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Hydroformylation of *m*-diisopropenylbenzene and 1-isopropyl-3-isopropenylbenzene for the preparation of the fragrance Florhydral®

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Abstract

An hydroformylation-based approach to the synthesis of the odorant Florhydral® has been investigated. The hydroformylation of *m*-diisopropenylbenzene (**2**) in the presence of rhodium catalysts leads to mixtures of 3-(3-isopropenylphenyl)butyraldehyde (**3**), which is an immediate precursor of Florhydral® and of the dialdehyde 3-[3-(1-methyl-3-oxopropyl)phenyl]butyraldehyde (**4**), which is a useless side product. The **3/4** ratio is dependent on the substrate conversion: when it is pushed over 40%, the formation of **4** becomes increasingly important. Interestingly, the reaction can be carried out in aqueous biphasic systems using a rhodium catalyst precursor either in the presence of sulphonated triphenyl phosphine or human serum albumin (HSA) as the ligands. Good results were also obtained using rhodium complexes immobilized on silica; in this case it was possible to exclusively obtain the sought aldehyde **3** by limiting the substrate conversion at about 41%.

As an alternative approach, 1-isopropyl-3-isopropenylbenzene (**8**) was synthesized and hydroformylated. In both homogeneous and biphasic systems, in the presence of rhodium catalysts, the reaction leads to the formation of Florhydral® with high reaction rates and complete chemo- and regioselectivity. The use of chiral phosphino ligands, in order to obtain enantiomerically enriched Florhydral®, gave very poor ees.

Keywords: Hydroformylation; Rhodium; Biphasic catalysis; Asymmetric catalysis; Fragrances; *m*-Diisopropenylbenzene

1. Introduction

The hydroformylation of functionalized olefins is a useful synthetic tool which can be conveniently employed in the preparation of a wide variety of fine chemicals [1–4]. In particular, hydroformylation-based synthetic approaches are of the foremost importance in perfume industry since they allow to transform a large number of readily available olefinic precursors into the corresponding aldehydes which represent one of the most important classes of odorants [5]. In this connection, it is worth mentioning that BASF has developed processes based on the hydroformylation of functionalized alkenes such as α-pinene [6], *tert*-butyldihydrodioxepine [7] or β-isophorone [8] and that also mono- or polycyclic aldehydes have been advantageously obtained by hydroformylation of the corresponding cyclic olefins [9–11]. In addition, it is to remind that differently substituted allyl- and propenylbenzenes such as safrole, isosafrole, eugenol and isoeugenol have been hydroformylated in the presence of rhodium complexes to produce the corresponding aldehydes which are valuable perfume components and/or odour boosters [12–14].

A new trend in modern perfumery is the preparation of fragrances having a delicate marine and watery touch [15]. Among the synthetic odorants employed to convey the fresh marine and ozonic note, one of the most important is 3-(3-isopropylphenyl)butyraldehyde (**1**) (Scheme 1), which is marketed by Givaudan under the trade name of Florhydral®. According to two patents issued by Givaudan, a very advantageous synthesis of Florhydral® implies the rhodium catalyzed hydroformylation of the cheap and readily available *m*-diisopropenylbenzene (**2**) (Scheme 1). The reaction affords the unsaturated aldehyde **3** which is then hydrogenated to give

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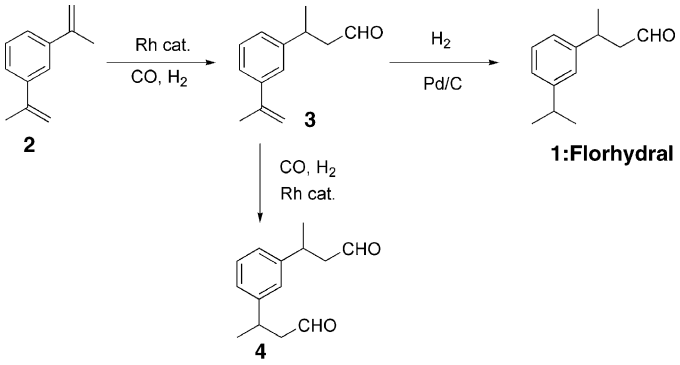


Scheme 1.

the sought fragrance. The major drawback of the process is represented by the formation of the undesired dialdehyde **4** which is formed by the double hydroformylation of the starting olefin [16,17].

Owing to our interest in the application of the oxo-reaction in fine chemistry [18–23], we deemed it interesting to reinvestigate the hydroformylation of *m*-diisopropenylbenzene in the presence of some rhodium catalysts modified with phosphino ligands looking for higher selectivities in the formation of aldehyde **3**; moreover, in order to easily recover and recycle the expensive rhodium-based catalyst, we decided to perform the oxo-process in biphasic systems by using water soluble or heterogenized rhodium catalysts.

Another aspect which spurred us to investigate the synthesis of **1** via hydroformylation is the presence of a chiral carbon atom in the Florhydral® molecule. As it happens with other fragrances, the two enantiomers induce a different biological activity and it has been shown by Fuganti and co-workers, who succeeded in independently preparing the two enantiomers resorting to an enzymatic approach [24], that (+)-Florhydral® is an odorant much more powerful than the opposite stereomer. There currently is a great interest in preparing chiral odorants as pure enantiomers; in fact, by producing and marketing only the more olfactory active isomer it will be possible to reduce the amount of these molecules which are eventually dispersed in the biosphere. These considerations encouraged us to devise an asymmetric hydroformylation-based scheme for the synthesis of enantiomerically enriched Florhydral®.

2. Experimental

2.1. General remarks

Commercial solvents (Fluka or Aldrich) were purified according to literature [25]. *m*-Diisopropenylbenzene, 3-isopropylphenol, trifluoromethanesulfonic anhydride, formic acid, 3-(mercapto)propyl-functionalyzed silica gel and 3-(1-thioureido)propyl-functionalyzed silica gel were purchased from Aldrich. $HRh(CO)(PPh_3)_3$, $Rh(CO)_2(acac)$, Xantphos and DPPB were Strem products. Sulfonated triphenylphosphine (TPPTS) was obtained from Fluka. Human serum albumin (HSA) was a Sigma product. (*R*)-BINAP (**III**), (*R*)-(−)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine (**IV**) and (*R*)-(−)-1[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl-di(3,5-dimethylphenyl)phosphine (**V**) were purchased from Strem. The silica gel tethered rhodium catalysts **Rh-I** and **Rh-II** were prepared according to Ref. [23].

Flash chromatographies were performed using Merck 60 silica gel, 230–400 mesh. NMR spectra were recorded on a Bruker Avance 300 spectrometer using $CDCl_3$ as the solvent. GLC analysis were carried out on an Agilent 6850A gas chromatograph, using an HP1 column (30 m × 0.32 mm × 0.25 μm). GC–MS analyses were performed by using an Agilent MS Network 5937 apparatus using an HP-5MS column (30 m × 0.25 mm × 0.25 μm). Optical rotation values were measured with a Perkin-Elmer Mod. 241 polarimeter.

2.2. Synthesis of 1-isopropyl-3-isopropenylbenzene (*8*)

2.2.1. 4-(3-Isopropylphenyl)-2-methylbut-3-yn-2-ol (*6*)

To an aqueous solution of NaOH (40.0 g in 400 mL) were added 40.3 g (0.30 mol) of 3-isopropylphenol and the mixture was stirred until complete dissolution. Then 83.5 g (0.30 mol) of trifluoromethanesulfonic anhydride dissolved in 85 mL of CCl_4 were added dropwise. After stirring for 2 h, the organic phase was separated and the aqueous layer washed with CCl_4 (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and rotoevaporated to give a brown oil. Distillation under reduced pressure afforded 65.0 g (81% yield) of trifluoromethanesulfonic acid 3-isopropylphenyl ester as a colourless oil (bp 49–51 °C/0.01 mmHg).

Trifluoromethanesulfonic acid 3-isopropylphenyl ester. MS: *m/z* 268 [M^+], 253, 135, 119, 103, 91. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, J = 7.0 Hz, 6H, CH_3), 2.98 (m, 1H, CH), 7.10–7.15 (m, 2H, arom.), 7.29 (s, 1H, arom.), 7.35–7.40 (m, 1H, arom.). ^{13}C NMR ($CDCl_3$, δ): 23.6, 33.9, 118.5, 118.8 (q, CF_3, J_{C-F} = 320.5 Hz), 119.3, 126.5, 130.0, 149.8, 152.0.

Under an inert atmosphere, in a 500 mL three-necked round bottom flask equipped with a reflux condenser and a nitrogen inlet, were placed, in the order, 41 mg of palladium(II) acetate (0.18 mmol), 140 mg of triphenylphosphine (0.54 mmol), 19.3 g (72.0 mmol) of trifluoromethanesulfonic acid 3-isopropylphenyl ester, 69 mg (0.36 mmol) of CuI, 6.0 g (72.0 mmol) of 2-methylbut-3-yn-2-ol and 125 mL of piperidine. The resulting solution was stirred at 75 °C for 20 h, then was cooled at rt and the piperidine was distilled off. The brown residue was treated with 70 mL of 5N HCl at 0 °C. The mixture was extracted with diethyl ether, and the aqueous phase washed with diethyl ether (3 × 50 mL), and with dichloromethane (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$, then with brine, dried over $MgSO_4$ and rotoevaporated. The resulting crude brown oil can be used in the subsequent step without further purification, but if needed, **6** can be obtained as a pale yellow oil after flash chromatography (silica gel, *n*-hexane/diethyl ether = 95/5).

4-(3-Isopropylphenyl)-2-methylbut-3-yn-2-ol (**6**). MS: *m/z* 202 [M^+], 187, 170, 159, 128, 91. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, J = 7.0 Hz, 6H, CH_3), 1.66 (s, 6H, CH_3), 2.45 (br s, 1H, OH), 2.98

(septet, 1H, CH), 7.17–7.33 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$, δ): 23.7, 31.5, 34.0, 65.5, 82.4, 93.3, 122.5, 126.6, 128.1, 129.0, 129.6, 148.8.

2.2.2. 1-(3-Isopropylphenyl)ethanone (7)

A mixture of 13.0 g (64.0 mmol) of crude **6** and 10 g (0.18 mol) of KOH in isopropanol (200 mL) was refluxed for 2.5 h, then the solvent was evaporated under vacuum. The resulting residue was diluted with *n*-hexane (100 mL) and the solution washed several times with water until pH 7. The combined aqueous phase was extracted three times with *n*-hexane (3 × 30 mL). The organic phase was dried over $MgSO_4$ and the solvent distilled off to afford a brown oil, from which 5.65 g (61% yield) of 1-ethynyl-3-isopropylbenzene were obtained by distillation under reduced pressure (colourless oil, bp 62 °C/0.01 mmHg).

1-Ethynyl-3-isopropylbenzene. MS: *m/z* 144 [M^+], 129, 115, 102, 77. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, 6H, CH_3), 2.93 (m, 1H, CH), 3.09 (s, 1H, CH), 7.23–7.43 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$, δ): 23.7, 33.9, 76.6, 84.0, 121.9, 127.1, 128.2, 129.5, 130.1, 148.9.

Four grams (26.0 mmol) of 1-ethynyl-3-isopropylbenzene and 16 mL of freshly distilled formic acid were placed in a 100 mL round bottom flask and refluxed under stirring for 1 h. After cooling to rt the mixture was diluted with dichloromethane (50 mL), then washed with water and with a 10% aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, and rotoevaporated. Vacuum distillation afforded 3.71 g (88% yield) of **7** as a pale yellow oil (bp 59 °C/0.01 mmHg).

1-(3-Isopropylphenyl)ethanone. MS: *m/z* 162 [M^+], 147, 119, 103, 91. ^{1}H NMR ($CDCl_3$, δ): 1.27 (d, J = 6.9 Hz, 6H, CH_3), 2.58 (s, 3H, CH_3), 2.96 (septet, 1H, CH), 7.34–7.44 (m, 2H, arom.), 7.76 (d, 1H, arom.), 7.83 (s, 1H, arom.). ^{13}C NMR ($CDCl_3$, δ): 23.7, 26.5, 34.0, 125.96, 126.00, 128.4, 131.2, 137.1, 148.9, 198.2.

2.2.3. 1-Isopropyl-3-isopropenylbenzene (8)

A solution of 2.0 g (12.3 mmol) of **7** in 5 mL of anhydrous diethyl ether was added dropwise to a cold (0 °C) solution of MeLi (17.0 mmol) in 40 mL of diethyl ether. After the addition was complete the resulting solution was allowed to warm to rt and stirred for 2.5 h. The reaction mixture was cautiously quenched with 10 mL of an aqueous 1 M NH_4Cl solution, and extracted with *n*-pentane (3 × 30 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvent distilled off. The crude tertiary alcohol was mixed with 30 mL of aqueous H_2SO_4 (5%) and refluxed for 4 h. The reaction mixture was extracted with *n*-pentane (3 × 20 mL), washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent distilled off. The residue was vacuum distilled to afford 1.14 g (58% yield) of **8** as a pale yellow oil (bp 35 °C/0.01 mmHg).

MS: *m/z* 160 [M^+], 145, 117, 105, 91. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, J = 6.9 Hz, 6H, CH_3), 2.25 (s, 3H, CH_3), 2.96 (septet, 1H, CH), 5.16 (br s, 1H, CH), 5.45 (br s, 1H, CH), 7.21–7.26 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$, δ): 22.4, 24.5, 34.7, 112.6, 123.6, 124.2, 125.9, 128.7, 141.8, 144.1, 149.2.

2.3. General procedure for hydroformylation in homogeneous phase

In a typical experiment (entry 1 of Table 1), the 150 mL stainless steel reaction vessel was charged under a nitrogen purge with 6.3 mmol of *m*-diisopropenylbenzene (**2**), 0.0063 mmol of $HRh(CO)(PPh_3)_3$ and 5 mL of anhydrous toluene. The autoclave was then pressurized to 70 atm with syngas (CO/H_2 = 1) and heated at 80 °C for 18 h. Then the reactor was cooled to rt and the residual gases vented off. Substrate conversion and products composition were determined by GLC. The aldehydes **3** and **4** can be separated from the raw reaction mixture by flash chromatography (silica gel, *n*-hexane/ether 7/3). They were identified by GC–MS and NMR spectroscopy.

Table 1
Rhodium catalyzed hydroformylation of *m*-diisopropenylbenzene (**2**)

Run	Catalytic precursor	T (°C)	t (h)	Conversion (%)	**3** Yield (%)	**4** Yield (%)	**3**/(**3**+**4**) (%)
1	$HRh(CO)(PPh_3)_3$	80	18	92.4	38.1	54.2	41.2
2	$HRh(CO)(PPh_3)_3$	100	20	70.3	53.2	17.1	75.7
3	$HRh(CO)(PPh_3)_3$	120	0.5	52.0	42.0	10.0	80.8
4	$HRh(CO)(PPh_3)_3$	150	0.25	33.1	30.1	3.0	90.9
5	$Rh(CO)_2(acac)$	60	64	72.0	51.0	21.0	70.8
6	$Rh(CO)_2(acac)$	80	24	91.3	42.1	49.2	46.1
7	$HRh(CO)(PPh_3)_3/PPh_3$[a,b]	80	20	3.0	3.0	–	100
8	$HRh(CO)(PPh_3)_3/PPh_3$[b]	80	48	59.0	49.0	10.0	83.1
9	$Rh(CO)_2(acac)$/DPPB[c]	80	24	17.2	17.2	–	100
10	$Rh(CO)_2(acac)$/DPPB[c]	80	48	45.0	41.0	4.0	91.1
11	$Rh(CO)_2(acac)$/Xantphos[d]	80	24	44.2	38.2	6.0	86.4
12	$Rh(CO)_2(acac)$/Xantphos[d,e]	80	24	6.0	6.0	–	100
13	$Rh(CO)_2(acac)$/Xantphos[d,e]	80	48	24.3	22.2	2.1	91.4

Reaction conditions: substrate = 6.3 mmol; substrate/Rh (molar ratio) = 1000/1; toluene = 5 mL; $p(CO) = p(H_2)$ = 35 atm.

[a] Substrate/Rh (molar ratio) = 10,000.

[b] P/Rh (molar ratio) = 80.

[c] DPPB: 1,4-bis(diphenylphosphino)butane, DPPB/Rh (molar ratio) = 3/1.

[d] Xantphos/Rh (molar ratio) = 2.2/1.

[e] $p(CO) = p(H_2)$ = 5 atm.

Table 2
Rhodium catalyzed hydroformylation of *m*-diisopropenylbenzene (**2**) in water/toluene biphasic system

Run	Catalyst	Ligand	*T* (°C)	*t* (h)	Conversion (%)	**3** Yield (%)	**4** Yield (%)	**3**/(**3**+**4**) (%)
1	$[Rh(COD)Cl]_2$	TPPTS[a]	60	42	81.3	52.2	29.1	64.2
2	$[Rh(COD)Cl]_2$	TPPTS[a]	60	22	49.6	41.6	8.0	83.8
3	$[Rh(COD)Cl]_2$	TPPTS	80	19	77.0	50.0	27.0	64.9
4	$Rh(CO)_2(acac)$	HSA[b]	60	24	19.1	19.1	–	100
5	$Rh(CO)_2(acac)$	HSA[b]	60	36	54.0	46.0	8.0	85.2
6	$Rh(CO)_2(acac)$	HSA[b]	60	48	73.5	55.3	18.2	75.2
7	$Rh(CO)_2(acac)$	HSA[b]	80	24	88.1	56.1	32.0	63.7

Reaction conditions: substrate = 6.3 mmol; toluene/water = 3/2 mL; $p(CO) = p(H_2) = 35$ atm.
[a] TPPTS/Rh (molar ratio) = 6; substrate/Rh (molar ratio) = 1000/1.
[b] Rh/HSA = 60/1 (atoms of rhodium/mol of protein) [29]; substrate/Rh (molar ratio) = 600/1.

Table 3
Hydroformylation of *m*-diisopropenylbenzene (**2**) catalyzed by **Rh-I** and **Rh-II**

Run	Catalyst	*T* (°C)	*t* (h)	Conversion (%)	**3** Yield (%)	**4** Yield (%)	**3**/(**3**+**4**) (%)
1	**Rh-I**	80	24	95.0	35.1	59.9	36.9
2	**Rh-I**	60	24	45.6	44.3	1.3	97.1
3	**Rh-II**	80	24	83.3	49.4	33.9	59.3
4	**Rh-II**	60	24	41.4	41.4	–	100

Reaction conditions: substrate = 6.3 mmol; substrate/Rh (molar ratio) = 800/1; toluene = 10 mL; $p(CO) = p(H_2) = 35$ atm.
Rh-I and **Rh-II** were obtained by reacting $[Rh(CO)_2(acac)]$ with 3-(mercapto)propyl- and 3-(1-thioureido)propyl-functionalized silica gel, respectively [23].

3-(3-Isopropenylphenyl)butyraldehyde (**3**). MS: *m/z* 188 [M^+], 173, 159, 145, 131, 117, 105, 91, 77, 65, 51. ^{1}H NMR ($CDCl_3$, δ): 1.34 (d, $J = 6.9$ Hz, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.68 (ddd, A part of a complex AB spin system, $J_{AB} = 16.5$ Hz, $J = 7.9$ and 1.8 Hz, 1H, CH*H*), 2.80 (ddd, B part of a complex AB spin system, $J_{AB} = 16.5$ Hz, $J = 6.6$ and 1.8 Hz, 1H, CH*H*), 3.38 (apparent sextet, $J = 6.8$ Hz, 1H, CH), 5.10 (m, 1H, =CH), 5.36 (s, 1H, =CH), 7.12–7.36 (m, 4H, arom.), 9.73 (t, $J = 1.8$ Hz, 1H, CHO).

3-[3-(1-Methyl-3-oxopropyl)phenyl]butyraldehyde (**4**). MS: *m/z* 218 [M^+], 200, 185, 172, 156, 117, 105, 91, 77, 65, 51. ^{1}H NMR ($CDCl_3$, δ): 1.32 (d, $J = 6.9$ Hz, 6H, CH_3), 2.67 (ddd, A part of a complex AB spin system, $J_{AB} = 16.4$ Hz, $J = 7.9$ and 1.8 Hz, 2H, CH*H*), 2.81 (ddd, B part of a complex AB spin system, $J_{AB} = 16.4$ Hz, $J = 6.6$ and 1.8 Hz, 2H, CH*H*), 3.38 (apparent sextet, $J = 6.8$ Hz, 2H, CH), 7.04–7.32 (m, 4H, arom.), 9.73 (t, $J = 1.8$ Hz, 2H, CHO).

The hydroformylation of olefin **8** was carried out in the same fashion affording 3-(3-isopropylphenyl)butyraldehyde (**1**) (Florhydral®).

3-(3-Isopropylphenyl)butyraldehyde (**1**). MS: *m/z* 190 [M^+], 175, 147, 133, 105, 91. ^{1}H NMR ($CDCl_3$, δ): 1.29 (d, $J = 6.8$ Hz, 6H, CH_3), 1.33 (d, $J = 6.9$ Hz, 3H, CH_3), 2.68 (ddd, A part of a complex AB spin system, $J_{AB} = 16.6$ Hz, $J = 7.7$ and 1.8 Hz, 1H, CH_2), 2.79 (ddd, B part of a complex AB spin system, $J_{AB} = 16.6$ Hz, $J = 6.6$ and 1.8 Hz, 1H, CH_2), 2.96 (septet, $J = 6.9$ Hz, 1H, CH), 3.35 (apparent sextet, $J = 6.8$ Hz, 1H, CH) 7.0–7.3 (m, 4H, arom.), 9.73 (t, $J = 1.8$ Hz, 1H, CHO).

2.4. Hydroformylation in water/toluene two-phase system

In a typical experiment (entry 1 of Table 2) in a Schlenk tube $[Rh(COD)Cl]_2$ (3.15×10^{-3} mmol) and TPPTS (3.8×10^{-2} mmol) were dissolved in water (2 mL) under nitrogen. Then, a solution of *m*-diisopropenylbenzene (**2**) (6.3 mmol) in toluene (3 mL) was then added to the aqueous solution. The Schlenk tube was transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized to 70 atm with syngas ($CO/H_2 = 1$), heated at 60 °C and maintained under vigorous magnetic stirring for 42 h. The reactor was then cooled to rt and the residual gases released. The organic phase was separated, dried on Na_2SO_4 and the substrate conversion and products composition were determined by GLC.

2.5. Hydroformylation catalyzed by SiO_2-tethered rhodium complexes

In order to avoid catalyst deterioration due to attrition by stirring, an autoclave lined with a modified glass vial was employed [23]. This apparatus allows to reuse the same catalyst for many reaction cycles. In a typical run, the basket containing the catalytic complex was introduced, under a nitrogen purge, in the glass vessel containing the substrate in toluene. The vessel was then transferred into a 150 mL stainless steel reactor which was pressurized with syngas at 70 atm and heated at 60–80 °C for 24 h (Table 3). After cooling at rt, the residual gases were released and the reaction mixture was analyzed by GLC.

3. Results and discussion

As described in the introduction, Givaudan patents claim the synthesis of Florhydral® by hydroformylation of *m*-diisopropenylbenzene in the presence of rhodium catalysts (Scheme 1) [16,17]. The reaction is carried out at 140 °C under 17 atm of syngas ($CO/H_2 = 1$); under these conditions, the aldehyde **3** can be obtained in about 41% yield by limiting the

substrate conversion at 50%. In fact, since the reactivity of the double bond present in aldehyde **3** is very close to that of the double bonds of the starting olefin **2**, at higher substrate conversions considerable amounts of the dialdehydic product **4** are formed.

Even if it is impossible to avoid the consecutive reaction of two equal and almost independent functional groups, we deemed interesting to test if it were possible to improve the selectivity towards aldehyde **3** by carrying out the hydroformylation of *m*-diisopropenylbenzene in the presence of ligands which may induce geometrical constraints such as diphosphines with different bite angles.

Since the *oxo*-process is affected by some drawbacks such as the technical difficulties associated with the separation of the reaction products from the solvent and the soluble and expensive catalytically active metal-complexes, we also tried to carry out the hydroformylation reaction in the water–toluene biphasic system or in the presence of heterogenized rhodium catalysts.

Preliminary hydroformylation experiments were carried out in homogeneous phase using some conventional catalysts such as rhodium carbonyls or rhodium complexes containing phosphino ligands (Table 1).

From the relevant data it comes into view that when the reaction is carried out at 60–150 °C using a substrate to rhodium molar ratio of 1000:1 or higher, ($p(CO) = p(H_2) = 5$–35 atm), the chemoselectivity and the regioselectivity of the process are complete, leading to the exclusive formation of the oxo-products **3** and **4** (Scheme 1), hydrogenation side products being absent.

It is interesting to note that the tertiary aldehyde **3a**, and hence the dialdehydes **4a** and **b** (Fig. 1) do not form at all: the reason for this remarkable regioselectivity can be found in the work of Lazzaroni et al. [26].

The temperature affects only the reaction rate since the **3/4** ratio seems to be essentially dictated by the reaction time. As a matter of fact, whichever is the catalyst employed, we observed that when the substrate conversion is driven over 30%, the formation of the dialdehyde **4** becomes increasingly important. For instance, at substrate conversions of about 90% the yield in **3** is only 40% and the major product is the aldehyde **4** (runs 1 and 6 of Table 1). The activities of the Wilkinson's catalyst and of $Rh(CO)_2(acac)$ appear to be comparable; on the other hand, when $HRh(CO)(PPh_3)_3$ is used in the presence of an excess of PPh_3 (P:Rh molar ratios of up to 80:1) the reaction rate decreases but the selectivity towards **3** seems to slightly increase (runs 7 and 8 of Table 1). Some hydroformylation experiments were carried out in the presence of the diphosphine DPPB [1,4-bis(diphenylphosphinobutane)], a chelating ligand having a relatively small bite angle near 98° and Xantphos, a diphosphine with a much larger bite angle close to 111° [27], but not significant improvements in selectivity were observed (runs 9–13 of Table 1).

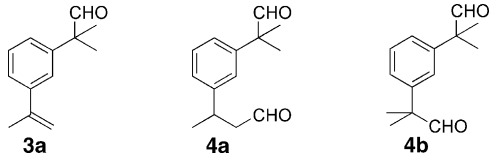


Fig. 1. Possible tertiary aldehydes deriving from the hydroformylation of *m*-diisopropenylbenzene.

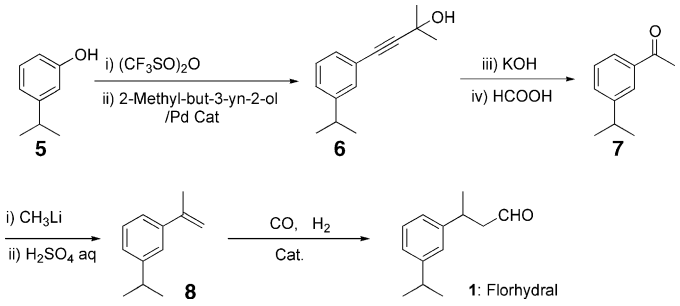
With the aim to combine the high activity of homogeneous catalysts and the easy separation of heterogeneous ones, we have studied the hydroformylation of *m*-diisopropenylbenzene in an aqueous biphasic system. The use of water soluble organometallic catalysts for chemical reactions offers considerable advantages providing a neat and inexpensive solution to the problem of conserving resources, making the process environmentally friendly for the chemical industry. As a matter of fact, the rhodium catalyzed aqueous biphasic hydroformylation is a well established industrial process by which about 600,000 t/a of butyraldehyde are produced combining the industrial requirement with the environmental benefit [28]. Accordingly, the hydroformylation of *m*-diisopropenylbenzene was carried out at 60–80 °C under 70 atm of syngas ($CO/H_2 = 1$), using a toluene/water biphasic system. The catalyst was prepared in situ by reacting $Rh(CO)_2(acac)$ or $[Rh(COD)Cl]_2$ with the appropriate amount of the water soluble phosphino ligand TPPTS.

Although the Rh/TPPTS system is the most used in biphasic hydroformylation, we have recently reported that $Rh(CO)_2(acac)$ in the presence of HSA is an highly efficient and chemoselective catalyst for olefin hydroformylation in toluene/water two-phase system [29,30]. Thus, some oxo-experiments on *m*-diisopropenylbenzene were carried out also in the presence of this catalytic system. At 60–80 °C and 70 atm of syngas pressure, with both these catalytic systems, the reaction proceeded affording only the two aldehydes **3** and **4** with complete chemo- and regioselectivity. As in the homogeneous process, the **3/4** ratio is dependent on the reaction time, therefore it was possible to selectively obtain the monoaldehyde **3** only at low substrate conversion (run 4 of Table 2). In any case, the reaction products were easily recovered by separation of the organic phase and the aqueous catalytic solution reused for five recycles with a very small efficiency loss.

A different interesting approach to an easy separation of the reaction products and a recycle of the catalytic system, is represented by the use of heterogenized homogeneous catalysts. Silica modified with donor ligands is one of the most commonly employed support to tether organometallic complexes; accordingly, we evaluated the catalytic activity of two SiO_2-tethered rhodium catalysts deriving from $Rh(CO)_2(acac)$ and the commercially available 3-(mercapto)propyl- and 3-(1-thioureido)propyl-functionalyzed silica gel [23]. These commercial supports contain sulfur and nitrogen ligands which can strongly bind the rhodium atom and, in principle, minimize metal leaching during the reaction [31].

Both the catalysts obtained, named **Rh-I** and **Rh-II**, respectively, were employed in some hydroformylation experiments and the most relevant results are reported in Table 3.

At 80 °C both the anchored catalysts showed a high activity and, analogously to that observed with the homogeneous catalysts, the selectivity towards the monoaldehyde turned out to be strongly dependent on the substrate conversion (runs 1 and 3 of Table 3). On lowering the reaction temperature at 60 °C the catalytic activity decreases, but the selectivity towards **3** is remarkably enhanced (runs 2 and 4 of Table 3): at the best,



Scheme 2.

using **Rh-II** it is possible to obtain exclusively the sought aldehyde **3** at about 40% substrate conversion (run 4 of Table 3). Since an alike selectivity is obtained with **Rh-I** at the same temperature, we tentatively attribute this intriguing effect to steric constraints introduced by the presence of the functionalized silica. This aspect will be the subject of future investigations.

Recycle experiments (not reported in Table 3) carried out at 80 °C showed that the anchored systems can be reused for three times with only little loss of activity.

The second goal of our study was to investigate the synthesis of Florhydral® in enantiomerically enriched form, employing the hydroformylation reaction as the enantioselective step. At the light of the above results we argued that the hydroformylation of *m*-diisopropenylbenzene in the presence of chiral rhodium catalysts should afford a complex mixture of stereomers. Therefore, we designed a different synthetic approach in which the key step is the hydroformylation of the monoolefin **8** which leads directly to Florhydral®. As shown in the Scheme 2, olefin **8** was synthesized starting from the commercially available 3-isopropylphenol (**5**). In two steps a Sonogashira reaction allowed to obtain the alkyne **6** [32,33]. Deprotection of **6** [34] followed by treatment with formic acid [35] afforded ketone **7** which was finally transformed into the sought olefin **8** via reaction with methyl lithium and subsequent dehydration of the intermediate benzyl alcohol.

At first, olefin **8** was subjected to the oxo-process in the presence of some different non-chiral catalytic precursors, both in homogeneous phase or in the water/toluene biphasic system.

At 80 °C under 80 atm of syngas ($CO/H_2 = 1$) using $HRh(CO)(PPh_3)_3$ or $Rh(CO)_2(acac)$ the reaction proceeds smoothly with almost quantitative substrate conversion and product yield. As a matter of fact the regioselectivity towards the desired Florhydral® is total: only insignificant amounts of *m*-diisopropylbenzene, arising from substrate hydrogenation and never exceeding 1%, were detected among the reaction products (runs 1 and 2 of Table 4).

Excellent results were also obtained when the oxo-reaction was carried out in the water/toluene biphasic system using $Rh(CO)_2(acac)$ modified with TPPTS or with the biopolymer HSA (Table 4). The hydroformylation in the presence of HSA was performed at 60 °C to avoid any protein denaturation phenomenon: accordingly, lower reaction rates were obtained (40% substrate conversion after 24 h), but the selectivity towards Florhydral® was complete (run 4 of Table 4).

Finally, olefin **8** was subjected to some hydroformylation experiments in the presence of rhodium carbonyl complexes modified with the chiral ligands **III–V** (Fig. 2) as the representatives of a wide class of chiral diphosphino ligands successfully employed in asymmetric catalysis.

The data in Table 5 show that also in the presence of these chelating diphosphines the hydroformylation proceeds with high chemo- and regioselectivity.

Regardless of the chiral ligands used, the enantiomeric excesses were practically negligible (Table 5), the maximum

Table 4
Rhodium catalyzed hydroformylation of 1-isopropyl-3-isopropenylbenzene (**8**)

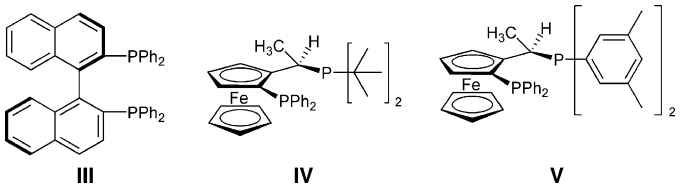
Run	Catalyst	*T* (°C)	*t* (h)	Conversion (%)	Florhydral® yield (%)[a]
1	$HRh(CO)(PPh_3)_3$	80	21	99.5	99.4
2	$Rh(CO)_2(acac)$	80	21	97.8	96.9
3	$Rh(CO)_2(acac)$/TPPTS[b]	100	24	99.6	98.6
4	$Rh(CO)_2(acac)$/HSA[c]	60	24	40.0	40.0

Reaction conditions: substrate = 6.3 mmol; substrate/Rh (molar ratio) = 1000/1; toluene = 5 mL; $p(CO) = p(H_2) = 40$ atm.
[a] In all cases, traces of *m*-diisopropylbenzene were detected in the reaction mixture.
[b] TPPTS/Rh (molar ratio) = 6/1; toluene/water = 3/2 mL.
[c] Rh/HSA = 60/1 (atoms of rhodium/mol of protein) [29]; toluene/water = 3/2 mL.

Table 5
Hydroformylation of 1-isopropyl-3-isopropenylbenzene (**8**) catalyzed by rhodium carbonyl complexes modified with chiral ligands

Run	Catalytic precursor	Ligand	Conversion (%)	Florhydral® yield (%)[a]	ee (%) (configuration) [b]
1	$Rh(CO)_2(acac)$	**IV**	47.3	45.8[a]	–
2	$Rh(CO)_2(acac)$	**V**	50.0	48.0[a]	–
3	$Rh(CO)_2(acac)$	**III**	90.0	90.0	2.0 (*R*)
4	$HRh(CO)(PPh_3)_3$	**III**	94.0	94.0	5.0 (*R*)

Reaction conditions: substrate = 6.3 mmol; substrate/Rh (molar ratio) = 1000/1; toluene = 5 mL; $T = 80$ °C, $t = 24$ h; $p(CO) = p(H_2) = 35$ atm; ligand/Rh (molar ratio) = 1.5/1.
[a] Traces of *m*-diisopropylbenzene were detected in the reaction mixture.
[b] Determined by polarimetry.



III IV V

Fig. 2. Structures of the chiral diphosphino ligands used.

enantiomeric induction reaching 5% in the presence of (*R*)-BINAP (**III**) (run 4 of Table 5) (the enantioselectivity of the reaction and the configuration of **1** were inferred on the basis of the specific rotation values reported by Fuganti and co-workers [24]). The poor enantioselectivity can be likely ascribed to the particular nature of the substrate; as a matter of fact, vinylidenic olefins usually give much lower enantiomeric excesses than those obtained with structurally correlated vinyl substrates [36].

4. Conclusive remarks

Two different hydroformylation-based approaches to the synthesis of the fragrance Florhydral® have been investigated and compared. The synthesis of Florhydral® via hydroformylation of *m*-diisopropenylbenzene suffers of the major drawback of the formation of the useless dialdehyde **4** which makes mandatory to limit the substrate conversion and no significant selectivity improvement could be obtained working with different ligands and conditions. Very interestingly, complete regioselective formation of the aldehyde **3** was obtained in the presence of the heterogenized systems **Rh-I** or **Rh-II** by limiting the substrate conversion at about 40%: the easy separation of the solid catalyst from the reaction products and the possibility to recycle the unreacted olefin makes this process attractive in the perspective of a possible scale-up.

Alternatively, the hydroformylation of olefin **8** also appears a very appealing process allowing to obtain the sought Florhydral® in almost quantitative yield. Analogously to the hydroformylation of *m*-diisopropenylbenzene, also this process can be suitably carried out in the environmentally friendly aqueous biphasic system in the presence of $Rh(CO)_2$acac modified with the sulphonated phospine TPPTS or with the biopolymer HSA, with comparable activity and selectivity. Attempts to obtain enantiomerically enriched Florhydral® by enantioselective hydroformylation of **8** were disappointing since almost no optical induction was obtained.

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