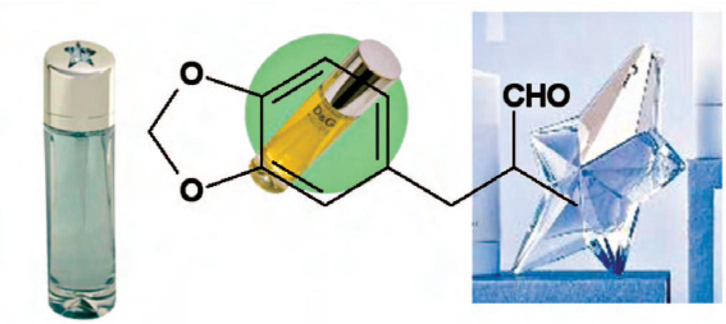

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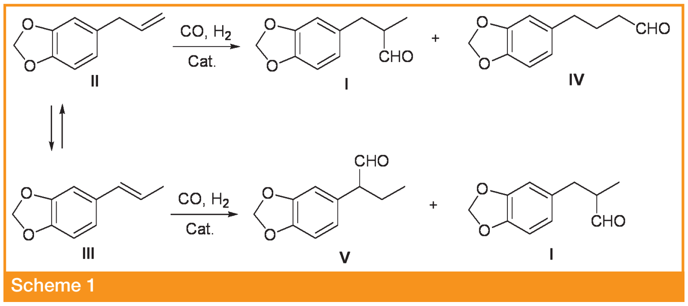
SYNTHESIS OF FRAGRANCES THROUGH SAFROLE AND ISOSAFROLE HYDROFORMYLATION

The hydroformylation reaction on safrole and isosafrole has been reinvestigated. An aqueous biphasic process, with a recyclable nanostructured Rh catalyst associated with a human serum albumin, was realized on isosafrole to afford a pleasant new aldehydic odorant mixture containing about 75% of valuable 3-benzo(1,3)dioxol-5-yl-2-methyl-propionaldehyde.

The hydroformylation of olefins, catalyzed by homogeneous cobalt and rhodium complexes, is one of the most important reactions for the industrial production of aldehydes (about 9 millions ton/year) [1, 2]. In particular, rhodium compounds, generally modified with phosphorous ligands, give rise to high reaction rates and good selectivities to the desired products [2-4] and therefore, the rhodium-catalyzed hydroformylation of functionalised olefins represents a useful tool for the preparation of several valuable intermediates for fine chemicals [5-11].

The fragrance and flavour industry, for example, is a field in which catalysis may play an important role and a great number of aldehydes, useful compounds for perfumery, can be easily obtained by hydroformylation of simple olefinic precursors [12]. Among these aldehydic odorants, 3-benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde **I**, commercialised with different trade names such as for example Helional®, is a fragrance used in many perfumes and presents a green, floral (cyclamen) odor profile with top notes of marine fresh, ozone and new mown hay [13, 14]. With the launches of *"New west for her"* (Aramis, 1990) and *"Escape for her"* (C. Klein, 1991), a marine trend was initiated in feminine perfumery, based on a very simple combination of raw materials as Helional [13]. Later, this fragrance was also employed in masculine perfumes: for example, *"l'Eau d'Issey masc"* (I. Miyake, 1994) contains about 13% of **I** [13]. More recently *"Masculine"* (Dolce e Gabbana, 1999) and *"Angel"* (T. Mugler, first top fragrance of 2005), both including **I**, shown the continue interest of introducing this synthetic odorant in many cosmetic products for men and women.

Many procedures have been reported [13-18] for the preparation of 3-benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde, the annual production of which is estimated higher than 300 tons, with a selling price of 25-28 $/kg. Very recently [19] the synthesis of both enantiomers of **I** showing different olfactory characteristics, has been accomplished too.



Scheme 1

In principle **I** could be obtained by regioselective hydroformylation of allyl benzene (safrole, **II**) and/or propenyl benzene (isosafrole, **III**) (Scheme 1). The rhodium catalyzed hydroformylation of differently substituted aryl propenes, included **II** and **III**, was actually investigated to produce oxo-aldehydes useful as perfume components and odour boosters [20-25]. Interestingly, Hoechst studied and patented a process to produce a new fragrance by hydroformylation of sassafras oil, an essential oil rich in safrole, catalyzed by rhodium carbonyl complexes modified with triphenylphosphine [26]. The reaction conditions adopted were almost drastic (120-140 °C and 20-30 MPa of syngas): a mixture of oxo products was obtained with the linear aldehyde **IV** as the major product (50-60%) [26]. More recently, some preliminary results on safrole and isosafrole hydroformylation catalyzed by Rh/diphosphine catalysts have been described in the literature [27]: at the best, carrying out the oxo-process on safrole (**II**), catalyzed by $[Rh(COD)(OAc)]_2$ modified with the diphosphino ligand dppp, at 80 °C and 2 MPa of syngas, the conversion was about 60% and the yield of **I** did not exceed 40%. By using the more sterically hindered phosphorous auxiliary Naphos, the yield of **I** was reduced to only 5%, the linear aldehyde **IV** being the prevailing product. When isosafrole (**III**) was hydroformylated, under the same reaction conditions adopted for safrole, the major oxo-product was the branched aldehyde **V** and, at the best, the regioselectivity towards **I** reached 21%.

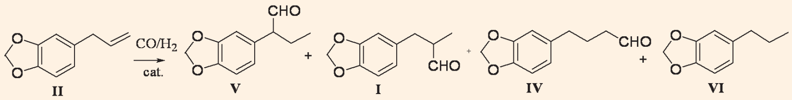
With the aim to enhance the selectivity towards the formation of this important fragrance we undertook a deeper investigation on the hydroformylation of **II** and **III** catalyzed by rhodium carbonyl complexes modified with various phopshino ligands, both in homogeneous and in aqueous biphasic system. All the hydroformylation experiments were carried out in a 150 ml stainless steel autoclave pressurized to 2-8 MPa of syngas (CO/H_2=1) and heated at 60-100 °C for the due time (see Tables 1-3). For analytical purposes the isomeric aldehydes **I**, **IV** and **V** were isolated from the reaction mixtures by flash silica gel chromatography (*n*-hexane/ether 9/1).

Results and discussion

Safrole hydroformylation

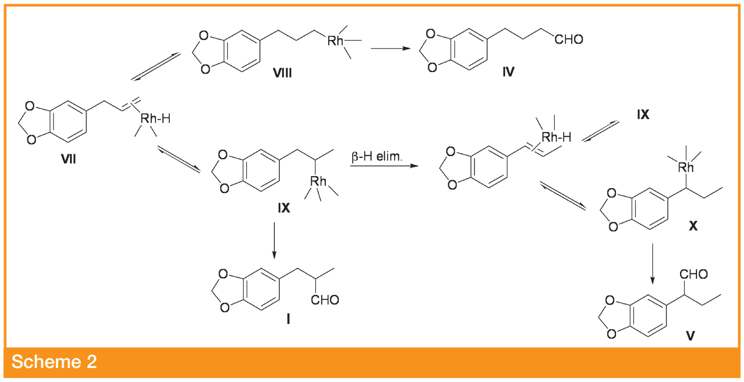
The hydroformylation of **II** is highly chemoselective, the only by-product, due to the olefinic double bond hydrogenation, being formed in a very small amount (see Table 1). The regioselectivity and the rate of the process correlates with the nature of the diphosphino ligand: in fact, we can observe that $Rh(CO)_2(acac)$, in the presence of a large excess of dppe or dppp, having bite angles near 90°, slightly favours the formation of the desired **I** (run 3 and 4 of Table 1) and the catalytic activity is depressed, while in the presence of the phosphorous auxiliary dppb (bite angle 98°), the major product is the linear aldehyde **IV** (run 5 of Table 1) with an activity and selec-

Tab. 1 - Rhodium catalyzed hydroformylation of safrole (II)

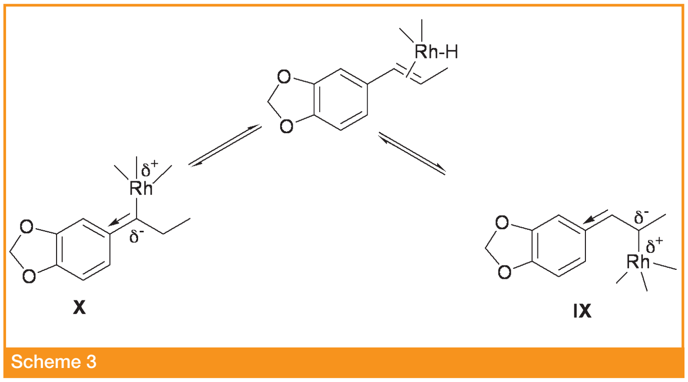


Run[a]	Catalyst	t (h)	Conv. (%)	V (%)	I (%)	IV (%)	VI (%)
1	$HRh(CO)(PPh_3)_3$	20	99.6	2.5	41.7	55.4	-
2	$Rh(CO)_2(acac)$	20	98.8	6.5	41.0	50.9	0.4
3	$Rh(CO)_2(acac)$/dppe (1/20)[b]	24	66.5	0.1	38.3	28.1	-
4	$Rh(CO)_2(acac)$/dppp (1/20)[b]	24	48.7	0.3	28.7	19.7	-
5	$Rh(CO)_2(acac)$/dppb (1/20)[b]	24	97.4	0.7	31.2	59.7	5.8

[a] General reaction conditions: substrate (8 mmol), toluene (5 ml), p(CO/H_2 1/1) = 8 MPa, T 80 °C, substrate/catalyst = 1,000 (molar ratio); [b] dppe = 1,2 bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, [Rh]/phosphine (molar ratio)



Scheme 2



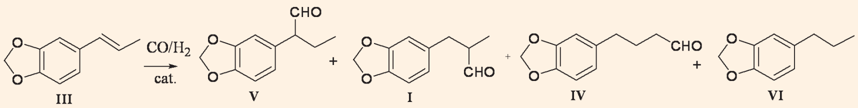
Scheme 3

tivity of the catalyst almost the same as that of monodentate triphenylphosphine. This result could be explained by the fact that by increasing flexibility of the ligand backbone in dppb vs. dppe and dppp raises the chance of an arm-off η^1 coordination [28]. It is interesting to note the formation, even if in a very small amount, of the isomeric aldehyde **V**. A plausible explanation could be given by supposing the initial formation of the π rhodium complex **VII** that, according to the generally accepted mechanism of the rhodium-catalyzed hydroformylation [3], generates both the primary and the secondary alkyl rhodium intermediates **VIII** and **IX**, respectively. The secondary alkyl rhodium specie **IX** could undergo a α-hydride elimination which brings to the σ complex **X** that under oxo conditions generates the branched aldehyde **V** (Scheme 2).

Isosafrole hydroformylation

Compound **III** was hydroformylated in the presence of rhodium carbonyl complexes modified with both mono- and bidentate phosphino ligands and at different experimental conditions. The data reported in Table 2 show that also in this case the regioselectivity of the reaction is strongly influenced by the nature of the phosphorous auxiliary. In fact, the branched aldehyde **V** is the major oxo-product when the hydroformylation experiments are carried out in the presence of PPh_3 or dppb. The prevalence of this isomer is probably due to the preferential formation of the σ-alkyl intermediate **X** stabilized by the delocalisation effect exerted by the aromatic ring in α-position to the carbon atom with a partial negative charge [29] (Scheme 3). Very interestingly, when the oxo-process is carried out in the presence of Xantphos, a diphosphine with a rigid backbone and a ligand bite angle near 111°, at lower pressure, the aldehyde **V** is produced in much lower amounts and the prevailing oxo-product is the less sterically hindered aldehyde **I**, as expected in accordance with other literature data [28, 30-31]. However a dramatic effect on the regioselectivity was observed changing the pressure: by increasing the syngas pressure from 2 to 8 MPa the regioselectivity towards **I** strongly decreased and the prevailing oxo-product was again the aldehyde **V** (run 4 vs run 5 of

Tab. 2 - Rhodium catalyzed hydroformylation of isosafrole (III)



Run[a]	Catalyst	t (h)	Conv. (%)	V (%)	I (%)	IV (%)	VI (%)
1	$HRh(CO)(PPh_3)_3$	18	100.0	54.1	36.0	2.5	7.4
2	$HRh(CO)(PPh_3)_3/PPh_3$ (1/20)[b]	21	97.2	61.3	32.1	1.6	2.2
3	$Rh(CO)_2(acac)$/dppb (1/4)[b]	24	99.2	62.5	32.4	2.1	2.2
4	$Rh(CO)_2(acac)$/Xantphos (1/4)[b,c]	45	74.0	51.3	21.3	-	1.4
5	$Rh(CO)_2(acac)$/Xantphos (1/4)[b,c,d]	48	67.5	15.5	29.4	20.6	2.0
6	$Rh(CO)_2(acac)$/Xantphos (1/8)[b,c,d]	48	17.9	1.6	11.2	0.9	4.2

[a]General reaction conditions as Table 1, if not otherwise specified; [b][Rh]/phosphine (molar ratio); [c]Xantophos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; [d]the temperature was 100 °C and the syngas pressure was 2 MPa

Tab. 3 - Rhodium catalyzed hydroformylation of safrole (II) and isosafrole (III) in aqueous biphasic medium

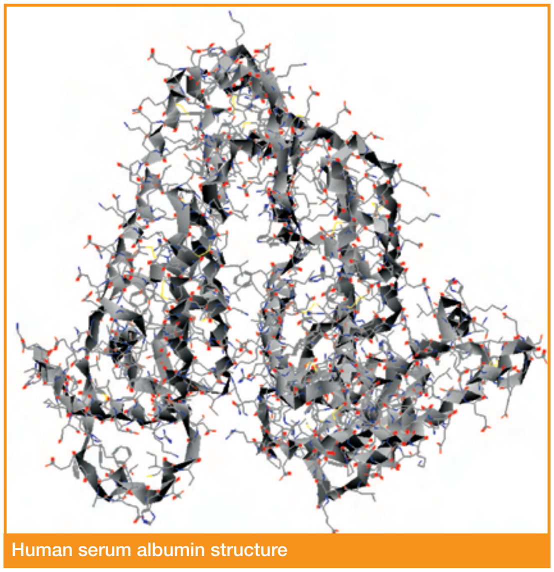
Run[a]	Catalyst[b]	Substrate	T (°C)	t (h)	Conv. (%)	V (%)	I (%)	IV (%)	VI (%)
1	$Rh(CO)_2(acac)$/TPPTS (1/6)[c]	II	80	24	99.7	14.5	44.3	40.9	-
2	$Rh(CO)_2(acac)$/HSA	II	60	6	7.0	-	3.5	3.5	-
3	$Rh(CO)_2(acac)$/HSA	II	60	24	99.0	-	45.0	51.0	3.0
4	$Rh(CO)_2(acac)$/TPPTS (1/6)[c]	III	80	24	99.9	72.6	27.2	-	-
5	$Rh(CO)_2(acac)$/HSA	III	60	6	5.0	1.3	3.7	-	-
6	$Rh(CO)_2(acac)$/HSA	III	60	24	100.0	25.0	75.0	-	-

[a]General reaction conditions: substrate (8 mmol), toluene/water (2 ml/4 ml), p(CO/H_2 1/1) = 8 MPa, substrate/catalyst = 1,000 (molar ratio) Rh/HSA = 60 (molar ratio); [b]TPPTS = triphenylphosphine-3,3',3"-trisulfonic acid trisodium salt; HSA = human serum albumin; [c][Rh]/phosphine (molar ratio)

Table 2). This effect could be explained by supposing an arm-off η^1 coordination of the ligand because of a competitive coordination of CO on the rhodium atom. Finally, the reaction rate of the experiment carried out in the presence of higher quantity of Xantphos was strongly depressed (run 6 of Table 2), even if the selectivity towards **I** reached about 82%. It is then to underline that unfortunately, the catalytic system Rh/Xantphos promotes also the formation of the linear aldehyde **IV** (Scheme 3).

Aqueous biphasic hydroformylation of safrole and isosafrole

We also tried to carry out the hydroformylation reaction 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. In particular, the rhodium catalyzed aqueous biphasic hydroformylation is a well established industrial process producing about 600,000 t/a of butyraldehyde so combining the industrial requirement with the environmental benefit [32]. Accordingly, we subjected both **II** and **III** to the oxo-process (Table 3) in the presence of $Rh(CO)_2(acac)$ modified with the water soluble phosphino ligand TPPTS or with the biopolymer HSA (Figure).



Human serum albumin structure

Among the large number of the available water soluble biopolymers we have chosen HSA because it is the principal protein component of plasma, which binds and transports a wide variety of substances including metal atoms [33]. The water-soluble complex derived from the interaction between $Rh(CO)_2(acac)$ and HSA contains 89 rhodium atoms for 4 protein molecules and had previously showed to be highly efficient and chemoselective in the hydroformylation of functionalised olefins [34, 35].

The results obtained in the aqueous biphasic hydroformylation experiments were very interesting and surprising. Both the catalytic systems Rh/TPPTS and Rh/HSA showed to be very active

Sintesi di fragranze tramite idroformilazione di safrolo e isosafrolo

RIASSUNTO

È stato effettuato uno studio approfondito sulla reazione di idroformilazione del safrolo e dell'isosafrolo finalizzato all'individuazione delle migliori condizioni per ottenere miscele di fragranze, di potenziale interesse applicativo, con un alto contenuto di Helional. È stato realizzato sull'isosafrolo un processo bifasico (toluene/acqua), utilizzando un catalizzatore riciclabile a base di Rh nanostrutturato associato a sieroalbumina umana che ha condotto a una nuova fragranza aldeidica, contenente circa il 75% di 3-benzo[1,3]diossol-5-il-2-metil-propionaldeide.

and chemoselective, but with a strongly different or opposite regioselectivity. Actually the hydroformylation of **II**, catalyzed by $Rh(CO)_2(acac)$/TPPTS, affords an almost relevant amount of the branched aldehyde **V** (about 15%) (run 1 of Table 3) while this isomer is absent with the other catalytic system. In any case, in the presence of both Rh/TPPTS and Rh/HSA the regioselectivity towards **I** remains rather low, not exceeding 47% (run 3 of Table 3). More stimulating results were obtained in the hydroformylation of **III**. In fact, we observed that, while the catalytic system $Rh(CO)_2(acac)$/TPPTS promotes the prevailing formation of the aldehyde **V** (run 4 of Table 3), the same rhodium carbonyl complex, modified with HSA, brings to a complete substrate conversion, with the formation of 75% of the desired **I** (run 6 of Table 3). Probably, the biopolymer acts as a matrix for the transition metal catalyst and the access of the substrate is constrained by the polymer backbone and site geometry, so favouring the formation of the less hindered reaction product. This water soluble catalytic system was noteworthy recycled five times and its activity maintained practically unchanged with no leaching of the metal, so to suggest a potential use for an industrial process.

Conclusive remarks

This study shows that according to the reaction conditions and the reagents used, it is possible to obtain mixtures of fragrances with different amount of aldehydic odorants and variety of fragrance notes. In one case a high content of the preferred Helional, never obtained previously with this type of reaction, was achieved and the process conditions appear valuable for a potential scaling-up.

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