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(*S*)-Selectivity in Phenylacetyl Carbinols Synthesis Using the Wild-Type Enzyme Acetoin:Dichlorophenolindophenol Oxidoreductase from *Bacillus licheniformis*

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Abstract. Thiamine diphosphate (ThDP)-dependent enzymes are well known biocatalysts for the asymmetric synthesis of α-hydroxy ketones with preferential (*R*)-selectivity. Pharmaceutically relevant phenylacetyl carbinol (PAC) is prepared with absolute (*S*)-configuration only in few occasions using enzyme variants suitably designed through rational site-directed mutagenesis approaches. Herein, we describe the synthesis of (*S*)-phenylacetyl carbinol products with extended reaction scope employing the readily available wild-type ThDP-dependent enzyme acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR) from *Bacillus licheniformis*. On a semipreparative scale, cross-benzoin-like condensations of methylacetoin (donor) and differently substituted benzaldehydes proceed with almost complete chemoselectivity yielding the target (*S*)-1-hydroxy-1-phenylpropan-2-one derivatives with high conversion efficiencies (up to 95%) and good enantioselectivities (up to 99%). Ao:DCPIP OR accepts hydroxy- and nitro-benzaldehydes and also sterically demanding substrates such as 1-naphthaldehyde and 4-(*tert*-butyl)benzaldehyde, which are typically poor acceptors in enzymatic transformations. The explorative synthesis of (*S*)-phenylpropionyl carbinol mediated by Ao:DCPIP OR via carboligation of benzaldehyde with 3,4-hexanedione is also reported.

Keywords: Asymmetric synthesis; C−C coupling; Enzyme catalysis; Thiamine diphosphate; Umpolung

Introduction

Chiral α-hydroxy ketones are key synthons in preparative organic chemistry for the synthesis of important molecules such as chiral amino alcohols and diols,[1] and structural subunits of many natural products and pharmaceuticals including antidepressants, antifungal agents, and antitumor antibiotics.[2] In virtue of their synthetic and biological relevance, several chemical approaches have been reported for their synthesis; the most common strategies rely on the α-hydroxylation of ketones with chiral oxidants,[3] the ketohydroxylation of olefins,[3,4] the asymmetric dihydroxylation of silyl enol ethers,[5] the mono-oxidation of 1,2-diols,[6] the organocatalytic α-oxygenation of ketones,[7] and the direct asymmetric condensation of two aldehyde molecules by the umpolung (polarity reversal) strategy (benzoin condensation). Organocatalytic strategies for the cross-benzoin-like condensation have been reported using azolium salt pre-catalysts with some level of success;[8] in general, however, chemical approaches suffer from chemoselectivity issues and high enantioselectivities are typically rare.[9] Biocatalysis with thiamine diphosphate (ThDP)-dependent enzymes constitutes a great opportunity to overcome the above limitations allowing the synthesis of chiral α-hydroxy ketones with high levels of chemo- and enantio-selectivity under environmentally benign conditions.[10] The production at industrial scale of (*R*)-phenylacetyl carbinol [(*R*)-PAC], the key precursor in the L-ephedrine synthesis, from pyruvic acid and

benzaldehyde mediated by pyruvate decarboxylase (PDC) is an illustrative example of the impact of ThDP-dependent enzymes on practical C−C bond-forming reactions.[11] A toolbox of different wild-type (wt) ThDP-dependent lyases, including several PDCs, benzoylformate decarboxylase (BFD), branched-chain keto acid decarboxylase (KdcA) and benzaldehyde lyase (BAL), is nowadays available for the chemoselective (cross-)benzoin condensation of various aliphatic and aromatic aldehydes (or their equivalents) to afford α-hydroxy ketones with high enantioselectivity and almost exclusive (*R*)-configuration.[12] Indeed, access to the corresponding (*S*)-isomers is almost precluded by using the above wild-type enzymes of the decarboxylase-subfamily[13] with two exceptions: the kinetic resolution of benzoins by BAL from *Pseudomonas fluorescens*,[14] and the formation of (*S*)-hydroxy propiophenone derivatives [(*S*)-HPPs] through condensation of benzaldehydes (donors) and acetaldehyde (acceptor) promoted by BFD from *Pseudomonas putida*.[15] Remarkably, mutagenesis studies based on structural analysis of the active-site architecture have permitted the design of (*S*)-selective variants of ThDP-dependent enzymes, thus paving the way for the formation of (*S*)-HPPs with wider substrate tolerance,[12c,15c] for the synthesis of (*S*)-5-hydroxy-4-oxo-5-phenylpentanoate derivatives (from α-ketoglutarate donor and benzaldehydes as acceptors),[16] and for the production of (*S*)-benzoins.[17] As far as the synthesis of pharmaceutically relevant phenylacetyl carbinols (PACs) is concerned, a variant of PDC from *Acetobacter pasteurianus* has been generated in a breakthrough study to produce PAC derivatives with (*S*)-selectivity for the first time.[18] While the mutant enzyme promoted the carboligation of benzaldehyde and acetaldehyde with modest efficiency,[12c,18a,19] (*S*)-PAC was suitably obtained using the same enzyme and pyruvate as donor (70% ee, 95% yield; Figure 1).[20] Very recently, a variant of PDC from *Zymomonas mobilis* has also been introduced for the highly chemoselective formation of (*S*)-PAC (76% ee, 95% yield; Figure 1).[21]

It results from the above survey that expanding the enzyme toolbox to efficiently access the valuable (*S*)-PAC structural motif with extended reaction scope and using readily available enzymes would be highly desirable. Herein, we describe the unprecedented (*S*)-selective synthesis of phenylacetyl carbinols mediated by the wt ThDP-dependent enzyme acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR; EC 2.3.1.190) via carboligation of methylacetoin (acetyl anion precursor) with a set of substituted benzaldehydes displaying different stereoelectronic properties. The results of this study clearly indicate Ao:DCPIP OR as a suitable candidate to fill the gap in the stereocontrolled synthesis of (*S*)-PAC derivatives by the catalysis of ThDP-dependent enzymes.

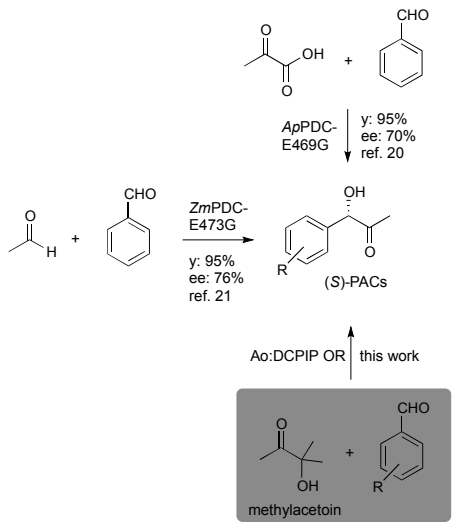


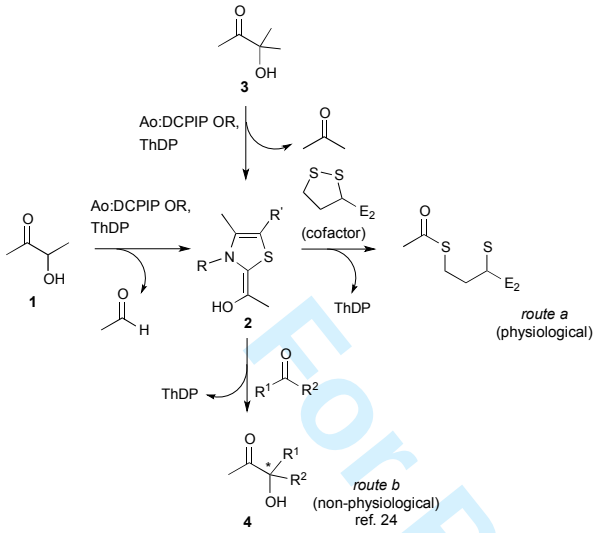
Figure 1. Enzymatic carboligations for the direct asymmetric synthesis of (*S*)-phenylacetyl carbinols (PACs).

Results and Discussion

Ao:DCPIP OR is the first enzyme of the bacterial acetoin dehydrogenase enzyme system (AoDH ES);[22,23] its physiological role is the oxidative cleavage of acetoin (**1**) with formation of acetaldehyde and transfer of the (hydroxyethyl)thiamine diphosphate intermediate **2** (acetyl anion equivalent) to the lipoamide cofactor of the second enzyme of the system (Scheme 1, *route a*). We have recently demonstrated that Ao:DCPIP OR from *Bacillus licheniformis*, cloned and overexpressed in *E. coli*, is also capable to mediate the non-physiological 1,2-addition of methylacetoin (donor) to activated ketones (acceptors) yielding chiral tertiary α-hydroxy ketones with high efficiency (Scheme 1, *route b*).[24]

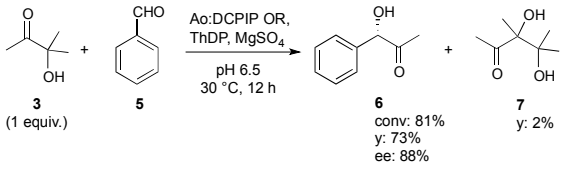
Complete control of chemoselectivity could be achieved in this transformation due to the hitherto unreported use of methylacetoin, whose activation occurs with elimination of unreactive acetone. In addition, some of the reaction products were formed with opposite stereochemistry compared to that obtained using other ThDP-dependent enzymes.[24] As a logical extension of that study on the formal aldehyde-ketone cross-carboligation reaction, we planned to examine the efficiency of the Ao:DCPIP OR-methylacetoin enzyme-substrate pair in the mixed benzoin-like reaction with aromatic aldehydes to access the class of valuable phenylacetyl carbinols, eventually with unusual (*S*)-configuration. Gratifyingly, condensation of methylacetoin (**3**) with benzaldehyde (**5**) under similar conditions to those previously described for the synthesis of chiral tertiary alcohols **4**[24] [**3** (20 mM), **5** (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% *v/v*), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR 0.5 mg mL^{-1}, 30 °C, 12 h], afforded the enantioenriched (*S*)-1-hydroxy-1-

phenylpropan-2-one [**6**, (*S*)-PAC] with 81% conversion (73% isolated yield) and 88% enantiomeric excess (ee), as determined by chiral-phase GC and optical rotation analyses (Scheme 2).



Scheme 1. Physiological and non-physiological activities of Ao:DCPIP OR. R = (4-amino-2-methylpyrimidin-5-yl)methyl; R' = ethyl diphosphate. Cofactor = lipoamide covalently bound to the second enzyme (E_2) of the acetoin dehydrogenase enzyme system (AoDH ES).

The (*S*)-configuration of **6** was further confirmed by comparison with an authentic sample of (*R*)-PAC prepared using the highly (*R*)-selective cyclohexane-1,2-dione hydrolase (CDH).[25] Hence, the first important result of this explorative study was the confirmation of Ao:DCPIP OR peculiarity to promote, in some occasions, carboligations with opposite stereochemical outcome compared to other wt ThDP-dependent enzymes. Moreover, the previously observed high level of chemoselectivity induced by Ao:DCPIP OR catalysis was established in the **3**/**5** coupling as well; indeed, the methylacetoin homocoupling product **7** was detected in very small amounts (2%) and in a racemic form,[26] whereas benzoin and 2-HPP byproducts were not observed in the crude reaction mixture (Scheme 2).



Scheme 2. Explorative study of the cross-benzoin-like reaction of methylacetoin (**3**) and benzaldehyde (**5**) catalyzed by Ao:DCPIP OR.

The effect of variation of the substrate molar ratio, reaction time, and enzyme amount on the efficiency of the model cross-benzoin-type condensation was evaluated next. Using equimolar concentrations of **3** and **5**, a decrease of benzaldehyde conversion was observed for reaction times of approximately 8−10 hours, and this effect was more pronounced increasing the enzyme concentration (from 0.5 to 4.0 mg mL^{-1}, Figure 2).

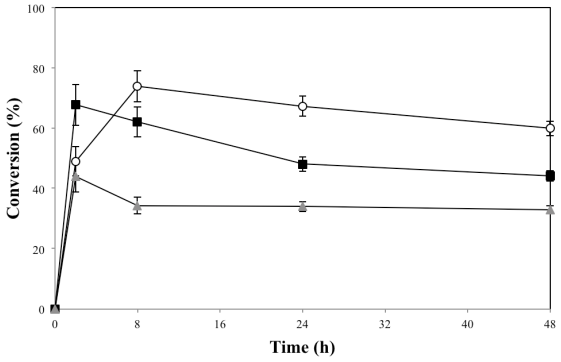


Figure 2. Conversion of benzaldehyde (**5**) as a function of time at different enzyme concentrations (○: 0.5 mg mL^{-1}; ■: 2.0 mg mL^{-1}; ▲: 4.0 mg mL^{-1}). Values are the mean ± SD of triplicates.

Intriguingly, the graph reporting the enantiomeric excess values as a function of time at different enzyme concentrations displayed a similar trend with erosion of enantioselectivity at long reaction times and high concentrations of enzyme (Figure 3).

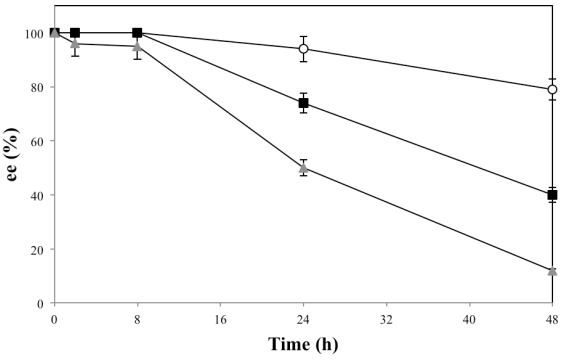
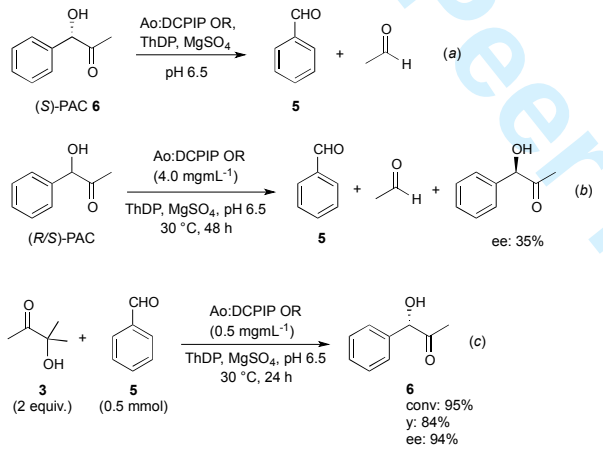


Figure 3. Enantiomeric excess of **6** as a function of time at different enzyme concentrations (○: 0.5 mg mL^{-1}; ■: 2.0 mg mL^{-1}; ▲: 4.0 mg mL^{-1}). Values are the mean ± SD of triplicates.

These results were rationalized assuming that Ao:DCPIP OR could also catalyze the cleavage of (*S*)-PAC (**6**) to yield benzaldehyde (**5**) and acetaldehyde (Scheme 3, eqn. *a*). This hypothesis was initially confirmed by ^{1}H NMR analysis of the crude

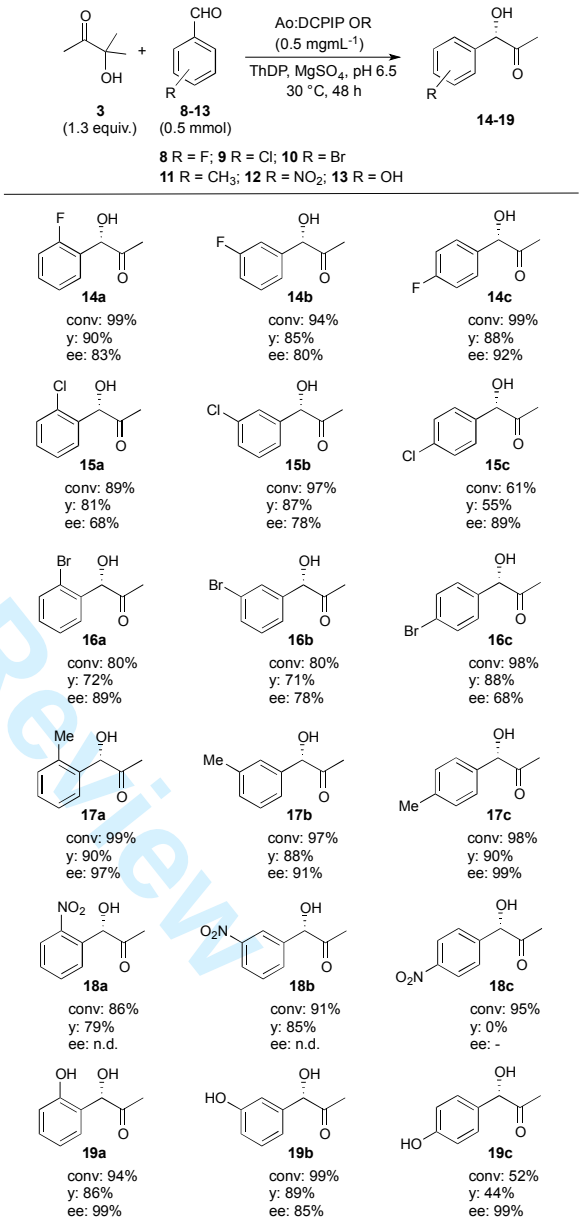
reaction mixture (Ao:DCPIP OR: 4 mg mL^{-1}; reaction time: 48 h) that showed, after extraction with $CDCl_3$, the presence of trace amounts of acetaldehyde. To unequivocally establish the postulated C−C bond-cleavage of **6**, two control experiments were performed where racemic PAC was incubated for 48 h under standard conditions with or without Ao:DCPIP OR. Indeed, benzaldehyde was formed only in the presence of the enzyme, which preferentially consumed the (*S*)-enantiomer of PAC, as determined by chiral GC analysis (Scheme 3, eqn. *b*). In light of these observations and with the aim to limit the reverse activity of Ao:DCPIP OR, the model cross-benzoin-type condensation was optimized by using a low amount of enzyme (0.5 mg mL^{-1}), an excess of methylacetoin (**3**, 2 equiv.), and by suitably controlling the reaction time (24 h). Under these conditions, (*S*)-PAC (**6**) was obtained in 84% yield (95% conversion) and 94% ee on a semipreparative scale (0.5 mmol; Scheme 3, eqn. *c*). A brief solvent screen was also undertaken and DMSO was found to be the best performing co-solvent among those tested (THF, EtOH, methyl *tert*-butyl ether), especially in terms of conversion efficiency (Figure S1).



Scheme 3. Cleavage of (*S*)- and (*rac*)-PAC (eqn. a,b) and optimized conditions for the synthesis of (*S*)-PAC (**6**).

The scope of the Ao:DCPIP OR-mediated cross-benzoin reaction was further investigated by testing the behavior of the *ortho*- (**a**), *meta*- (**b**), and *para*-substituted (**c**) benzaldehydes **8a,b,c**–**13a,b,c** (Table 1). Preliminary experiments run on an analytical scale (enzyme concentration: 0.5 mg mL^{-1}; equimolar donor/acceptor) showed no decrease of conversion efficiency and enantioselectivity in the formation of the corresponding PACs **14a**,**b**,**c**–**19a**,**b**,**c** within 8−48 hours (Figure S2: methylacetoin/*p*-tolualdehyde condensation as representative example). This result was in contrast with the trend observed for **6**, thus suggesting that the cleavage of PAC derivatives with substituted aromatic portions is a slow reaction. Therefore, the reaction time was set at 48 h for the subsequent screening study on a semipreparative scale (0.5 mmol) using a slight excess (1.3 equiv.) of methylacetoin (**3**). The absolute configuration of all the synthesized PAC products (Table 1) was assigned to be (*S*) on the basis of circular dichroism analysis (appearance of a positive band centered at 270-290 nm)[25] and confirmed for products **14a-c**, **15a-c**, **17a**, **17c** and **26** by comparison of their optical rotations with literature values (Experimental Section).[27]

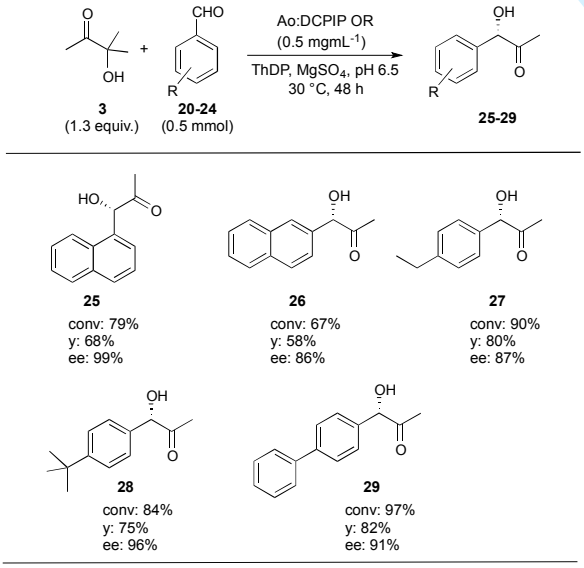
Table 1. Synthesis of PAC derivatives **14–19** catalyzed by Ao:DCPIP OR.[a]



[a]Conditions: **3** (26 mM), aldehyde (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% *v/v*), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1}). Conversion determined by ^1H NMR analysis; enantiomeric excess determined by chiral-phase GC analysis. Yields refer to the isolated product after column chromatography.

No racemization was observed for compounds **14-19** under the reaction conditions; this was verified in a control experiment with isolated **14c** (92% ee), which maintained its enantiomeric integrity over a period of 48 h (**14c** (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% *v/v*), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), 30 °C). Overall, the electronic properties and position of the substituent on the aromatic ring were found to have little effect on the conversion (52–99%) and enantioselectivity (68–99% ee) of the cross-benzoin processes, with the exceptions of *o*-chloro- and *p*-bromo-benzaldehydes **9a** and **10c**, which gave the corresponding PAC derivatives **15a** and **16c** with modest enantioselectivity (68% ee for both), and *p*-nitrobenzaldehyde **12c**. In this latter case, the full consumption of **3**/**12c** substrates occurred with formation of a quite complex reaction mixture not containing the expected PAC derivative **18c** (^{1}H NMR and MS analyses). It is worth emphasizing, however, that Ao:DCPIP OR accepted nitro- and hydroxy-benzaldehydes **12** and **13**, which are suitable substrates only for a very limited number of ThDP-dependent enzymes.[25,28]
Ao:DCPIP OR proved also to be an effective biocatalyst in the condensation of methylacetoin (**3**) with the sterically demanding aromatic aldehydes **20**–**24** furnishing the PAC products **25**–**29** with good conversions (67–97%) and enantioselectivities (87–99% ee; Table 2).

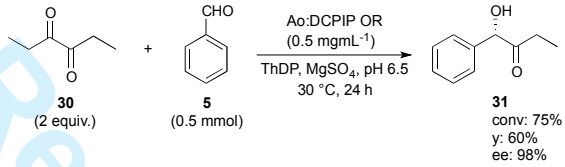
Table 2. Synthesis of sterically demanding PAC derivatives **25–29** catalyzed by Ao:DCPIP OR.[a]



[a]Conditions: **3** (26 mM), aldehyde (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% *v/v*), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1}). Conversion determined by ^{1}H NMR analysis; enantiomeric excess determined by chiral-phase GC analysis. Yields refer to the isolated product after column chromatography.

The combinations of **3** with 1-naphthaldehyde (**20**) and with 4-(*tert*-butyl)benzaldehyde (**23**) are of particular relevance as these acceptors are notoriously poor substrates in enzymatic transformations for steric and solubility reasons.[25,29]

The donor substrate range of the Ao:DCPIP OR-catalyzed cross-benzoin reaction was briefly investigated in an explorative study on the carboligation of benzaldehyde (**5**) with 3,4-hexanedione (**30**) for the challenging synthesis of 1-hydroxy-1-phenylbutan-2-one (phenylpropionyl carbinol, PPC) **31** with (*S*)-selectivity (Scheme 4).[30] It is important to remember that alkyl α-diketones are highly reactive donors in Ao:DCPIP OR catalysis;[24,31] however, their utilization in mixed condensations with carbonyl acceptors is complicated by the occurrence of the α-diketone homocoupling side-reaction, which reduces the chemoselectivity of the coupling process. Nevertheless, the cross-benzoin-type reaction of **30** and **5** was attempted to gain information about the Ao:DCPIP OR capability to promote the (*S*)-selective synthesis of PPC derivatives. Satisfyingly, under standard conditions [**30** (40 mM), **5** (20 mM), phosphate buffer pH 6.5 (50 mM), DMSO (10% *v/v*), $MgSO_4$ (0.9 mM), ThDP (0.4 mM), purified and lyophilized Ao:DCPIP OR (0.5 mg mL^{-1}); 30 °C, 24 h] the target (*S*)-1-hydroxy-1-phenylbutan-2-one (**31**) was prepared in 60% isolated yield and 98% ee (Scheme 4).



Scheme 4. Approaching the class of (*S*)-phenylpropionyl carbinol derivatives (PPCs) by Ao:DCPIP OR catalysis.

Conclusions

In summary, we have demonstrated that the wild-type ThDP-dependent acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR) serves as an efficient biocatalyst for the (*S*)-selective synthesis of valuable phenylacetyl carbinol products (PACs). Indeed, the carboligation of methylacetoin (**3**) (acetyl anion donor) with differently substituted benzaldehydes afforded the target α-hydroxy ketone derivatives with good levels of conversion efficiency and enantioselectivity and, significantly, with almost complete chemoselectivity. In anticipation of a future improvement based on the use of the higher homolog of methylacetoin, the propionyl anion transfer on benzaldehyde was attempted in this study employing the α-diketone 3,4-hexanedione (**30**) as donor substrate; the (*S*)-selectivity induced by Ao:DCPIP OR catalysis was established in the formation of phenylpropionyl carbinol (PPC) as well. Ao:DCPIP

OR belongs to the narrow group of ThDP-dependent enzymes capable to promote asymmetric aldehyde-ketone cross-couplings yielding chiral tertiary alcohols;[24] this constitutes a further evidence of the tremendous catalytic potential of Ao:DCPIP OR in asymmetric carboligation reactions. The straightforward production, robustness and facile immobilization of Ao:DCPIP OR[31b] are additional values of this enzyme for the development of novel synthetic applications and technological improvements. The evaluation of aliphatic aldehydes as acceptor substrates and the operation of Ao:DCPIP OR-functionalized packed-bed reactors for the continuos-flow cross-benzoin and aldehyde-ketone cross-coupling reactions are currently under investigation in our laboratories. Moreover, determination of the three-dimensional structure of the enzyme will offer new perspectives on thiamine catalysis in respect to mechanistic information and the design of variants with novel catalytic activities.

Experimental Section

General methods. 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). 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}. ^1H (300 MHz), ^{13}C (75 MHz), and ^{19}F (282 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature. Peak assignments were aided by 1H-1H COSY and gradient-HMQC experiments. For HR-MS measurements, the compounds were analyzed in positive ion mode by Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) using a quadrupole, a hexapole, and a time-of-flight unit to produce spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and 5 L min^{-1}, respectively. The MS analyzer was externally calibrated with ESI-L low concentration tuning mix from *m/z* = 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H_2O/ACN 0.1% TFA into the system at a flow rate of 0.4 µL min^{-1}. Chiral phase HPLC analyses were carried out on a HP 1100 chromatography system (Agilent) using a Chiralpak ID column (250 × 4.6 mm, particle size: 5 µm) for compounds **15a-c**, **16a-c**, **25**, a Phenomenex Lux Cellulose-1 column (250 × 4.6 mm, particle size: 5 µm) for compounds **19a** and **19b**, and a Phenomenex Amylose-2 lux (250 × 4.6 mm, particle size: 5 µm) for compounds **19c**, **26** and **29**. Analyses were performed using a detection wavelength of 254 nm and hexane/2-propanol (90:10) as eluent (flow rate: 1 mL/min), a part from compound **19c** (eluent: hexane/2-propanol/acetic acid 185:14:1). GC analyses were performed on a Carlo Erba 6000, equipped with a FID detector and a Megadex 5 column (25 m × 0.25 mm) with the temperature programs below specified. CD spectra of the products dissolved in acetonitrile were recorded on a Jasco J-810 spectrometer. Purified Ao:DCPIP OR was obtained as described in Ref. 24.

Effect of enzyme concentration and reaction time on the synthesis of (*S*)-1-hydroxy-1-phenylpropane-2-one (6) [(*S*)-PAC]. Three reactions were performed by adding 0.75, 3 and 6 mg of lyophilized Ao:DCPIPOR, respectively, to a solution of benzaldehyde (**5**) (3.0 µL, 30 µmol), methylacetoin (**3**) (3.2 µL, 30 µmol), ThDP (0,4 mg, 0.6 µmol) and Mg_2SO_4 (0.16 mg, 1.3 µmol) in 50 mM phosphate buffer at pH 6.5 (1.5 mL) containing DMSO (10% v/v). The reactions were gently shaken at 30 °C and after 2, 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 ^1H NMR and chiral-phase GC to determine conversion and ee, respectively.

Optimized synthesis of (*S*)-1-hydroxy-1-phenylpropane-2-one (6) [(*S*)-PAC]. Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of benzaldehyde (**5**) (51 µL, 0.50 mmol), methylacetoin (**3**) (105 µL, 1.00 mmol), ThDP (4.5 mg, 10 µmol) and Mg_2SO_4 (2.7 mg, 20 µmol) in 50 mM phosphate buffer at pH 6.5 (25 mL) containing DMSO (10% v/v). The reaction mixture was gently shaken at 30 °C for 24 h and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel using cyclohexane/ethyl acetate (4:1) as eluent to afford pure (*S*)-**6** (ee 94%) as a yellow pale oil (63 mg, 84%). $[\alpha]_D$ = +313 (*c* 0.3, $CHCl_3$), lit.:[32a] +413 (*c* 0.82, $CHCl_3$); GC, temperature program from 100 to 200 °C rate 1 °C min^{-1}, r.t. 28.6 min (*R*), 30.2 min (*S*); ^1H NMR: δ = 7.46-7.28 (m, 5 H, Ar), 5.09 (d, *J* = 4.2 Hz, 1 H, H-1), 4.30 (d, *J* = 4.2 Hz, 1 H, OH), 2.07 (s, 3 H, CH_3); ^{13}C NMR: δ = 207.1, 137.9, 129.0 (2 C), 128.7 (2 C), 127.3, 80.1, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 173.0605, calcd. for $C_9H_{10}O_2Na$ $[M+Na]^+$: 173.0578.

3,4-Dihydroxy-3,4-dimethylpentan-2-one 7: obtained as described before from the reaction of equimolar **3** and **5** (0.50 mmol). ^1H NMR: δ = 2.24 (s, 3 H, $C(O)CH_3$), 1.38 (s, 3 H, $C(OH)CH_3$), 1.24 (s, 6 H, 2 CH_3).

General procedure for the synthesis of the PAC analogues 14a,b,c–19a,b,c on analytical scale. Lyophilized Ao:DCPIPOR (0.75 mg) was added to a solution of the substituted benzaldehyde **8a,b,c–13a,b,c** (30 µmol), methylacetoin (**3**) (3.2 µL, 30 µmol), ThDP (0,4 mg, 0.6 µmol) and Mg_2SO_4 (0.16 mg, 1.3 µmol) in 50 mM phosphate buffer at pH 6.5 (1.5 mL) containing DMSO (10% v/v). After 2, 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 ^1H NMR and chiral-phase GC to determine conversion and ee, respectively.

General procedure for the synthesis of the PAC analogues 14a,b,c–19a,b,c and 25–29 on semipreparative scale. Lyophilized Ao:DCPIP OR (12 mg) was added to a solution of the substituted benzaldehyde **7a,b,c–12a,b,c** and **20–24** (0.50 mmol), methylacetoin (**3**) (63 µL, 0.60 mmol), ThDP (4.5 mg, 10 µmol) and Mg_2SO_4 (2.7 mg, 20 µmol) in 50 mM phosphate buffer at pH 6.5 (25 mL) containing DMSO (10% v/v). The reaction mixture was gently shaken at 30 °C for 48 h and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel with the suitable elution system.

(*S*)-1-(2-Fluorophenyl)-1-hydroxypropan-2-one 14a: colorless oil, 90% yield. $[\alpha]_D$ = +176 (c 1.0, MeOH), lit. for (*R*)-enantiomer:[32b] -186 (*c* 0.56, MeOH); GC, temperature program from 100 to 200 °C, rate 1 °C min^{-1}, r.t. 22.3 min (*R*), 23.2 min (*S*); ee 83% (*S*); ^1H NMR: δ = 7.34-7.25 (m, 2 H, Ar), 7.19-7.07 (m, 2 H, Ar), 5.41 (s, 1 H, H-1), 4.26 (bs, 1 H, OH), 2.13 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.2, 160.5 (d, *J* = 246 Hz), 130.5, 128.8, 125.1, 124.9, 116.0, 73.6, 25.0; ^{19}F NMR: δ = -118.3 (m); HR-MS (ESI/Q-TOF): *m/z*= 168.0531, calcd. for $C_9H_9FO_2$ $[M]^+$: 168.0587.

(*S*)-1-(3-Fluorophenyl)-1-hydroxypropan-2-one 14b: colorless oil, 85% yield. $[\alpha]_D$ = +242.2 (*c* 0.93, $CHCl_3$), lit. for (*R*)-enantiomer:[32b] -221 (*c* 0.14, MeOH); GC, temperature program from 100 to 200 °C, rate 5 °C min^{-1},

r.t. 13.1 min (*R*), 13.2 min (*S*); ee 80% (*S*); ^{1}H NMR: δ = 7.40-7.33 (m, 1 H, Ar), 7.14 (dd, *J* = 7.9, 0.8 Hz, 1 H, Ar), 7.07-7.01 (m, 2 H), 5.09 (s, 1 H, H-1), 4.33 (s, 1 H, OH), 2.10 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.4, 163.2 (d, *J* = 248 Hz), 140.4, 130.7, 123.1, 115.9, 114.3, 79.6, 25.3; ^{19}F NMR: δ = -111.83 (m); HR-MS (ESI/Q-TOF): *m/z*= 168.0611, calcd. for $C_9H_9FO_2$ $[M]^+$: 168.0587.

(*S*)-1-(4-Fluorophenyl)-1-hydroxypropan-2-one 14c: colorless oil, 88% yield, $[\alpha]_D$ = +330.3 (*c* 0.35, $CHCl_3$), lit. for (*R*)-enantiomer:[32b] -197 (*c* 0.69, MeOH); GC, temperature program from 100 to 200 °C, rate 1 °C min^{-1}, r.t. 33.6 min (*R*), 36.1 min (*S*); ee 92% (*S*); ^{1}H NMR: δ = 7.38-7.18 (m, 2 H, Ar), 7.15-6.99 (m, 2 H, Ar), 5.07 (s, 1 H, H-1), 4.28 (bs, 1 H, OH), 2.07 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.98, 163.0 (d, *J* = 247 Hz), 133.87, 129.2 (2 C), 116.1 (2 C), 79.5, 25.3; ^{19}F NMR: δ = -112.91 (m); HR-MS (ESI/Q-TOF): *m/z*= 168.0524, calcd. for $C_9H_9FO_2$ $[M]^+$: 168.0587.

(*S*)-1-(2-Chlorophenyl)-1-hydroxypropan-2-one 15a: colorless oil, 81% yield. $[\alpha]_D$ = +179.5 (*c* 0.22, MeOH), lit. for (*R*)-enantiomer:[32b] -207 (*c* 0.34, MeOH); HPLC, r.t. 11.7 min (*S*), 12.7 min (*R*); ee 68% (*S*); ^{1}H NMR: = δ 7.50-7.35 (m, 1 H, Ar), 7.35-7.18 (m, 3 H, Ar), 5.58 (s, 1 H, H-1), 4.35 (bs, 1 H, OH), 2.13 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.3, 135.6, 133.4, 130.1, 129.9, 128.9, 127.5, 76.4, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 207.0150, calcd. for $C_9H_9ClO_2Na$ $[M+Na]^+$: 207.0189.

(*S*)-1-(3-Chlorophenyl)-1-hydroxypropan-2-one 15b: colorless oil, 87% yield. $[\alpha]_D$ = +218.8 (*c* 0.70, $CHCl_3$), lit. for (*R*)-enantiomer:[32c] -115 (*c* and solvent not reported); HPLC, r.t. 9.7 min (*S*), 12.3 min (*R*); ee 78% (*S*); ^{1}H NMR: δ = 7.34-7.31 (m, 3 H, Ar), 7.25-7.19 (m, 1 H, Ar), 5.06 (s, 1 H, H-1), 4.31 (bs, 1 H, OH), 2.11 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.3, 139.9, 135.1, 130.4, 129.1, 127.6, 125.6, 79.6, 25.4; HR-MS (ESI/Q-TOF): *m/z*= 207.0212, calcd. for $C_9H_9ClO_2Na$ $[M+Na]^+$: 207.0189.

(*S*)-1-(4-Chlorophenyl)-1-hydroxypropan-2-one 15c: colorless oil, 55% yield; $[\alpha]_D$ = +222,5 (*c* 0.16, $CHCl_3$), lit. for (*R*)-enantiomer:[32b] -158 (*c* 0.58, MeOH); HPLC, r.t. 10.7 min (*R*), 11.6 min (*S*); ee 89% (*S*). ^{1}H NMR: δ = 7.42-7.32 (m, 2 H, Ar), 7.29-7.25 (m, 2 H, Ar), 5.06 (s, 1 H, H-1), 4.29 (s, 1 H, OH), 2.08 (s, 3 H, CH^3); ^{13}C NMR: δ = 206.6, 136.5, 134.8, 129.3 (2 C), 128.7 (2 C), 79.5, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 207.0158, calcd. for $C_9H_9ClO_2Na$ $[M+Na]^+$: 207.0189.

(*S*)-1-(2-Bromophenyl)-1-hydroxypropan-2-one 16a: colorless oil, 72% yield. $[\alpha]_D$ = +157.8 (*c* 0.32, $CHCl_3$); HPLC, r.t. 12.4 min (*S*), 13.3 min (*R*); ee 89% (*S*); ^{1}H NMR: δ = 7.71-7.48 (m, 1 H, Ar), 7.45-7.26 (m, 1 H, Ar), 7.25-7.14 (m, 2 H, Ar), 5.60 (d, *J* = 3.5 Hz, 1 H, H-1), 4.38 (d, *J* = 3.50 Hz, 1 H, OH), 2.14 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.3, 137.3, 133.4, 130.2, 128.9, 128.2, 123.7, 78.6, 25.5; HR-MS (ESI/Q-TOF): *m/z*= 227.9762, calcd. for $C_9H_9BrO_2$ $[M]^+$: 227.9786.

(*S*)-1-(3-Bromophenyl)-1-hydroxypropan-2-one 16b: yellow pale oil, 71% yield. $[\alpha]_D$ = +223.5 (*c* 0.90, $CHCl_3$); HPLC, r.t. 10.1 min (*S*), 12.3 min (*R*); ee 78% (*S*); ^{1}H NMR: δ = 7.58-7.36 (m, 2 H, Ar), 7.34-7.10 (m, 2 H, Ar), 5.05 (s, 1 H, H-1), 4.31 (s, 1 H, OH), 2.10 (s, 3 H, CH_3); ^{13}C NMR: δ = 206.2, 140.1, 131.9, 130.5, 130.3, 125.9, 123.1, 79.4, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 227.9806, calcd. for $C_9H_9BrO_2$ $[M]^+$: 227.9786.

(*S*)-1-(4-Bromophenyl)-1-hydroxypropan-2-one 16c: colorless oil,[36b] 88% yield. $[\alpha]_D$ = +170.5 (*c* 1.19, $CHCl_3$); HPLC, r.t. 11.1 min (*R*), 11.7 min (*S*); ee 68% (*S*); ^{1}H NMR: δ = 7.52 (d, *J* = 8.4 Hz, 2 H, Ar), 7.21 (d, *J* = 8.4 Hz, 2 H, Ar), 5.05 (s, 1 H, H-1), 4.28 (bs, 1 H, OH), 2.08 (s, 3 H, CH_3). ^{13}C NMR: δ = 206.5, 137.0, 132.3 (2 C), 129.1 (2 C), 122.9, 79.6, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 227.9711, calcd. for $C_9H_9BrO_2$ $[M]^+$: 227.9786.

(*S*)-1-Hydroxy-1-(*o*-tolyl)propan-2-one 17a: colorless oil, 90% yield. $[\alpha]_D$ = +173.0 (*c* 0.30, $CHCl_3$), lit. for (*R*)-enantiomer:[32d] -363 (*c* 0.25, $CHCl_3$); GC, temperature program from 100 to 200 °C rate 5 °C min^{-1}, r.t. 14.1 min (*S*), 14.2 min (*R*); ee 97% (*S*); ^{1}H NMR: δ = 7.24-7.08 (m, 4 H, Ar), 5.26 (d, *J* = 3.8 Hz, 1 H, H-1), 4.16 (d, *J* = 3.8 Hz, 1 H, OH), 2.40 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3); ^{13}C NMR: δ = 207.6, 136.4, 135.9, 131.3, 128.7, 128.3, 126.6, 78.1, 25.4, 19.3; HR-MS (ESI/Q-TOF): *m/z*= 164.0912, calcd. for $C_{10}H_{12}O_2$ $[M]^+$: 164.0837.

(*S*)-1-Hydroxy-1-(*m*-tolyl)propan-2-one 17b: yellow pale oil, 88% yield. $[\alpha]_D$= +351.1 (*c* 0.88, $CHCl_3$); GC, temperature program from 100 to 200 °C rate 1 °C min^{-1}, r.t. 34.3 min (*R*), 35.5 min (*S*); ee 91% (*S*); ^{1}H NMR: δ = 7.33-7.20 (m, 1 H, Ar), 7.20-7.03 (m, 3 H, Ar), 5.05 (s, 1 H, H-1), 4.26 (bs, 1 H, OH), 2.35 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3); ^{13}C NMR: δ = 207.3, 138.9, 137.9, 129.6, 128.9, 127.9, 124.7, 80.2, 25.4, 21.5; HR-MS (ESI/Q-TOF): *m/z*= 164.0927 calcd. for $C_{10}H_{12}O_2$ $[M]^+$: 164.0837.

(*S*)-1-Hydroxy-1-(*p*-tolyl)propan-2-one 17c: yellow pale oil, 90% yield, $[\alpha]_D$= +394.0 (*c* 0.55, $CHCl_3$), lit. for (*R*)-enantiomer:[32d] –385 (*c* and solvent not reported); GC, temperature program from 100 to 200 °C rate 1 °C min^{-1}, r.t. 37.5 min (*R*), 39.6 (*S*); ee 99% (*S*); ^{1}H NMR: δ = 7.22-7.17 (m, 4 H, Ar), 5.06 (d, *J* = 4.2 Hz, 1 H, H-1), 4.25 (d, *J* = 4.2 Hz, 1 H, OH), 2.35 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3); ^{13}C NMR: δ = 207.4, 138.7, 135.1, 129.8 (2 C), 127.4 (2 C), 80.0, 25.4, 21.3. HR-MS (ESI/Q-TOF): *m/z*= 164.0711, calcd. for $C_{10}H_{12}O_2$ $[M]^+$: 164.0837.

(*S*)-1-Hydroxy-1-(2-nitrophenyl)propan-2-one 18a: yellow amorphous solid, 79% yield. $[\alpha]_D$= +183.0 (*c* 1.40, $CHCl_3$). ^{1}H NMR: δ = 8.00 (d, *J* = 8.1 Hz, 1 H, Ar), 7.76-7.57 (m, 1 H, Ar), 7.59-7.39 (m, 2 H, Ar), 5.61 (s, 1 H, H-1), 4.38 (s, 1 H, OH), 2.21 (s, 3 H, CH_3). ^{13}C NMR: δ = 205.3, 133.7, 133.3, 130.6, 130.5, 129.6, 125.1, 76.0, 25.6; HR-MS (ESI/Q-TOF): *m/z*= 196.0697, calcd. for $C_9H_{10}NO_4$ $[M+H]^+$: 196.0610.

(*S*)-1-Hydroxy-1-(3-nitrophenyl)propan-2-one 18b: yellow amorphous solid, 85% yield. $[\alpha]_D$= +59.0 (*c* 0.80, $CHCl_3$). ^{1}H NMR: δ = 8.30-8.24 (m, 2 H, Ar), 7.70-7.66 (m, 1 H, Ar), 7.60-7.55 (m, 1 H, Ar), 5.21 (s, 1 H, H-1), 4.39 (bs, 1 H, OH), 2.14 (s, 3 H, CH_3); ^{13}C NMR: δ = 205.5, 140.0, 133.1, 130.1, 125.0, 123.7, 122.3, 79.2, 77.3, 25.2. HR-MS (ESI/Q-TOF): *m/z*= 196.0671, calcd. for $C_9H_{10}NO_4$ $[M+H]^+$: 196.0610.

(*S*)-1-Hydroxy-1-(2-hydroxyphenyl)propan-2-one 19a: colorless oil, yield 86%. $[\alpha]_D$ = +275.6 (*c* 0.64, MeOH); HPLC, r.t. 20.0 min (*R*), 27.2 min (*S*); ee 99% (*S*). ^{1}H NMR: = δ 7.34-7.13 (m, 2 H, Ar), 6.98-6.90 (m. 1 H, Ar), 6.88-6.75 (m, 1 H, Ar), 5.22 (s, 1 H, H-1), 2.11 (s, 3 H, CH_3). ^{13}C NMR: δ = 207.4, 154.9, 130.3, 129.4, 122.1, 120.9, 117.2, 78.7, 25.1. HR-MS (ESI/Q-TOF): *m/z*= 189.0601, calcd. for $C_9H_{10}O_3Na$ $[M+Na]^+$: 189.0528.

(*S*)-1-Hydroxy-1-(3-hydroxyphenyl)propan-2-one 19b: white amorphous solid, yield 89%. $[\alpha]_D$ = +101.2 (*c* 0.68, MeOH); HPLC, r.t. 42.7 min (*S*), 45.0 min (*R*); ee 85% (*S*). ^{1}H NMR: δ = 7.28-7.06 (m, 1 H, Ar), 6.92-6.79 (m, 2 H, Ar), 6.74 (dd, *J* = 8.1, 1.0 Hz, 1 H, Ar), 5.07 (s, 1 H, H-1), 2.04 (s, 3 H, CH_3); ^{13}C NMR: δ = 209.4, 158.9, 141.4, 130.8, 119.3, 116.3, 114.8, 81.1, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 189.0433, calcd. for $C_9H_{10}O_3Na$ $[M+Na]^+$: 189.0528.

(S)-1-Hydroxy-1-(4-hydroxyphenyl)propan-2-one 19c: white amorphous solid, yield 44%. $[\alpha]_D$ = +131.2 (*c* 0.42, MeOH); HPLC, r.t. 27.4 min (*R*), 31.9 min (*S*); ee 99% (*S*). ^{1}H NMR (CD_3OD): δ = 7.19 (d, *J* = 8.6 Hz, 2 H, Ar), 6.78 (d, *J* = 8.6 Hz, 2 H, Ar), 5.07 (s, 1 H, H.1), 3.31 (s, 1 H, OH), 2.01 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD): δ = 209.7, 158.9, 130.6, 129.6 (2 C), 116.6 (2 C), 80.7, 25.4; HR-MS (ESI/Q-TOF): *m/z*= 189.0645, calcd. for $C_9H_{10}O_3Na$ $[M+Na]^+$: 189.0528.

(*S*)-1-Hydroxy-1-(naphthalen-1-yl)propan-2-one 25: yellow amorphous solid, 68% yield. $[\alpha]_D$ = +284.3 (*c* 1.30, $CHCl_3$); HPLC, r.t. 10.1 min (*S*), 10.8 min (*R*); ee 99% (*S*). ^{1}H NMR: δ = 8.10-7.95 (m, 1 H, Ar), 7.90-7.80 (m, 2 H, Ar), 7.60-7.40 (m, 4 H, Ar), 5.61 (s, 1 H, H-1), 2.05 (s, 3 H, CH_3); ^{13}C NMR: δ = 208.3, 134.3, 133.3, 131.1, 129.7, 129.0, 127.7, 126.9, 126.1, 125.4, 123.4, 79.3, 25.5; HR-MS (ESI/Q-TOF): *m/z*= 223.0829, calcd. for $C_{13}H_{12}O_2Na$ $[M+Na]^+$: 223.0735.

(*S*)-1-Hydroxy-1-(naphthalen-2-yl)propan-2-one 26: white solid, 58% yield, $[\alpha]_D$ = +308.5 (*c* 1.00, $CHCl_3$), lit. for (*R*)-enantiomer:[32d] -101 (*c* 0.08, $CHCl_3$); HPLC, r.t. 19.5 min (*S*), 22.7 min (*R*); ee 92% (*S*). ^{1}H NMR: δ = 8.01-7.72 (m, 4 H, Ar), 7.61-7.43 (m, 2 H, Ar), 7.37 (dd, *J* = 8.5 Hz, *J* = 1.8, 1 H, Ar), 5.26 (s, 1 H, H-1), 4.42 (bs, 1 H, OH), 2.11 (s, 3 H, CH_3); ^{13}C NMR: δ = 207.1, 135.2, 133.3, 133.2, 128.9, 127.9, 127.7, 127.10, 126.5, 126.4, 124.1, 80.2, 25.3; HR-MS (ESI/Q-TOF): *m/z*= 223.0612, calcd. for $C_{13}H_{12}O_2Na$ $[M+Na]^+$: 223.0735.

(*S*)-1-(4-Ethylphenyl)-1-hydroxypropan-2-one 27: colorless oil, 80% yield. $[\alpha]_D$ = + 326.0 (*c* 1.00, $CHCl_3$); GC temperature program from 100 to 200 °C rate 1 °C min^{-1}, r.t. 45.4 min (*R*), 47.5 min (*S*); ee 87% (*S*); ^{1}H NMR: δ = 7.26-7.19 (m, 4 H, Ar), 5.07 (s, 1 H, H-1), 4.25 (bs, 1 H, OH), 2.64 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.09 (s, 3 H, CH_3), 1.23 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3); ^{13}C NMR: δ = 207.3, 144.9, 135.1, 128.5 (2 C), 127.3 (2 C), 79.9, 28.5, 25.3, 15.5; HR-MS (ESI/Q-TOF): *m/z*= 223.0628, calcd. for $C_{11}H_{14}O_2Na$ $[M+Na]^+$: 223.0735.

(*S*)-1-(4-(*tert*-Butyl)phenyl)-1-hydroxypropan-2-one 28: colorless oil, 75% yield. $[\alpha]_D$ = + 195.8 (*c* 1.70, $CHCl_3$); GC temperature program from 100 to 200 °C, rate 1 °C min^{-1}, r.t. 56.4 min (*R*), 57.9 min (*S*); ee 96% (*S*); ^{1}H NMR δ = 7.54-7.30 (m, 2 H, Ar), 7.34-7.07 (m, 2 H, Ar), 5.07 (s, 1 H, H-1), 4.23 (bs, 1 H, OH), 2.09 (s, 3 H, CH_3), 1.31 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR: δ = 207.3, 151.8, 134.9, 127.0 (2 C), 125.9 (2 C), 79.8, 34.6, 31.3, 25.4; HR-MS (ESI/Q-TOF): *m/z*= 229.1098, calcd. for $C_{13}H_{18}O_2Na$ $[M+Na]^+$: 229.1204.

(*S*)-1-([1,1'-Biphenyl]-4-yl)-1-hydroxypropan-2-one 29: yellow amorphous solid, 82% yield. $[\alpha]_D$ = + 267.1 (*c* 2.10, $CHCl_3$); HPLC, r.t. 29.7 min (*S*), 34.7 min (*R*); ee 91% (*S*). ^{1}H NMR: δ = 7.71-7.50 (m, 4 H, Ar), 7.54-7.28 (m, 5 H, Ar), 5.15 (s, 1 H, H-1), 4.32 (bs, 1 H, OH), 2.14 (s, 3 H, CH_3); ^{13}C NMR: δ = 207.0, 141.7, 140.4, 136.9, 128.8 (2 C), 127.8 (2 C), 127.7 (2 C), 127.6, 127.1 (2 C), 79.9, 25.4; HR-MS (ESI/Q-TOF): *m/z*= 226.0727, calcd. for $C_{15}H_{14}O_2$ $[M]^+$: 226.0994.

(*S*)-1-Hydroxy-1-phenylbutan-2-one 31: lyophilized Ao:DCPIP OR (12 mg) was added to a solution of benzaldehyde **5** (0.50 mmol) and 3,4-hexandione (**30**) (121 µL, 1.0 mmol), ThDP (4.5 mg, 10 µmol) and Mg_2SO_4 (2.7 mg, 20 µmol) in 50 mM phosphate buffer at pH 6.5 (25 mL) containing DMSO (10% v/v). The reaction mixture was gently shaken at 30 °C for 48 h and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. After chromatography on silica gel with cyclohexane-ethyl acetate (4:1) as eluent, the product 31 was obtained as a colorless oil, 60% yield. $[\alpha]_D$ = +254 (*c* 0.3, $CHCl_3$), lit.:[32e] +389.8 (*c* 2.06, $CHCl_3$); GC, temperature program from 100 to 200 °C rate 2 °C min^{-1}, r.t. 19.0 min (*R*), 19.1 min (*S*); ee 98% (*S*); ^{1}H NMR: δ = 7.45-7.25 (m, 5 H, Ar), 5.10 (s, 1 H, H-1), 4.35 (bs, 1 H, OH), 2.40-2.15 (m, 2 H, CH_2), 1.01 (t, 3 H, *J* = 7.0 Hz, CH_3); ^{13}C NMR: δ = 210.1, 138.2, 129.1 (2 C), 128.7, 127.4 (2 C), 79.5, 31.2, 7.7; HR-MS (ESI/Q-TOF): *m/z*= 164.0801, calcd. for $C_{10}H_{12}O_2$ $[M]^+$: 164.0837.

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[27] Taking advantage of the reverse activity of AO:DCPIP OR (Scheme 3, eqn. *b*), the synthesis of **14c** was attempted using the (*S*)-PAC (**6**) as donor and 4-fluorobenzaldehyde (**8c**; 5 equiv.) as acceptor. The expected PAC derivative **14c** was obtained after 24 h in 63% conversion and 90% ee (for the experimental details see the Supporting Information and Figure S3). The use of **6** as donor in cross-benzoin-type reactions is currently under investigation in our laboratories and it will be the object of a forthcoming publication.

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FULL PAPER

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