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Asymmetric Bio- and Chemoreduction of 2-Benzylidenecyclopentanone Derivatives

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Dedicated to Professor Emeritus Miha Tišler, University of Ljubljana, on the occasion of his 90th birthday.

Abstract

Highly efficient asymmetric reduction of 2-benzylidenecyclopentanone derivatives to give the respective exocyclic allylic alcohols in *ee*'s up to 96% was performed with chiral oxazaborolidine-based catalysts. Complete enantioselectivity furnishing (*S*)-configured alcohol product could be achieved by bioreduction of 2-(4-chlorobenzylidene)cyclopentanone with *Daucus carota* root. The synthesized compounds may be used as enantiomerically enriched standards for the monitoring of the enzyme-catalyzed redox processes.

Keywords: Enantioselective reduction, cyclopentanone, AKR1C inhibitors, oxazaborolidine, bioreduction

1. Introduction

Chiral alcohols are important building blocks and intermediates in the synthesis of pharmaceuticals, fine chemicals, agrochemicals, flavors and fragrances, as well as functional materials.[1] Since ketones represent one of the most common families of unsaturated compounds, their asymmetric reduction represents the simplest and most powerful method for the preparation of enantiomerically enriched alcohols. The stereospecific reduction of carbonyl groups to the corresponding alcohols is also a functionalization reaction involved in the metabolism of endogeneous compounds and xenobiotics containing these groups. Thus, it is often catalyzed by enzymes belonging to either dehydrogenase/reductase superfamily or the aldo-keto reductase (AKR) superfamily.[2] The human members of the AKR subfamily 1C are involved in the biosynthesis and inactivation of steroid hormones, and also in the biosynthesis of neurosteroids and prostaglandins.[3] These enzymes reduce carbonyl containing substrates to alcohols and also function in vivo as ketosteroid reductases, and thus regulate the activity of androgens, estrogens and progesterone in target tissues, and ligand occupancy and transactivation of their corresponding receptors.[4] Aberrant expression and action of AKR1C enzymes may lead to an imbalance in the metabolism of steroid hormones, and to further development of different pathophysiological conditions.[5] These enzymes thus represent promising therapeutic targets in the development of new drugs. In the literature, structurally different compounds have been evaluated as AKR1C inhibitors, for example dietary phytoestrogens,[6] benzodiazepines,[7] cinnamic acids,[8] benzofurans, and phenolphthalein derivatives,[9] Ru(II) complexes,[10] salicylic and aminobenzoic acids derivatives, as well as some nonsteroidal anti-inflammatory drugs and their analogues.[11,12] In spite of a plethora of potent inhibitors of steroid metabolizing enyzmes that have emerged, the search for new and more selective ones is an important field of investigation. Štefane *et al.*[13] indentified compounds based on cyclopentane scaffold, which are AKR1C1 and AKR1C3 substrates active in the low micromolar range, and thus represent promising starting points in the development of potential agents for treatment of hormone-dependent forms of cancer and other diseases involving these enzymes. AKR1C inhibitors are not only interesting as potential agents for the treatment of diseases, but also as molecular tools in the study of the pathophysiological roles of these enzymes. In the recent study Beranič *et al.* introduced new enzymatic assays employing racemic 2-(4-chlorobenzylidene)cyclopentanol (CBCP-ol) and its ketone counterpart 2-(4-chlorobenzylidene)cyclopentanone that allow monitoring of AKR1C-catalyzed reactions in the reductive and oxidative directions.[14] Since enzymes perform highly stereoselective reactions, it seems

useful to know, which enantiomer of CBCP-ol is involved in the redox process. For this reason we present herein the synthesis of enantiomerically enriched cyclopentyl alcohols (CBCP-ol and its 4-methoxy analogue) via the asymmetric chemo- and bioreduction of substituted 2-benzylidenecyclopentanones, which can serve as standards in monitoring of AKR1C-catalyzed reactions. The reduction of the benzene-fused analogue, indanone-derived chalcone, to the corresponding secondary allylic alcohol is also included.

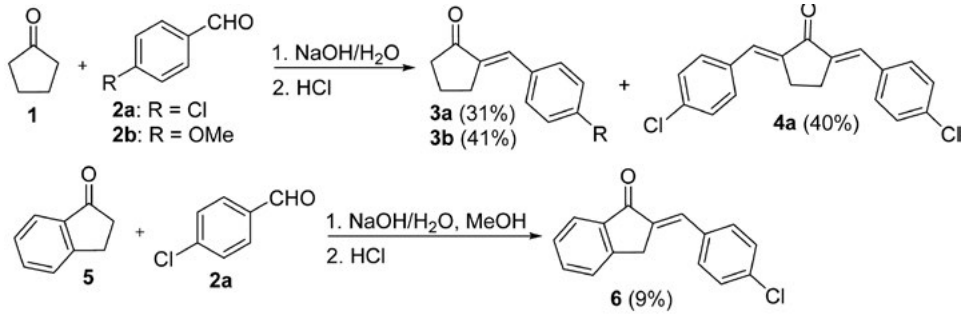
2. Results and Discussion

The starting compounds, α-arylmethylene cyclic ketones **3** and **6** were synthesized in a base-induced aldol condensation from cyclopentanone (**1**) or 1-indanone (**5**) and the corresponding *p*-substituted benzaldehydes **2** following slightly modified literature procedure[15] (Scheme 1). The reaction of cyclopentanone with *p*-methoxybenzaldehyde (**2b**) towards benzylidenecyclopentanone **3b** proceeded smothly, while using *p*-chlorobenzaldehyde (**2a**), besides the desired product **3a**, symmetrical abis(benzylidene) derivative **4a** was isolated as the by-product. 1-Indanone reacted with *p*-chlorobenzaldehyde leading to the product **6** in a very low 9% isolated yield. We were not, however, interested in the optimization of these aldol condensation reactions.

With α,β-unsaturated ketones **3** and **6** in hand, we investigated different methods for the selective carbonyl reduction to obtain the highest possible enantiomeric excess of the corresponding allylic alcohol products with exocyclic C=C double bond.

The most elegant method for the asymmetric reduction of prochiral ketones is either homogeneous or heterogeneous hydrogenation or transfer hydrogenation catalyzed by chiral metal catalysts.[16] Highly efficient asymmetric hydrogenation of α-arylmethylene cyclopentanones was realized by chiral tailor-made iridium–spiroaminophosphine catalysts;[17] for example, reduction of **3b** gave **7b** with 95% *ee* (enantiomeric excess). Unfortunately, in our case the use of some commercially available chiral rhodium and ruthenium catalysts **C1**–**C4** (Figure 1) in hydrogenation of cyclopentanone **3a** with molecular hydrogen (80 bars) led to very low yields and *ee* values of the secondary alcohol **7a**; the best *ee* of 12% (31% isolated yield) was obtained with Noyori's bifunctional ruthenium catalyst **C4**.

After report by Itsuno[18] that chiral aminoalcohols together with BH_3 effected the enantioselctive reduction of prochiral ketones, Corey[19] isolated the primarily formed oxazaborolidine derivative, and developed a powerful catalytic version of an original stoichometric reduction. Con-



Scheme 1. Synthesis of α-arylmethylene cyclic ketones **3**, **4** and **6**.

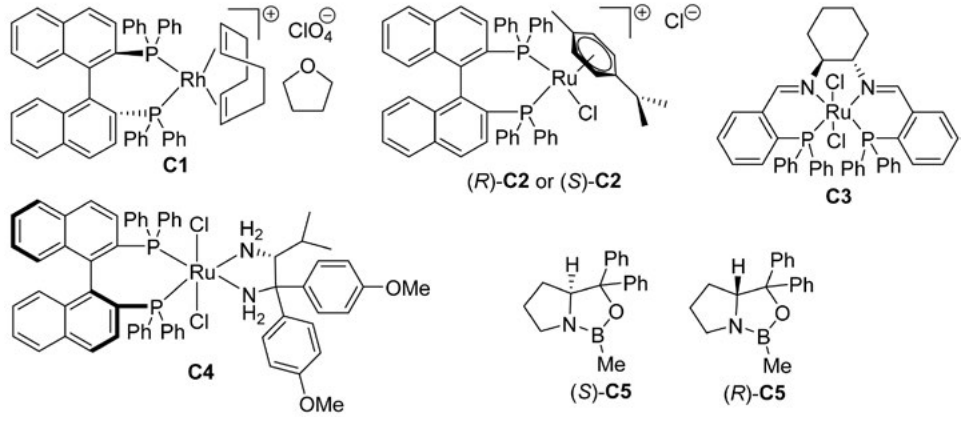
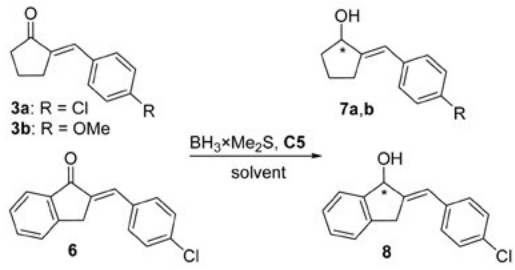


Figure 1. Chiral catalysts employed in the asymmetric reduction of cyclic ketones **3** and **6**.

sequently, enantioselective reduction of prochiral ketones with borane (or its derivatives) catalyzed by chiral oxazaborolidines has emerged as an excellent route to alcohols of high enantiomerical purity.[20] Since this method has many advantages such as predictable absolute configuration and high *ee* of chiral secondary alcohol products, it seemed logical to investigate whether oxazaborolidine-catalysed reduction of ketones **3** and **6** could afford the desired exocyclic allylic alcohols in high enantioselectivity. Indeed, the borane reduction of chlorobenzylidenecyclopentanone **3a** in the presence of 10 mol% of oxazaborolidine catalyst (*S*)-**C5** at room temperature afforded the desired alcohol (*R*)-**7a** in 77% *ee* (as juged by chiral HPLC) (Table 1, entry 1). By varying different solvents, reaction temperatures, amount of reductant, and catalyst loading (Table 1, entries 2–8), the highest *ee* of 96% in reduction of **3a** was achieved with 1.88 equiv. $BH_3 \times Me_2S$, 20 mol% (*S*)-**C5** in toulene at 0 °C. Typically, reduction was carried out by slow addition of a toluene solution of the ketone to an ice-cooled toluene solution of $BH_3 \times Me_2S$ and catalyst (stirred for 10 min prior to adding the ketone). The same protocol was used in the reduction of the methoxy-substituted analogue **3b** giving (*R*)-**7b** but with significant loss of enantioselectivity (Table 1, entry 9). The opposite enantiomers, (*S*)-**7a** and (*S*)-**7b**, were obtained by the borane reduction with the oxazaborolidine catalyst (*R*)-**C5** (Table 1, entries 10 and 11). Interestingly, chloro-substituted alcohols (*S*)-**7a** and (*R*)-**7a** were obtained with practically identical *ee* values (~95%), while catalyst (*R*)-**C5** reduced methoxy-benzylidenecyclopentanone **3b** with increased enantioselectivity compared to catalyst (*S*)-**C5** (90% vs. 82% *ee*). A dramatic drop in chemical yield and optical purity of the indanol alcohol **6** was observed in reduction of the indanone derivative **6** with either (*S*)-**C5** or (*R*)-**C5** catalyst. In spite of applying different reaction conditions (Table 1, entries 12–17), the corresponding alcohol **8** was not obtained in *ee* higher than 33%. Lower *ee* values associated with asymmetric reduction of indanone **6** as compared to cyclopentanone **3** may suggest that a fused benzene ring has a pronounced influence on the level of asymmetric induction with oxazaborolidine catalysts **C5**. Additionally, low isolated yield of indanol **8** might be due to its decomposition (or of parent ketone) under applied reaction conditions as was also established for reduction of analogous indanone-derived chalcones.[21]

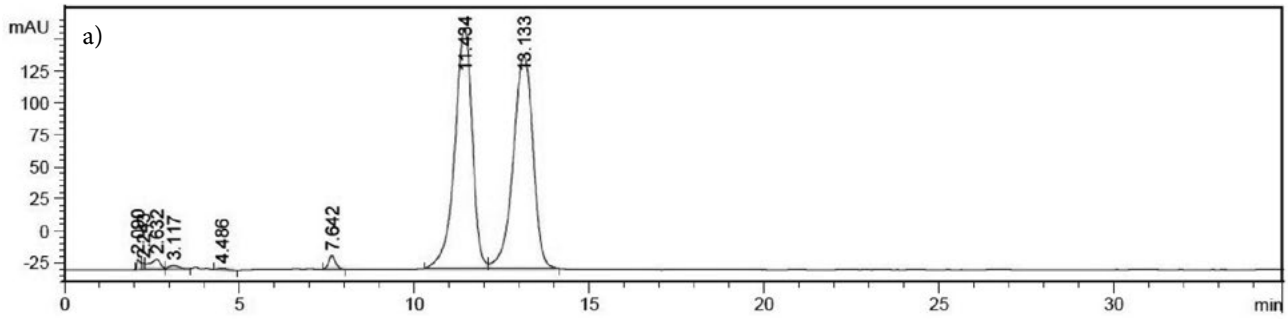
The enantiomeric excess of the allylic alcohols **7** and **8** was determined by chiral stationary phase HPLC. The corresponding racemic alcohols were synthesized by che-

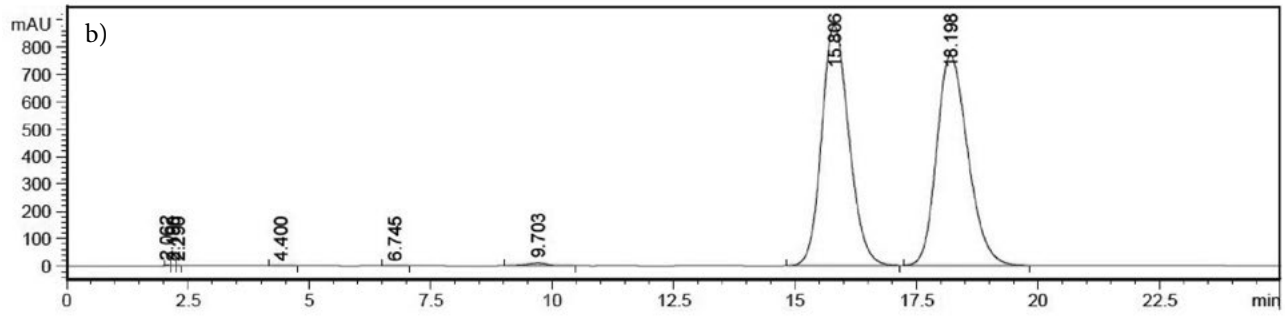
Table 1: Asymmetric reduction of cyclic ketones **3a**,**b** and **6** with oxazaborolidine catalysts **C5**.

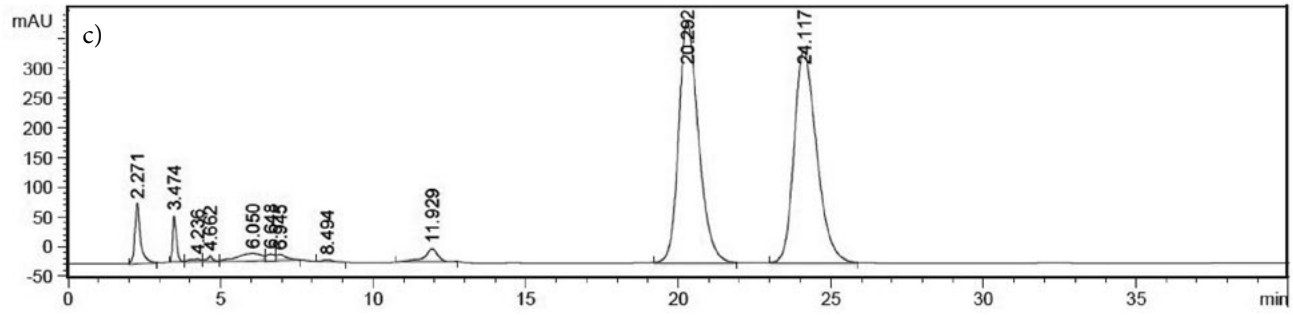


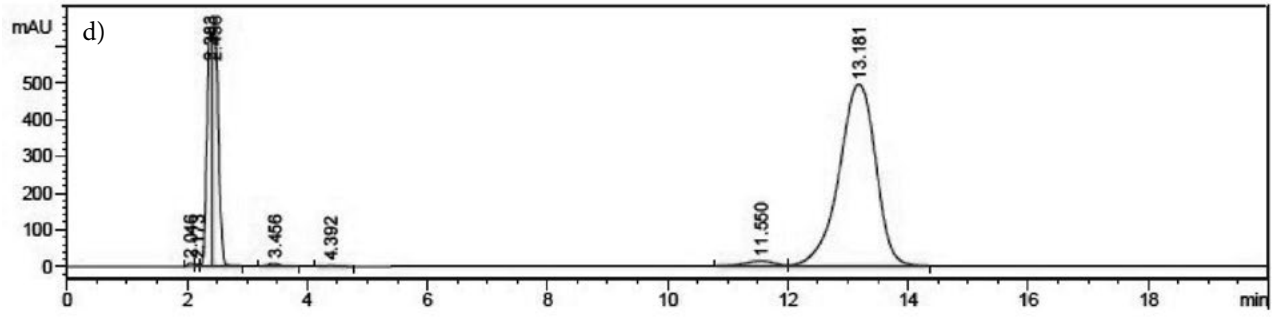
entry	ketone	catalyst (mol%)	solvent	$BH_3 \times Me_2S$ (equiv.)	T (°C)	product	yield[a] (%)	*ee*[b] (%)
1	**3a**	(*S*)-**C5**, 10	THF	1.10	r. t.	**7a**	n.d.	77 (*R*)
2	**3a**	(*S*)-**C5**, 10	THF	2.74	–20	**7a**	88	81 (*R*)
3	**3a**	(*S*)-**C5**, 10	THF	1.70	–20	**7a**	67	32 (*R*)
4	**3a**	(*S*)-**C5**, 10	THF	3.42	–20	**7a**	91	75 (*R*)
5	**3a**	(*S*)-**C5**, 20	DCM	1.70	–6	**7a**	84	90 (*R*)
6	**3a**	(*S*)-**C5**, 10	THF	2.74	0	**7a**	82	88 (*R*)
7	**3a**	(*S*)-**C5**, 10	THF	1.70	0	**7a**	80	90 (*R*)
8	**3a**	(*S*)-**C5**, 20	toluene	1.88	0	**7a**	77	96 (*R*)
9	**3b**	(*S*)-**C5**, 20	toluene	1.88	0	**7b**	67	82 (*R*)
10	**3a**	(*R*)-**C5**, 20	toluene	1.88	0	**7a**	70	95 (*S*)
11	**3b**	(*R*)-**C5**, 20	toluene	1.88	0	**7b**	59	90 (*S*)
12	**6**	(*R*)-**C5**, 20	toluene	1.88	0	**8**	15	23
13[c,d]	**6**	(*R*)-**C5**, 20	toluene/CH_2Cl_2	2.10	0	**8**	21	24
14[d]	**6**	(*S*)-**C5**, 20	toluene/CH_2Cl_2	1.27	0	**8**	20	33
15	**6**	(*S*)-**C5**, 20	CH_2Cl_2	1.27	0	**8**	19	21
16[e,f]	**6**	(*S*)-**C5**, 20	THF	1.27	–30	–	–	–
17[e]	**6**	(*S*)-**C5**, 20	CH_2Cl_2	1.27	–30	**8**	22	19

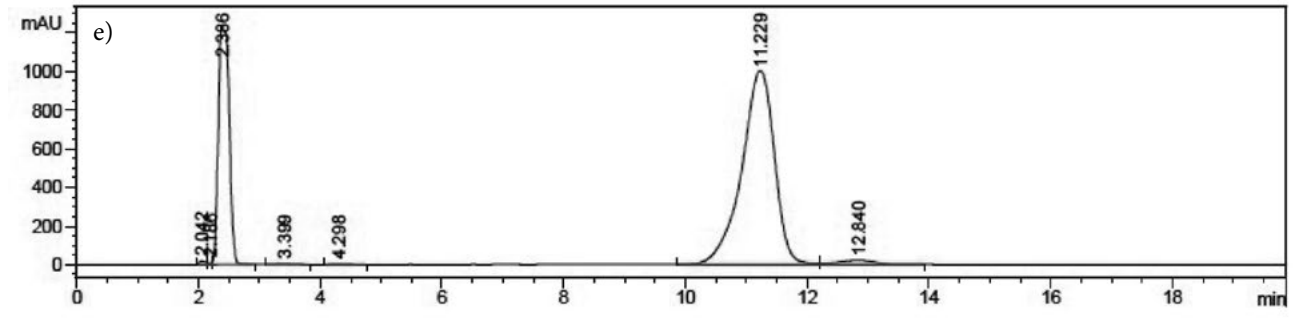
[a]Isolated yield is given. [b]Determined by chiral HPLC. [c]First solution of **6** added to a solution of (*R*)-**C5**, then $BH_3 \times Me_2S$. [d]Ketone dissolved in CH_2Cl_2, and catalyst in toluene. [e]Reaction quenched with MeOH. [f]The desired alcohol was not isolated.


a)
mAU
11.434
13.133
7.642
4.486
3.117
min


b)
mAU
15.806
18.198
4.400
6.745
9.703
min


c)
mAU
20.292
24.117
2.271
3.474
6.050
8.494
11.929
min


d)
mAU
13.181
11.550
3.456
4.392
min


e)
mAU
2.386
11.229
12.840
3.399
4.298
min

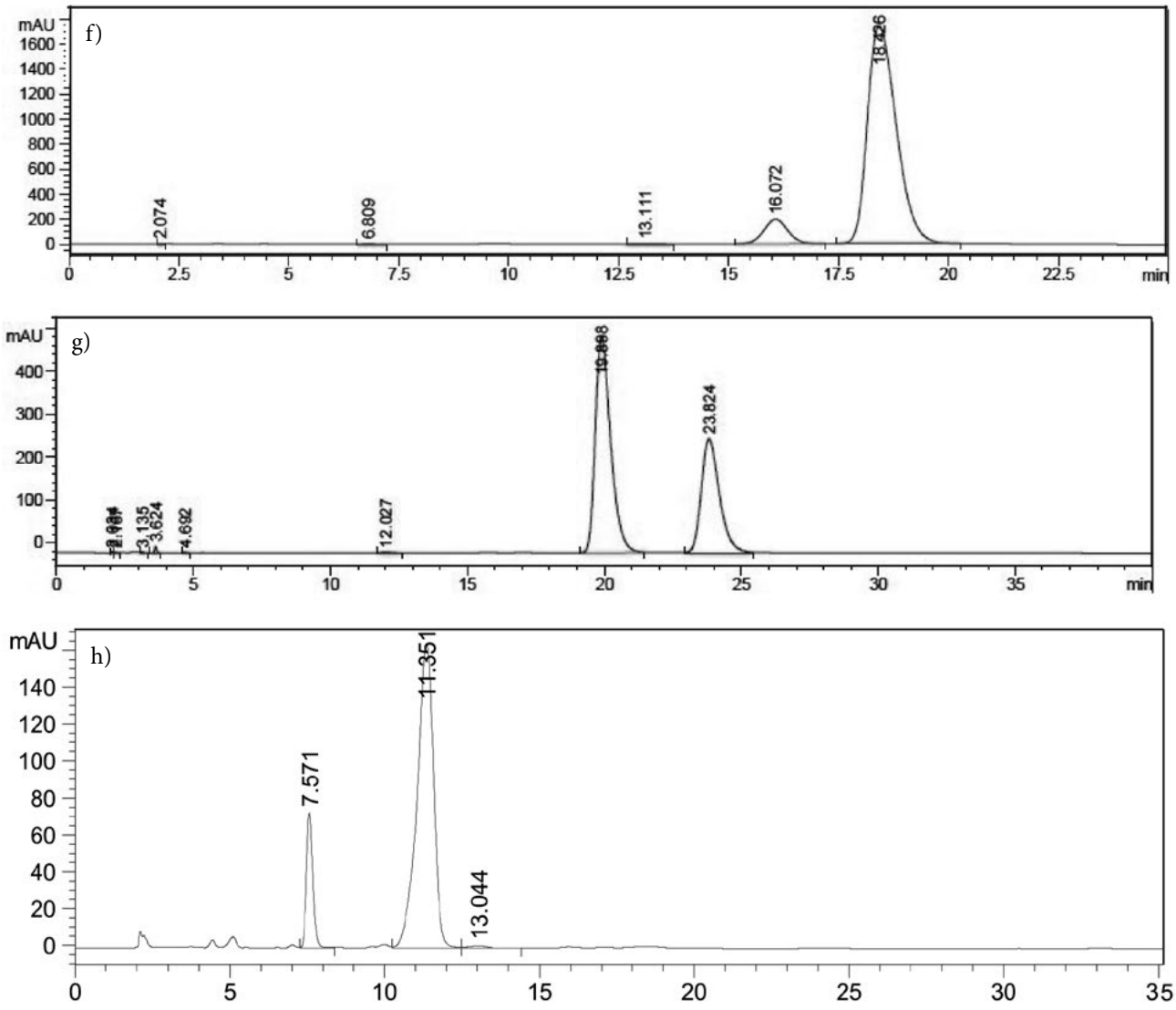


Figure 2. Chromatograms of **(a)** racemic alcohol **7a**, **(b)** racemic alcohol **7b**, (**c**) racemic alcohol **8**, (**d**) enantiomerically enriched (*R*)-**7a** obtained with (*S*)-**C5**, **(e)** enantiomerically enriched (*S*)-**7a** obtained with (*R*)-**C5**, **(f)** enatiomerically enriched (*R*)-**7b** obtained with (*S*)-**C5**, **(g)** alcohol **8** obtained with (*R*)-**C5**, **(h)** enantiomerically enriched (*R*)-**7a** obtained with *Daucus carota* root reduction.

moselective reduction with $NaBH_4$ in the presence of $CeCl_3 \times 6H_2O$. They were used to find the optimal HPLC conditions for the separation of the pairs of the enatiomeric alcohols.

Although Corey's (*S*)-proline-derived or stereochemically related oxazaborolidines in general delivered *R*-configured allylic alcohols in reduction of enones,[22] the *R* absolute configuration of chlorobenzylidenecyclopentanol **7a** obtained from reduction with (*S*)-**C5** was unambigously confirmed by X-ray crystallography (Figure 3). Additionally, this established also the configuration around the exocyclic C=C double bond as *E*. It should be made clear that stereochemical assignment for (*R*)-**7a** has not been previously made, although the absolute stereochemistry of related 2-benzylidenecyclopentanol obtained with Corey (*S*)-oxazaborolidine catalyst was determined to be *R*.[23] Thus, formation of the alcohol (*R*)-**7a** from chloro-substituted cyclopentanone **3a** in the presence of oxazaborolidine catalyst (*S*)-**C5** is also consistent with the sense of asymmetric induction predicted by the Corey mechanistic model.[24] Consequently, we ascribed the *R* stereochemistry also to the methoxy-substituted alcohol **7b** provided by oxazaborolidine catalyst (*S*)-**C5**, while for alcohols **7a**,**b** arising from the borane reduction with catalyst (*R*)-**C5** the *S* configuration was concluded. This was further supported by comparison of the sense of optical rotation and HPLC elution sequence of the enantiomeric forms of the alcohols **7a** and **7b** obtained with catalysts (*S*)-**C5** and (*R*)-**C5**, respectively. Examination of the chromatogram **(d)** depicted in Figure 2 reveals, that for chloro-cyclopentanol **7a** delivered with catalyst (*S*)-**C5**, the (+)-(*R*)-form of the enantiomers separated on chiral column is eluted second.

Methoxy-cyclopentanol **7b** obtained with catalyst (*S*)-**C5** (Figure 2, chromatogram **(f)**) is also eluted second and returned a specific rotation of $[\alpha]_D^{25}$ + 3.8, identical in sign to that of (*R*)-**7a**; consequently its configuration was proposed to be *R*. The opposite enantiomers of **7a** and **7b**, obtained with catalyst (*R*)-**C5**, both eluted on column first and the samples show levorotatory character. The dominant enantiomer of the indanol alcohol **8** obtained with (*R*)-**C5**, though in low excess, also eluted first on chiral column (Figure 2, chromatogram **(g)**), and the optical rotation of the sample was measured as $[\alpha]_D^{25}$ – 13.4. On this basis it can be speculated that catalyst (*R*)-**C5** preferentially delivers the (*S*)-indanol **8** in the reduction of indanone **6**, while with catalyst (*S*)-**C5** the (*R*)-alcohol **8** is obtained as the major enantiomer.

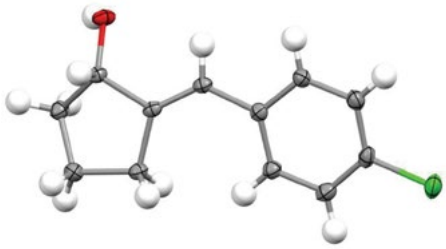
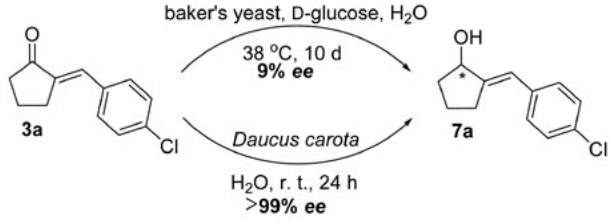


Figure 3. X-ray crystal structure of (*R*)-**7a**; thermal ellipsoids are set at 40% probability.

Table 2 Crystallographic data, structure refinement summary, selected bond lengths, bond angles, and torsion angles for compound (*R*)-**7a**.

Property	**Compound (*R*)-7a**
Empirical formula	$C_{12}H_{13}ClO$
Formula weight	208.67
Temperature	150(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	4.99305(10)
b (Å)	9.3428(2)
c (Å)	22.2446(4)
α (°)	90.00
b (°)	90.00
γ (°)	90.00
Volume (Å^3)	1037.69(4)
Z	4
F (000)	440
Crystal size (mm3)	0.08 × 0.25 × 0.60
μ (CuK\a) (/mm)	0.079
*N*ref	6371
R	0.0327
$_wR_2$	0.0876
S	1.08
Bond length (Å)	
C2(1) – Cl(1)	1.7440(16)
C(8) – C(9)	1.336(2)
O(1) – C(10)	1.4238(19)
Bond angles (°)	
C(5) – C(7) – C(8)	125.0(1)
C(8) – C(9) – C(11)	129.9(2)
C(8) – C(9) – C(10)	122.4(1)
C(9) – C(10) –O(1)	115.2(1)
Torsion angles (°)	
C(5) – C(7) – C(8) – C(9)	10.0(1)
C(7) – C(8) – C(9) – C(11)	–4.5(1)

Efficient asymmetric reduction of carbonyl compounds can also be achieved by means of bioreduction employing either isolated enzymes or whole cells system as mild and environmentally benign reduction systems. Fogliato *et al.* used baker's yeast[25] for the reduction of arylidene cyclopentanones and cyclohexanones reaching satisfactory enantioselectivity, while the secondary alcohols of excellent optical purity were obtained from *Daucus carota*[26] root reduction of structurally different prochiral ketones (up to 100% *ee*). Similarly, an α,β-unsaturated ketone *trans*-4-phenylbut-3-en-2-one was regio- and stereoselectively reduced using carrot, celeriac, and beetroot enzyme systems to the corresponding (*S*)-allylic alcohol in *ee*'s 72–99%.[27] In our case, the baker's yeast reduction of chlorobenzylidenecyclopentanone **3a** gave very low isolated yield (5%) and optical purity (*ee* = 9%) of the corresponding alcohol **7a** even after incubating the reaction mixture at 38 °C for 10 days. On the contrary, the 24-hour-bioreduction with *Daucus carota* root (substrate/carrot, 1/134 (w/w)) delivered alcohol (*S*)-**7a** with >99% *ee* as determined in the crude product (Figure 2, chromatogram **(h)**), the amount of which was, however, very low after removal of the biomaterial (Scheme 2). Interestingly, asymmetric induction turned out to be time-dependent, namely *ee* value of (*S*)-**7a** reduced to 92% after incubating reaction mixture for four days at room temperature. It is noteworthy that isolation of the desired alcohol product from bioreduction is intrinsically messy, as the aqueous media contains the cellular mass, usual metabolites, nutrients, and the starting ketone.



Scheme 2. Bioreduction of benzylidenecyclopentanone **3a**.

3. Experimental

General. Toluene was dried with sodium and distilled. All other reagents and solvents were used as received from commercial suppliers. Melting points were deter-

mined on a Kofler micro hot stage. The NMR spectra were recorded at 302 K either on a Bruker Avance DPX 300 or Avance III 500 MHz spectrometer operating at 300 MHz or 500 MHz and 75.5 MHz or 126 MHz for ^{1}H and ^{13}C nuclei. The ^{1}H NMR spectra in $CDCl_3$ are referenced with respect to TMS as the internal standard. The ^{13}C NMR spectra are referenced against the central line of the solvent signal ($CDCl_3$ triplet at δ = 77.0 ppm). The coupling constants (*J*) are given in Hz. The multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad). IR spectra were obtained on a Bruker FTIR Alpha Platinum ATR spectrophotometer. MS spectra were recorded with an Agilent 6224 Accurate Mass TOF LC/MS instrument. Elemental analyses (C, H, N) were performed with a Perkin-Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica gel TLC-cards. Column chromatography was performed on 230–400-mesh silica gel. Merck silica gel 60 PF254 containing gypsum was used to prepare chromatotron plates. Radial chromatography was performed with Harrison Research, model 7924T chromatotron. HPLC analyses were performed with Agilent Technology 1260 Infinity HPLC instrument with UV detection. The known compounds were characterized by comparison of their physical or spectrosopic data with those in the literature.

Synthesis of ketones 3a and 4a: Cyclopentanone (**1**) (5.0 g, 59.4 mmol) and *p*-chlorobenzaldehyde (**2a**) (4.22 g, 30.02 mmol) were added into a 0.2 M aqueous NaOH solution (210 mL), and stirred at room temperature for 72 h. The reaction was quenched with water (210 mL), and the reaction mixture was acidified with 3.6% aqueous HCl solution (60 mL) to *p*H ~ 4. The product was extracted with CH_2Cl_2 (3 × 150 mL), and combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by SiO_2 column chromatography (petroleum ether : EtOAc = 20 : 1) to give 1.90 g (31%) of **3a** and 4.00 g (40%) of **4a**.

2-(4-Chlorobenzylidene)cyclopentanone (3a): mp 74–76 °C (lit.[28] 77–79 °C).

2,5-Bis(4-chlorobenzylidene)cyclopentanone (4a): mp 225–227 °C (lit.[29] 224–226 °C).

Synthesis of 2-(4-methoxybenzylidene)cyclopentanone (3b): Cyclopentanone (**1**) (1.0 g, 11.89 mmol) and *p*-methoxybenzaldehyde (**2b**) (896 mg, 6.58 mmol) were added into a 0.2 M aqueous NaOH solution (90 mL), and stirred at room temperature for 24 h, to which additional amount of cyclopentanone (298 mg, 3.54 mmol) was added, and stirred for further 12 h. The reaction was quenched with water (90 mL), and the reaction mixture was acidified with 3.6% aqueous HCl solution (20 mL) to *p*H ~ 4. The product was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by SiO_2 column chromatography (petroleum ether : EtOAc = 10 : 1) to give 843 mg (41%) of yellow crystalline product. Mp 65.4–66.3 °C (lit.[28] 68–69 °C).

Synthesis of 2-(4-chlorobenzylidene)-2,3-dihydro-1*H*-inden-1-one (6): To a solution of 1-indanone (**5**) (4.0 g, 30.27 mmol) and *p*-chlorobenzaldehyde (**2a**) (5.32 g, 37.85 mmol) in MeOH (20 mL), a 0.2 M aqueous NaOH solution (250 mL) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with water (200 mL), and the reaction mixture was acidified with 3.6% aqueous HCl solution (60 mL) to *p*H ~ 1. The product was extracted with CH_2Cl_2 (3 × 150 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by SiO_2 column chromatography (petroleum ether : EtOAc = 50 : 1; 20 : 1; 10: 1; 5 : 1; 2 : 1) to give 732 mg (9%) of light yellow crystalline product. Mp 180.4–181.0 °C (lit.[30] 179 °C).

Typical procedure for the synthesis of racemic alcohols – (±)-2-(4-chlorobenzylidene)cyclopentanol (±)-(7a): 2-(4-Chlorobenzylidene)cyclopentanone (**3a**) (400 mg, 1.94 mmol) and $CeCl_3 \times 6H_2O$ were dissolved in MeOH (20 mL), and stirred at room temperature for 30 min. Then solid $NaBH_4$ (296 mg, 7.83 mmol) was added portion-wise. After 15 min additional amount of $NaBH_4$ (140 mg, 3.70 mmol) was added, and stirred for further 1 h. The reaction was quenched with 1 M aqueous HCl solution (10 mL) and water (40 mL). The reaction mixture was stirred for 30 min and then extracted with EtOAc (3 × 50 mL). The combined organic layers were successively washed with 5% aqueous $NaHCO_3$ solution (50 mL), water (30 mL), and brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated in a vacuo to give 360 mg (89%) of white crystalline product (±)-(**7a**), mp 76–77 °C. IR (ATR) ν 3358, 2964, 1911, 1705, 1620, 1493, 1405, 1325, 1243, 1166, 1143, 1090, 1027, 1009, 980, 940, 887, 823, 730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (br s, 1H, OH), 1.61–1.68 and 1.70–1.79 (2 × m, 2 × 1H, CH_2), 1.93–2.02 (m, 2H, CH_2), 2.51–2.59 and 2.65–2.74 (2 × m, 2 × 1H, CH_2), 4.59 (m, 1H, OCH), 6.53 (br q, *J* 2.5 Hz, 1H, C=CH), 7.28 (AA'BB', *J* 8.8 Hz, 2H, Ar), 7.30 (AA'BB', *J* 8.8 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 29.2, 34.7, 77.1, 122.4, 128.4, 129.5, 132.1, 136.2, 148.3. ESI–HRMS (*m/z*): $[M+H-H_2O]^+$ calcd for $C_{12}H_{12}Cl$, 191.0622; found, 191.0627.

(±)-2-(4-Methoxybenzylidene)cyclopentanol (±)-(7b): Prepared by the above procedure from **3b** (100 mg, 0.49 mmol). Yield 71%, mp 75.5–78.3 °C. IR (ATR) ν 3252, 2998, 2955, 2931, 2833, 1604, 1510, 1463, 1420, 1294, 1242, 1178, 1112, 1034, 973, 938, 886, 831, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 1H, OH), 1.62–1.69 and 1.72–1.79 (2 × m, 2 × 1H, CH_2), 1.89–2.01 (m, 2H, CH_2), 2.50–2.59 and 2.67–2.75 (2 × m, 2 × 1H, CH_2), 3.82 (s, 3H, Me),

4.58 (m, 1H, OCH), 6.52 (br q, *J* 2.5 Hz, 1H, C=CH), 6.88 (AA'BB', *J* 8.8 Hz, 2H, Ar), 7.30 (AA'BB', *J* 8.8 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 29.3, 34.9, 55.2, 77.5, 113.7, 123.2, 129.6, 130.5, 145.5, 158.2. ESI–HRMS (*m/z*): $[M+H-H_2O]^+$ calcd for $C_{13}H_{15}O$, 187.1117; found, 187.1114. Analytical data are in agreement with the literature data.[17]

(±)-2-(4-Chlorobenzylidene)-2,3-dihydro-1*H*-inden-1-ol (±)-(8): Prepared by the above procedure from **6** (125 mg, 0.49 mmol). Yield 39%, mp 105.8–108.6 °C. IR (ATR) ν 3319, 3069, 3025, 2887, 2321, 2155, 2107, 1904, 1692, 1677, 1608, 1586, 1490, 1461, 1405, 1354, 1312, 1296, 1255, 1212, 1186, 1176, 1133, 1092, 1009, 954, 895, 866, 844, 823, 806, 745, 732 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97 (br s, 1H, OH), 3.79–3.99 (m, 2H, CH_2), 5.62 (br s, 1H, OCH), 6.86 (br q, *J* 2.5 Hz, 1H, C=CH), 7.27–7.32 (m, 3H, Ar), 7.34–7.37 (m, 4H, Ar), 7.51–7.55 (m, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.5, 78.3, 124.8, 124.9, 125.1, 127.3, 128.6, 128.8, 129.8, 132.7, 135.5, 140.7, 142.9, 145.5. ESI–HRMS (*m/z*): $[M+H-H_2O]^+$ calcd for $C_{16}H_{12}Cl$, 239.0622; found, 239.0612.

Typical procedure for the asymmetric reduction with oxazaborolidines – synthesis of (*R*)-2-(4-chlorobenzylidene)cyclopentanol (*R*)-(7a). To the ice-cooled (0 °C) solution of (*S*)-**C5** (0.1 mL, 0.1 mmol; 1 M in toluene) in dry toluene (1 mL), BH_3:Me_2S (470 µL, 0.94 mmol; 2 M in toluene) was added dropwise, and the mixture was strirred for 10 min. A solution of ketone **3a** (0.5 mmol) in dry toluene (1 mL) was slowly added to the previously prepared solution of reductant at 0 °C. After completion (jugded by TLC) of the reaction, the mixture was evaporated, and the residue purified by SiO_2 radial chromatography (petroleum ether : EtOAc = 5 : 1) to give 80 mg (77%) of enantiomerically enriched product. 96% *ee*; t_R = 11.6 min (minor), 13.2 min (major), (chiracel OD-H chiral column, mobile phase: *i*-PrOH/hexane = 98/2, flow rate: 1.5 mL/min, wavelength: 240 nm), $[\alpha]_D^{25}$ + 41.3 (1.13, CH_2Cl_2).

(*S*)-2-(4-Chlorobenzylidene)cyclopentanol (*S*)-(7a): for the synthesis details see Table 1, entry 10. Yield 70%, 95% *ee*; t_R = 11.2 min (major), 12.8 min (minor) (chiracel OD-H chiral column, mobile phase: *i*-PrOH/hexane = 98/2, flow rate: 1.5 mL/min, wavelength: 240 nm), $[\alpha]_D^{25}$ – 31.9 (1.17, CH_2Cl_2).

(*R*)-2-(4-Methoxybenzylidene)cyclopentanol (*R*)-(7b): for the synthesis details see Table 1, entry 9. Yield 67%, 82% *ee*; t_R = 16.1 min (minor), 18.4 min (major), (chiracel OD-H chiral column, mobile phase: *i*-PrOH/hexane = 98/2, flow rate: 1.5 mL/min, wavelength: 240 nm), $[\alpha]_D^{25}$ + 3.8 (1.11, CH_2Cl_2).

(*S*)-2-(4-Methoxybenzylidene)cyclopentanol (*S*)-(7b): for the synthesis details see Table 1, entry 11. Yield 59%, 90% *ee*; t_R = 16.0 min (major), 18.7 min (minor) (chiralcel OD-H), *i*PrOH:heksan = 98:2, 1.5 ml/min, $[\alpha]_D^{25}$ – 9.9 (1.08, CH_2Cl_2).

2-(4-Chlorobenzylidene)-2,3-dihydro-1*H*- inden-1-ol (8): for the synthesis details see Table 1, entry 13. Yield 21%, 24% *ee*; t_R = 19.9 min (major), t_R = 23.8 min (minor) (chiracel OD-H chiral column, mobile phase: *i*-PrOH/hexane = 98/2, flow rate: 1.5 mL/min, wavelength: 240 nm), $[\alpha]_D^{25}$ – 13.4 (0.96, CH_2Cl_2).

2-(4-Chlorobenzylidene)-2,3-dihydro-1*H*-inden-1-ol (6): for the synthesis details see Table 1, entry 14. Yield 20%, 33% *ee*; t_R = 20.3 min (minor), t_R = 24.1 min (major) (chiracel OD-H chiral column, mobile phase: *i*-PrOH/hexane = 98/2, flow rate: 1.5 mL/min, wavelength: 240 nm).

Hydrogenation of 3a with Noyori's catalyst C4: 2-(4-Chlorobenzylidene)cyclopentanone (**3a**) (103 mg, 0.498 mmol), catalyst **C4** (6 mg, 4.9 µmol) and isopropanol (2 mL) were added to hydrogenation vessel under nitrogen atmosphere. Then K_2CO_3 (10 mg, 0.072 mmol) was added, the autoclave was pressurized to 80 bars of H_2, and the reaction mixture was stirred at room temperature. After 2 days additional amount of **C4** (4.6 mg, 3.8 µmol) was added (ketone **3a** still present). Because the ketone **3a** was still not consumed after 7 days, additional amount of K_2CO_3 (50 mg, 0.362 mmol) was added. After additional 5 days the reaction was still not complete, therefore K_2CO_3 (10 mg, 0.072 mmol), catalyst **C4** (5 mg, 4.1 µmol) and isopropanol (1 mL) were added, and hydrogenated for further 4 days. The solvent was evaporated and the residue was purified by SiO_2 column chromatography (petroleum ether : EtOAc = 5 : 1) to afford 32 mg (31%) of the product **7a**; *ee* = 12%.

Reduction of 3a with baker's yeast: To a stirred solution of D-glucose (10.0 g, 55.5 mmol) and baker's yeast (56.0 g) in water (200 mL) at 38 °C, 2-(4-chlorobenzylidene)cyclopentanone (**3a**) (1.0 g, 4.84 mmol) dissolved in the minimum amount of EtOH (5 mL) was added; the reaction mixture was stirred for 10 days. Then EtOAc (100 mL) was added and the crude reaction mixture was filtered through a pad of Celite. The filtrate was extracted with EtOAc (3 × 100 mL), the organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by SiO_2 column chromatography (petroleum ether : EtOAc = 5 : 1) to afford 45 mg (5%) of the product **7a** as a light yellow oil; *ee* = 9%.

Reduction of 3a with *Daucus carota* root: An ethanolic (5 mL) solution of 2-(4-chlorobenzylidene)cyclopentanone (**3a**) (100 mg, 0.484 mmol) was added to a suspension of freshly grated carrot root (13.4 g) in water (70 mL). The raction mixture was stirred at room temperature for

24 h, then carrot root was filtered off and washed with water. Filtrate was extracted with EtOAc (3 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give 10 mg (10%) of crude red oily product **7a**; *ee* >99%.

4. Conclusion

In summary, we synthesized enantiomerically enriched exocyclic allylic alcohols by asymmetric reduction of cyclic α-arylmethylene cyclic ketones. Highly enantioselective chemoreduction of 2-benzylidenecyclopentanone derivatives was achieved by applying chiral oxazaborolidine-derived catalysts under mild reaction conditions. The sense of asymmetric induction was in accordance with Corey mechanistic model, thus (*S*)-catalyst delivered (*R*)-alcohols, while (*R*)-catalyst gave (*S*)-alcohol products with *ee* values of up to 96%. The indanone-derived chalcone was much less efficiently reduced regarding the chemical yield and optical purity (33% *ee*). Bioreduction of 2-(4-chlorobenzylidene)cyclopentanone with baker's yeast gave very low *ee* of the corresponding allylic alcohol, while reduction with *Daucus carota* root turned out to be completely enantioselective. The synthesized allylic alcohols can serve as enantioenriched probes for the monitoring of oxidation-reduction processes catalyzed by AKR1C enzymes; these studies are currently under progress.

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Povzetek

Učinkovita asimetrična redukcija 2-benzilidenciklopentanonskih derivatov s kiralnimi oksazaborolidinskimi katalizatorji vodi selektivno do nastanka eksocikličnih alilnih alkoholov z enantiomernimi presežki do 96 %. Popolno enantioselektivnost lahko dosežemo z bioredukcijo 2-(4-klorobenziliden)ciklopentanona s korenjem, pri čemer nastane ustrezen alkohol z *S* konfiguracijo. Sintetizirane spojine lahko služijo kot enantiomerno obogateni standardi pri spremljanju encimsko kataliziranih