Synthesis V. Beghetto et al. Paper

A Practical, Enantioselective Synthesis of the Fragrances Canthoxal and Silvial®, and Evaluation of Their Olfactory Activity

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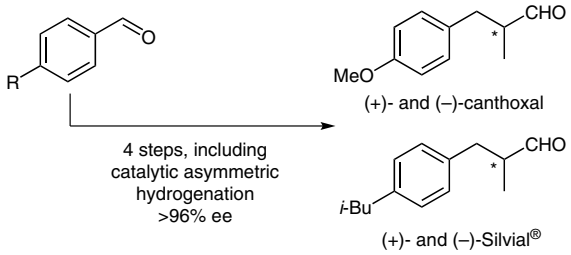


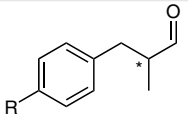
Received: 31.07.2014
Accepted after revision: 18.09.2014
Published online: 24.10.2014
DOI: 10.1055/s-0034-1379254; Art ID: ss-2014-z0478-op

Abstract The fragrances (*S*)-(+)- and (*R*)-(–)-canthoxal [(*S*)-(+)- and (*R*)-(–)-3-(4-methoxyphenyl)-2-methylpropanal] and (+)- and (–)-Silvial® [(+)- and (–)-3-(4-isobutylphenyl)-2-methylpropanal] have been synthesized in high enantiopurity via a simple four-step strategy starting from the commercially available 4-substituted benzaldehydes. The key synthetic step is the catalytic asymmetric hydrogenation of the appropriate 3-aryl-2-methylacrylic acid which has been carried out employing an in situ prepared ruthenium/axially chiral phosphine catalyst (up to 98% ee). The olfactory activity of the single enantiomers has been evaluated.

Key words fragrance synthesis, asymmetric hydrogenation, ruthenium, canthoxal, Silvial®

We have long been interested in the synthesis of enantiomerically enriched fragrances and in the evaluation of their olfactive notes, since the olfactory activities of two enantiomeric fragrances can be different both in quality and in intensity.[1] Accordingly, the availability of the single stereoisomers of a fragrance is of great interest, as they could be employed as new perfumery materials.[2] Environmental concerns provide further impetus for the synthesis of enantiopure fragrances. In fact, since fragrance ingredients are eventually dispersed in the biosphere, the use of the most active stereoisomer instead of a racemate could lead to a lower consumption of these chemicals and hence reduce their impact on the environment.[3] Further motivations derive from patentability opportunities,[2] and the important role that the availability of single stereoisomers plays in studying molecular structure–odour relationships.[4]

Canthoxal (**1a**), Silvial® (**1b**), lilial (**1c**) and cyclamal (**1d**) are four fragrances characterized by a common aldehydic structural motif (Figure 1), so that the differences in their olfactive profiles can be ascribed to the group present in the para position of the aromatic ring. It is worth noting that this substituent plays an important role in determining not only the olfactory activity, but also the biological impact of these molecules. Thus, allergenic and possible carcinogenic activities have been demonstrated for lilial, but not for the other three fragrances.[5,6]



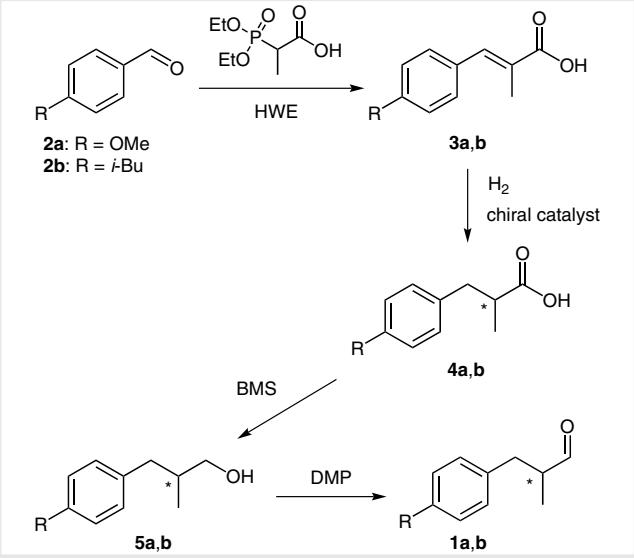
canthoxal (**1a**) R = OMe
Silvial® (**1b**) R = *i*-Bu
lilial (**1c**) R = *t*-Bu
cyclamal (**1d**) R = *i*-Pr

Figure 1 Arylpropanal fragrances

There are papers dealing with the preparation of the enantiomers of **1c**,[7,8] and the odour profiles of (+)-**1c** and (–)-**1c** have been reported.[9] Only recently, two different research groups have reported the preparation of enantioenriched cyclamal;[8,10] in particular, Kawasaki and co-workers have developed an enzymatic enantioselective synthesis of (*R*)-**1d** or (*S*)-**1d** and have described the olfactive profiles of the enantiomers.[10]

In contrast, the olfactive notes of the enantiomers of **1a** and **1b** have not yet been reported. Accordingly, we deemed it interesting to synthesize enantiopure canthoxal (its partial deracemization has been reported[8]) and Silvial in order to evaluate their odour profiles.[11]

Asymmetric catalytic hydrogenation of a prochiral olefin[12] is one of the most efficient and practical approaches used to form a chiral centre. Thus, in order to synthesize nonracemic **1a** and **1b**, we devised the synthetic strategy outlined in Scheme 1.



Scheme 1 The designed canthoxal (**1a**) and Silvial (**1b**) syntheses

We chose as starting compounds the para-substituted benzaldehydes **2a** and **2b**, which are commercially available. Horner–Wadsworth–Emmons (HWE) olefination employing 2-(diethoxyphosphoryl)propanoic acid[13] stereoselectively transformed **2a** and **2b** into the corresponding α,β-unsaturated acids (*E*)-**3a** and (*E*)-**3b** in >85% yield. HWE olefination was the selected methodology because it usually proceeds with high control of the C=C stereoisomerism. This is a key issue, since the asymmetric hydrogenation of the *E*- or *Z*-isomer of an olefin often leads to the formation of opposite enantiomers.[7b,14]

The key step of the synthetic strategy is the asymmetric catalytic hydrogenation of the α,β-unsaturated carboxylic acids **3a** and **3b**. Nowadays, a large number of chiral phosphorus auxiliaries are available for transition-metal-catalyzed asymmetric hydrogenation. According to our experience,[14] the most convenient approach is to employ a catalytic system allowing for a rapid screening of the candidate ligands. A particularly handy system is that prepared by combining, in situ, benzeneruthenium(II) chloride dimer $\{[RuCl_2(C_6H_6)]_2\}$ and a chiral bidentate phosphine ligand in a 1:2 molar ratio.[15]

Keeping in mind the excellent results obtained in the synthesis of other fragrances,[16a] in the first experiments the ferrocenylphosphine ligand (*S*,*R*)-Mandyphos-4[16] (see Figure 2) was employed as the chiral auxiliary, and (*E*)-**3a** was chosen as the model substrate (see Table 1).

In an exploratory experiment, carried out at 30 °C under 40 atm of hydrogen, a moderately good (50%) enantiomeric excess (ee) was obtained (Table 1, entry 1). This result prompted us to investigate whether the enantioselectivity could be improved by some fine-tuning of the reaction conditions. Thus, a second experiment was carried out in the presence of triethylamine as promoter (amine/substrate molar ratio = 1:1), since it is known that the hydrogenation rate with ruthenium catalytic systems can often be improved by the addition of tertiary amines as promoters, even though their presence does not always have a favourable effect on the enantioselectivity.[17]

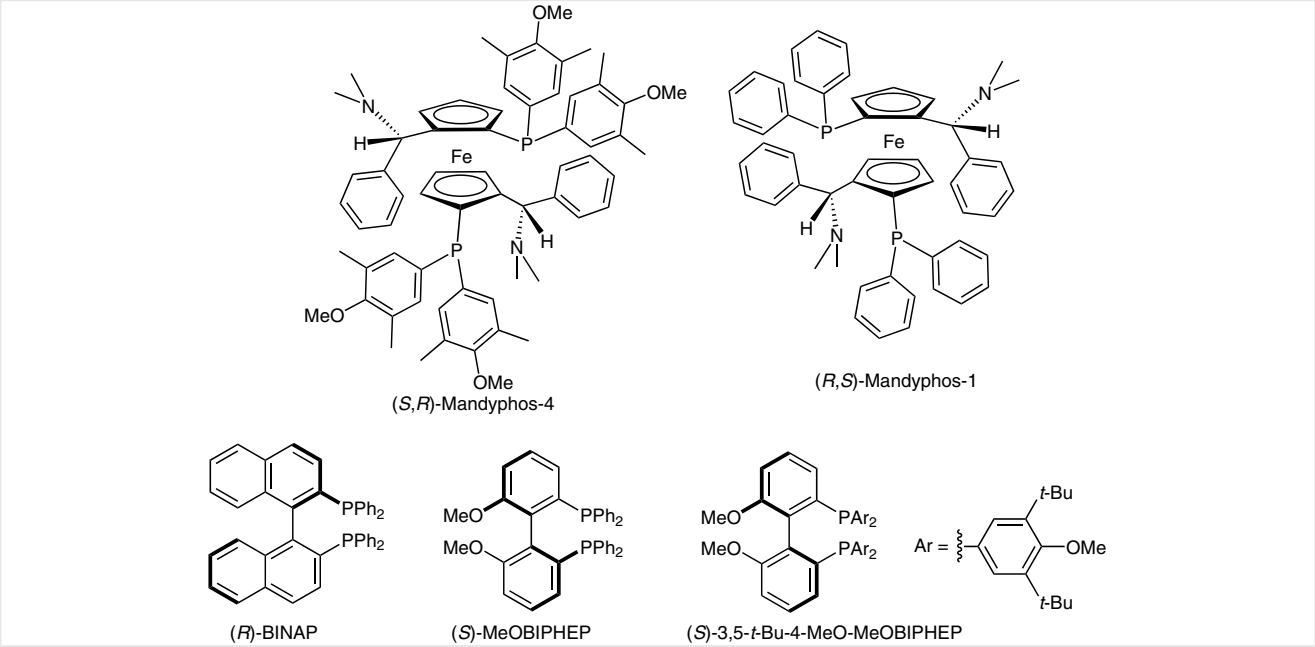


Figure 2 Molecular structures of the employed chiral ligands

Table 1 Asymmetric Hydrogenation of (*E*)-**3a** and (*E*)-**3b** in the Presence of the $[RuCl_2(C_6H_6)]_2$/(*S*,*R*)-Mandyphos-4 Catalytic System[a]

Entry	Substrate	Temp (°C)	H_2 (atm)	Time (h)	Et_3N/**3a**,**b**	**3a**,**b**/Ru	Conv[b] (%)	ee[c] (%)
1	**3a**	30	40	3	0	100:1	91	50[d]
2	**3a**	30	40	3	1:1	100:1	100	65[d]
3	**3a**	0	40	18	1:1	100:1	100	71[d]
4	**3a**	0	100	18	1:1	100:1	100	75[d]
5	**3b**	0	40	24	1:1	50:1	100	84[e]
6	**3b**	0	100	24	1:1	50:1	100	86[e]

[a] Reaction conditions: substrate (0.91 mmol), $[RuCl_2(C_6H_6)]_2$ (4.5 μmol); Ru/ligand, 1:1 (mol/mol)], Et_3N (0.9 mmol), MeOH (10 mL).
[b] Determined by GLC.
[c] All acids have a positive specific rotation (determined by polarimetry).
[d] Determined by HPLC analysis of the anilide using a Chiralcel OD-H column.
[e] Determined by chiral GLC (β-Dex 120 column).

The use of triethylamine led to an enhancement of the asymmetric induction up to 65% ee and, when the temperature was lowered to 0 °C, the ee increased to 71%, although a longer reaction time was necessary to reach total substrate hydrogenation (Table 1, entries 2 and 3). A further, modest improvement of the enantioselectivity (up to 75% ee) was obtained by increasing the hydrogen pressure to 100 atm (Table 1, entry 4), in agreement with the frequently observed positive effect of hydrogen pressure on the enantioselectivity in ruthenium-catalyzed hydrogenations.

Entries 5 and 6 in Table 1 report the results of the asymmetric hydrogenation of (*E*)-**3b** under the best reaction conditions found for (*E*)-**3a**. According to these data, it appears that higher asymmetric inductions (up to 86% ee) can be obtained with (*E*)-**3b**. This very good result can be tentatively attributed to the higher steric hindrance of (*E*)-**3b**. In this connection, it is worth noting that such a level of enantioselectivity, albeit not completely satisfactory, could be considered acceptable for an application in fragrance synthesis.

With the aim of achieving higher enantioselectivities, a different set of ligands was tested (Table 2). The experiments were carried out at 0 °C in the presence of the amine promoter and the hydrogen pressure was kept constant at 40 atm.

At first, we tested (*R*,*S*)-Mandyphos-1, a ferrocenyl ligand which differs from (*S*,*R*)-Mandyphos-4 in that it has no hindered aryl substituents on the phosphorus atoms (see Figure 2). Employing this ligand, we obtained complete substrate hydrogenation (Table 2, entry 1), but the resulting enantioselectivity was significantly lower than with (*S*,*R*)-Mandyphos-4. As also suggested by the data in Table 1, this indicates that steric hindrance, either on the substrate or on the ligand, has a significant positive effect on the asymmetric induction.

Ligands with axial chirality, such as (*R*)-BINAP and (*S*)-MeOBIPHEP (Figure 2), gave significantly better enantioselectivities than (*R*,*S*)-Mandyphos-1, although they were somewhat less effective than (*S*,*R*)-Mandyphos-4 (Table 2, entries 2 and 3).

Considering the observed steric hindrance effect, we deemed it may be possible to obtain better results using (*S*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine] [(*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP], a highly hindered homologue of (*S*)-MeO-BIPHEP. In fact, when we employed this ligand, enantioselectivity values close to 96% ee were obtained with both **3a** and **3b** (Table 2, entries 4 and 5).

With the optimized asymmetric hydrogenation reaction conditions in hand, we prepared the sought saturated acids on a 1-gram scale. When (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP was employed, enantiomerically enriched (+)-**4a** and (+)-**4b** were obtained in 95% ee and 97% ee, respectively. Analogously, when (*R*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP was employed, enantiomerically enriched (–)-**4a** and (–)-**4b** were obtained in 95% ee and 98% ee, respectively.

According to the synthetic plan depicted in Scheme 1, the enantiomerically enriched acids **4** were reduced to the corresponding primary alcohols **5** by reaction with borane–

Table 2 Asymmetric Hydrogenation of (*E*)-**3a** and (*E*)-**3b** in the Presence of $[RuCl_2(C_6H_6)]_2$/Chiral Ligand Catalytic Systems[a]

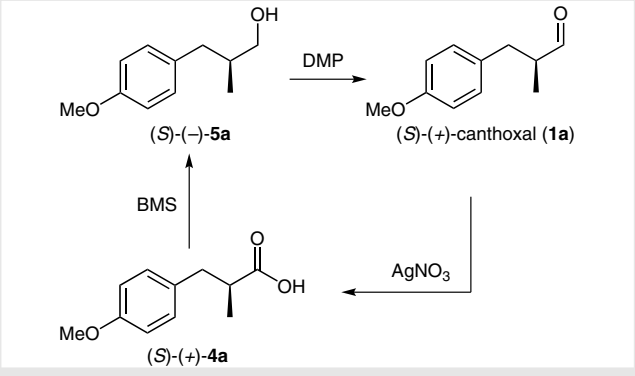
Entry	Substrate	Ligand	Time (h)	**3a**,**b**/Ru	Conv[b] (%)	ee[c] (%)
1	**3a**	(*R*,*S*)-Mandyphos-1	18	100:1	100	45[d] (–)
2	**3a**	(*R*)-BINAP	18	100:1	100	62[d] (–)
3	**3b**	(*S*)-MeOBIPHEP	24	50:1	100	67[e] (+)
4	**3a**	(*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP	18	100:1	100	96[d] (+)
5	**3b**	(*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP	24	100:1	100	96[e] (+)

[a] Reaction conditions: substrate (0.91 mmol), $[RuCl_2(C_6H_6)]_2$ (4.5 μmol); Ru/ligand, 1:1 (mol/mol); substrate/Et_3N, 1:1 (mol/mol)], MeOH (10 mL), H_2 (40 atm), 0 °C.
[b] Determined by GLC.
[c] Specific rotation sign determined by polarimetry.
[d] Determined by HPLC analysis of the anilide using a Chiralcel OD-H column.
[e] Determined by chiral GLC (β-Dex 120 column).

methyl sulfide complex (BMS), a reducing reagent which assures complete configuration retention at the α-carbon[18] and short reaction times. In fact, at room temperature, 1-gram-scale reductions of (+)-**4a** and (–)-**4a** were complete in 1 hour, giving (–)-**5a** and (+)-**5a**, respectively. The chiral alcohols were obtained in about 90% isolated yield and with complete retention of the enantiomeric purity. Analogously, reductions of (+)-**4b** and (–)-**4b** afforded (–)-**5b** and (+)-**5b** in about 89% yield.

The last step of the canthoxal and Silvial syntheses required the partial oxidation of the **5a** and **5b** enantiomers to the corresponding aldehydes (Scheme 1). The reaction was conveniently carried out employing Dess–Martin periodinane (DMP), and the single enantiomers of **1a** and **1b** were obtained in about 70% isolated yield. As we were unable to directly determine the enantiomeric excesses of the obtained aldehydes via chiral GLC or HPLC, samples (+)-**1a**,**b** and (–)-**1a**,**b** were further oxidized with silver nitrate[19] to give the parent acids (+)-**4a**,**b** and (–)-**4a**,**b** whose enantiomeric purities were found to be unchanged with respect to the corresponding acids obtained by asymmetric hydrogenation.

According to the literature,[20] the absolute configuration of (–)-**5a** is (*S*) and that of (+)-**5a** is (*R*); since reduction of (+)-**4a** leads to (–)-**5a**, it can be inferred that the absolute configuration of (+)-**4a** is (*S*) and that of (–)-**4a** is (*R*). Upon oxidation, (–)-**5a** affords (+)-**1a** whose absolute configuration is hence (*S*); thus, the configuration of (–)-**1a** is (*R*) (Scheme 2).



Scheme 2 Specific rotation–absolute configuration relationship for canthoxal

Samples of (+)-**1a**, (–)-**1a**, (+)-**1b** and (–)-**1b** were submitted to a panel of skilled perfumers (Givaudan) for the evaluation of odour profiles and odour detection thresholds (ODT). The following descriptions were obtained:

(*S*)-(+)-**1a**: floral, anisic, fruity-watery odour with a sweet fennel-type character recalling anethol (ODT: 31.1 ng/L).

(*R*)-(–)-**1a**: floral, anisic, fruity-watery odour with green accents and slightly rubbery aspects; weaker than (*S*)-(+)-**1a** (ODT: 45.2 ng/L).

(+)-**1b**: strong, floral, Silvial, fatty, creamy, green, aldehydic, typically lily of the valley, more powerful than Silvial (ODT: 1.50 ng/L).

(–)-**1b**: weak, floral, muguet, lilial-like, aldehydic, green (ODT: 7.45 ng/L).

Summing up, we have devised a new synthesis of the single enantiomers of canthoxal and Silvial. The developed approach entails a minimum number of simple and high-yielding atom-economical steps. The chiral centre is formed by catalytic asymmetric hydrogenation which can be carried out with excellent enantioselectivity by using a convenient in situ formed ruthenium catalyst derived from an axially chiral ligand of the MeOBIPHEP family. It was, thus, possible to evaluate the odour profiles of the single stereoisomers of both fragrances: even if no particularly striking differences were perceived, it is worth noting that whatever the fragrance, the (+)-enantiomer is always stronger; in particular, the odour detection threshold of (+)-Silvial is about five times lower than the opposite enantiomer.

All manipulations were carried out under nitrogen using standard Schlenk techniques. The starting aldehydes were purchased from TCI Europe. All other reagents and solvents and were purchased from Aldrich and purified according to literature procedures.[21] (*S*)-MeOBIPHEP, (*R*)- and (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP, (*R*,*S*)-Mandyphos-1 and (*S*,*R*)-Mandyphos-4 were a generous gift from Solvias. (*R*)-BINAP was a generous gift from Rhodia UK Ltd. $[RuCl_2(C_6H_6)]_2$[22] and 2-(diethoxyphosphoryl)propanoic acid were prepared as described in the literature.[23]

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance AC 300 spectrometer operating at 300.21 and 75.44 MHz, respectively. GC-MS analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph interfaced with an HP 5971 quadrupole mass detector. GLC analyses were performed on an Agilent 6850 gas chromatograph. Enantiomeric excesses were determined by chiral GLC using a β-Dex 120 column (30 m × 0.25 mm) or by chiral HPLC using a Chiralcel OD-H column (250 mm × 4.6 mm) on an Agilent 1100 HPLC system equipped with a UV detector at 254 nm. Specific rotations (α) were determined using a Perkin-Elmer 241 polarimeter (Na lamp at 25 °C). High-resolution mass spectra were recorded on a Thermo Finnigan MAT 95 XP mass spectrometer.

(*E*)-3-(4-Methoxyphenyl)-2-methylacrylic Acid (3a)

Under inert atmosphere, to chilled (–60 °C) anhydrous THF (120 mL) were sequentially added a 2.5 M solution of *n*-BuLi in *n*-hexane (31 mL, 79 mmol) and 2-(diethoxyphosphoryl)propanoic acid (8.3 g, 39.5 mmol) in THF (40 mL); the mixture was stirred for 1 h at –60 °C, then 4-methoxybenzaldehyde (**2a**; 5.25 g, 39.6 mmol) in THF (20 mL) was added. The yellow solution was stirred at –60 °C for 2 h, then was allowed to warm to r.t. and kept under stirring overnight. The reaction mixture was quenched with H_2O (100 mL), leading to the precipitation of a white solid which was removed by filtration. The filtrate was then basified to pH 11 with a 10% aq solution of Na_2CO_3, concentrated and then extracted with Et_2O (3 × 40 mL). The combined aqueous phases were acidified with 1 M HCl to give **3a** as a white powder. Spectroscopic and analytical data were in complete agreement with the corresponding literature data[24,25] (see Supporting Information).

Yield: 6.4 g (85%); white powder; mp 154–156 °C.

(*E*)-3-(4-Isobutylphenyl)-2-methylacrylic Acid (3b)

Compound **3b** was prepared from aldehyde **2b** according to the procedure above for **3a**.

Yield: 7.7 g (88%); white powder; mp 90–92 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.36 (s, 1 H), 7.81 (s, 1 H), 7.37 (d, *J* = 8.1 Hz, 2 H), 7.19 (d, *J* = 8.1 Hz, 2 H), 2.51 (d, *J* = 7.2 Hz, 2 H), 2.18 (s, 3 H), 1.91 (m, 1 H), 0.93 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 142.9, 141.3, 133.1, 130.0 (2 C), 129.4 (2 C), 126.7, 45.4, 30.3, 22.5 (2 C), 13.9.

GC-MS (EI): *m*/*z* = 218 $[M]^+$, 175, 129, 115, 91, 77.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1295.

(*S*)-(+)-3-(4-Methoxyphenyl)-2-methylpropanoic Acid [(*S*)-(+)-4a]; Typical Procedure

The asymmetric hydrogenation experiments were carried out in a 150-mL stainless steel autoclave with magnetic stirring. In a typical experiment (Table 2, entry 4), **3a** (175 mg, 0.91 mmol) was introduced into a Schlenk tube together with anhydrous MeOH (10 mL). Under inert atmosphere, $[RuCl_2(C_6H_6)]_2$ (2.3 mg, 4.5 μmol), (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP (10.4 mg, 9.0 μmol) and anhydrous Et_3N (125 μL, 91.0 mg, 0.9 mmol) were added to the solution which was stirred for about 30 min. The reaction mixture was then transferred via cannula into the autoclave which was pressurized to 40 atm with H_2 and thermostated at 0 °C under stirring. After 18 h, the autoclave was warmed to r.t.; the residual gas was vented off and the reaction mixture was analyzed by GLC. The crude reaction mixture was concentrated to dryness and then diluted with Et_2O (50 mL). The organic phase was extracted with a 10% aq solution of Na_2CO_3 (3 × 30 mL). The combined aqueous layers were acidified to pH 1 with a 10% aq solution of HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and, after chromatographic purification, the solvent was removed under reduced pressure to give (*S*)-(+)-**4a** as a colourless oil in 85% yield. Spectroscopic and analytical data were in complete agreement with the corresponding literature data[24] (see Supporting Information). To determine the ee, a sample of (*S*)-(+)-**4a** was treated with aniline to give the corresponding anilide;[24] the ee was 95% [Chiralcel OD-H column; *n*-hexane–*i*-PrOH, 92:8, 0.8 mL/min; detection: UV at 254 nm; t_R = 17.15 min (minor), 21.2 min (major)].

Yield: 150 mg (85%); colourless oil.

$[\alpha]_D^{25}$ +31.0 (*c* 0.51, acetone) [Lit.[24] $[\alpha]_D^{25}$ +30.3 (*c* 0.50, acetone)].

R_f = 0.47 (*n*-hexane–EtOAc, 7:3).

(*R*)-(–)-3-(4-Methoxyphenyl)-2-methylpropanoic Acid [(*R*)-(–)-4a]

The asymmetric hydrogenation of **3a** was carried out as described above, but employing (*R*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP as the ligand to give (*R*)-(–)-**4a** in 83% yield. The ee was 95% [anilide analysis; Chiralcel OD-H column; *n*-hexane–*i*-PrOH, 92:8, 0.8 mL/min; t_R = 17.15 min (major), 21.2 min (minor)].

Yield: 146 mg (83%); colourless oil.

$[\alpha]_D^{25}$ –30.0 (*c* 0.50, acetone).

(+)-3-(4-Isobutylphenyl)-2-methylpropanoic Acid [(+)-4b]

The asymmetric hydrogenation of **3b** was carried out in the presence of (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP, as described above for **3a**, giving (+)-**4b** as a colourless oil in 87% yield after chromatographic purification. The ee was determined to be 97% by chiral GLC [β-Dex 120 capillary column, 30 m × 0.25 mm × 0.25 μm, carrier gas N_2, 3.0 mL/min; t_R = 138.13 min (major), 143.07 min (minor)].

Yield: 171 mg (87%); colourless oil.

$[\alpha]_D^{25}$ +19.8 (*c* 0.50, acetone).

R_f = 0.43 (*n*-hexane–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.0 (br s, 1 H), 7.10–7.00 (m, 4 H), 3.10–3.03 (m, 1 H), 2.80–2.61 (m, 2 H), 2.44 (d, *J* = 7.1 Hz, 2 H), 1.85 (m, 1 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.8, 139.9, 136.4, 129.3 (2 C), 128.8 (2 C), 45.2, 41.4, 39.0, 30.4, 22.5 (2 C), 16.6.

GC-MS (EI): *m*/*z* = 220 $[M]^+$, 177, 147, 105, 91, 77, 51.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{20}O_2$: 220.1463; found: 220.1453.

(–)-3-(4-Isobutylphenyl)-2-methylpropanoic Acid [(–)-4b]

The asymmetric hydrogenation of **3b** was carried out in the presence of (*R*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP, as described above for **3a**, giving (–)-**4b** as a colourless oil in 85% yield. The ee was determined to be 98% by chiral GLC [β-Dex 120 capillary column; t_R = 138.13 min (minor), 143.07 min (major)].

Yield: 167 mg (85%); colourless oil.

$[\alpha]_D^{25}$ –19.8 (*c* 0.5, acetone).

(*S*)-(–)-3-(4-Methoxyphenyl)-2-methylpropan-1-ol [(*S*)-(–)-5a]

Under inert atmosphere, to cooled (0 °C) anhydrous Et_2O (50 mL), (*S*)-(+)-**4a** (1.09 g, 5.6 mmol) and a 2 M THF solution of BMS (3.7 mL, 7.3 mmol) were sequentially added. The mixture was allowed to warm to r.t.; after 1 h, the mixture was cooled to 0 °C and a mixture of H_2O and glycerin (3:1, 8 mL) was slowly added. The mixture was then extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and, after chromatographic purification, the solvent was removed under reduced pressure to give (*S*)-(–)-**5a** as a pale yellow oil in 92% yield. Spectroscopic and analytical data were in complete agreement with the corresponding literature data[20] (see Supporting Information). The ee was 96% [Chiralcel OD-H column; *n*-hexane–*i*-PrOH, 95:5, 1.0 mL/min; t_R = 21.34 min (minor), 23.55 min (major)].

Yield: 928 mg (92%); pale yellow oil.

$[\alpha]_D^{25}$ –11.0 (*c* 1, $CHCl_3$) [Lit.[20] $[\alpha]_D^{25}$ –11.4 (*c* 1.02, $CHCl_3$)].

R_f = 0.63 (*n*-hexane–EtOAc, 7:3).

(*R*)-(+)-3-(4-Methoxyphenyl)-2-methylpropan-1-ol [(*R*)-(+)-5a]

The synthesis was carried out from (*R*)-(–)-**4a**, as described above for (*S*)-(–)-**5a**, to give (*R*)-(+)-**5a** in 89% yield. The ee was 97% [Chiralcel OD-H column; t_R = 21.34 min (major), 23.55 min (minor)].

Yield: 905 mg (89%); pale yellow oil.

$[\alpha]_D^{25}$ +11.5 (*c* 1.02, $CHCl_3$).

(–)-3-(4-Isobutylphenyl)-2-methylpropan-1-ol [(–)-5b]

The synthesis was carried out from (+)-**4b**, as described above for (*S*)-(–)-**5a**, to give (–)-**5b** in 92% yield as a colourless oil after chromatographic purification.

Yield: 1.070 g (92%); colourless oil.

$[\alpha]_D^{25}$ –14.6 (*c* 0.5, $CHCl_3$).

R_f = 0.60 (*n*-hexane–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.07 (m, 4 H), 3.54–3.48 (m, 2 H), 2.78–2.72 (m, 1 H), 2.48 (d, *J* = 7.2 Hz, 2 H), 2.47–2.35 (m, 1 H), 2.29 (s, 1 H), 1.98–1.88 (m, 2 H), 0.95–0.93 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 137.9, 129.0 (2 C), 128.9 (2 C), 67.7, 45.1, 39.4, 37.9, 30.3, 22.5 (2 C), 16.6.

GC-MS (EI): *m*/*z* = 206 $[M]^+$, 163, 147, 131, 105, 91, 77, 51.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1663.

(+)-3-(4-Isobutylphenyl)-2-methylpropan-1-ol [(+)-5b]

The synthesis was carried out from (–)-**4b** as described above for (–)-**5b**.

Yield: 1.022 g (88%); colourless oil.

$[\alpha]_D^{25}$ +14.5 (*c* 0.5, $CHCl_3$).

(*S*)-(+)-3-(4-Methoxyphenyl)-2-methylpropanal [(*S*)-(+)-Canthoxal, (*S*)-(+)-1a]

To cooled (0 °C) CH_2Cl_2 (100 mL) were sequentially added (*S*)-(–)-**5a** (910 mg, 5.0 mmol), $NaHCO_3$ (1.89 g, 22.5 mmol) and a 3 M solution of Dess–Martin periodinane (2.5 mL, 7.5 mmol). After 1 h, the solution was allowed to warm to r.t. and then was hydrolyzed with an aq solution of Na_2SO_3 (50 mL) and a sat. aq solution of $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (4 × 70 mL) and the combined organic phases were dried over $MgSO_4$. After concentration to a small volume and chromatographic purification, the solvent was removed under reduced pressure to give (*S*)-(+)-**1a** as a colourless oil in 70% yield. Spectroscopic and analytical data were in complete agreement with the corresponding literature data[26] (see Supporting Information). To establish the ee of (*S*)-(+)-**1a** and the sign–configuration relationship, to a solution of (+)-**1a** (100 mg, 0.57 mmol) in EtOH (3 mL) was added $AgNO_3$ (100 mg, 0.58 mmol) in H_2O (2 mL). Then, to the resulting mixture, a solution of NaOH (96 mg) in H_2O (2 mL) was slowly added under stirring. After being stirred for 1 h at r.t., the mixture was diluted with H_2O (15 mL) and filtered. The filtrate was acidified to pH 1 with a 10% aq solution of HCl and extracted with CH_2Cl_2 (2 × 10 mL). Concentration of the extracts under reduced pressure afforded (+)-**4a** (85 mg) which was transformed into the corresponding anilide and analyzed by chiral HPLC as reported above; the ee was found to be 97%.

Yield: 625 mg (70%); colourless oil.

$[\alpha]_D^{25}$ +3.61 (*c* 1.5, $CHCl_3$).

R_f = 0.80 (*n*-hexane–Et_2O, 1:1).

(*R*)-(–)-3-(4-Methoxyphenyl)-2-methylpropanal [(*R*)-(–)-Canthoxal, (*R*)-(–)-1a]

The synthesis was carried out from (+)-**5a**, as described above for (+)-**1a**, to give (–)-**1a** in 72% yield. The ee was determined to be 96%, according to the procedure reported for (*S*)-(+)-**1a**.

Yield: 640 mg (72%); colourless oil.

$[\alpha]_D^{25}$ –3.57 (*c* 1.5, $CHCl_3$).

(+)-3-(4-Isobutylphenyl)-2-methylpropanal [(+)-Silvial, (+)-1b]

The synthesis was carried out from (–)-**5b**, as described above for (+)-**1a**, to give (+)-**1b** in 77% yield as a colourless oil after chromatographic purification. According to the procedure described above for (+)-**1a**, the ee was found to be 96%.

Yield: 795 mg (77%); colourless oil.

$[\alpha]_D^{25}$ +7.15 (*c* 0.55, acetone).

R_f = 0.75 (*n*-hexane–Et_2O, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (s, 1 H), 7.09–7.06 (m, 4 H), 3.09–3.03 (m, 1 H), 2.68–2.55 (m, 2 H), 2.44 (d, *J* = 7.2 Hz, 2 H), 1.85 (m, 1 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.7, 139.9, 136.0, 129.3 (2 C), 128.8 (2 C), 48.2, 45.1, 36.4, 30.3, 22.5 (2 C), 13.3.

GC-MS (EI): *m*/*z* = 204 $[M]^+$, 161, 147, 105, 91, 77.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1506.

(–)-3-(4-Isobutylphenyl)-2-methylpropanal [(–)-Silvial, (–)-1b]

The synthesis was carried out from (+)-**5b**, as described above for (+)-**1b**, to give (–)-**1b** in 75% yield as a colourless oil. According to the procedure described above for (+)-**1a**, the ee was found to be 98%.

Yield: 770 mg (75%); colourless oil.

$[\alpha]_D^{25}$ –7.20 (*c* 0.55, acetone).

Acknowledgment

Dr. P. Kraft, Mrs. K. Grman, Mr. A. Alchenberger and Mrs. D. Lelievre (Givaudan) are kindly acknowledged for the olfactory evaluations. Solvias is acknowledged for the generous gift of a chiral ligands kit. Rhodia UK Ltd is acknowledged for generously supplying (*R*)-BINAP.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379254.

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