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FULL PAPER

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Enzymatic Cross-Benzoin-Type Condensation of Aliphatic Aldehydes: Enantioselective Synthesis of 1-Alkyl-1-hydroxypropan-2-ones and 1-Alkyl-1-hydroxybutan-2-ones

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Abstract. Benzoin-type reactions have been intensively exploited as a synthetic strategy for the preparation of α-hydroxy ketones. Thiamine diphosphate (ThDP) dependent enzymes are excellent catalysts for asymmetric versions of such reaction types. In particular, in cross-benzoin condensations of aromatic reactants and mixed aromatic/aliphatic reactions, use of these enzymes has resulted in high levels of chemo-, regio- and stereoselectivity. The present work, which confirms this trend for aliphatic reactants, outlines results obtained in the formal cross-benzoin-type condensation of the 'umpoled' acetaldehyde and propionaldehyde with various aliphatic aldehydes catalyzed by the ThDP-dependent enzyme acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR). In these reactions, 3-hydroxy-3-methylbutan-2-one (methylacetoin) was used as the activated acetaldehyde donor, while 4-hydroxy-4-methylhexan-3-one was employed for the first time as the precursor of activated propionaldehyde. With the exception of 3-hydroxypentan-2-one and 3-hydroxyhexan-2-one, which were obtained in almost racemic form by the condensation of methylacetoin with propanal and butanal, respectively, all other products achieved from reactions performed using the same donor with more hindered aldehyde acceptors were obtained with high conversions (89–99%) and in good to high enantiomeric excess (72–99% *ee*). In a similar way, high conversions (75–99%) and good *ee* (76–99%) were observed in reactions performed with the same set of aldehyde acceptors, but using 4-hydroxy-4-methylhexan-3-one as propionyl anion donor. This is the first time that most of the products described herein have been prepared via benzoin-type condensation.

Keywords: asymmetric synthesis; C–C coupling; enzyme catalysis; thiamine diphosphate; umpolung

Introduction

The development of efficient asymmetric synthetic methodologies is of fundamental importance for the production of chiral bioactive compounds.[1] Huge efforts in this area are devoted to the production of enantiopure building blocks, the availability of which allows for the directed control of the stereochemical course of complex synthetic pathways.[2] Many bioactive molecules contain an α-hydroxy ketone motif, in which the configuration of the carbinolic center is often critical for the biological activity.[3] Thus, the development of new catalytic strategies for the asymmetric synthesis of α-hydroxy ketones is of high interest.[4] Significant results in this area have been achieved through the α-oxidation of ketones[5] or of their enolate and enol ether derivatives.[6] Alternative approaches are the ketohydroxylation of olefins,[7] and the monooxidation of diols.[8] Furthermore, thanks to the recent development of chiral N-heterocyclic carbene (NHC) catalysts,[9] the umpolung coupling of aldehydes (benzoin-type condensation) can be added to this list of methodologies.

Concurrently with the introduction of these chemocatalytic strategies, several biocatalytic methodologies have been developed.[3a] Enantioenriched α-hydroxy ketones have been obtained via the kinetic resolution of their racemates by enantioselective acylation catalyzed by lipases.[10] Alternative enzymatic approaches are the monoreduction of α-diketones and the monooxidation of vicinal diols, both catalyzed in a stereoselective manner by NAD(P)-dependent dehydrogenases.[11] Also worthy of mention is the unique example of the enantioselective α-oxidation of ketones promoted by a cytochrome P450 enzyme.[12]

An alternative, straightforward biocatalytic approach is offered by catalysis using thiamine diphosphate (ThDP) dependent lyases. Thanks to their tightly bound cofactor ThDP, the enzymes of this family catalyze benzoin-type condensations with

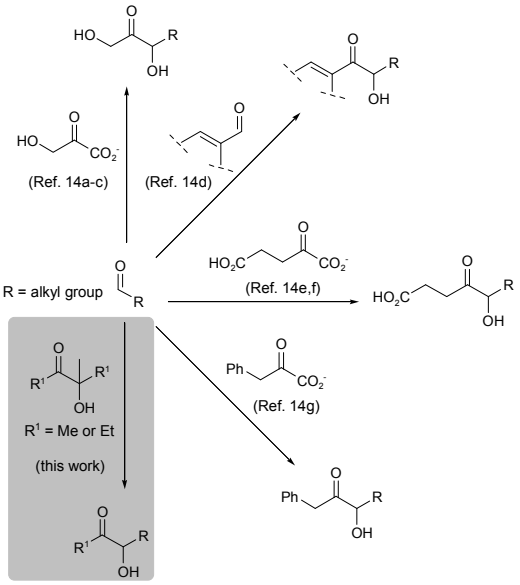
the same umpolung mechanism as the above-noted NHC catalysts, often with a high level of enantio-selectivity.[13] Furthermore, while the NHC catalysts need at least one aromatic aldehyde in order to direct the chemo- and regioselectivity of the cross-benzoin condensation,[9] various ThDP-dependent lyases are known to efficiently catalyze the chemo- and stereoselective formation of fully aliphatic acyloins.[14] Scheme 1 shows generic structures of the more significant products achieved via these enzymatic approaches. Although the efficiency of acetaldehyde and propionaldehyde as both donor and acceptor has been demonstrated in ThDP-dependent enzyme-catalyzed homo-benzoin-type reactions,[15] there are only rare examples of cross-benzoin-type reactions involving these aldehydes or their α-keto acids precursors (pyruvate and 2-oxobutyrate, respectively) as donors with aliphatic acceptors and few of the resulting products have been characterized.[16]

We herein report the results obtained in benzoin-type condensations of 3-hydroxy-3-methylbutan-2-one (Scheme 1, R^1 = Me) and 4-hydroxy-4-methylhexan-3-one (Scheme 1, R^1 = Et), which act as precursors of activated acetaldehyde and propionaldehyde, respectively, with various aliphatic aldehydes as acceptors catalyzed by the ThDP-dependent enzyme acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR).

Results and Discussion

We recently highlighted the synthetic value of the substrate–enzyme pair constituted by methylacetoin (**1**, Scheme 2) and Ao:DCPIP OR from *Bacillus licheniformis* by demonstrating its efficiency in the enantioselective synthesis of tertiary acyloins **4** and phenylacetylcarbinol (PAC) analogues **6** through the addition of the activated acetaldehyde **2**, derived from **1**, to various activated methyl ketones **3** (Scheme 2, route a)[17] and aromatic aldehydes **5** (Scheme 2, route b),[18] respectively. Most of the resulting products were highly enantioenriched. Noteworthy, reactions with the aromatic aldehydes afforded the (*S*)-enantiomers of the PAC analogues, a behavior not observed with other wild-type ThDP-dependent enzymes.[19]

These encouraging results prompted us to investigate the activity of Ao:DCPIP OR in benzoin-type reactions between donor **1** and various aliphatic aldehydes **7** as acceptors (Scheme 2, route c). In fact, apart from acetoin, which represents a case study,[13a,b] few other α-hydroxy ketones of type **8** (Scheme 2, route c) have been produced exploiting the ThDP-dependent enzyme pyruvate decarboxylase (PDC). Furthermore, the conversion levels were low and, for most products, the enantiomeric excess (*ee*) was not determined.[16]

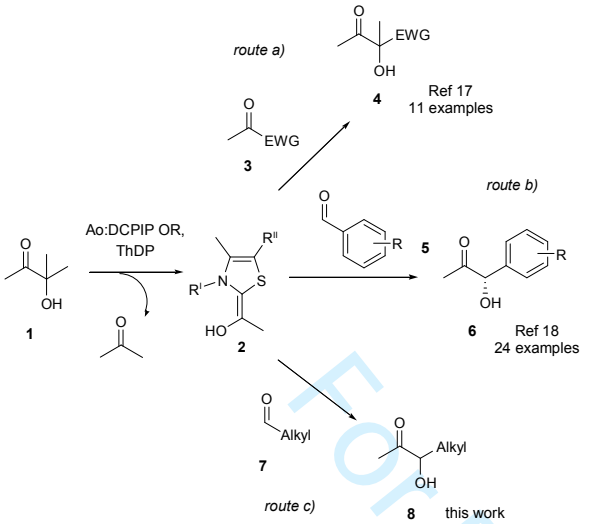


Scheme 1. Generic structures of the main aliphatic acyloins achievable via ThDP-dependent enzyme catalysis.

The activity of the Ao:DCPIP OR–methylacetoin enzyme–substrate system was tested on analytical scale reactions (1.5 mL reaction volume), using the linear aliphatic aldehydes propanal and butanal (**7a** and **7b**, Table 1) as acceptors. By employing reaction conditions similar to those adopted for the synthesis of the PAC analogues **6**[18] [methylacetoin (**1**; 30 mM), **7a** or **7b** (20 mM), phosphate buffer pH 6.5 (50 mM), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1})], after 48 hours at 30 °C we observed the formation of the expected products **8a** and **8b** with complete and 57% conversion, respectively (Table 1, entries 1 and 2). ^{1}H NMR analyses of the reaction mixtures did not reveal the presence of products arising from the homo-coupling of aldehydes **7a** or **7b**. The non-occurrence of such a reaction was further confirmed by experiments performed without donor **1**. These results agree with those reported in previous synthetic applications of Ao:DCPIP OR,[18] namely that although aldehydes are good acceptors, they cannot act as acyl-anion donors since this enzyme needs α-hydroxy ketones or α-diketones for this role. Chiral-phase GC analyses of crude **8a** and **8b** indicated low *ee* for both products (43% and 29%, respectively). Previous studies on the synthesis of the same products, conducted using PDC as catalyst and pyruvate as donor, reported low conversions for **8a**[16b] and **8b**[16a] formation (41% and 2%, respectively) and did not provide information about the optical purity of the products. The results achieved with the short-chain linear aldehydes **7a** and **7b** were encouraging concerning the chemo- and regioselectivity of the enzymatic approach. Hence, we investigated the activity of Ao:DCPIP OR in the condensation of methylacetoin (**1**) with more hindered acceptors, such as the α-branched aliphatic and alicyclic aldehydes **7c**–**g** (Table 2). Gratifyingly,

in a preliminary study conducted on an analytical scale (1.5 mL reaction volume) with different donor to acceptor molar ratios,

all the aldehydes **7c**–**g** were accepted as substrates by Ao:DCPIP OR.



Scheme 2. Ao:DCPIP OR catalyzed benzoin-type condensation of methylacetoin (**1**) with activated ketones (route a), aromatic aldehydes (route b) and aliphatic aldehydes (route c). R^{I} = (4-amino-2-methylpyrimidin-5-yl)methyl, R^{II} = 2-diphosphate ethyl.

A slight excess of the donor (1.5 equivalents) was sufficient to obtain almost complete conversion of the acceptors (see Supporting Information). Products **8c**–**g** have not been obtained previously via ThDP-dependent enzyme-catalyzed benzoin-type reactions (aldehydes **7e**–**g** have been used as acceptors in condensations with hydroxypyruvate catalyzed by engineered transketolases).[14b] Reactions repeated on a preparative scale (Table 1, entries 3–7) confirmed the high conversion levels (89–99%) observed on the smaller scale. After purification by column chromatography, products **8e**–**g** were obtained in high yields (81–89%), while part of products **8c** and **8d** was lost during the purification procedure, probably due to their high volatility (49% and 42% isolated yield for **8c** and **8d**, respectively). Attempts to use volatile solvents like pentane, diethyl ether, chloroform or dichloromethane did not afford appreciable results in terms of separation and recovery of the products as well. Unlike the short-chain linear products **8a** and **8b**, acyloins **8c**–**g** were highly enantioenriched, with *ee* values ranging from 72% to 99%.

These results indicate that the α-branched structure of the substrates does not limit their access to the enzyme active site, but orientates them within this site, thus ensuring highly stereoselective attack of the activated acetaldehyde **2**. To assess the robustness of the enzymatic procedure, the α-oxygenated aldehydes **7h** and **7i** were employed as acceptor substrates. By virtue of their protected alcoholic and aldehydic functionalities, the expected products **8h** and **8i** (Table

Table 1. Ao:DCPIP OR catalyzed synthesis of 1-alkyl-1-hydroxypropan-2-ones **8a**–**j** using methylacetoin (**1**) as donor.[a]

			Conversion [%][b] (yield [%])[c]	ee [%][d]
1[e]	**7a**	**8a**	99 (n.d.)[f]	43
2[e]	**7b**	**8b**	57 (n.d.)[f]	29
3	**7c**	**8c**	99 (49)	99
4	**7d**	**8d**	99 (42)	99(*S*)
5	**7e**	**8e**	99 (81)	72
6	**7f**	**8f**	89 (82)	86
7	**7g**	**8g**	99 (89)	92(*S*)
8	**7h**	**8h**	99 (92)	72(*S*)[g]
9	**7i**	**8i**	99 (61)	n.d.[f]
10	**7j**	**8j**	99 (93)	84(*S*)[g]

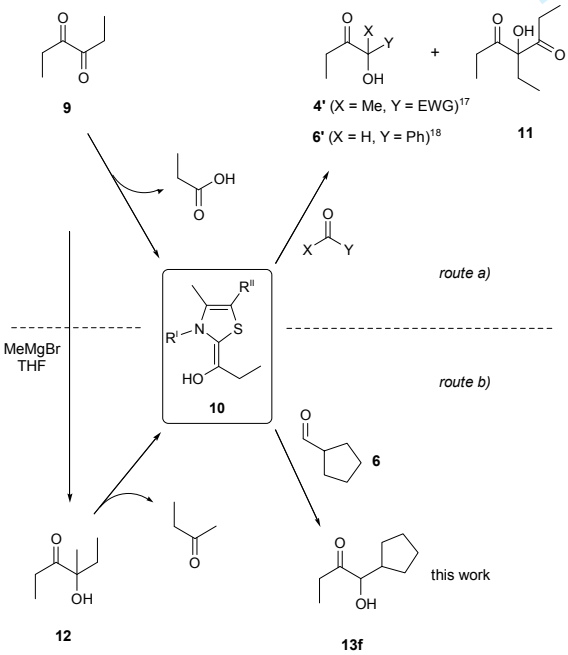
[a] *Conditions*: reaction volume 25 mL, **1** (30 mM), aldehyde **7** (20 mM), phosphate buffer pH 6.5 (50 mM), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1}). [b] Determined by ^1H NMR analysis. [c] Refers to the isolated product after column chromatography. [d] Determined by chiral-phase GC or HPLC analysis. [e] Reaction performed on an

analytical scale only. [f] Not determined. [g] Absolute configuration determined by ^{1}H-NMR analysis of the Mosher's esters derivatives (see Supporting Information).

1, entries 8 and 9) are interesting building blocks for asymmetric synthesis.

The two aldehydes **7h** and **7i** have been used as donor and acceptor, respectively, in a cross-benzoin-type reaction catalyzed by benzaldehyde lyase;[20] however, neither has been used as an acceptor of the activated acetaldehyde **2**.

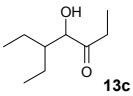
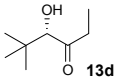
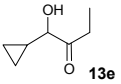
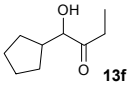
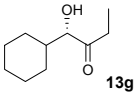
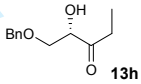
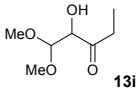
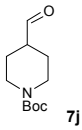
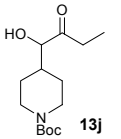
Gratifyingly, the reactions conducted with donor **1** and Ao:DCPIP OR as catalyst afforded the corresponding products **8h** and **8i** with almost complete conversion and a satisfactory 72% *ee* for **8h**. Likewise what described in previous work[14d] for analogous products, also for **8i** a low isolated yield (34%) was achieved after chromatography on conventional silica gel. This drawback, probably due to the low stability of the acetal group on the acidic stationary phase, has been overcome by performing the chromatographic purification on neutral silica gel. Under this conditions a considerably higher yield of 61% was obtained (Table 1, entry 9). Finally, the tolerance of the procedure for bulky substrates was confirmed by the use of 1-Boc-substituted piperidine-4-carboxaldehyde **7j** as acceptor. In this case, the enzymatic reaction provided the expected product **8j** in high isolated yield (93%) and good *ee* (84%).



Scheme 3. Synthesis and exploitation of 4-hydroxy-4-methylhexan-3-one (**12**) as a propionyl anion donor alternative to hexane-3,4-dione (**9**). R^I = (4-amino-2-methylpyrimidin-5-yl)methyl, R^{II} = 2-diphosphate ethyl.

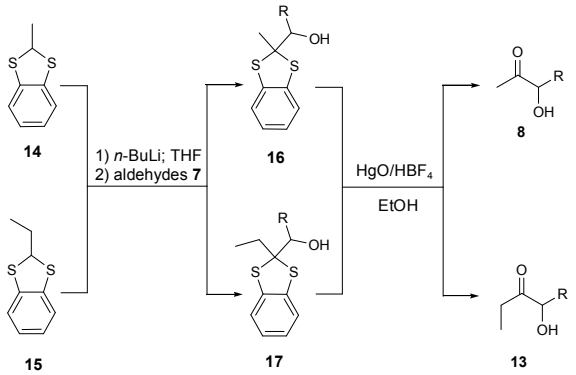
The successful results thus far were thanks to the employment of the non-natural donor **1** whose higher potential in carboligation reactions, with respect to the natural substrate acetoin, is due to the release of unreactive acetone during formation of the activated acetaldehyde **2** (Scheme 2).[17] On the other hand, as we have demonstrated previously, Ao:DCPIP OR is also able to catalyze the cleavage of hexane-3,4-dione (**9**) and addition of the resulting activated propionaldehyde **10** to various activated ketones[17] and benzaldehydes[18] (Scheme 3, route a). The synthetic efficiency of **9** as a donor, however, is negatively affected by the unavoidable formation of byproduct **11** (homo-coupling of **9**), which necessitates the use of an excess of the donor with the consequent complication of product purification.

Table 2. Ao:DCPIP OR catalyzed synthesis of 1-alkyl-1-hydroxybutan-2-ones **13c–j** using **12** as donor.[a]

Entry	Acceptor	Product	Conversion [%][b] (yield [%])[c]	ee [%][d]
1	 **7c**	 **13c**	99 (52)	90
2	 **7d**	 **13d**	95 (45)	99(*S*)
3	 **7e**	 **13e**	83 (70)	n.d.[e]
4	 **7f**	 **13f**	90 (82)	78
5	 **7g**	 **13g**	85 (78)	59(*S*)
6	 **7h**	 **13h**	75 (68)	92(*S*)[f]
7	 **7i**	 **13i**	99 (62)	n.d.[e]
8	 **7j**	 **13j**	99 (91)	76

[a] *Conditions*: reaction volume 25 mL, **12** (30 mM), aldehyde **7** (20 mM), phosphate buffer pH 6.5 (50 mM), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1}). [b] Determined by ^{1}H NMR analysis. [c] Refers to the isolated product after column chromatography. [d] Determined by chiral-phase GC or HPLC analysis, apart from **13g**.[21] [e] Not determined. [f] Absolute configuration determined by ^{1}H-NMR analysis of the Mosher's esters derivatives (see Supporting Information).

Searching for a more efficient propionyl anion donor reminiscent of the structure of **1**, we aimed to convert diketone **9** into 4-hydroxy-4-methylhexan-3-one (**12**) through reaction with a methyl Grignard reagent. In the event, the addition of methylmagnesium bromide (1.2 equivalent) to **9**, followed by refluxing of the resulting mixture (2 h) and aqueous workup, afforded the expected racemic product **12**. Under these conditions we did not observe the formation of the diol and the product **12** was purified by distillation (48% yield). The so-obtained acyloin **12** was tested as donor (1.5 equivalents) in the model reaction with acceptor **7f** (Scheme 3, route b). Gratifyingly, this afforded a 90% conversion and the expected product **13f** was enantioenriched (78% *ee*) (Table 2, entry 4). Noteworthy, in forming the activated aldehyde **10**, Ao:DCPIP OR catalyzes the cleavage of **12** with comparable rates for both enantiomers, as demonstrated by chiral-phase GC analysis of the residual donor in the reaction mixture (see Supporting Information). Additionally, ^{1}H NMR analysis of the same mixture excluded the presence of byproducts derived from donor homo-coupling. These features, added to the complete non-reactivity of the methyl ethyl ketone released upon donor cleavage,[22] contribute to increasing the synthetic value of **12** as propionyl anion donor and encouraged us to extend the methodology to the complete set of acceptors **7c**–**j** successfully used with donor **1**. As observed for the reactions with methylacetoin (**1**), a study conducted with different donor **12** to acceptor **7f** molar ratios (see Supporting Information) indicated that the best conversion and optical purity of product **13f** were achieved using 1.5 equivalents of donor. Hence, these conditions were adopted in all reactions performed on a preparative scale (25 mL) with donor **12** and acceptor substrates **7c**–**j**, the results of which are summarized in Table 2. The conversions and yield and *ee* values of products **13c**–**j** are comparable with the results obtained for the lower homologues **8c**–**j**; therefore, **12** is a suitable propionyl anion donor in reactions catalyzed by Ao:DCPIP OR. The absolute configuration of products **8d**,[23] **8g**,[24] **8h**, **13d**[25] **13g**[21] and **13h** show that, with acceptors **7d**, **7g** or **7h**, the enzyme is (*S*)-stereoselective independently from the use of **1** or **12** as donor.[26] These results are congruent with those we previously reported using aromatic aldehydes as acceptors.[18]



Scheme 4. Synthesis of racemic samples of products **8c**,**d**,**g**,**h**,**j** and **13c**,**d**,**f**,**h**,**j**.

Finally, preparation of racemic samples to assess the optical purity of the enzymatic products by chiral-phase chromatographic analysis was required. Initial attempts to racemize the optically active products by acidic or basic treatment afforded the expected samples only for products **8e** and **8f**, albeit with very low conversions.[27] Therefore, most of the acyloins were synthesized in their racemic form by addition of the carbanions generated from 2-methyl-1,3-benzodithiole (**14**) and 2-ethyl-1,3-benzodithiole (**15**)[28] to the aldehyde acceptors **7**, followed by hydrolysis of the resulting adducts[29] **16** and **17**, as depicted in Scheme 4 (see Supporting Information).

Conclusion

We have demonstrated that the benzoin-type coupling of methylacetoin (**1**) with α-substituted aliphatic aldehydes catalyzed by the ThDP-dependent enzyme Ao:DCPIP OR is a valuable synthetic strategy to produce a broad range of enantioenriched 1-alkyl-1-hydroxypropan-2-ones **8c**–**j**. Most of these products have not been synthesized previously via enzymatic or organocatalytic benzoin-type reactions. Additionally, we have disclosed the unprecedented use of 4-hydroxy-4-methylhexan-3-one (**12**) as propionyl anion donor that has allowed us to significantly extend the range of optically active aliphatic acyloins obtainable through Ao:DCPIP OR catalysis. Surprisingly, this enzyme is sterically unselective in the cleavage of the racemic compound **12**, while being highly stereoselective in the addition of the resulting activated propionaldehyde **10** to the α-substituted aliphatic aldehydes. The results obtained with both donors **1** and **12** seem to confirm the (*S*)-enantioselectivity observed in previous biocatalytic exploitations of Ao:DCPIP OR.[17,18] Additionally, since neither **1** and **12** nor the ketones released from their cleavage (acetone and methyl ethyl ketone, respectively) act as acceptors, methylacetoin (**1**) and 4-hydroxy-4-methylhexan-3-one (**12**) become valuable alternatives to pyruvate and 2-oxobutyrate, respectively, in ThDP catalysis. Our results provide further evidence for the general

applicability of what can be defined as the 'methylacetoin approach' which can be successfully employed to catalyze the asymmetric addition of activated acetaldehyde and propionaldehyde to the carbonyl group of various kinds of acceptors, namely activated ketones, variously substituted benzaldehydes and, as here demonstrated, also α-substituted aliphatic aldehydes.

Experimental Section

General Methods

All commercially available reagents were used as received without further purification, unless otherwise stated. Liquid aldehydes were freshly distilled before use. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh) or on Florisil (60–100 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers at room temperature using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in ppm relative to residual solvent signals. High-resolution mass spectra (HRMS) were recorded in positive ion mode with an Agilent 6520 HPLC-Chip Q/TOF-MS nanospray system using a time-of-flight, quadrupole or hexapole unit to produce spectra. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The enantiomeric excess (*ee*) of products was determined by chiral-phase HPLC or GC analysis. For the HPLC analyses, a Phenomenex Amylose-2 Lux (250 × 4.6 mm, 5 μm particle size) or a Phenomenex Lux Cellulose-1 (250 × 4.6 mm, 5 μm particle size) column was used, together with a UV detector operating at 254 nm. GC analyses were performed using a flame ionization detector and a Megadex 5 column (25 m × 0.25 mm), with the temperature programs as specified. Purified Ao:DCPIP OR was obtained as previously described.[17]

General Procedure for the Synthesis of Products 8a–j on an Analytical Scale

Lyophilized Ao:DCPIP OR (0.75 mg) was added to a solution of aldehyde **7a**–**j** (30 μmol), methylacetoin (**1**; 4.7 μL, 45 μmol), ThDP (0.4 mg, 0.9 μmol) and $MgSO_4$ (0.16 mg, 1.3 μmol) in 50 mM phosphate buffer at pH 6.5 (1.5 mL). The reaction mixture was gently shaken at 30 °C and, after 8, 24 and 48 h, samples (0.5 mL) were withdrawn and extracted with $CDCl_3$ (1.0 mL). The organic extracts were dried with anhydrous Na_2SO_4 and analyzed by ^{1}H NMR spectroscopy and chiral-phase GC to determine the conversion and the *ee*, respectively.

General Procedure for the Synthesis of Products 8c–j on a Semipreparative Scale

Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of aldehyde **7c**–**j** (0.50 mmol), methylacetoin (**1**; 79 μL, 0.75 mmol), ThDP (4.5 mg, 10 μmol) and $MgSO_4$ (2.7 mg, 20 μmol) in 50 mM phosphate buffer at pH 6.5 (25 mL). The reaction mixture was gently shaken at 30 °C for 48 h and then extracted with Et_2O (3 × 5 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with the noted elution system.

4-Ethyl-3-hydroxyhexan-2-one (8c)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8c** as a colorless oil, 49% yield. $[\alpha]_D$ +117 (*c* 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): t_R (min) = 23.8 (minor), 25.1 (major); 99% *ee*; ^{1}H NMR (300 MHz): δ = 4.24 (s, 1H, H-3), 3.38 (bs, 1H, OH), 2.19 (s, 3H, CH_3), 1.69–1.36 (m, 3H), 1.30–1.06 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H, CH_3), 0.89–0.79 (m, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 210.9, 78.3, 44.7, 25.4, 23.3, 21.4, 12.2, 12.0; HRMS (ESI/Q-TOF): m/z = 167.1048, calcd for $C_8H_{16}NaO_2$ $[M+Na]^+$: 167.1060.

(*S*)-3-Hydroxy-4,4-dimethylpentan-2-one [(*S*)-8d]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8d** as a colorless oil, 42% yield. $[\alpha]_D$ +93 (*c* 1.0, $CHCl_3$), lit. for (*S*)-enantiomer +133.2 (*c* 1.0, $CHCl_3$);[23] GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): t_R (min) = 16.7 (*R*), 17.8 (*S*); 99% *ee*; ^{1}H NMR (300 MHz): δ = 3.88 (d, J = 6.3 Hz, 1H, H-3), 3.25 (d, J = 6.3 Hz, 1H, OH), 2.24 (s, 3H, CH_3), 0.99 (s, 9H); ^{13}C NMR (101 MHz): δ = 211.0, 84.5, 35.5, 29.4, 26.3; HRMS (ESI/Q-TOF): m/z = 153.0891, calcd for $C_7H_{14}NaO_2$ $[M+Na]^+$: 153.0879.

1-Cyclopropyl-1-hydroxypropan-2-one (8e)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **8e** as a colorless oil, 81% yield. $[\alpha]_D$ +112 (*c* 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): t_R (min) = 6.3 (minor), 6.7 (major); 72% *ee*; ^{1}H NMR (300 MHz): δ = 3.64 (dd, J = 7.7, 4.3 Hz, 1H, H-1), 3.50 (d, J = 4.3 Hz, 1H, OH), 2.31 (s, 3H, CH_3), 1.05–0.88 (m, 1H, CH_{cprop}), 0.73–0.35 (m, 4H); ^{13}C NMR (101 MHz): δ = 209.1, 79.1, 25.6, 14.2, 2.9, 2.0; HRMS (ESI/Q-TOF): m/z = 137.0578, calcd for $C_6H_{10}NaO_2$ $[M+Na]^+$: 137.0590.

1-Cyclopentyl-1-hydroxypropan-2-one (8f)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8f** as a colorless oil, 82% yield. $[\alpha]_D$ +47 (*c* 1.0, $CHCl_3$); GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): t_R (min) = 17.7 (minor), 19.0 (major); 86% *ee*; ^{1}H NMR (300 MHz): δ = 4.23 (dd, J = 4.8, 3.4 Hz, 1H, H-1), 3.42 (d, J = 4.8 Hz, 1H, OH), 2.38–2.23 (m, 1H, CH_{Cpent}), 2.20 (s, 3H, CH_3), 1.72–1.49 (m, 5H), 1.40–1.16 (m, 3H); ^{13}C NMR (101 MHz): δ = 209.8, 78.5, 42.0, 29.5, 27.0, 26.0, 25.5, 24.7; HRMS (ESI/Q-TOF): m/z = 165.0891, calcd for $C_8H_{14}NaO_2$ $[M+Na]^+$: 165.0878.

(*S*)-1-Cyclohexyl-1-hydroxypropan-2-one [(*S*)-8g]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **8g** as a colorless oil, 89% yield. $[\alpha]_D$ +146 (*c* 1.0, $CHCl_3$), lit. for (*S*)-enantiomer +54.9 (*c* 1.0, $CHCl_3$);[24] 92% *ee* (determined by chiral-phase HPLC analysis after conversion into **16g**, as described in the Supporting Information); ^{1}H NMR (300 MHz): δ = 4.04 (d, J = 2.4 Hz, 1H, H-1), 3.36 (bs, 1H, OH), 2.19 (s, 3H, CH_3), 1.88–1.58 (m, 5H), 1.55–1.39 (m, 1H), 1.37–1.09 (m, 5H); ^{13}C NMR (101 MHz): δ = 209.9, 81.1, 41.1, 30.1, 26.5, 26.0, 25.8, 25.5, 25.0; HRMS (ESI/Q-TOF): m/z = 179.1048, calcd for $C_9H_{16}NaO_2$ $[M+Na]^+$: 179.1058.

4-(Benzyloxy)-3-hydroxybutan-2-one (8h)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **8h** as a colorless oil, 92% yield. $[\alpha]_D$ +17 (*c* 1.0, $CHCl_3$); GC (temperature program: 120 to 210 °C, rate 2 °C min^{-1}): t_R (min) = 33.0 (minor), 34.0 (major); 72% *ee*; ^{1}H NMR (300 MHz): δ = 7.43–7.27 (m, 5H), 4.61 (d, J = 12.0 Hz, 1H, Ha_{Bn}), 4.49 (d, J = 12.0 Hz, 1H, Hb_{Bn}), 4.26 (m, 1H, H-3), 3.83 (dd, J = 10.4, 3.7 Hz, 1H, OCHa), 3.72 (dd, J = 10.4, 3.7 Hz, 1H, OCHb), 3.63 (d, J = 5.1 Hz, 1H, OH), 2.22 (s, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 207.8, 137.4, 128.5, 127.9, 127.8, 77.2, 76.9, 73.7, 70.8, 25.7; HRMS (ESI/Q-TOF): m/z = 217.0841, calcd for $C_{11}H_{14}NaO_3$ $[M+Na]^+$: 217.0856.

3-Hydroxy-4,4-dimethoxybutan-2-one (8i)

Column chromatography on florisil gel with cyclohexane/EtOAc 10:3 afforded **8i** as a colorless oil, 61% yield. $[\alpha]_D$ +76 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz): δ = 4.40 (d, *J* = 3.2 Hz, 1H, H-4), 4.21 (m, 1H, H-3), 3.64 (bs, 1H, OH), 3.49 (s, 3H, CH_3O), 3.46 (s, 3H, CH_3O), 2.29 (s, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 207.2, 106.2, 77.7, 57.3, 55.8, 27.3; HRMS (ESI/Q-TOF): *m/z* = 171.0633, calcd for $C_6H_{12}NaO_4$ $[M+Na]^+$: 171.0647.

***tert*-Butyl 4-(1-Hydroxy-2-oxopropyl)piperidine-1-carboxylate (8j)**

Column chromatography with cyclohexane/EtOAc 6:4 afforded **8j** as a white waxy solid, 93% yield. $[\alpha]_D$ +91 (*c* 1.0, $CHCl_3$); 84% *ee* (determined by chiral-phase HPLC analysis after conversion into **16j**, as described in the Supporting Information); ^1H NMR (300 MHz): δ = 4.25–4.10 (m, 2H, CH_2), 4.10–4.06 (m, 1H, H-1′), 3.39 (bs, 1H, OH), 2.79–2.50 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.01–1.81 (m, 1H, H-4), 1.65 (m, 4H, 2 × CH_2), 1.43 (s, 9H, 3 × CH_3); ^{13}C NMR (101 MHz): δ = 209.1, 154.6, 80.0, 79.5, 43.7, 39.4, 28.9, 28.4, 25.7, 24.4; HRMS (ESI/Q-TOF): *m/z* = 258.1705, calcd for $C_{13}H_{24}NO_4$ $[M+H]^+$: 258.1721.

Synthesis of 4-Hydroxy-4-methylhexan-3-one (12)

To a stirred solution of hexane-3,4-dione (**9**; 9.4 g, 82.4 mmol) in anhydrous THF (30 mL), a 3.0 M MeMgBr solution in Et_2O (33 mL, 99 mmol) was added dropwise, at room temperature. The resulting mixture was refluxed for 2 h and then a saturated aqueous solution of NH_4Cl (50 mL) was slowly added. The organic layer was separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue (6.3 g, 6.6 mL) was purified by vacuum distillation (70 °C/10 mmHg) to obtain the expected product **12** as a yellow oil, 5.2 g (40 mmol, 48% yield). ^1H NMR (400 MHz): δ = 3.89 (bs, 1H, OH), 2.60–2.41 (m, 2H, CH_2), 1.79–1.66 (m, 2H, CH_2), 1.34 (s, 3H, CH_3), 1.10 (t, *J* = 7.3 Hz, 3H, CH_3), 0.78 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 215.1, 78.9, 32.5, 28.9, 25.3, 7.8, 7.7; HRMS (ESI/Q-TOF): *m/z* = 153.0891, calcd for $C_7H_{14}NaO_2$ $[M+Na]^+$: 153.0905.

General Procedure for the Synthesis of Products 13c–j on an Analytical Scale

The reactions were performed and analyzed as described for the synthesis of products **8a**–**j** on an analytical scale, using 4-hydroxy-4-methylhexan-3-one (**12**; 6.2 μL, 45 μmol) instead of methylacetoin.

General Procedure for the Synthesis of Products 13c–j on a Semipreparative Scale

The reactions were performed and worked up as described for the synthesis products **8c**–**j** on a semipreparative scale, using 4-hydroxy-4-methylhexan-3-one (**12**; 103 μL, 0.75 mmol) instead of methylacetoin.

5-Ethyl-4-hydroxyheptan-3-one (13c)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13c** as a colorless oil, 52% yield. $[\alpha]_D$ +60.8 (*c* 0.5, $CHCl_3$); 90% *ee* (determined by chiral-phase HPLC analysis after conversion into **17c**, as described in the Supporting Information); ^1H NMR (300 MHz): δ = 4.28–4.22 (m, 1H, H-4), 3.41 (d, *J* = 4.5 Hz, 1H, OH), 2.60–2.33 (m, 2H, CH_2), 1.67–1.37 (m, 4H), 1.29–1.15 (m, 1H), 1.12 (t, *J* = 7.3 Hz, 3H, CH_3), 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 0.83 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (76 MHz): δ = 213.9, 77.8, 45.3, 31.4, 23.6, 21.6, 12.4, 12.3, 8.0; HRMS (ESI/Q-TOF): *m/z* = 181.1204, calcd for $C_9H_{18}NaO_2$ $[M+Na]^+$: 181.1217.

(*S*)-4-Hydroxy-5,5-dimethylhexan-3-one [(*S*)-13d]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13d** as a colorless oil, 45% yield. $[\alpha]_D$ +135 (*c* 0.6, $CHCl_3$), lit. for (*S*)-enantiomer +94.5 (*c* 2.2, $CHCl_3$);[25] GC (temperature program: 80 to 200 °C, rate 2 °C min^{-1}): t_R (min) = 25.0 (*R*), 26.0 (*S*); 99% *ee*; ^1H NMR (300 MHz): δ = 3.87 (s, 1H, H-4), 2.66–2.37 (m, 2H, CH_2), 1.10 (t, *J* = 7.2 Hz, 3H, CH_3), 0.98 (s, 9H, 3 × CH_3); ^{13}C NMR (76 MHz): δ = 214.2, 84.0, 35.6, 27.1, 26.5, 8.0; HRMS (ESI/Q-TOF): *m/z* = 167.1048, calcd for $C_8H_{16}NaO_2$ $[M+Na]^+$: 167.1062.

1-Cyclopropyl-1-hydroxybutan-2-one (13e)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **13e** as a colorless oil, slightly contaminated with unknown compounds, 70% yield. ^1H NMR (300 MHz): δ = 3.64 (d, *J* = 7.7 Hz, 1H), 3.55 (bs, 1H, OH), 2.89–2.70 (m, 1H, Ha_{CH2}), 2.60–2.40 (m, 1H, Hb_{CH2}), 2.06–1.89 (m, 1H, CH_{cprop}), 1.16 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (76 MHz): δ = 201.8, 78.8, 37.1; HRMS (ESI/Q-TOF): *m/z* = 151.0735, calcd for $C_7H_{12}NaO_2$ $[M+Na]^+$: 151.0723.

1-Cyclopentyl-1-hydroxybutan-2-one (13f)

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13f** as a colorless oil, 82% yield. $[\alpha]_D$ +60.0 (*c* 0.5, $CHCl_3$); 78% *ee* (determined by chiral-phase HPLC analysis after conversion into **17f**, as described in the Supporting Information); ^1H NMR (300 MHz): δ = 4.24 (d, *J* = 3.2 Hz, 1H, H-1), 3.46 (bs, 1H, OH), 2.63–2.38 (m, 2H, CH_2), 2.37–2.21 (m, 1H, CH), 1.85–1.42 (m, 6H), 1.39–1.19 (m, 2H), 1.15–1.09 (m, 3H, CH_3); ^{13}C NMR (76 MHz): δ = 212.8, 78.0, 42.4, 31.6, 29.7, 26.2, 26.1, 25.0, 7.9; HRMS (ESI/Q-TOF): *m/z* = 179.1048, calcd for $C_9H_{16}NaO_2$ $[M+Na]^+$: 179.1039.

(*S*)-1-Cyclohexyl-1-hydroxybutan-2-one [(*S*)-13g]

Column chromatography with cyclohexane/EtOAc 7:3 afforded **13g** as a colorless oil, 78% yield. $[\alpha]_D$ +73.6 (*c* 1.0, $CHCl_3$), lit. for (*R*)-enantiomer –112.5 (*c* 1.0, $CHCl_3$);[21] 59% *ee*;[21] ^1H NMR (300 MHz): δ = 4.24 (d, *J* = 1.7 Hz, 1H, H-1), 2.56–2.39 (m, 2H, CH_2), 1.89–1.56 (m, 10H), 1.55–1.41 (m, 1H), 1.11 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 212.8, 80.5, 41.4, 31.4, 30.1, 29.7, 26.6, 26.0, 25.8, 25.1, 7.6; HRMS (ESI/Q-TOF): *m/z* = 193.1204, calcd for $C_{10}H_{18}NaO_2$ $[M+Na]^+$: 193.1219.

1-(Benzyloxy)-2-hydroxypentan-3-one (13h)

Column chromatography with cyclohexane/EtOAc 8:2 afforded **13h** as a colorless oil, 68% yield. $[\alpha]_D$ +48.1 (*c* 1.0, $CHCl_3$); chiral-phase HPLC (Phenomenex Amylose-2 Lux column, *n*-hexane/propan-2-ol 9:1, flow 1.0 mL min^{-1}): t_R (min) = 14.9 (major), 34.0 (minor); 92% *ee*; ^1H NMR (300 MHz): δ = 7.38–7.23 (m, 5H), 4.60 (d, *J* = 12.1 Hz, 1H, Ha_{Bn}), 4.49 (d, *J* = 12.1 Hz, 1H, Hb_{Bn}), 4.30–4.22 (m, 1H, H-2), 3.81 (dd, *J* = 10.4, 3.7 Hz, 1H, OCHa), 3.71 (dd, *J* = 10.4, 3.7 Hz, 1H, OCHb), 2.69–2.34 (m, 2H, CH_2), 1.10 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (76 MHz): δ = 210.8, 137.7, 128.7, 128.1, 128.0, 76.5, 73.9, 71.3, 71.2, 31.8, 7.6; HRMS (ESI/Q-TOF): *m/z* = 231.0997, calcd for $C_{12}H_{16}NaO_3$ $[M+Na]^+$: 231.0985.

2-Hydroxy-1,1-dimethoxypentan-3-one (13i)

Column chromatography on florisil gel with cyclohexane/EtOAc 12:3 afforded **13i** as a colorless oil, 62% yield. $[\alpha]_D$ +72.7 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz): δ = 4.37 (d, *J* = 3.2 Hz, 1H, H-1), 4.19 (dd, *J* = 5.3, 3.2 Hz, 1H, H-2), 3.62 (d, *J* = 5.3 Hz, 1H, OH), 3.45 (s, 3H,

CH_3O), 3.42 (s, 3H, CH_3O), 2.82–2.65 (m, 1H, Ha_{CH2}), 2.55–2.37 (m, 1H, Hb_{CH2}), 1.05 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (76 MHz, $CDCl_3$): δ = 210.2, 106.4, 76.8, 57.4, 55.9, 33.4, 7.5; HRMS (ESI/Q-TOF): m/z = 185.0790, calcd for $C_7H_{14}NaO_4$ $[M+Na]^+$: 185.0803.

tert-Butyl 4-(1-Hydroxy-2-oxobutyl)piperidine-1-carboxylate (13j)

Column chromatography with cyclohexane/EtOAc 6:4 afforded **13j** as a white waxy solid, 91% yield. $[\alpha]_D$ +34.6 (c 1.0, $CHCl_3$); 76% *ee* (determined by chiral-phase HPLC analysis after conversion into **17j**, as described in the Supporting Information); ^{1}H NMR (300 MHz): δ = 4.16 (bs, 2H), 4.09 (bs, 1H, H-1′), 3.40 (bs, 1H, OH), 2.82–2.38 (m, 5H), 1.97–1.80 (m, 1H), 1.71–1.57 (m, 3H), 1.43 (s, 9H, 3 × CH_3), 1.12 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (101 MHz): δ = 212.0, 154.6, 79.5, 79.4, 43.6, 39.7, 31.6, 29.7, 28.9, 28.4, 24.4, 7.6; HRMS (ESI/Q-TOF): m/z = 272.1862, calcd for $C_{14}H_{26}NO_4$ $[M+H]^+$: 272.1879.

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References

[1] G.-Q. Lin, Y.-M. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, John Wiley & Sons, Inc., New York, **2001**, pp 47–65.

[2] W. A. Szabo, H. T. Lee, *Aldrichimica Acta* **1980**, *13*, 13–20.

[3] a) P. Hoyos, J. V. Sinisterra, F. Molinari, A. R. Alcantara, P. Domínguez de María, *Acc. Chem. Res*. **2010**, *43*, 288–299; b) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev*. **2012**, *41*, 4150–4164.

[4] J. Streuff, *Synlett* **2013**, *24*, 276–280.

[5] a) O. A. Hame, A. El-Qisairi, H. Qaseer, E. M. Hamed, P. M. Henry, D. P. Becker, *Tetrahedron Lett*. **2012**, *53*, 2699–2701; b) P. Merino, T. Tejero, *Angew. Chem. Int. Ed*. **2004**, *43*, 2995–2997.

[6] a) F. A. Davis, B.-C. Chen, *Chem. Rev*. **1992**, *92*, 919–934; b) A. Yanagisawa, S. Takeshita, Y. Izumi, K. Yoshida, *J. Am. Chem. Soc*. **2010**, *132*, 5328–5329; c) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc*. **2003**, *125*, 6038–6039; d) N. Momiyama, H. Yamamoto, *Angew. Chem. Int. Ed*. **2002**, *41*, 2986–2988.

[7] B. Plietker, *Eur. J. Org. Chem*. **2005**, 1919–1929.

[8] a) D. Minato, H. Arimoto, Y. Nagasue, Y. Demizu, O. Onomura, *Tetrahedron* **2008**, *64*, 6675–6683; b) O. Onomura, H. Arimoto, Y. Matsumura, Y. Demizu, *Tetrahedron Lett*. **2007**, *48*, 8668–8672.

[9] a) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev*. **2015**, *115*, 9307–9387; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev*. **2007**, *107*, 5606–5655; c) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem*. **2011**, *76*, 347–357; d) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *Chem. Sci*. **2012**, *3*, 735–740.

[10] a) W. Adam, M. T. Diaz, R. T. Fell, C. R. Saha-Möller, *Tetrahedron: Asymmetry* **1996**, *7*, 2207–2210; b) P. Hoyos, M. Fernandez, J. V. Sinisterra, A. R. Alcántara, *J. Org. Chem*. **2006**, *71*, 7632–7637; c) P. Hoyos, P. Domínguez de María, J. V. Sinisterra, A. R. Alcántara, in: *Biotechnology: Research, Technology and Applications* (Ed.: F. W. Richter), Nova Science Publishers, Inc., New York, **2009**, pp 97–119; d) C. Tanyeli, I. Akhmedov, C. Iyigun, *Tetrahedron: Asymmetry* **2006**, *17*, 1125–1128; e) G. Scheid, E. Ruijter, M. Konarzycka-Bessler, U. T. Bornscheuer, L. A. Wessjohann, *Tetrahedron: Asymmetry* **2004**, *15*, 2861–2869; f) P. Ödman, L. A. Wessjohann, U. T. Bornscheuer, *J. Org. Chem*. **2005**, *70*, 9551–9555; g) A. Petrenz, P. Domínguez de María, A. Ramanathan, U. Hanefeld, M. B. Ansorge-Schumacher, S. Kara, *J. Mol. Catal. B: Enzym*. **2015**, *114*, 42–49.

[11] a) M. Kurina-Sanz, F. R. Bisogno, I. Lavandera, A. A. Orden, V. Gotor, *Adv. Synth. Catal*. **2009**, *351*, 1842–1848; b) K. Edegger, W. Stampfer, B. Seisser, K. Faber, S. F. Mayer, R. Oehrlein, A. Hafner, W. Kroutil, *Eur. J. Org. Chem*. **2006**, 1904–1909; c) R. Médici, H. Stammes, S. Kwakernaak, L. G. Otten, U. Hanefeld, *Catal. Sci. Technol*. **2017**, *7*, 1831–1837; d) J. Zhang, T. Xu, Z. Li, *Adv. Synth. Catal*. **2013**, *355*, 3147–3153; e) P. P. Giovannini, G. Fantin, A. Massi, V. Venturi, P. Pedrini, *Org. Biomol. Chem*. **2011**, *9*, 8038–8045.

[12] R. Agudo, G. D. Roiban, R. Lonsdale, A. Ilie, M. T. Reetz, *J. Org. Chem*. **2015**, *80*, 950–956.

[13] a) P. P. Giovannini, O. Bortolini, A. Massi, *Eur. J. Org. Chem*. **2016**, 4441–4459; b) M. Pohl, C. Wechsler, M. Müller, in: *Science of Synthesis. Biocatalysis in Organic Synthesis 2* (Eds.: K. Faber, W.-D. Fessner, N. J. Turner), Georg Thieme Verlag KG, Stuttgart, **2015**, pp 93–131; c) N. G. Schmidt, E. Eger, W. Kroutil, *ACS Catal*. **2016**, *6*, 4286–4311; d) S. Schmidt, T. Pedroso de Almeida, D. Rother, F. Hollmann, *Green Chem*. **2017**, *19*, 1226–1229; e) M. Beigi, E. Gauchenova, L. Walter, S. Waltzer, F. Bonina, T. Stillger, D. Rother, M. Pohl, M. Müller, *Chem. Eur. J*. **2016**, *22*, 13999–14005.

[14] a) H. C. Hailes, D. Rother, M. Müller, R. Westphal, J. M. Ward, J. Pleiss, C. Vogel, M. Pohl, *FEBS J*. **2013**, *280*, 6374–6394; b) A. Cázares, J. L. Galman, L. G. Crago, M. E. B. Smith, J. Strafford, L. Ríos-Solís, G. J. Lye, P. A. Dalby, H. C. Hailes, *Org. Biomol. Chem*. **2010**, *8*, 1301–1309; c) A. Ranoux, U. Hanefeld, *Top. Catal*. **2013**, *56*, 750–764; d) A. Cosp, C. Dresen, M. Pohl, L. Walter, C. Röhr, M. Müller, *Adv. Synth. Catal*. **2008**, *350*, 759–771; e) M. Beigi, S. Waltzer, A. Fries, L. Eggeling, G. A. Sprenger, M. Müller, *Org. Lett*. **2013**, *15*, 452–455; f) A. Kurutsch, M. Richter, V. Brecht, G. A. Sprenger, M. Müller, *J. Mol. Catal. B: Enzym*. **2009**, *61*, 56–66; g) Z. Guo, A. Goswami, V. B. Nanduri, R. N. Patel, *Tetrahedron: Asymmetry* **2001**, *12*, 571–577.

[15] P. Domínguez de María, M. Pohl, D. Gocke, H. Gröger, H. Trauthwein, T. Stillger, L. Walter, M. Müller, *Eur. J. Org. Chem*. **2007**, 2940–2944.

[16] a) F. Neuser, H. Zorn, R. G. Berger, *Z. Naturforsch., C* **2000**, *55*, 560–568; b) D. H. G. Crout, H. Dalton, D. W. Hutchinson, M. Miyagoshi, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1329–1334.

[17] G. Bernacchia, O. Bortolini, M. De Bastiani, L. A. Lerin, S. Loschonsky, A. Massi, M. Müller, P. P. Giovannini, *Angew. Chem. Int. Ed.* **2015**, *54*, 7171–7175.

[18] P. P. Giovannini, L. A. Lerin, M. Müller, G. Bernacchia, M. De Bastiani, M. Catani, G. Di Carmine, A. Massi, *Adv. Synth. Catal*. **2016**, *358*, 2767–2776.

[19] T. Sehl, S. Bock, L. Marx, Z. Maugeri, L. Walter, R. Westphal, C. Vogel, U. Menyes, M. Erhardt, M. Müller, M. Pohl, D. Rother, *Green Chem*. **2017**, *19*, 380–384.

[20] a) P. Ayhan, İ. Şimşek, B. Çifçi, A. S. Demir, *Org. Biomol. Chem*. **2011**, *9*, 2602–2605; b) A. S. Demir, Ö. Şeşenoglu, P. Dünkelmann, M. Müller, *Org. Lett*. **2003**, *5*, 2047–2050.

[21] Due to difficulties encountered in the chiral-phase chromatographic analysis, the optical purity of product **13g** was deduced by comparison of its optical rotation value with that reported for the (*R*)-enantiomer (89% *ee*) in: K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc*. **2003**, *125*, 3442–3443. This information needs to be considered taking into account the limitation of using polarimetry to evaluate enantiomeric composition described in: R. E. Gawley, *J. Org. Chem*. **2006**, *71*, 2411–2416.

[22] Methyl ethyl ketone and other simple ketones could act as acceptors under particular conditions, such as those described for the *in vivo* conversion of acetone into methylacetoin in: X. Jiang, H. Zhang, J. Yang, Y. Zheng, D. Feng, W. Liu, X. Xu, Y. Cao, H. Zou, R. Zhang, T. Cheng, F. Jiao, M. Xian, *Sci. Rep.* **2013**, *3*, 2445.

[23] W.-Y. Zhang, D. J. Jakiela, A. Maul, C. Knors, J. W. Lauher, P. Helquist, D. Enders, *J. Am. Chem. Soc.* **1988**, *110*, 4652–4660.

[24] M. Hatano, T. Mizuno, K. Ishihara, *Chem. Commun*. **2010**, *46*, 5443–5445.

[25] N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, C. H. Heathcock, *J. Org. Chem*. **1991**, *56*, 2499–2506.

[26] Although Mosher ester derivatives of other products (**8c**, **8f**, **13c**, **13f**, and **13j**) have been synthetized, the comparison of the ^{1}H NMR spectra of the corresponding diastereoisomers did not allow an unambiguous deduction of the absolute configurations.

[27] a) Racemic samples of compounds **8e** and **8f** were prepared by treating the optically active products dissolved in *n*-hexane/water with Amberlyst 15, as described in reference 10f; b) For experimental details, see the Supporting Information.

[28] a) S. Ncube, A. Pelter, K. Smith, P. Blatcher, S. Warren, *Tetrahedron Lett*. **1978**, 2345–2348; b) D. R. Boyd, N. D. Sharma, J. H. Dorman, R. Dunlop, J. F. Malone, R. A. S. McMordie, A. F. Drakeb, *J. Chem. Soc., Perkin Trans. 1* **1992**, 1105–1110.

[29] D. Cheng, J. Zhou, E. Saiah, G. Beaton, *Org. Lett*. **2002**, *4*, 4411–4414.

FULL PAPER

Enzymatic Cross-Benzoin-Type Condensation of Aliphatic Aldehydes: Enantioselective Synthesis of 1-Alkyl-1-hydroxypropan-2-ones and 1-Alkyl-1-hydroxybutan-2-ones

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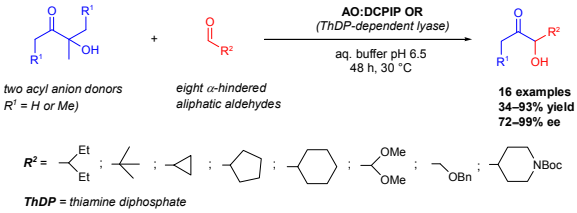

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