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ScienceDirect
Tetrahedron: *Asymmetry* 18 (2007) 797–802
Tetrahedron: *Asymmetry*

Asymmetric catalysis in fragrance chemistry: a new synthetic approach to enantiopure Phenoxanol®, Citralis® and Citralis Nitrile®

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Received 9 March 2007; accepted 13 March 2007

Abstract—A new approach to the synthesis of the single stereomers of the fragrances Phenoxanol®, Citralis® and Citralis Nitrile® is reported. The key step of the synthesis is the asymmetric hydrogenation of (*Z*)- or (*E*)-3-methyl-5-phenyl-pent-2-en-1-ol, which leads to the single enantiomers of Phenoxanol® from which both enantiomers of Citralis® are obtained by oxidation. Treatment of these compounds with hydroxylamine finally led to Citralis Nitrile® without any loss of enantiopurity. The odour profiles of the single enantiomers of these fragrances are reported as well.

1. Introduction

An answer to the continuing quest for new odour profiles by the fragrance industry can come not only from the creation of new olfactory active molecules, but also by the synthesis of the single stereomers of already known odorants which until now has been used as racemic or diastereomeric mixtures.[1–3] As a matter of fact, 'our sense of smell is enantioselective' so that the opposite enantiomers of an odorant may show odour profiles different both in quality and in intensity.[1–3] Accordingly, the synthesis of fragrances in highly enantiomerically enriched form and the evaluation of their odour properties is currently of great interest. Further interest is due to environmental concerns regarding the increasing use of these compounds in many formulations, from fine fragrances to household products. Different odorants have been found in the sediments of lakes, and even in living creatures;[4] accordingly, next year legal restrictions will apply to some fragrance ingredients in the European Union and Switzerland.[5] The manufacture and use of the most olfactory active stereomer of a fragrance, instead of its racemic mixture, might be enough to achieve the desired scent of a formulation and could contribute to lower the amount of these compounds finally dispersed in the environment.

Odorants displaying floral notes (rose, jasmine, lily-of-the valley, etc.[6]) are of particular interest for the fragrance industry, as they are very much appreciated and widely used. 3-Methyl-5-phenyl-pentan-1-ol (Phenoxanol®, IFF, Fig. 1), 3-methyl-5-phenyl-pentanaldehyde (Citralis®, Innospec, Fig. 1) and 3-methyl-5-phenyl-pentanenitrile (Citralis Nitrile®, Innospec, Fig. 1) are three synthetic fragrances, which belong to the floral odorants domain being reminiscent, albeit with some differences, of rose, lily-of-the-valley and citrus. All three of these molecules have a stereogenic centre but the odour profiles of the single enantiomers have not yet been reported.

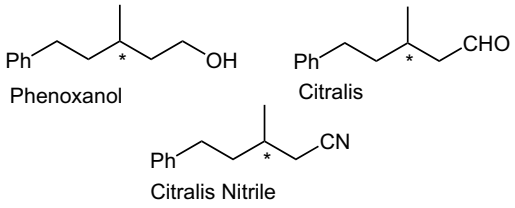

Figure 1. Chemical structures of Phenoxanol®, Citralis® and Citralis Nitrile®.

Transition-metal asymmetric catalysis is among the most powerful tools available for the synthesis of enantiomerically enriched substances on a practical scale,[7] and our group has been involved for years in the research of the application of homogeneous asymmetric catalysis processes to the synthesis of enantiomerically enriched

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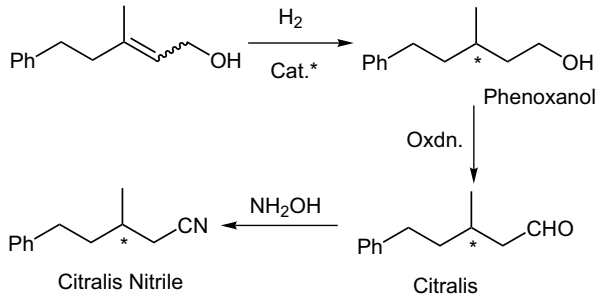
doi:10.1016/j.tetasy.2007.03.014

fragrances.[8] Herein we report a new approach to the enantioselective synthesis of Phenoxanol®, Citralis® and Citralis Nitrile® based on the catalytic asymmetric hydrogenation of 3-methyl-5-phenyl-pent-2-en-1-ol (see Scheme 1); the evaluation of the odour profiles of the single stereomers is also reported. It is worth mentioning that the (*R*)-isomer of Phenoxanol® has been prepared in 82% ee by Brenna et al.[9] through an enzymatic approach, while previous syntheses of enantiomerically enriched Citralis Nitrile® have been described by Pfaltz[10] (ee up to 70%, by a cobalt catalyzed asymmetric reduction of (*E*)- or (*Z*)-3-methyl-5-phenyl-pentenenitrile with $NaBH_4$), and by our group[8d] (ee up to 98% via asymmetric hydrogenation of 2-phenethylacrylic acid).

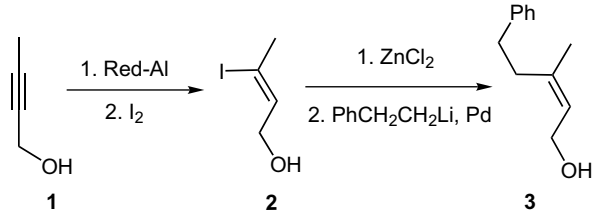


Scheme 1. Synthetic approach.

2. Results and discussion

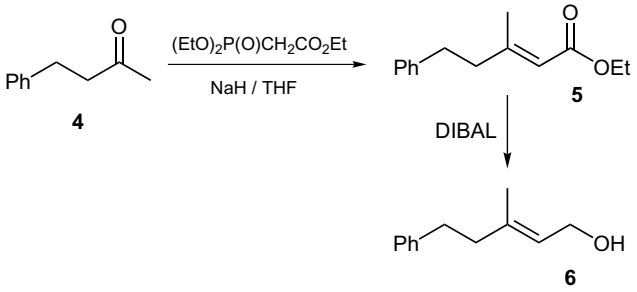
The devised synthesis has as the key step the asymmetric hydrogenation of (*Z*)- or (*E*)-3-methyl-5-phenyl-pent-2-en-1-ol to give enantiomerically enriched Phenoxanol, which is, then, oxidized to Citralis which is in turn transformed in Citralis Nitrile (Scheme 1).

Since asymmetric hydrogenation usually requires stereochemically well defined substrates in order to be carried out with high asymmetric inductions,[8b,11] two different approaches were adopted in order to prepare diastereopure (*Z*)- or (*E*)-3-methyl-5-phenyl-pent-2-en-1-ol. To obtain the (*Z*)-isomer, commercial 2-butyn-1-ol **1** was treated with Red-Al® and then with I_2 to give (*Z*)-3-iodo-2-buten-1-ol **2** (91% yield).[12] Negishi coupling of **2** with (2-phenylethyl)lithium[13] afforded pure (*Z*)-3-methyl-5-phenyl-pent-2-en-1-ol **3** (55% yield, Scheme 2).



Scheme 2. Preparation of (*Z*)-3-methyl-5-phenyl-pent-2-en-1-ol.

On the other hand, (*E*)-allyl alcohol **6** was prepared by a Horner–Wadsworth–Emmons reaction[14] by reacting benzylacetone with triethyl phosphonoacetate in the presence of NaH to give the α,β-unsaturated ester **5** (50% yield), which was then reduced with DIBAL[15] (45% total yield, Scheme 3).



Scheme 3. Preparation of (*E*)-3-methyl-5-phenyl-pent-2-en-1-ol.

The stereogenic centre is then formed by the asymmetric hydrogenation of allylic alcohols **3** and **6**, which are both tri-substituted weakly coordinating functionalized olefins. For the enantioselective hydrogenation of this type of substrate, the literature suggests the use of chiral catalysts based on iridium,[16] or ruthenium.[11,17]

Among the iridium species which have been successfully used in the asymmetric hydrogenation of allylic alcohols, the ones containing chiral phosphooxazolines developed by Pfaltz[16a] appear particularly well suited at being able to give ees up to 97%[16b] (see Fig. 2).

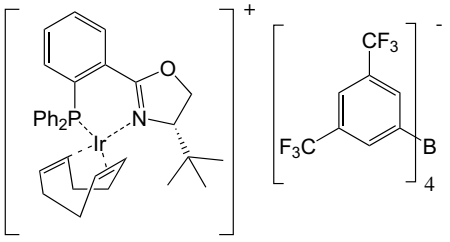
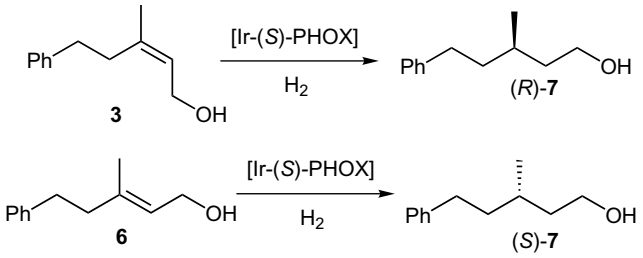


Figure 2. Structure of [Ir-(*S*)-PHOX].

The asymmetric hydrogenation of **3** in the presence of [Ir((*S*)-2-(*o*-diphenylphosphinophenyl)-3-*tert*-butyl-oxazoline)COD](BARF) ([Ir-(*S*)-PHOX]) proceeded with complete chemoselectivity; using 2% of catalyst, total substrate hydrogenation was observed after 21 h in all the experiments carried out (see Scheme 4 and Table 1).

A preliminary experiment carried out at room temperature under 10 atm of hydrogen showed that [Ir-(*S*)-PHOX] afforded (*R*)-Phenoxanol as the prevailing stereomer in about 67% ee (entry 1 of Table 1).

While aiming at raising the enantioselectivity, two other experiments were carried out at room temperature, increasing the hydrogen pressure to 50 and then up to 100 atm (entries 1–3 of Table 1). Unfortunately, the asymmetric induction turned out to be almost insensitive to the hydrogen pressure so that these experiments did not lead to significant improvements, even though a maximum enantioselectivity is obtained working at 50 atm. The influ-



Scheme 4. Asymmetric hydrogenation of **3** and **6** catalyzed by [Ir-(*S*)-PHOX].

Table 1. Asymmetric hydrogenation of **3** and **6** in the presence of [Ir-(*S*)-PHOX][a]

Entry	Substrate	*T* (°C)	$P(H_2)$ (atm)	ee[b]	Config.
1	**3**	23	10	67.5	(*R*)
2	**3**	23	50	69.0	(*R*)
3	**3**	23	100	66.0	(*R*)
4	**3**	0	100	46.0	(*R*)
5	**3**	60	100	67.0	(*R*)
6	**6**	23	50	64.4	(*S*)

[a] Reaction conditions: substrate: 0.57 mmol; cat.: 1.14×10^{-2} mmol; substrate/cat. = 50:1; solvent: CH_2Cl_2 (10 mL); $t = 21$ h.
[b] Determined by chiral GLC on the corresponding aldehydes.

ence of the temperature is shown in entries 3–5, Table 1: on increasing the temperature to 60 °C an almost negligible increase in the enantioselectivity is observed; conversely, the enantioselectivity dramatically decreased when lowering the temperature from 23 to 0 °C. This is a quite unusual behaviour; however, it should be noted that a similar trend has previously been reported by Pfaltz[16d] and also by us[8d] when using Ir-PHOX catalysts.

No improvement was obtained when using (*E*)-allylic alcohol **6** instead of (*Z*)-isomer **3** (entry 6): starting from **6**, (*S*)-Phenoxanol is obtained as the prevailing stereomer (64.4% ee).

The inversion of the configuration of the prevailing enantiomer on changing the stereochemistry of the C=C double bond is a well known phenomenon[8b,11] in asymmetric hydrogenation and it is one of the compelling reasons to use stereochemically pure unsaturated substrates. Even though the above enantioselectivities might be considered interesting, owing to the peculiar type of application of these molecules, the results appear somewhat disappointing, in particular when compared with the very high asymmetric inductions attained by Pfaltz when using [Ir-PHOX] catalysts in the hydrogenation of prochiral allyl alcohols.[16a]

A possible explanation can be found by taking into account the structural differences between Pfaltz's and our substrates. In fact, the allyl alcohols studied by Pfaltz have as a common structural feature, a phenyl ring conjugated with the C=C double bond: in our opinion, such a combination of moieties could contribute to enhance the selectivity of the interaction of the substrates with the catalytic centre and hence the enantioselectivity of the process. Indeed, the literature reveals that asymmetric inductions not greater than 68% have been obtained by using [Ir-(*S*)-PHOX] to hydrogenate olefinic diols in which the C=C double bond is not conjugated with aromatic moieties.[18]

While attempting to obtain better enantioselectivities, we turned our attention to ruthenium based catalysts. In fact, ruthenium complexes in combination with atropisomeric diphosphines are exceedingly good catalysts for the asymmetric hydrogenation of allylic alcohols as confirmed by many examples reported in the literature.[17]

In order to verify the usefulness of ruthenium catalysts in the asymmetric hydrogenation of **3** and **6**, we used a catalyst prepared in situ by reacting $[Ru(C_6H_6)Cl_2]_2$ with an (*R*)- or (*S*)-BINAP (ligand/complex = 2:1 molar ratio).[19] The relevant data are collected in Table 2.

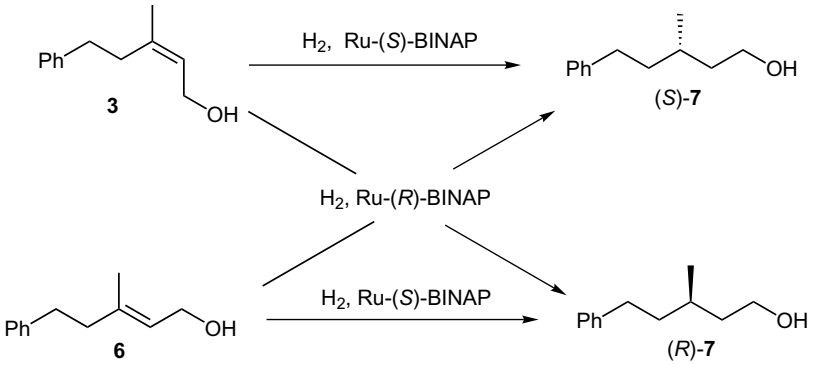
In all the experiments, the asymmetric inductions were very high (ee >96%) thus demonstrating the practical applicability of the devised synthetic approach. Using the ruthenium catalytic system, the reaction is slower than in the presence of the iridium catalyst; however, by increasing the reaction time it is possible to attain total conversion of the olefin, maintaining complete chemoselectivity. Attempting to obtain higher reaction rates, 95% aqueous methanol was used as the solvent, as suggested in the literature;[17c] however, no increase in the reaction rate was noticed and even worse the enantioselectivity decreased (entry 2 of Table 2).

As shown in Scheme 5, using (*S*)-BINAP, the hydrogenation of (*Z*)-allyl alcohol **3** led to (*S*)-**7** as the prevailing

Table 2. Asymmetric hydrogenation of **3** and **6** in the presence of the Ru/BINAP system[a]

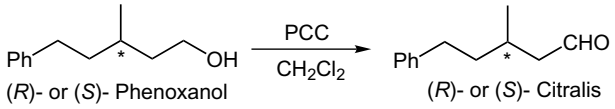
Entry	Substrate	Ligand	Solv.	*t* (h)	Conv.[b] (%)	ee[c] (%)	Config.
1	**3**	(*S*)-BINAP	MeOH	21	48	97	(*S*)
2	**3**	(*S*)-BINAP	aq MeOH[d]	21	40	86	(*S*)
3	**3**	(*S*)-BINAP	MeOH	48	100	97	(*S*)
4	**3**	(*R*)-BINAP	MeOH	48	100	96	(*R*)
5	**6**	(*S*)-BINAP	MeOH	48	100	97	(*R*)
6	**6**	(*R*)-BINAP	MeOH	48	100	98	(*S*)

[a] Reaction conditions: substrate: 0.57 mmol; (*R*)- or (*S*)-BINAP: 1.14×10^{-2} mmol; $[Ru(C_6H_6)Cl_2]_2$: 0.57×10^{-2} mmol; substrate/ruthenium = 50:1; solvent: 10 mL, $T = 23$ °C, $P(H_2) = 100$ atm.
[b] Determined by GLC.
[c] Determined by chiral GLC on the corresponding aldehydes.
[d] 95% aqueous methanol.



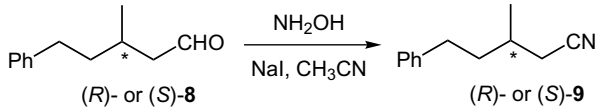
Scheme 5. Asymmetric hydrogenation of **3** and **6** in the presence of the $[Ru(C_6H_6)Cl_2]_2$/BINAP catalytic system.

stereomer, instead the hydrogenation of the (*E*)-isomer gives (*R*)-**7**. Accordingly, it is possible to obtain in high enantiomeric purity, both enantiomers of **7** by choosing the configuration either of the substrate or of the ligand (Scheme 5). It is worth noting that in order to determine the ees by chiral GLC (Chiraldex G-TA capillary column) it was necessary to oxidize (*R*)-**7** or (*S*)-**7** to the corresponding aldehydes (*R*)-**8** or (*S*)-**8** (Scheme 6) thus demonstrating the feasibility of this step of our synthetic approach.



Scheme 6.

Indeed, in the presence of pyridinium chlorochromate, the oxidation of alcohol **7**[20] proceeds on a preparative scale affording the desired Citralis in 90% yield (Scheme 6). The final transformation of Citralis into Citralis Nitrile was accomplished by treating the aldehydes with $NH_2OH \cdot HCl$ in the presence of NaI and CH_3CN (Scheme 7), as described by Ballini et al.[21] (43% yield).



Scheme 7.

3. Odour profiles evaluation

Enantiopure samples of **7**, **8** and **9** were submitted to a panel of skilled perfumers (Givaudan) for the evaluation of the odour profiles. The following descriptions were obtained: (*R*)-(+)-Phenoxanol is 'reminiscent of racemic Phenoxanol, but weaker. Its rose character is harsher, fattier and more metallic compared to the racemate and its antipode' (odour threshold: 12.5 ng/L air); (*S*)-(−)-Phenoxanol® is 'also reminiscent of a typical Phenoxanol note, but stronger; softer, with a more powdery rose character of pronounced floralcy with fruity facets in the direction of red fruits and rhubarb, and a fresh even slightly aquatic tonality' (odour threshold: 5.0 ng/L air); (*R*)-(+)-Citralis is 'very close to racemic Citralis, and stronger than its antipode; aldehydic, fresh, floral, citronellal-like odour, reminiscent of verbena and lemongrass; a somewhat slightly latex and plastic connotation is present as well' (odour threshold: 2.5 ng/L air); (*S*)-(−)-Citralis is 'citronellal-like, floral-aldehydic, but less fresh, more fruity in the direction of red fruits, and with a fatty-rosy undertone that somewhat even reminds of Phenoxanol' (odour threshold: 7.9 ng/L air); (*S*)-(+)-Citralis Nitrile is 'typical citrus, reminiscent of lemon peel and geranyl nitrile, with fresh, fruity and slightly green nuances' (odour threshold: 12.5 ng/L air); (*R*)-(−)-Citralis Nitrile is 'similar in smell, but slightly stronger, and with additional waxy aspects, and a more pronounced green, leafy side' (odour threshold: 6.8 ng/L air).

4. Conclusion

In conclusion the devised synthetic scheme allowed us to obtain the single enantiomers of three different floral fragrances: Phenoxanol®, Citralis® and Citralis Nitrile® in very high enantiopurity. The synthesis appears convenient since with a single enantioselective transformation it is possible to obtain three different fragrances. The Ru/BINAP system prepared in situ appears very versatile allowing us to prepare the sought after enantiomer by choosing the configuration of either the olefin or the ligand.

It was thus possible to evaluate the odour profiles of the single stereomers of the three fragrances: even if no particularly striking differences were perceived, it is worth to note that whatever the fragrance, one of the enantiomers is always stronger. It is also interesting to note that the (*S*)-Phenoxanol presents an olfactory activity not only more intense than its opposite but also more complex and interesting olfactive notes.

5. Experimental

5.1. General methods

Commercial solvents (J. T. Baker) were dried according to literature methods.[22] (*S*)- and (*R*)-BINAP were kindly sup-

plied by Rhodia Phosphines UK. Anhydrous $ZnCl_2$ was prepared by treating commercial $ZnCl_2$ according to a literature method.[23] [Ir((*S*)-2-(*o*-diphenylphosphinophenyl)-3-*tert*-butyl-oxazoline)COD](BARF)[16a] and $[Ru(C_6H_6)Cl_2]_2$[24] were prepared as described in the literature. All other reagents were available from commercial sources (Aldrich) and used without further purification, unless otherwise noted. Flash-chromatographies were performed on MN Kieselgel 60, 70–230 mesh. Yields refer to isolated compounds of greater than 95% purity, as estimated by GLC, and ^{1}H NMR. All compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AC300 spectrometer operating at 300.213 and 75.44 MHz, respectively. GLC analyses were performed on an Agilent 6850 gas chromatograph with a FID detector. GC–MS analyses were performed on a Hewlett-Packard 5890 SERIES II gas chromatograph interfaced with an HP 5971 quadrupole mass detector. Enantiomeric excesses (ee) were determined by chiral GLC using a Chiraldex G-TA column (50 m × 0.25 mm) installed on a Agilent 6850 gas chromatograph with a FID detector. Optical rotations (α) were determined using a Perkin–Elmer 241 polarimeter (Na lamp at 25 °C).

5.2. Synthesis of the unsaturated alcohols 3 and 6

5.2.1. (*Z*)-3-Iodo-2-buten-1-ol. Compound **2** was obtained as a pale yellow oil in 91% yield according to a literature method.[12] The GC–MS and ^{1}H NMR data were identical to those reported in the literature. ^{13}C NMR ($CDCl_3$): δ 33.6, 67.3, 102.3, 134.1.

5.2.2. (*Z*)-3-Methyl-5-phenylpent-2-en-1-ol. Compound **3** was prepared as described by Negishi[13] by reaction of the lithium derivative of (2-iodoethyl)benzene[25] with the zinc derivative of **2**. Olefin **3** was isolated as a pale yellow oil in 55% yield. The GC–MS and ^{1}H NMR data[26] were identical to those reported in the literature.^{13}C NMR ($CDCl_3$): δ 23.3, 33.9, 34.2, 58.9, 125.2, 126.1, 128.3, 128.6, 138.4, 141.7.

5.2.3. (*E*)-Ethyl-3-methyl-5-phenylpent-2-enoate. Compound **5** was prepared in 50% yield as described by Buchwald.[14] The spectral data were identical to those reported in the literature.

5.2.4. (*E*)-3-Methyl-5-phenylpent-2-en-1-ol. Compound **6** was obtained by reduction of ester **5** in the presence of DIBAL as described for the synthesis of (*E*)-3-phenyl-2-buten-1-ol.[15] Olefin **6** was isolated as a pale yellow oil (90% yield). The GC–MS and ^{1}H NMR data[26] were identical to those reported in the literature. ^{13}C NMR ($CDCl_3$): δ 16.4, 34.3, 41.4, 59.3, 123.8, 125.8, 128.29, 128.34, 139.2, 141.9.

5.3. Enantioselective hydrogenations

5.3.1. In the presence of [Ir-(*S*)-PHOX]. In a typical experiment (entry 1 of Table 1), to a solution of [Ir((*S*)-2-(*o*-diphenylphosphinophenyl)-3-*tert*-butyl-oxazoline)(COD)]BARF (17.68 mg, 0.0114 mmol) in 10 mL of anhydrous CH_2Cl_2 contained in a small Schlenk flask were added 100 mg (0.57 mmol) of (*Z*)-3-methyl-5-phenyl-pent-2-en-1-ol under an inert atmosphere. The resulting solution was transferred via cannula into a 150 mL stainless steel autoclave which was then pressurized with 50 atm of H_2, and heated at 60 °C by means of a thermostatic bath. The system was kept under stirring for 21 h, then the residual gas vented off. The solvent was evaporated off and the solid residue dissolved in *n*-pentane/diethyl ether (50:50), and the solution passed through a short silica plug to remove the catalyst. After solvent elimination, 98.0 mg (96.5% yield) of (*R*)-**7** (69.0% ee) were obtained as a yellow oil.

5.3.2. In the presence of the $[Ru(C_6H_6)Cl_2]_2$–BINAP catalyst. In a typical experiment (entry 6 of Table 2), 10 mL of anhydrous methanol was introduced in a small Schlenk flask, which was then evacuated and filled with nitrogen. Under a nitrogen flow were then added 7.1 mg (11.4×10^{-3} mmol) of (*R*)-BINAP, 2.9 mg (5.7×10^{-3} mmol) of $[Ru(C_6H_6)Cl_2]_2$ and 100 mg (0.57 mmol) of (*E*)-3-methyl-5-phenyl-pent-2-en-1-ol to give a pale yellow solution which was transferred via cannula to a 150 mL stainless steel autoclave. The reactor was pressurized with 100 atm of H_2, and kept at 23 °C under stirring by means of a thermostatic bath. After 48 h, the residual gas was vented off, the solvent evaporated and the solid residue dissolved in diethyl ether. The resulting solution was passed through a short silica plug to remove the catalyst. After solvent elimination, 100.6 mg (99.0% yield) of (*S*)-**7** were obtained (98.0% ee) as a yellow oil. The GC–MS and ^{1}H NMR data[20] of (*R*)- or (*S*)-**7** were identical to those reported in the literature. ^{13}C NMR ($CDCl_3$): δ 19.5, 29.2, 33.3, 39.0, 39.7, 61.0, 125.6, 128.26, 128.28, 142.8. The enantiomeric excesses of (*R*)- or (*S*)-**7** were determined by chiral GC after their oxidation to the corresponding aldehydes with pyridinium chlorochromate (see below). $[\alpha]_D^{25} = -14.7$ (*c* 5, CH_2Cl_2); (*S*)-(−)-3-methyl-5-phenyl-pentanol. $[\alpha]_D^{25} = +14.5$, (*c* 5, CH_2Cl_2); (*R*)-(+)-3-methyl-5-phenyl-pentanol.

5.4. Synthesis of fragrances 8 and 9

5.4.1. (*R*)- and (*S*)-3-Methyl-5-phenyl-pentanaldehyde. Compound (*R*)- or (*S*)-**8**, was obtained by treating a dichloromethane solution of (*R*)- or (*S*)-**7** with an excess of pyridinium chlorochromate; after removal of the solvent, the residue was diluted with diethyl ether and filtered through a short plug of silica gel to afford a pale yellow oil (90% yield). MS (*m*/*z*): 176 $[M]^+$; 158, 143, 131, 117, 105, 91. ^{1}H NMR ($CDCl_3$): δ 1.04 (d, 3H, CH_3, $J = 6.8$ Hz); 1.63 (m, 2H, CH_2); 2.06–2.17 (m, 1H, CH), 2.24–2.33 (m, 1H, CH_2); 2.41–2.49 (m, 1H, CH_2); 2.55–2.73 (m, 2H, CH_2); 7.16–7.31 (m, 5H, arom.); 9.75 (t, 1H, CHO, $J = 2.1$ Hz). ^{13}C NMR ($CDCl_3$): δ 19.8, 27.8, 33.2, 38.6, 50.9, 61.0, 125.8, 128.3, 128.4, 142.0, 202.7. Chiral GC conditions: Chiraldex G-TA column, $T = 110$ °C (isotherm); nitrogen flow = 3.5 mL/min; $t_R = 47.03$ min (*S*); $t_R = 47.61$ min (*R*). $[\alpha]_D^{25} = -23.2$ (*c* 1, CH_2Cl_2); (*S*)-(−)-3-methyl-5-phenyl-pentanaldehyde; $[\alpha]_D^{25} = +22.9$ (*c* 1, CH_2Cl_2); (*R*)-(+)-3-methyl-5-phenyl-pentanaldehyde.

5.4.2. (*R*)- or (*S*)-3-Methyl-5-phenyl-pentanenitrile. Compound (*R*)- or (*S*)-**9**, was obtained by treatment of (*R*)- or (*S*)-**8** with $NH_2OH{\cdot}HCl$ in the presence of a catalytic amount of NaI according to the method developed by Ballini et al.[21] (90% yield). The GC–MS and ^1H NMR data[27] of (*R*)- or (*S*)-**9** were identical to those reported in the literature. ^{13}C NMR ($CDCl_3$): δ 19.3, 24.5, 29.9, 33.0, 37.5, 118.7, 126.0, 128.2, 128.5, 141.3. Chiral GC conditions: Chiraldex GT-A column, $T = 120$ °C (isotherm), nitrogen flow = 3.5 mL/min, $t_R = 63.79$ min (*S*), $t_R = 64.96$ min (*R*). $[\alpha]_D^{25} = +2.4$ (*c* 2.2, EtOH); (*S*)-(+)-3-methyl-5-phenyl-pentanenitrile; $[\alpha]_D^{25} = -2.3$ (*c* 2.2, EtOH); (*R*)-(−)-3-methyl-5-phenyl-pentanenitrile.

Acknowledgements

Rhodia UK Ltd—Phosphorus Specialties and Derivatives is acknowledged for generously supplying the BINAP ligands. Dr. P. Kraft, Mr. A. Alchenberger, Mr. A. Vinksnaitis and Mr. K. Grman from Givaudan AG are kindly acknowledged for all the olfactory evaluations. The work has been performed with the Financial Support of the MIUR (COFIN 2004).

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