for 24 h. Then, the mixture was extracted with ethyl acetate (2 × 500 μL), the organic layers separated by centrifugation (2 min, 5700 × *g*), combined and finally dried over Na₂SO₄. Conversion, diastereomeric excess and enantiomeric excess values of 1,4-diphenylbutane-1,4-diol (**1b**) were determined by HPLC.

4.7. Preparative Bioreductions of 1,4-Diarylbutane-1,4-Diones **1–5a**, **7a**, and **8a** Using Overexpressed *E. coli/RasADH*

Lyophilized *E. coli/RasADH* cells (50 mg for 1,4-diketone **1a**, 20 mg for 1,4-diketones **2–4a**, 100 mg for 1,4-diketone **5a**, and 150 mg for 1,4-diketone **7a**). THF (5% *v/v*), NADP⁺ (1 mM), glucose (50 mM), and GDH (50–100 U), were added into an Erlenmeyer flask containing a suspension of the corresponding 1,4-diketone (25 mM) in Tris·HCl buffer 50 mM pH 7.5. The reaction was incubated at 30 °C and 250 rpm for 24 h (**1a–5a**) or at 40 °C and 250 rpm for 48 h (**7a**). Then, the mixture was

extracted with ethyl acetate (3 × 15 mL). The organic layers were separated by centrifugation (5 min, 4000 × g), combined, and finally dried over Na₂SO₄. The reaction crude was purified by column chromatography (EtOAc/hexane mixtures), isolating the enantiopure (1*S*,4*S*)-diols in moderate to high yields (10%–73%).

(–)-(1*S*,4*S*)-1,4-Diphenylbutane-1,4-diol [(1*S*,4*S*)-**1b**]. Yield: 37 mg (73%). *R*_f = 0.36 (40% EtOAc/hexane). Mp: 74–75 °C. ¹H NMR (300.13 MHz, CDCl₃): δ 1.76–1.96 (m, 2H), 1.88–2.02 (m, 2H), 2.59 (s, 2OH), 4.72 (dd, *J*_{HH} = 6.5, 3.9 Hz, 2H), 7.08–7.50 (m, 10H) ppm. ¹³C NMR (300.13 MHz, CDCl₃): δ 35.9 (2CH₂), 74.6 (2CH), 125.8 (4CH), 127.5 (2CH), 128.4 (4CH), 144.6 (2C) ppm. HRMS (ESI⁺, *m/z*): calcd for (C₁₆H₁₈NaO₂)⁺ (M + Na)⁺ 265.1204; found 265.1199. [α]_D²¹ = –57.2 (*c* = 0.5, CHCl₃), described in the literature [52]: [α]_D²⁵ = –59.0 (*c* = 1.0, CHCl₃) for *syn*-(*S*,*S*)-diol.

(–)-(1*S*,4*S*)-1,4-Bis(4-methoxyphenyl)butane-1,4-diol [(1*S*,4*S*)-**2b**]. Yield: 9 mg (41%). *R*_f = 0.21 (40% EtOAc/hexane). ¹H NMR (300.13 MHz, CDCl₃): δ 1.71–1.85 (m, 2H), 1.85–2.00 (m, 2H), 3.82 (s, 6H), 4.68 (m, 2H), 6.88 (d, *J*_{HH} = 8.5, 4H), 7.27 (d, *J*_{HH} = 8.1 Hz, 4H) ppm. ¹³C NMR (300.13 MHz, CDCl₃): δ 34.4 (2CH₂), 53.6 (2CH₃), 81.0 (2CH), 113.9 (4CH), 127.5 (2CH), 135.2 (2C), 159.1 (2C) ppm. HRMS (ESI⁺, *m/z*): calcd for (C₁₈H₂₂NaO₄)⁺ (M + Na)⁺ 325.1415; found 325.1410. [α]_D²¹ = –43.0 (*c* = 0.1, CHCl₃), described in the literature [11]: [α]_D²² = +41.6 (*c* = 1.0, CHCl₃) for *syn*-(*R*,*R*)-diol.

(–)-(1*S*,4*S*)-1,4-Bis(4-methylphenyl)butane-1,4-diol [(1*S*,4*S*)-**3b**]. Yield: 14 mg (69%). *R*_f = 0.27 (40% EtOAc/hexane). Mp: 114–115 °C. ¹H NMR (300.13 MHz, CDCl₃): δ 1.72–1.80 (m, 2H), 1.88–2.04 (m, 2H), 2.28 (s, 2OH), 2.36 (s, 6H), 4.70 (dd, *J*_{HH} = 6.8, 4.4 Hz, 2H), 7.16 (d, *J*_{HH} = 8.0 Hz, 4H), 7.24 (d, *J*_{HH} = 8.0 Hz, 4H) ppm. ¹³C NMR (300.13 MHz, CDCl₃): δ 21.1 (2CH₃), 35.8 (2CH₂), 74.5 (2CH), 125.8 (4CH), 129.1 (4CH), 137.2 (2C), 141.7 (2C) ppm. HRMS (ESI⁺, *m/z*): calcd for (C₁₈H₂₂NaO₂)⁺ (M + Na)⁺ 293.1517; found 293.1512. [α]_D²¹ = –45.2 (*c* = 0.2, CH₂Cl₂), described in the literature [4]: [α]_D²⁵ = –47.0 (*c* = 1.0, CHCl₃) for *syn*-(*S*,*S*)-diol.

(–)-(1*S*,4*S*)-1,4-Bis(4-chlorophenyl)butane-1,4-diol [(1*S*,4*S*)-**4b**]. Yield: 11 mg (57%). *R*_f = 0.45 (40% EtOAc/hexane). Mp: 112–113 °C. ¹H NMR (300.13 MHz, CDCl₃): δ 1.69–2.01 (m, 4H), 2.31 (s, 2OH), 4.71 (d, *J*_{HH} = 5.9 Hz, 2H), 7.09–7.46 (m, 8H) ppm. ¹³C NMR (300.13 MHz, CDCl₃): δ 35.8 (2CH₂), 73.8 (2CH), 127.1 (4CH), 128.5 (4CH), 133.2 (2C), 142.9 (2C) ppm. HRMS (ESI⁺, *m/z*): calcd for (C₁₆H₁₆Cl₂NaO₂)⁺ (M + Na)⁺ 333.0425; found 333.0419. [α]_D²¹ = –22.1 (*c* = 0.2, CHCl₃), described in the literature [11]: [α]_D²¹ = +24.4 (*c* = 1.05, CHCl₃) for *syn*-(*R*,*R*)-diol.

(–)-(1*S*,4*S*)-1,4-Bis[4-(trifluoromethyl)phenyl]butane-1,4-diol [(1*S*,4*S*)-**5b**]. Yield: 63 mg (64%). *R*_f = 0.51 (40% EtOAc/hexane). Mp: 159–160 °C. ¹H NMR (300.13 MHz, MeOD): δ 1.67–1.77 (m, 2H), 1.78–1.92 (m, 2H), 3.30 (s, 2OH), 4.73 (apparent t, *J*_{HH} = 5.6 Hz, 2H), 7.49 (d, *J*_{HH} = 8.2 Hz, 4H), 7.60 (d, *J*_{HH} = 8.2 Hz, 4H) ppm. ¹³C NMR (300.13 MHz, MeOD): δ 34.8 (2CH₂), 72.5 (2CH), 124.4 (q, *J*_{CF} = 271.2 Hz, 2CF₃), 124.7 (q, *J*_{CF} = 3.6 Hz, 4CH), 126.1 (4CH), 128.9 (q, *J*_{CF} = 32.0 Hz, 2C), 149.6 (2C) ppm. HRMS (ESI⁺, *m/z*): calcd for (C₁₈H₁₆F₆NaO₂)⁺ (M + Na)⁺ 401.0952; found 401.0951. [α]_D²⁵ = –20.1 (*c* = 0.4, CHCl₃), described in the literature [3]: [α]_D²⁴ = +19.0 (*c* = 0.1, CHCl₃) for *syn*-(*R*,*R*)-diol.

(–)-(1*S*,4*S*)-1,4-Bis(3-chlorophenyl)butane-1,4-diol [(1*S*,4*S*)-**7b**]. Yield: 8 mg (10%). *R*_f = 0.35 (40% EtOAc/hexane). ¹H NMR (300.13 MHz, CDCl₃): δ 1.80–1.93 (m, 4H), 2.54 (s, 2OH), 4.71 (m, 2H), 7.02–7.51 (m, 8H) ppm. ¹³C NMR (300.13 MHz, CDCl₃): δ 35.8 (2CH₂), 74.0 (2CH), 124.0 (2CH), 126.1 (2CH), 127.8 (2CH), 129.9 (2CH), 134.5 (2C), 146.7 (2C) ppm. HRMS (ESI⁺, *m/z*): calcd for (C₁₆H₁₆Cl₂NaO₂)⁺ (M + Na)⁺ 333.0425; found 333.0426. [α]_D¹⁹ = –41.0 (*c* = 0.1, CHCl₃).

To obtain the hydroxy ketone **8c**, lyophilized *E. coli*/RasADH cells (80 mg), THF (5% *v/v*), NADP⁺ (1 mM), glucose (50 mM), and GDH (50 U), were added into an Erlenmeyer flask containing a suspension of the 1,4-diketone **8a** (20 mg, 25 mM) in Tris·HCl buffer 50 mM pH 7.5. The reaction was

incubated at 30 °C and 250 rpm for 24 h. Then, the mixture was extracted with ethyl acetate (3 × 15 mL) and the organic layers were separated by centrifugation (5 min, 4000× g), combined and finally dried over Na₂SO₄. The reaction crude was purified by column chromatography (EtOAc/hexane mixtures), isolating **8c** (2 mg, 10% yield).

4-Hydroxy-1,4-bis(2-methoxyphenyl)butan-1-one (**8c**). $R_f = 0.41$ (40% EtOAc/hexane). ¹H NMR (300.13 MHz, CDCl₃): δ 2.13–2.36 (m, 2H), 3.00 (s, OH), 3.05–3.29 (m, 2H), 3.85 (s, OCH₃), 3.88 (s, OCH₃), 6.79–7.07 (m, 4H), 7.25 (m, 1H), 7.38 (d, $J_{HH} = 7.5$ Hz, 1H), 7.40–7.51 (t, $J_{HH} = 7.8$ Hz, 1H), 7.69 (dd, $J_{HH} = 7.7, 1.8$ Hz, 1H) ppm. HRMS (ESI⁺, m/z): calcd for (C₁₈H₂₀NaO₄)⁺ (M + Na)⁺ 323.1259; found 323.1260.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/8/4/150/s1>. Substrates and products studied in this contribution, 2. HPLC separations, 3. HPLC chromatograms of optically active 1,4-diaryl-1,4-diols, 4. NMR spectra.

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References

1. Robinson, A.; Aggarwal, V. Asymmetric total synthesis of solandelactone E: Stereocontrolled synthesis of the 2-ene-1,4-diol core through a lithiation–borylation–allylation sequence. *Angew. Chem.* **2010**, *122*, 6823–6825. [[CrossRef](#)]
2. Seebach, D.; Beck, A.K.; Heckel, A. TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries. *Angew. Chem. Int. Ed.* **2001**, *40*, 92–138. [[CrossRef](#)]
3. Denmark, S.E.; Chang, W.-T.T.; Houk, K.N.; Liu, P. Development of chiral bis-hydrazone ligands for the enantioselective cross-coupling reactions of aryldimethylsilanolates. *J. Org. Chem.* **2015**, *80*, 313–366. [[CrossRef](#)] [[PubMed](#)]
4. Chen, H.; Sweet, J.A.; Lam, K.-C.; Rheingold, A.; McGrath, D.V. Chiral amine–imine ligands based on *trans*-2,5-disubstituted pyrrolidines and their application in the palladium-catalyzed allylic alkylation. *Tetrahedron Asymmetry* **2009**, *20*, 1672–1682. [[CrossRef](#)]
5. Melchiorre, P.; Jorgensen, K.A. Direct enantioselective Michael addition of aldehydes to vinyl ketones catalyzed by chiral amines. *J. Org. Chem.* **2003**, *68*, 4151–4157. [[CrossRef](#)] [[PubMed](#)]
6. Foubelo, F.; Nájera, C.; Yus, M. Catalytic asymmetric transfer hydrogenation of ketones: Recent advances. *Tetrahedron Asymmetry* **2015**, *26*, 769–790. [[CrossRef](#)]
7. Hynes, J.T.; Klinman, J.P.; Limbach, H.-H.; Schowen, R.L. (Eds.) *Hydrogen Transfer Reactions*; Wiley-VCH: Weinheim, Germany, 2007; Volumes 1–4.
8. Zheng, L.-S.; Llopis, Q.; Echeverria, P.-G.; Férand, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. Asymmetric transfer hydrogenation of (hetero)arylketones with tethered Rh(III)–*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-1,2-diamine complexes: Scope and limitations. *J. Org. Chem.* **2017**, *82*, 5607–5615. [[CrossRef](#)] [[PubMed](#)]
9. Corey, E.J.; Helal, C.J. Reduction of carbonyl compounds with chiral oxazaborolidine catalyst: A new paradigm for enantioselective catalysis and a powerful new synthetic method. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012. [[CrossRef](#)]
10. Mathre, D.J.; Thomson, A.S.; Douglas, A.W.; Hoogsteen, K.; Carroll, J.D.; Corley, E.G.; Grabowski, E.J.J. A practical process for the preparation of tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole-borane. A highly enantioselective stoichiometric and catalytic reducing agent. *J. Org. Chem.* **1993**, *58*, 2880–2888. [[CrossRef](#)]

11. Li, X.; Zhao, G.; Cao, W.-G. An efficient method for catalytic asymmetric reduction of diketones and application of synthesis to chiral 2,5-diphenylpyrrolidine and 2,5-diphenylthiolane. *Chin. J. Chem.* **2006**, *24*, 1402–1405. [[CrossRef](#)]
12. Aldous, D.J.; Dutton, W.M.; Steel, P.G. A simple enantioselective preparation of (2*S*,5*S*)-2,5-diphenylpyrrolidine and related diaryl amines. *Tetrahedron Asymmetry* **2000**, *11*, 2455–2462. [[CrossRef](#)]
13. Hudlicky, T.; Reed, J.W. Applications of biotransformations and biocatalysis to complexity generation in organic synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3117–3132. [[CrossRef](#)] [[PubMed](#)]
14. Clouthier, C.M.; Pelletier, J.M. Expanding the organic toolbox: A guide to integrating biocatalysis in synthesis. *Chem. Soc. Rev.* **2012**, *41*, 1585–1605. [[CrossRef](#)] [[PubMed](#)]
15. Milner, S.E.; Maguire, A.R. Recent trends in whole cell and isolated enzymes in enantioselective synthesis. *Arkivoc* **2012**, *2012*, 321–382.
16. Torrelo, G.; Hanefeld, U.; Hollmann, F. Biocatalysis. *Catal. Lett.* **2015**, *145*, 309–345. [[CrossRef](#)]
17. Albarrán-Velo, J.; González-Martínez, D.; Gotor-Fernández, V. Stereoselective Biocatalysis. A mature technology for the asymmetric synthesis of pharmaceutical building blocks. *Biocatal. Biotransform.* **2018**, *36*, 102–130. [[CrossRef](#)]
18. Mattson, A.; Öhrner, N.; Hult, K.; Norin, T. Resolution of diols with C₂-symmetry by lipase catalysed transesterification. *Tetrahedron Asymmetry* **1993**, *4*, 925–930. [[CrossRef](#)]
19. Nagai, H.; Morimoto, T.; Achiwa, K. Facile enzymatic synthesis of optically active 2,5-hexanediol derivatives and its application to the preparation of optically pure cyclic sulfate for chiral ligands. *Synlett* **1994**, *1994*, 289–290. [[CrossRef](#)]
20. Caron, G.; Kazlauskas, R.J. Isolation of racemic 2,4-pentanediol and 2,5-hexanediol from commercial mixtures of racemic and *meso* isomers by way of cyclic sulfites. *Tetrahedron Asymmetry* **1994**, *6*, 657–664. [[CrossRef](#)]
21. Persson, B.A.; Larsson, A.L.E.; Le Ray, M.; Bäckvall, J.-E. Ruthenium- and enzyme-catalyzed dynamic kinetic resolution of secondary alcohols. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650. [[CrossRef](#)]
22. Persson, B.A.; Huerta, F.; Bäckvall, J.-E. Dynamic kinetic resolution of secondary diols via coupled ruthenium and enzyme catalysis. *J. Org. Chem.* **1999**, *64*, 5237–5240. [[CrossRef](#)]
23. Edin, M.; Bäckvall, J.-E. On the mechanism of the unexpected facile formation of *meso*-diacetate products in enzymatic acetylation of alkanediols. *J. Org. Chem.* **2003**, *68*, 2216–2222. [[CrossRef](#)] [[PubMed](#)]
24. Martín-Matute, B.; Edin, M.; Bäckvall, J.-E. Highly efficient synthesis of enantiopure diacetylated C₂-symmetric diols by ruthenium- and enzyme-catalyzed dynamic kinetic asymmetric transformation (DYKAT). *Chem. Eur. J.* **2006**, *12*, 6053–6061. [[CrossRef](#)] [[PubMed](#)]
25. Borén, L.; Leijondahl, K.; Bäckvall, J.-E. Dynamic kinetic asymmetric transformation of 1,4-diols and the preparation of trans-2,5-disubstituted pyrrolidines. *Tetrahedron Lett.* **2009**, *50*, 3237–3240. [[CrossRef](#)]
26. Martín-Matute, B.; Bäckvall, J.-E. Ruthenium- and enzyme-catalyzed dynamic kinetic asymmetric transformation of 1,4-diols: Synthesis of γ -hydroxy ketones. *J. Org. Chem.* **2004**, *69*, 9191–9195. [[CrossRef](#)] [[PubMed](#)]
27. Yang, B.; Lihammar, R.; Bäckvall, J.-E. Investigation of the impact of water on the enantioselectivity displayed by CALB in the kinetic resolution of δ -functionalized alkan-2-ol derivatives. *Chem. Eur. J.* **2014**, *20*, 13517–13521. [[CrossRef](#)] [[PubMed](#)]
28. Hollmann, F.; Arends, I.W.C.E.; Holtmann, D. Enzymatic reductions for the chemist. *Green Chem.* **2011**, *13*, 2285–2313. [[CrossRef](#)]
29. Magano, J.; Dunetz, J.R. Large-scale carbonyl reductions in the pharmaceutical industry. *Org. Process Res. Dev.* **2012**, *16*, 1156–1184. [[CrossRef](#)]
30. Nealon, C.M.; Musa, M.M.; Patel, J.M.; Phillips, R.S. Controlling substrate specificity and stereospecificity of alcohol dehydrogenases. *ACS Catal.* **2015**, *5*, 2100–2114. [[CrossRef](#)]
31. Kratzer, R.; Woodley, J.M.; Nidetzky, B. Rules for biocatalyst and reaction engineering to implement effective, NAD(P)H-dependent, whole cell bioreductions. *Biotechnol. Adv.* **2015**, *33*, 1641–1655. [[CrossRef](#)] [[PubMed](#)]
32. Kurina-Sanz, M.; Bisogno, F.R.; Lavandera, I.; Orden, A.A.; Gotor, V. Promiscuous substrate-binding explains the enzymatic stereo- and regiocontrolled synthesis of enantiopure hydroxy ketones and diols. *Adv. Synth. Catal.* **2009**, *351*, 1842–1848. [[CrossRef](#)]
33. Chen, Y.; Chen, C.; Wu, X. Dicarboxyl reduction by single enzyme for the preparation of chiral diols. *Chem. Soc. Rev.* **2012**, *41*, 1742–1753. [[CrossRef](#)] [[PubMed](#)]

34. Goldberg, K.; Edegger, K.; Kroutil, W.; Liese, A. Overcoming the thermodynamic limitation in asymmetric hydrogen transfer reactions catalyzed by whole cells. *Biotechnol. Bioeng.* **2006**, *95*, 192–198. [[CrossRef](#)] [[PubMed](#)]
35. De Gonzalo, G.; Lavandera, I.; Faber, K.; Kroutil, W. Enzymatic reduction of ketones in “micro-aqueous” media catalyzed by ADH-A from *Rhodococcus ruber*. *Org. Lett.* **2007**, *9*, 2163–2166. [[CrossRef](#)] [[PubMed](#)]
36. Machielsen, R.; Leferink, N.G.H.; Hendriks, A.; Brouns, S.J.J.; Hennemann, H.-G.; Daussmann, T.; Oost, J. Laboratory evolution of *Pyrococcus furiosus* alcohol dehydrogenase to improve the production of (2S,5S)-hexanediol at moderate temperatures. *Extremophiles* **2008**, *12*, 587–594. [[CrossRef](#)] [[PubMed](#)]
37. Müller, M.; Katzberg, M.; Bertau, M.; Hummel, W. Highly efficient and stereoselective biosynthesis of (2S,5S)-hexanediol with a dehydrogenase from *Saccharomyces cerevisiae*. *Org. Biomol. Chem.* **2010**, *8*, 1540–1550. [[CrossRef](#)] [[PubMed](#)]
38. Mizar, P.; Wirth, T. Flexible stereoselective functionalizations of ketones through umpolung with hypervalent iodine reagents. *Angew. Chem. Int. Ed.* **2014**, *53*, 5993–5997. [[CrossRef](#)] [[PubMed](#)]
39. Hua, G.; Henry, J.B.; Li, Y.; Mount, A.R.; Slawin, A.M.Z.; Woollins, J.D. Synthesis of novel 2,5-diarylselenophenes from selenation of 1,4-diarylbutane-1,4-diones or methanol/arylacetylenes. *Org. Biomol. Chem.* **2010**, *8*, 1655–1660. [[CrossRef](#)] [[PubMed](#)]
40. Nevar, N.M.; Kel'in, A.V.; Kulinkovich, O.G. One step preparation of 1,4-diketones from methyl ketones and α -bromomethyl ketones in the presence of $ZnCl_2 \cdot t-BuOH \cdot Et_2NR$ as a condensation agent. *Synthesis* **2000**, *9*, 1259–1262. [[CrossRef](#)]
41. Lavandera, I.; Kern, A.; Ferreira-Silva, B.; Glieder, A.; de Wildeman, S.; Kroutil, W. Stereoselective bioreduction of bulky-bulky ketones by a novel ADH from *Ralstonia* sp. *J. Org. Chem.* **2008**, *73*, 6003–6005. [[CrossRef](#)] [[PubMed](#)]
42. Leuchs, S.; Greiner, L. Alcohol dehydrogenase from *Lactobacillus brevis*: A versatile robust catalyst for enantioselective transformations. *Chem. Biochem. Eng. Q.* **2011**, *25*, 267–281.
43. Lavandera, I.; Kern, A.; Resch, V.; Ferreira-Silva, B.; Glieder, A.; Fabian, W.M.F.; de Wildeman, S.; Kroutil, W. One-way biohydrogen transfer for oxidation of *sec*-alcohols. *Org. Lett.* **2008**, *10*, 2155–2158. [[CrossRef](#)] [[PubMed](#)]
44. Heiss, C.; Laivenieks, M.; Zeikus, J.G.; Phillips, R.S. Mutation of cysteine-295 to alanine in secondary alcohol dehydrogenase from *Thermoanaerobacter ethanolicus* affects the enantioselectivity and substrate specificity of ketone reductions. *Bioorg. Med. Chem.* **2001**, *9*, 1659–1666. [[CrossRef](#)]
45. Stampfer, W.; Kosjek, B.; Moitzi, C.; Kroutil, W.; Faber, K. Biocatalytic asymmetric hydrogen transfer. *Angew. Chem. Int. Ed.* **2002**, *41*, 1014–1017. [[CrossRef](#)]
46. Abu, R.; Woodley, J. Application of enzyme coupling reactions to shift thermodynamically limited biocatalytic reactions. *ChemCatChem* **2015**, *7*, 3094–3105. [[CrossRef](#)]
47. Man, H.; Kędziora, K.; Kulig, J.; Frank, A.; Lavandera, I.; Gotor-Fernández, V.; Rother, D.; Hart, S.; Turkenburg, J.P.; Grogan, G. Structures of alcohol dehydrogenases from *Ralstonia* and *Sphingobium* spp. reveal the molecular basis for their recognition of ‘bulky–bulky’ ketones. *Top. Catal.* **2014**, *57*, 356–365. [[CrossRef](#)]
48. García-Cerrada, S.; Redondo-Gallego, L.; Martínez-Olid, F.; Rincón, J.A.; García-Losada, P. Practical manufacture of 4-alkyl-4-aminocyclohexylalcohols using ketoreductases. *Org. Process Res. Dev.* **2017**, *21*, 779–784. [[CrossRef](#)]
49. Ceylan, M.; Gürdere, M.B.; Budak, Y.; Kazaz, C.; Seçen, H. One-step preparation of symmetrical 1,4-diketones from α -halo ketones in the presence of $Zn-I_2$ as a condensation agent. *Synthesis* **2004**, *35*, 1750–1754. [[CrossRef](#)]
50. Fujita, K.; Shinokubo, H.; Oshima, K. Highly diastereoselective tandem reduction–allylation reactions of 1,4-diketones with zirconocene–olefin complexes. *Angew. Chem. Int. Ed.* **2003**, *42*, 2550–2552. [[CrossRef](#)] [[PubMed](#)]
51. Xuan, J.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. Visible-light-induced C-S bond activation: Facile access to 1,4-diketones from β -ketosulfones. *Chem: Eur. J.* **2014**, *20*, 3045–3049. [[CrossRef](#)] [[PubMed](#)]
52. Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Hametner, C.; Fröhlich, J.; Kirchner, K. Synthesis and characterization of new chiral palladium β -diimine complexes. *J. Organomet. Chem.* **2007**, *692*, 1048–1057. [[CrossRef](#)]

