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Chemoenzymatic Deracemization of Secondary Alcohols by using a TEMPO–Iodine–Alcohol Dehydrogenase System

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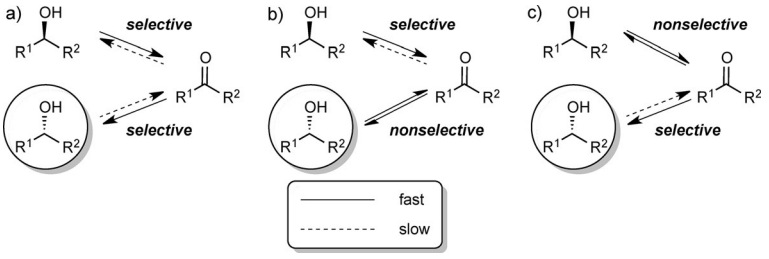
A deracemization system for secondary alcohols was established after the analysis of individual steps and their compatibility in one pot. The chemical oxidation and bioreduction occurred in a sequential manner to yield 1-arylethanols and lineal aliphatic alcohols with excellent conversions and enantiomeric excess values. The oxidation step was performed by using 2,2,6,6-tetramethylpiperidin-1-oxyl and iodine. This chemical process was extremely favored by sonication, which allowed quantitative formation of the corresponding ketone intermediates after just 1 h. Simple destruction of iodine in the same pot allowed sequential bioreduction of the ketones by using either Prelog or antiPrelog enzymes, which led to the preparation of the enantiopure alcohols in excellent yields.

Enzymes have stormed over the last decades as useful tools in the search of sustainable methodologies towards chiral compounds in theoretical 100% yield, breaking the inherent limitations associated with classical kinetic resolutions.[1] The possibility of developing dynamic kinetic resolutions, deracemization from racemates,[2] or stereoselective desymmetrizations starting from prochiral or *meso* compounds[3] allows a reduction in cost and the elimination of waste, both of which are particularly attractive for the implementation of biocatalytic strategies in the chemical industry. In this context, the most common deracemization strategies involve stereoinversion or cyclic modes.

Deracemization of a racemate by stereoinversion (Scheme 1 a) consists in the selective transformation of one substrate enantiomer into a nonchiral intermediate, which subsequently reacts to give the final product with opposite configuration ideally to obtain a single enantiomer.[4] A few (chemo)-enzymatic deracemization protocols have been described for the asymmetric synthesis of broad families of organic compounds, such as amino acid and amino derivatives.[4,5] Nevertheless, the deracemization of secondary alcohols has attracted much attention on the basis of simple oxidation–reduction sequences and is usually accomplished by multienzymatic combinations.[4,6] With that purpose, the action and high selectivity of oxidoreductases such as alcohol dehydrogenases (ADHs) has been fully exploited.[7] Redox enzymes are useful biocatalysts for both the oxidation of alcohols and the selective reduction of ketones by using whole cells and semipurified or purified enzymes.[8] In addition, it is worth mentioning that these fully enzymatic deracemizations occur under mild reaction conditions that permit the presence of additional functional groups in the reactive substrate such as esters[9] and carboxylic acids.[10]



Scheme 1. Different pathways to deracemize secondary alcohols by combining a) two stereoselective steps, b) one selective step for oxidation and one nonselective step for reduction, and c) one nonselective step for oxidation and one selective step for reduction. The approach used in this article belongs to pathway c.

The main difficulty of deracemization through stereoinversion resides in the perfect combination of enantioselective oxidation and stereoselective reduction steps without detriment to the conversion or the enantiomeric excess of the target optically active alcohol. In this sense, cyclic deracemization systems of secondary alcohols (Scheme 1 b, c) provide less exigent reaction conditions, as they make use of a nonselective process. One approach can be the selective (enzymatic) oxidation of one enantiomer into the ketone, followed by nonselective chemical reduction in a stepwise fashion (Scheme 1 b).[11] On the other hand, it is also possible to achieve deracemization by combining a nonselective oxidation step of the alcohol with stereoselective (enzymatic) reduction of the prochiral ketone

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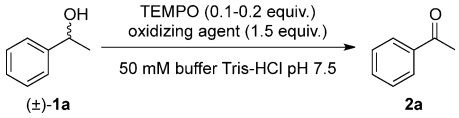
formed (Scheme 1 c). This synthetic strategy has been satisfactorily reported by using a metal complex as the oxidant[12] and by applying other redox biocatalysts such as laccases in combination with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO).[13] Clearly, in this case the oxidation reaction must be quantitative to obtain a proper deracemization protocol.

Herein, we report a versatile and commonly applicable deracemization strategy for secondary alcohols involving nonselective chemical oxidation by employing the iodine/TEMPO system and a stereoselective bioreduction step. After optimization of the individual processes, both were combined in a one-pot and stepwise manner to yield the (*R*)- or (*S*)-alcohols depending on the stereopreference of the ADH used in the reduction of the ketone intermediate.

The oxidation of alcohols for the formation of carbonyl compounds is a key reaction in organic synthesis.[14] Therefore, a number of strategies have appeared in the literature involving metal or organic oxidants such as chromium(VI) salts, manganese dioxide, activated dimethyl sulfoxides, and hypervalent iodine reagents, among others. In the search for a simple and compatible approach with the bioreduction process, the use of a catalytic amount of TEMPO in combination with several oxidizing agents was tested to oxidize the model substrate 1-phenylethanol (**1 a**). A premise for this study was the development of the oxidative process in a buffer system, which is the medium required for the ADH-catalyzed bioreduction (Scheme 2). Tris-HCl buffer pH 7.5 and a catalytic amount of



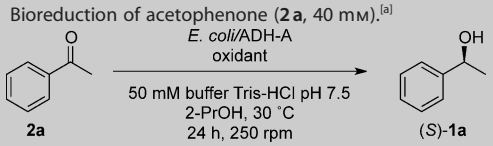
Scheme 2. Oxidation of (±)-1-phenylethanol (**1 a**) with a catalytic amount of TEMPO and different oxidizing agents in Tris-HCl buffer pH 7.5.

TEMPO were initially selected for screening. A series of oxidants including sodium hypochlorite (NaOCl),[15] phenyliodine(III) diacetate (PIDA),[16] *N*-chlorosuccinimide (NCS),[17] and iodine[18] were tested and used in slight excess amounts at different temperatures (30–50 °C), and significant conversions into acetophenone (**2 a**) were found.

Once the chemical oxidation of a series of secondary alcohols was explored, we focused on the bioreduction step of **2 a** by using a Prelog ADH, such as the one from *Rhodococcus ruber* (ADH-A),[19] and 2-PrOH (6.4% v/v) as the hydrogen donor in a "coupled-substrate" approach.[20] To identify compatible conditions with the oxidizing systems, the bioreduction of **2 a** was studied in the presence of the previously tested chemical oxidants by using favorable conditions for the overexpressed ADH-A mediated reductions (Table 1).

The enantiomeric excess (*ee*) of (*S*)-1-phenylethanol was slightly affected by the presence of TEMPO or PIDA, which resulted in a notable decrease in the conversion (Table 1, entries 2–4) that dramatically diminished upon using NCS (Table 1, entry 5). In the search for compatible redox conditions for the overall deracemization process, iodine was then selected as the oxidant, as it can be easily quenched afterwards by sodium thiosulfate, which converts the excess amount of iodine into harmless iodide anions (Table 1, entries 6 and 7). With this treatment, the activity of ADH-A remained unaltered in the stereoselective reduction of acetophenone and a total conversion was obtained in the bioreduction step (Table 1, entry 7). In summary, iodine was selected as a mild oxidant for two main and important reasons. On the one hand, it allows the simple reoxidation of TEMPO (0.1 equiv.) in aqueous medium under mild reaction conditions. On the other hand, the destruction of the excess amount of iodine into iodide ions can be accomplished in one pot without detriment to the enzymatic activity, which is in contrast to the inhibition or competitive oxidative reverse reaction observed with other oxidants tested in this study.

Table 1. Bioreduction of acetophenone (**2 a**, 40 mM).[a]



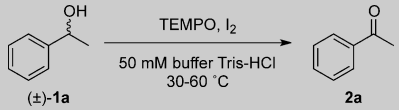
Entry	Oxidant (equiv.)	*c* [%][b]	*ee* [%][b]
1	–	>99	>99
2	TEMPO (0.1)	85	96
3	PIDA (2)	91	>99
4	TEMPO/PIDA (0.1/2)	73	>99
5	TEMPO/NCS (0.1/1.5)	2	n.d.
6	TEMPO/PIDA (0.1/2)[c]	85	99
7	TEMPO/I_2 (0.1/2)[c]	>99	>99

[a] Bioreduction was performed by using ADH-A and 2-PrOH (6.4% v/v) in the presence of the different oxidizing agents at 30 °C for 24 h at 250 rpm. [b] Conversion and enantiomeric excess values were measured by GC analyses (see the Supporting Information for details). n.d. = not determined. [c] $Na_2S_2O_3$ saturated aqueous solution (200 μL) was supplemented before enzyme addition.

Once a convenient oxidation protocol was found, an exhaustive optimization study was performed by searching for suitable conditions for the complete oxidation of 1-phenylethanol (Table 2). Different parameters that could affect the reactivity of the catalytic TEMPO/iodine system were analyzed, such as the amount of TEMPO, number of equivalents of iodine, substrate concentration, pH, and temperature.

The first attempts for the oxidation of **1 a** were performed by using a 50 mM Tris-HCl buffer pH 7.5, a catalytic amount of TEMPO (0.1–0.2 equiv.), and an excess amount of iodine (1.5–2 equiv.), but low conversions were obtained (Table 2, entries 1–3). The presence of a hydrophobic cosolvent such as hexane (10% v/v; Table 2, entry 4) did not lead to any improvement. A significant increase in the conversion values was achieved at pH 9 (Table 2, entry 5), which allowed the 50% conversion to be surpassed if 0.2 equivalents of TEMPO were employed (Table 2, entry 6). This is due to the fact that TEMPO works better under basic conditions. Unfortunately, the activity of the system dramatically decreased at higher substrate concentrations (80-160 mM; Table 2, entries 7 and 8). Similar results were attained by using lower concentrations of the alcohol or higher temperatures (Table 2, entries 9–11). A similar

Table 2. TEMPO/iodine-catalyzed oxidation of (±)-1-phenylethanol (**1 a**) in aqueous medium.



(±)-**1a** **2a**

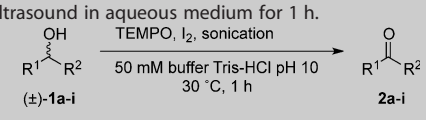
Entry	TEMPO [equiv.]	I_2 [equiv.]	**1 a** [mM]	pH	*T* [°C]	*t* [h]	*c* [%][a]
1	0.1	1.5	40	7.5	30	16	16
2	0.2	1.5	40	7.5	30	16	23
3	0.1	2	40	7.5	30	16	18
4[b]	0.1	1.5	40	7.5	30	16	14
5	0.1	1.5	40	9	30	16	48
6	0.2	1.5	40	9	30	16	54
7	0.2	1.5	80	9	30	16	30
8	0.2	1.5	160	9	30	16	22
9	0.2	1.5	20	9	30	16	49
10	0.2	1.5	40	9	60	16	52
11	0.2	1.5	20	9	60	16	57
12	0.2	1.5	20	10	30	16	52
13	0.2	1.5	20	10	60	16	60
14[c]	0.2	1.5	20	10	30	1	98

[a] Conversion values were measured by GC analyses (see the Supporting Information for details). [b] Hexane (10% v/v) was used as the cosolvent. [c] Ultrasound was used over a period of 1 h.

trend was observed by using Tris-HCl buffer pH 10 (Table 2, entries 12 and 13). Remarkably, the oxidation of **1 a** was almost complete after sonication of the reaction mixture for 1 h (Table 2, entry 14).

Once the optimal conditions were found for the oxidation of **1 a**, extension of this methodology to a series of aromatic and aliphatic racemic alcohols was considered (Table 3). Different

Table 3. TEMPO/iodine-catalyzed oxidation of racemic alcohols **1** (20 mM) by using ultrasound in aqueous medium for 1 h.



(±)-**1a-i** **2a-i**

Entry	R^1	R^2	*c* [%][a]
1	C_6H_5 (**1 a**)	Me	>99
2	3-$MeOC_6H_4$ (**1 b**)	Me	>99
3	3-$O_2NC_6H_4$ (**1 c**)	Me	39
4	3-ClC_6H_4 (**1 d**)	Me	>99
5	4-ClC_6H_4 (**1 e**)	Me	>99
6	2-ClC_6H_4 (**1 f**)	Me	>99
7	2,4-$Cl_2C_6H_3$ (**1 g**)	CH_2Cl	<1
8	cyclohexyl (**1 h**)	Me	>99
9	$(CH_2)_5Me$ (**1 i**)	Me	>99

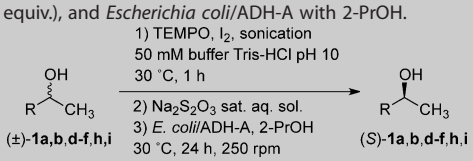
[a] Conversion values were measured by GC analyses (see the Supporting Information for details).

substitution patterns were chosen in the *meta* position of the aromatic ring (methoxy, chloro, and nitro; Table 3, entries 2–4), and we also studied the effect of the same substituent at different positions on the phenyl moiety (chloro group; Table 3, entries 4–6). In addition, β-chlorinated (Table 3, entry 7) and aliphatic (Table 3, entries 8 and 9) alcohols were finally selected to have a broader overview of the potential of this oxidizing system.

Focusing on *meta*-substituted substrates, complete conversions were found with a moderately activating (Table 3, entry 2) or deactivating group (Table 3, entry 4). On the contrary, a strong electron-withdrawing group such as the nitro functionality led to poor 39% conversion upon using this oxidizing system (Table 3, entry 3). Regardless of the position of the chloro substituent, the catalytic system was active, and in all cases quantitative conversions were found (Table 3, entries 4–6). Nevertheless, the oxidation of substrate **1 g** with a chlorine atom at the β position did not proceed at any extension (Table 3, entry 7). This result can be explained, as these activated alcohols can be oxidized under strong conditions.[21] Finally, aliphatic alcohols reacted effectively to yield 1-cyclohexylethanone (Table 3, entry 8) and 2-octanone (Table 3, entry 9) in quantitative conversions.

Once the TEMPO/iodine system was found to be efficient for the complete chemical oxidation of secondary alcohols (Table 3), *E. coli*/ADH-A, without the need of an external cofactor,[19] was used in a stepwise fashion to reduce the corresponding ketones on the basis of the excellent activity of this enzyme under the conditions for the oxidative process shown in Table 1. Gratifyingly, the corresponding (*S*)-alcohols were produced in enantiopure form and with conversions over 95% starting from the racemic forms (Table 4).

Table 4. Deracemization of alcohols **1** (20 mM) with TEMPO (0.2 equiv.), iodine (2 equiv.), and *Escherichia coli*/ADH-A with 2-PrOH.



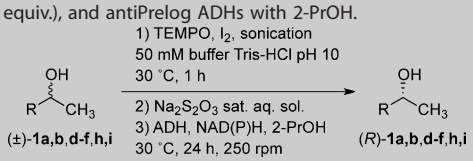
(±)-**1a,b,d-f,h,i** (*S*)-**1a,b,d-f,h,i**

Entry	R	*c* [%][a]	*ee* [%][b]
1	C_6H_5 (**1 a**)	96	>99
2	3-$MeOC_6H_4$ (**1 b**)	96	>99
3	3-ClC_6H_4 (**1 d**)	99	>99
4	4-ClC_6H_4 (**1 e**)	99	>99
5	2-ClC_6H_4 (**1 f**)	99	>99
6	cyclohexyl (**1 h**)	98	>99
7	$(CH_2)_5Me$ (**1 i**)	96	>99

[a] Conversion values of the bioreduction reaction were measured by GC analyses (see the Experimental Section for details). [b] Enantiomeric excess values of the resulting deracemized alcohols were measured by GC analysis on a chiral stationary phase (see the Supporting Information for details).

Trying to obtain their alcohol antipodes, antiPrelog ADHs were tested in the bioreduction step of the sequential deracemization (Table 5). For this study, two different semipurified enzymes were considered: the NADPH-dependent ADH from *Lactobacillus brevis* (LBADH)[22] and the NADH-dependent and commercially available evo-1.1.200.[23] Satisfactorily, all the substrates were recognized by both enzymes, so after the chemical oxidation and quenching, the stereoselective bioreduction

Table 5. Deracemization of alcohols **1** (20 mM) with TEMPO (0.2 equiv.), iodine (2 equiv.), and antiPrelog ADHs with 2-PrOH.



Entry	R	ADH	Yield [%][a]	*ee* [%][b]
1	C_6H_5 (**1a**)	LB	91	99
2	C_6H_5 (**1a**)	evo-1.1-200	91	99
3	3-MeOC_6H_4 (**1b**)	LB	99	>99
4	3-MeOC_6H_4 (**1b**)	evo-1.1-200	99	>99
5	3-ClC_6H_4 (**1d**)	LB	92	>99
6	3-ClC_6H_4 (**1d**)	evo-1.1-200	95	>99
7	4-ClC_6H_4 (**1e**)	LB	99	>99
8	4-ClC_6H_4 (**1e**)	evo-1.1-200	99	>99
9	2-ClC_6H_4 (**1f**)	LB	99	>99
10	2-ClC_6H_4 (**1f**)	evo-1.1-200	99	>99
11	cyclohexyl (**1h**)	LB	98	>99
12	cyclohexyl (**1h**)	evo-1.1-200	98	>99
13	$(CH_2)_5$Me (**1i**)	LB	95	>99
14	$(CH_2)_5$Me (**1i**)	evo-1.1-200	94	>99

[a] Conversion values of the alcohols were measured by GC analysis (see the Experimental Section for details). [b] Enantiomeric excess values of the resulting deracemized alcohols were measured by GC analysis with a chiral stationary phase (see the Supporting Information for details).

of the corresponding ketones led to the enantiopure (*R*)-alcohols with conversions over 90%.

In conclusion, chemoenzymatic deracemization strategies offer significant advantages in chemical synthesis for the preparation of enantiopure compounds with high yields. Dynamic kinetic resolution has been fully exploited over the last two decades, whereas other deracemization strategies involving the use of redox processes in combination with chemical and enzymatic catalysts have been less explored. Herein, we have developed a deracemization protocol for secondary alcohols on the basis of the chemical oxidation of the racemates and the sequential bioreduction of the intermediate ketones formed in the same vessel. A simple and cheap system such as TEMPO together with iodine allowed the effective oxidation of the alcohols, which required ultrasound conditions for the fast quantitative formation of the ketones after just 1 h. This system was fully compatible with the alcohol dehydrogenase-catalyzed bioreduction of the resulting ketones, after quenching of the excess amount of iodine with an aqueous $Na_2S_2O_3$ saturated solution. Gratifyingly, different Prelog and antiPrelog alcohol dehydrogenases efficiently mediated the preparation of enantiopure (*S*)- and (*R*)-alcohols with conversions over 90%, starting from inexpensive racemates.

Experimental Section

General Methods

Chemical reagents were purchased from different commercial sources (Sigma–Aldrich, Acros, and Fluka) and were used without further purification. The alcohol dehydrogenase from *Lactobacillus brevis* (LBADH, 300 U mL^{-1}) was purchased from Codexis. Evo-1.1.200 (1716 U mg^{-1}) was acquired from Evocatal. *Escherichia coli* strains to overexpress ADH-A from *Rhodococcus ruber* were kindly provided by Prof. Wolfgang Kroutil (University of Graz). GC analyses were performed for conversion and enantiomeric excess measurements (see the Supporting Information).

Chemical oxidations

Iodine (30 mg, 1.5 equiv.) and TEMPO (2.5–5 mg, 0.1–0.2 equiv.) were successively added over a solution of alcohol **1a–i** (0.08 mmol, 20 mM) in 50 mM Tris-HCl buffer at pH 10 (4 mL) in a 15 mL falcon tube. The mixture was sonicated for 1 h and conversions were measured by GC analysis.

General procedure for the bioreduction of ketones 2a–i with ADH-A overexpressed in *E. coli*

E. coli/ADH-A cells (15 mg) and 2-PrOH (32 μL) were successively added to an Eppendorf tube containing **2a–i** (0.08 mmol) in 50 mM Tris-HCl buffer pH 10 (468 μL). The mixture was shaken at 30 °C and 250 rpm for 24 h. Then, the mixture was extracted with EtOAc (2×500 μL), centrifuged (13 000 rpm, 90 s), and dried (Na_2SO_4). The substrate conversion and the enantiomeric excess of alcohol **1a–i** were measured by GC analysis.

General procedure for the bioreduction of ketones 2a–i with LBADH

LBADH (10 μL, 3 U), 1 mM NADPH (60 μL of a 10 mM stock solution), 1 mM $MgCl_2$ (60 μL of a 10 mM stock solution), and 2-PrOH (32 μL) were successively added to an Eppendorf tube containing **2a–i** (0.08 mmol) in 50 mM Tris-HCl buffer pH 10 (468 μL). The mixture was shaken at 30 °C and 250 rpm for 24 h. Then, the mixture was extracted with EtOAc (2×500 μL), centrifuged (13 000 rpm, 90 s), and dried (Na_2SO_4). The substrate conversion and the enantiomeric excess of alcohol **1a–i** were measured by GC analysis.

General procedure for the bioreduction of ketones 2a–i with evo-1.1.200

Evo-1.1.200 (50 μL, 3 U), 1 mM NADH (60 μL of a 10 mM stock solution), 1 mM $MgCl_2$ (60 μL of a 10 mM stock solution), and 2-PrOH (25 μL) were successively added to an Eppendorf tube containing **2a–i** (0.08 mmol) in 50 mM Tris-HCl buffer pH 10 (468 μL). The mixture was shaken at 30 °C and 250 rpm for 24 h. Then, the mixture was extracted with EtOAc (2×500 μL), centrifuged (13 000 rpm, 90 s), and dried (Na_2SO_4). The substrate conversion and the enantiomeric excess of alcohol **1a–i** were measured by GC analysis.

Deracemization experiments by using ADH-A overexpressed in *E. coli*

Iodine (30 mg, 1.5 equiv.) and TEMPO (2.5 mg, 0.1 equiv.) were successively added over a solution of alcohol **1a–i** (0.8 mmol, 20 mM) in 50 mM Tris-HCl buffer pH 10 (4 mL). The mixture was sonicated for 1 h at room temperature until complete conversion to ketone **2a–i**. After this time, the reaction was stopped by adding a saturated $Na_2S_2O_3$ aqueous solution (300 μL). An aliquot (500 μL) was then withdrawn, and *E. coli*/ADH-A cells (15 mg) and 2-propanol (32 μL) were successively added. The mixture was shaken at 30 °C

and 250 rpm for additional 24 h. Then, the mixture was extracted with EtOAc (2×500 μL), centrifuged (13000 rpm, 90 s), and dried (Na_2SO_4). The substrate conversion and enantiomeric excess of (*S*)-alcohols **1a–i** were measured by GC analysis.

Deracemization experiments by using LBADH

Iodine (30 mg, 1.5 equiv.) and TEMPO (2.5 mg, 0.1 equiv.) were successively added over a solution of alcohol **1a–i** (0.8 mmol, 20 mM) in 50 mM Tris-HCl buffer pH 10 (4 mL). The mixture was sonicated for 1 h at room temperature until complete conversion to ketone **2a–i**. After this time, the reaction was stopped by adding a saturated $Na_2S_2O_3$ aqueous solution (300 μL). An aliquot (500 μL) was then withdrawn, and LBADH stock (10 μL, 3 U) in 50 mM Tris-HCl buffer pH 10, 1 mM $MgCl_2$ (60 μL of a 10 mM stock solution), 2-PrOH (32 μL), and 1 mM NADPH (60 μL of a 10 mM stock solution) were successively added. The mixture was shaken at 30 °C and 250 rpm for additional 24 h. Then, the mixture was extracted with EtOAc (2×500 μL), centrifuged (13000 rpm, 90 s), and dried (Na_2SO_4). The substrate conversion and enantiomeric excess of (*R*)-alcohols **1a–i** were measured by GC analysis.

Deracemization experiments by using ADH evo-1.1.200

Iodine (30 mg, 1.5 equiv.) and TEMPO (2.5 mg, 0.1 equiv.) were successively added over a solution of alcohol **1a–i** (0.8 mmol, 20 mM) in 50 mM Tris-HCl buffer pH 10 (4 mL). The mixture was sonicated for 1 h at room temperature until complete conversion to ketone **2a–i**. After this time, the reaction was stopped by adding a saturated $Na_2S_2O_3$ aqueous solution (300 μL). An aliquot (500 μL) was then withdrawn, and evo-1.1.200 (3 U), 10 mM NADH (50 μL), 10 mM $MgCl_2$ (50 μL), and 2-PrOH (25 μL) were successively added. The mixture was shaken at 30 °C and 250 rpm for additional 24 h. Then, the mixture was extracted with EtOAc (2×500 μL), centrifuged (13000 rpm, 90 s), and dried (Na_2SO_4). The substrate conversion and enantiomeric excess of (*R*)-alcohols **1a–i** were measured by GC analysis.

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Keywords: alcohols · biocatalysis · deracemization · oxidoreductases · TEMPO

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