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Synthesis of 2-chromanol by hydroformylation of 2-hydroxystyrene derivatives

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Abstract

2-Benzyloxy- and 2-tosyloxystyrene were hydroformylated under different reaction conditions with the aim to obtain the corresponding linear aldehydes, valuable intermediates to 2-chromanol, a structural moiety present in several interesting therapeutically active molecules. The best results were obtained by using the catalytic precursor $Pt(Xantphos)Cl_2$ in toluene or the water-soluble catalytic system $Rh(CO)_2acac/Xantphos(SO_3Na)_2$ in the biphasic medium water/toluene. Rather good regioselectivities were also achieved employing the unmodified complex $Rh_4(CO)_{12}$ at high temperature and low pressure for very short reaction times: unfortunately the chemoselectivity of the process was not satisfactory, due to the extensive formation of the substrate hydrogenation product.

Keywords: Hydroformylation; Rhodium complexes; Platinum complexes; Hydroxystyrene; 2-Chromanol

1. Introduction

Several therapeutically active molecules as the antipsycotic *Sarizotan* [1], the neuroprotectant *Repinotan* [2] and others [3,4] embody in their framework structural moieties deriving from 3,4-dihydrobenzopyran (chroman). In this connection we focused our attention on 2-chromanol (**II**) as one of the most interesting precursors of the above class of pharmaceuticals. This structurally simple intermediate is prepared in good yields by several methods: however, none of them seems to be fully suitable for a semi-industrial scale production. A survey of the literature reveals that 2-chromanol is generally obtained from easily accessible coumarin or dihydrocoumarin by reduction under various experimental conditions [5–7]. However, this reduction requires low temperature reaction ($<-20\,^{\circ}C$) with DIBAL, preferential reagent but very sensitive towards air oxidation and moisture [8]; it is possible to work at higher temperature by using more expensive metal hydrides or homogeneous metal catalysts but very often a substantial amount of *o*-(3-hydroxypropyl)phenol is produced as by-product [9].

In principle, the hydroformylation of 2-hydroxystyrene (**I**) could represent a convenient route to

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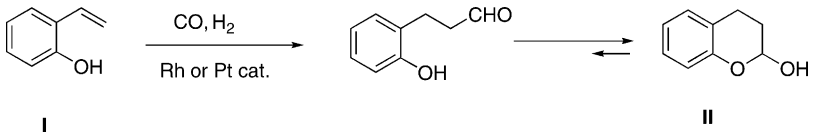


Scheme 1.

2-chromanol (**II**), if the linear aldehyde 3-(2-hydroxyphenyl)propanal is produced with high regioselectivity (Scheme 1).

The substrate **I** is accessible through several expeditous experimental procedures that could be suitable for industrial production, especially by using continuous processes and heterogeneous acid catalysts. They include the alkylation reaction of phenol with ethylene oxide promoted by an acid catalyst [10], the condensation between phenol and vinyl acetate under similar conditions [11], the rearrangement of 2-phenoxyethanol in the presence of sulfuric acid [12], the decarboxylation of *o*-hydroxycinnamic acid [13] and the pyrolysis of 2,4-dimethyl-1,3-benzodioxane [14]. As laboratory procedure, 2-hydroxystyrene may be produced by Wittig reaction of salicylaldehyde and methylene triphenylphosphorane [15]. In all cases, an extensive amount of dimerization and polymerization by-products is formed, due to the rather low stability of the hydroxy olefin **I**, even at room temperature. The formation of the dimer is very likely due to a Diels–Alder reaction between the obtained 2-hydroxystyrene and the diene derivative 2-ethylidencyclohexadienon, a product formed by 1,5-sigmatropic transposition of 2-hydroxystyrene [16] (Scheme 2).

In this paper we wish to describe the results obtained during our study on the hydroformylation of 2-hydroxystyrene derivatives catalyzed by different rhodium and platinum carbonyl complexes with the aim to obtain **II** in satisfactory yield.

2. Experimental

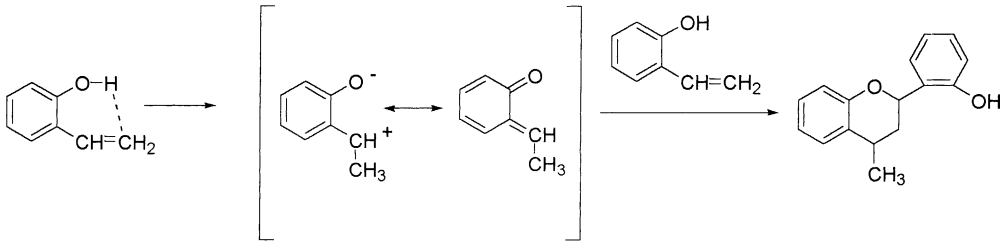
2.1. Materials

$HRh(CO)(PPh_3)_3$ [17], $[Rh(COD)Cl]_2$ [18], $Pt(COD)Cl_2$ [19], $(DPPB)PtCl_2$ [20] and $Pt(Xantphos)Cl_2$ [21] were prepared following well-known procedures. $Rh(CO)_2acac$ was purchased from Aldrich and TPPTS from Fluka. Xantphos was prepared as described in the literature [22]. 2,7-bis$(SO_3Na)_2$Xantphos was a generous gift from Prof. P. van Leeuwen. Merck silica gel 60 (240–400 mesh) was used for column chromatography. NMR spectra were measured for solutions in $CDCl_3$ using a Bruker AC 200 spectrometer operating at 200 MHz. Solvents were purified following well-known procedures [23].

2.2. Synthesis of 2-benzyloxystyrene (*IV*)

2.2.1. 2-Benzyloxybenzaldehyde [24]

A mixture of salicylaldehyde (10.0 g, 82.0 mmol), benzyl bromide (14.02 g, 82.0 mmol) and K_2CO_3 (12.46 g, 90.2 mmol) in anhydrous acetone (110 ml)



Scheme 2.

was heated at reflux for 2 h, after which it was cooled to RT. The mixture was filtered and the solvent distilled in vacuo. The obtained crude oil was purified by distillation at reduced pressure (135 °C/0.06 mmHg), so furnishing 2-benzyloxybenzaldehyde as a colorless oil (95% yield). ^{1}H NMR δ: 10.55 (s, 1H), 7.71–7.02 (m, 9H), 5.21 (s, 2H). MS: *m/e* 212 (M^+), 183, 121, 91, 65, 39. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.69. Found: C, 78.98; H, 5.67.

2.2.2. 2-Benzyloxystyrene (IV) [25]

A solution of 2-benzyloxybenzaldehyde (4.87 g, 23.0 mmol) in anhydrous diethyl ether (30 ml) was added dropwise, under a nitrogen purge, to a mixture of methyltriphenylphosphonium bromide and sodium amide (10.0 g, 24.0 mmol), in anhydrous diethyl ether (60 ml). The reaction mixture was stirred at room temperature overnight, then filtered and the solvent eliminated in vacuo. Pure **IV** was obtained by flash chromatography (*n*-hexane/diethyl ether 7/3) as a colorless oil in 90% yield. ^{1}H NMR δ: 7.63–6.99 (m, 9H), 5.86 (dd, $J_{\mathrm{H-H}\,trans} = 17.7$, $J_{\mathrm{H-H}\,gem} = 1.22$, 2H), 5.35 (dd, $J_{\mathrm{H-H}\,cis} = 11.0$, $J_{\mathrm{H-H}\,gem} = 1.2$, 1H), 5.17 (s, 2H). MS: *m/e* 210 (M^+), 119, 91, 65, 51, 39. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.85; H, 6.72.

2.3. Synthesis of 2-tosyloxystyrene (V)

2.3.1. 2-Tosyloxyacetophenon [26]

A mixture of 2-hydroxyacetophenon (10.0 g, 73.5 mmol), *p*-toluenesulfonylchloride (16.57 g, 86.9 mmol) and K_2CO_3 (20.15 g, 146.0 mmol) in anhydrous acetone (150 ml) was heated at reflux for 5 h, and then cooled to RT. The mixture was filtered and the solvent distilled in vacuo. The obtained crude oil was purified by flash chromatography (*n*-hexane/diethyl ether 7/3), so furnishing 2-tosyloxyacetophenon as a colorless oil (86% yield). ^{1}H NMR δ: 7.72–7.10 (m, 8H), 2.53 (s, 3H), 1.57 (s, 3H). MS: *m/e* 290 (M^+), 275, 248, 155, 139, 121, 91, 65, 43. Anal. Calcd for $C_{15}H_{14}SO_4$: C, 62.05; H, 4.86. Found: C, 61.81; H, 4.84.

2.3.2. (2-Tosyloxy)-1-phenylethanol [27]

A solution of $NaBH_4$ (0.75 g, 19.7 mmol) in H_2O (10 ml) and 1 M NaOH (1 ml) was dropwise added to a solution of 2-tosyloxyacetophenon (10.0 g, 34.5 mmol) in methanol (165 ml). The reaction mixture was stirred at room temperature for 1 h, then diluted with water and extracted with diethyl ether. The organic phase was dried on Na_2SO_4 and the solvent distilled in vacuo: (2-tosyloxy)-1-phenylethanol was obtained in almost quantitative yield. ^{1}H NMR δ: 7.82–6.86 (m, 8H), 5.15 (q, $J = 6.1$, 1H), 2.49 (s, 3H), 1.42 (d, $J = 6.7$, 3H). MS: *m/e* 292 (M^+), 274, 248, 155, 119, 91, 65, 43, 39. Anal. Calcd for $C_{15}H_{16}SO_4$: C, 61.62; H, 5.52. Found: C, 61.44; H, 5.50.

2.3.3. 2-Tosyloxystyrene (V)

A mixture of (2-tosyloxy)-1-phenylethanol (10.0 g, 32.4 mmol), *p*-toluenesulfonic acid (1.0 g, 5.3 mmol) and a small amount of hydroquinone in benzene (100 ml) was heated at reflux for 5 h. The solution was then cooled to RT, washed with a 10% Na_2CO_3 solution and then with water. The organic phase was dried on Na_2SO_4, filtered and the solvent distilled in vacuo. Pure **V** was obtained as a white solid by flash chromatography (*n*-hexane/diethyl ether 7/3) in about 40% yield (mp 41.5–42 °C). ^{1}H NMR δ: 7.79–7.07 (m, 8H), 6.7 (dd, $J_{\mathrm{H-H}\,trans} = 17.7$, $J_{\mathrm{H-H}\,cis} = 11.0$, 1H), 5.6 (dd, $J_{\mathrm{H-H}\,trans} = 17.7$, $J_{\mathrm{H-H}\,gem} = 1.2$, 1H), 5.15 (dd, $J_{\mathrm{H-H}\,cis} = 11.0$, $J_{\mathrm{H-H}\,gem}$=1.2, 1H), 1.55 (s, 3H). MS: *m/e* 274 (M^+), 155, 119, 91, 77, 65, 39. Anal. Calcd for $C_{15}H_{14}SO_3$: C, 65.67; H, 5.14. Found: C, 65.80; H, 5.15.

2.4. Rhodium catalyzed hydroformylation

A 150 ml stainless steel reaction vessel was charged under a nitrogen purge with 0.0018 mmol of $Rh(CO)_2$acac, 0.0039 mmol of Xantphos and 3 ml of anhydrous toluene. The reactor was then pressurized with 10 atm of syngas ($CO/H_2 = 1$), heated at 60–100 °C for 2 h, then cooled to RT and the gases vented off. Olefin **IV** or **V** (1.8 mmol) dissolved in 2 ml of toluene was added to the catalytic solution under nitrogen and then the autoclave was pressurized to 10–100 atm of syngas ($CO/H_2 = 1$) and heated at 60–100 °C for the due time (see Tables 1 and 2). For analytical purposes the desired linear aldehyde 3-(2-tosyloxyphenyl)propanal (**VII**) or 3-(2-benzyloxyphenyl)propanal (**IX**) was recovered from the reaction mixture by flash silica gel chromatography (*n*-hexane/ether 8/2).

Table 1
Hydroformylation of 2-tosyloxystyrene (**V**) catalyzed by rhodium/Xantphos complexes

Run	Catalytic precursor	Temperature (°C)	*t* (h)	*P* (atm)	Conversion (%)[a]	Linear to branched aldehyde (%)[a]
1	$HRh(CO)(PPh_3)_3$	60	4	100	95	5.5/94.5
2[b]	$HRh(CO)(PPh_3)_3$/L	60	4	100	18.7	17.6/82.4
3[c]	$HRh(CO)(PPh_3)_3$/L	60	18	100	8.5	57.8/42.2
4	$Rh(CO)_2$acac/L	60	24	10	6.9	70.1/29.9
5	$Rh(CO)_2$acac/L	80	4	10	7.2	69.6/30.4
6	$Rh(CO)_2$acac/L	80	24	10	88.7	69.5/30.5
7	$Rh(CO)_2$acac/L	80	24	100	99.0	18.8/81.2
8	$Rh(CO)_2$acac/L	100	24	100	>99	19.6/80.4
9	$Rh(CO)_2$acac/L	100	24	10	92.0	70.9/29.1

Reaction conditions: substrate = 1.8 mmol; substrate-to-catalyst (molar ratio) = 1000; ligand/Rh (molar ratio) = 2.2/1; L = Xantphos; toluene = 5 ml; $p(CO) = p(H)_2$.
[a] Determined by GC, only aldehyde products were present in the reaction mixture.
[b] Ligand/Rh (molar ratio) = 3/1.
[c] Ligand/Rh (molar ratio) = 9/1.

Compound **VII**. ^{1}H NMR δ: 9.74 (t, $J = 1.8$, 1H), 7.80–6.99 (m, 8H), 2.86–2.78 (m, 2H), 2.72–2.64 (m, 2H), 2.47 (s, 3H). MS: *m/e* 304 (M^+), 155, 149, 121, 91, 65, 39. Anal. Calcd for $C_{16}H4_{16}SO_4$: C, 63.14; H, 5.29. Found: C, 62.95; H, 5.27.

Compound **IX**. ^{1}H NMR δ: 9.70 (t, $J = 1.8$, 1H), 7.70–6.92 (m, 9H), 5.15 (s, 2H), 2.80–2.72 (m, 2H), 2.66–2.54 (m, 2H). MS: *m/e* 240 (M^+), 184, 149, 120, 91, 65, 39. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.69; H, 6.69.

2.5. Hydroformylation of 2-benzyloxystyrene (*IV*) catalyzed by $Rh_4(CO)_{12}$

A solution of **IV** (0.52 g, 2.5 mmol) and $Rh_4(CO)_{12}$ (2.0 mg, 0.0027 mmol) in benzene (5 ml) was introduced by suction into an evacuated 25 ml stainless steel autoclave equipped with a magnetic stirrer. The reactor was transferred to an oil bath, and carbon monoxide was introduced; the autoclave was then heated to 130 °C, and hydrogen was rapidly introduced

Table 2
Hydroformylation of 2-benzyloxystyrene (**IV**) catalyzed by $Rh(CO)_2$acac/Xantphos complexes

Run	Ligand	*P* (atm)	Temperature (°C)	*t* (h)	Conversion (%)[a]	Linear to branched aldehyde (%)[a]
1	Xantphos	20	60	72	8.8	70.1/29.9
2	Xantphos	100	60	72	25.9	20.2/79.8
3	Xantphos	10	80	24	73.0	70.7/29.3
4	Xantphos	20	80	24	85.4	52.0/48.0
5	Xantphos	100	80	24	99.0	16.9/83.1
6[b]	Xantphos	10	80	24	62.0	67.4/32.6
7[b]	Xantphos	10	80	72	99.0	64.7/35.6
8	DPPB	10	80	24	76.6	27.4/72.6
9	DPPB	100	80	24	99.8	12.2/87.8

Reaction conditions: substrate = 1.8 mmol; substrate-to-catalyst (molar ratio) = 1000; ligand/Rh (molar ratio) = 2.2/1; toluene = 5 ml. DPPB = 1,4-bis(diphenylphosphino)butane.
[a] Determined by GC, only aldehyde products were present in the reaction mixture.
[b] Ligand/Rh (molar ratio) = 10/1.

Table 3
Hydroformylation of 2-benzyloxystyrene (**IV**) catalyzed by $Rh_4(CO)_{12}$

Run	$p(H_2)$	$p(CO)$	Conversion (%)[a]	Aldehyde yield (%)[a]	Hydrogen yield (%)[a]	Linear to branched aldehyde (%)[a]
1	10	10	75.1	40.6	34.5	72.2/27.8
2	40	10	98.3	60.0	38.3	72.2/27.8
3	20	10	95.4	73.2	22.2	79.0/21.0
4[b]	15	5	83.1	31.0	52.1	71.3/28.7
5[c]	40	10	94.0	26.6	67.4	67.6/32.4

Reaction conditions: substrate = 2.5 mmol; substrate-to-Rh (molar ratio) = 234/1; benzene = 5 ml; reaction time = 10 min; temperature = 140 °C.
[a] Determined by GC.
[b] Reaction time = 12 min.
[c] Temperature = 150 °C.

up to the desired pressure (CO/H_2 = 1:1). After 10 min the reaction was cooled and the gases vented off. The degree of conversion was measured by GLC, using *o*-xylene as an internal standard (See Table 3).

2.6. Hydroformylation in aqueous biphasic medium

In a Schlenk tube $[Rh(COD)Cl]_2$ (1.2 mg, 0.0024 mmol) and TPPTS (6.0 mg, 0.0106 mmol) were dissolved under nitrogen in H_2O (4 ml). The Schlenk tube was transferred to a 150 ml stainless steel autoclave under nitrogen, pressurized to 20 atm with syngas (CO/H_2 = 1:1) and heated at 100 °C for 2 h. The reactor was then cooled to RT and the residual gases released. A solution of **IV** (1.0 g, 4.8 mmol) in toluene (6 ml) was then added to the aqueous solution and the autoclave pressurized to the desired pressure with syngas (CO/H_2 = 1) and heated at 100 °C for 24 h (see Table 4). The reactor was then cooled to RT and the gases vented off; the organic phase was separated, dried on $MgSO_4$ and toluene removed in vacuo: the aldehyde **IX** was recovered and identified as previously described.

2.7. Platinum catalyzed hydroformylation

A 150 ml stainless steel reaction vessel was charged under a nitrogen purge with 0.0036 mmol of $Pt(Xantphos)Cl_2$, 0.0036 mmol of $SnCl_2{\cdot}H_2O$ and

Table 4
Hydroformylation of 2-benzyloxystyrene (**IV**) in the water/toluene biphasic system catalyzed by water-soluble rhodium carbonyl complexes

Run	Catalytic precursor	Ligand	Conversion (%)[a]	Linear to branched aldehyde (%)[a]
1[b]	$[Rh(COD)Cl]_2$	TPPTS	99.0	30.0/70.0
2[c]	$[Rh(COD)Cl]_2$	TPPTS	5.8	65.9/34.1
3[d]	$[Rh(COD)Cl]_2$	TPPTS	3.8	71.7/28.3
4[b]	$Rh(CO)_2acac$	TPPTS	99.0	27.0/73.0
5[b]	$Rh(CO)_2acac$	L	24.3	59.5/40.5
6[e]	$Rh(CO)_2acac$	L	55.4	85.6/14.4

Reaction conditions: substrate = 1.8 mmol; substrate-to-catalyst (molar ratio) = 1000; $p(CO) = p(H_2)$ = 5 atm; temperature = 100 °C; reaction time = 24 h; TPPTS = triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt. L = $Xantphos(SO_3Na)_2$.
[a] Determined by GC, only aldehyde products were present in the reaction mixture.
[b] Ligand/Rh (molar ratio) = 2.2/1.
[c] Ligand/Rh (molar ratio) = 6.6/1.
[d] Ligand/Rh (molar ratio) = 10/1.
[e] Ligand/Rh (molar ratio) = 6.6/1; reaction time = 240 h.

Table 5
Hydroformylation of 2-tosyloxystyrene (**V**) catalyzed by $Pt/SnCl_2$ complexes

Run	Catalytic precursor	Conversion (%)	Aldehyde yield (%)[a]	Hydrogen yield (%)[a]	By-products (%)[a]	Linear to branched aldehyde (%)[a]
1[b]	(DPPB)$PtCl_2$	99.0	35.3	43.2	20.5	59.2/40.8
2[b]	(COD)$PtCl_2$/L	99.0	61.6	2.3	35.1	87.1/12.9
3[c]	Pt(Xantphos)Cl_2	66.3	39.9	20.4	6.0	84.7/15.3
4[c,d]	Pt(Xantphos)Cl_2	85.5	64.3	13.2	8.0	>99/<1

Reaction conditions: substrate = 1.8 mmol; substrate-to-catalyst (molar ratio) = 500; temperature = 80 °C; reaction time = 24 h; toluene = 5 ml; $p(CO) = p(H_2) = 5$ atm; L = Xantphos; L/Pt (molar ratio) = 2.2/1. All the experiments have been carried out in the presence of $SnCl_2$.

[a] Determined by GC.

[b] $Pt/SnCl_2 = 1/5$ (molar ratio).

[c] $Pt/SnCl_2 = 1/1$ (molar ratio).

[d] Experiment carried out in CH_2Cl_2.

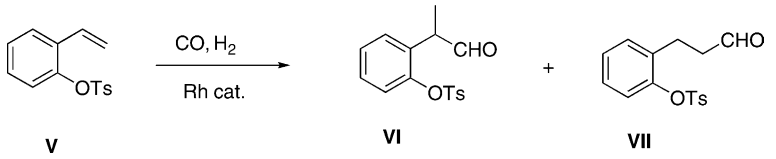
5 ml of CH_2Cl_2 and maintained under stirring for 30 min. The reactor was then pressurized to 10 atm with syngas (CO/H_2 = 1:1) and heated at 80 °C for 30 min, then cooled to RT and the gases vented off. Olefin **V** (1.8 mmol) dissolved in 2 ml of CH_2Cl_2 was added to the catalytic solution under nitrogen and then the autoclave was pressurized to 10 atm of syngas (CO/H_2 = 1:1) and heated at 80 °C for 24 h (see Table 5). The reactor was cooled to RT and the gases vented off: the aldehyde **VII** was recovered and identified as previously described.

3. Results and discussion

Hydroxystyrenes are substrates which have not attracted the interest of researchers involved in the *oxo*-process to date [28–30]. Only 3-hydroxy- and 4-hydroxystyrenes were subjected to hydroformylation and in this latter case 90% yield of 2-(4-hydroxyphenyl)propanal was reported, operating at 65 °C and 60 atm in the presence of $HRh(CO)(PPh_3)_3$ [31,32].

We prepared 2-hydroxystyrene (**I**) by decarboxylation of *o*-hydroxycinnamic acid [13b] with no more than 30% yield: owing to the pronounced tendency to thermal dimerization of **I**, we subjected it to the *oxo*-process as soon as formed. The hydroformylation experiments were carried out at 80 °C and 100 atm (CO/H_2 = 1) with a substrate to rhodium catalyst molar ratio 250/1. In the best case, using the catalytic system $[Rh(COD)Cl]_2/PPh_3$ (Rh/P = 1/3 molar ratio), the aldehyde yield reached 50% and only 5% of the desired linear aldehyde was obtained: both aldehydes were identified as the corresponding hemiacetalic forms, 3-methyl-2,3-dihydrobenzofuran-2-ol and 2-chromanol, respectively. Even operating as carefully as possible, it was impossible to avoid a very extensive substrate dimerization (>40%). When the reaction was carried out in the aqueous biphase system (water/cyclohexane) in the presence of $[Rh(COD)Cl]_2$/TPPTS (Rh/P = 1/3 molar ratio) using the same reaction conditions, the aldehyde yield was 40% and the regioselectivity towards the linear isomer was unsatisfactory, reaching only 16%; moreover, also in this case, about 30% of dimer was formed. In any case, carrying out the *oxo*-experiments in both homogeneous and in biphasic aqueous system the results were not always reproducible, due to the high instability of 2-hydroxystyrene (**I**) even at room temperature.

To avoid all the problems connected with the formation of the dimeric product deriving from 2-hydroxystyrene (**I**), we prepared its derivatives 2-benzyloxy (**IV**) and 2-tosyloxystyrene (**V**), having the phenol group protected. We chose these relatively bulky protecting groups hoping that their steric hindrance would contribute to direct the *oxo*-process preferentially towards the desired linear aldehydes **VII** and **IX**. Whereas compound **V** was obtained from 2-hydroxyacetophenone in three simple steps in about 40% overall yield, **IV** was prepared in 80–85% yield from salicylaldehyde by Wittig reaction (see Section 2).



Scheme 3.

The hydroformylation reactions on substrates **IV** and **V** were carried out between 60 and 100 °C at different pressure using rhodium complexes such as $Rh(CO)_2$acac and $HRh(CO)(PPh_3)_3$ modified with Xantphos as catalytic systems. Xantphos, this large bite-angle ligand, is known to promote the preferential formation of the linear aldehyde in the rhodium catalyzed hydroformylation of 1-alkenes including styrene [29,33]. A first set of *oxo*-reactions was carried out on substrate **V** and the results are reported in Table 1 (Scheme 3).

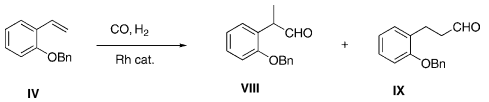
As expected, the chemoselectivity of all *oxo*-experiments was practically quantitative. The presence of the external ligand Xantphos considerably reduced the reaction rate: therefore, it appeared rather difficult to find a combination of experimental conditions useful to achieve high aldehyde yields.

As for the regioselectivity to linear aldehyde is concerned, it was very low if the catalytic system was not modified with Xantphos (run 1), and very similar to that typical of unsubstituted styrene.

Xantphos generally promoted the formation of the desired aldehyde **VII**; however, only at low pressure and 80 °C at a ligand-to-rhodium molar ratio = 2.2 it was possible to reach regioselectivity values up to 70% (run 6). The increase of the pressure exerted a strong negative influence on the yield of **VII** (compare runs 6 and 7).

Analogous results were found in the hydroformylation of 2-benzyloxystyrene (**IV**) effected under similar reaction conditions (Table 2). The figures reported in Table 2 confirm that the total pressure of the catalytic process is the crucial factor in determining the regioselectivity of the *oxo*-reaction catalyzed by Rh(I)/Xantphos complexes (Scheme 4).

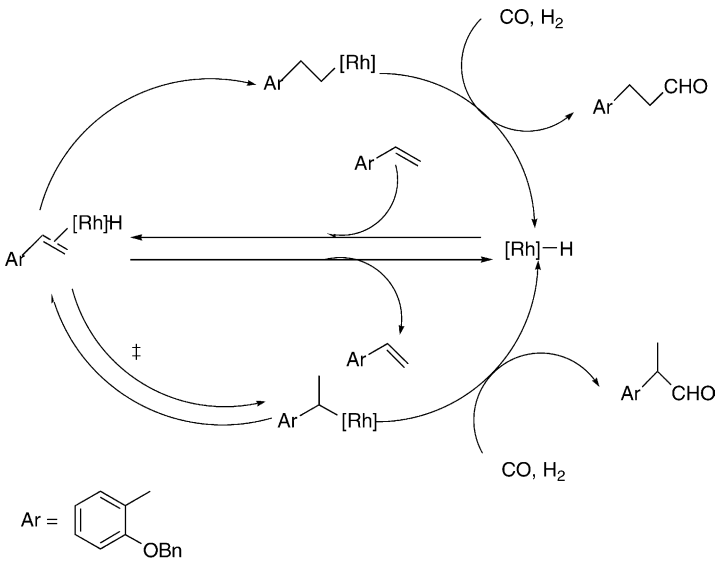
Again, only Xantphos was able to drive the regioselectivity up to 70%, while DPPB containing complexes produced a proportion of linear aldehyde not exceeding 27% (run 8).



Scheme 4.

A different approach to the preparation of the linear aldehyde **IX** from **IV** relies on the use of an unmodified rhodium catalytic precursor, for instance $Rh_4(CO)_{12}$, at high temperature (130–140 °C) and low pressure of synthesis gas. The results obtained in a set of *oxo*-experiments are collected in Table 3: high substrate conversions (75–98%) were achieved carrying out the reaction at 140 °C for very short reaction times (10 min) and the linear aldehyde resulted the prevailing product (linear to branched isomer = 72/28). The chemoselectivity of the reaction was, however, not satisfactory due to the formation of considerable amount of the substrate hydrogenation product. The best outcomes were obtained working at 140 °C and 20 atm H_2 and 10 atm CO (run 3). By decreasing CO pressure and increasing temperature (run 5), the proportion of the substrate hydrogenation product remarkably grew, whereas the regioselectivity resulted practically unaffected.

The hydroformylation of substrate **IV** catalyzed by $Rh_4(CO)_{12}$ without employing any external ligand afforded high proportion of linear aldehyde with nearly quantitative conversions and very short reaction times (Table 3). The co-production of high amount of reduction compound strongly lowered the aldehyde **IV** yield. The remarkable increasing of the proportion of linear *oxo*-product by increasing the reaction temperature and decreasing the gas pressure is very likely due to the complete reversibility step in the formation of isomeric σ-alkylrhodium and σ-acylrhodium species under these reaction conditions. Indeed, it was demonstrated that the branched σ-alkylrhodium



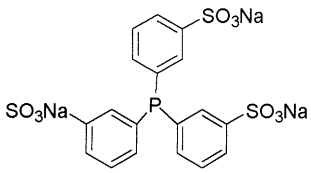
Scheme 5.

complex in both styrene and 1-hexene hydroformylation undergoes more easily β-hydride elimination than the linear one [34]. Thus, one can assume that the branched σ-alkylrhodium intermediate species, favored by electronic effect, is transformed into the linear σ-alkylcomplex, which affords the linear aldehyde, being more reactive towards the CO migratory insertion and the subsequent hydrogen oxidative addition (Scheme 5).

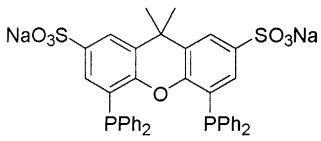
Rather promising results were obtained in the hydroformylation of substrate **IV** in the aqueous biphasic reaction medium water/toluene using water-soluble rhodium carbonyl complexes such as $[Rh(COD)Cl]_2$/TPPTS, $Rh(CO)_2(acac)$/TPPTS and $Rh(CO)_2(acac)$/Xantphos$(SO_3Na)_2$ as catalysts at 100 °C and 10 atm ($CO/H_2 = 1$) (Fig. 1).

The data collected in Table 4 demonstrate that it is possible to obtain the linear aldehyde **IX** in more than 70% yield using a nor chelating ligand like TPPTS, but only at very low conversion degrees and at high metal-to-ligand molar ratio (run 3).

Xantphos$(SO_3Na)_2$ promoted the highest regioselectivity value: more than 85% of aldehyde **IX** was formed at 55% conversion. The excess ligand, however, reduced considerably the reaction rate.

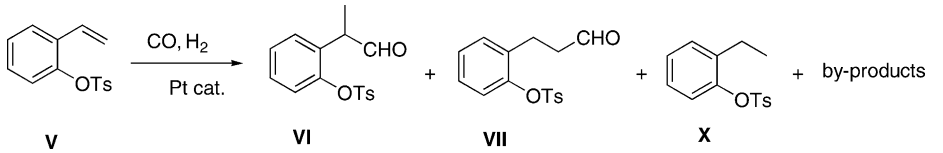


TPPTS



2,7-bis$(SO_3Na)_2$Xantphos

Fig. 1. Water-soluble phosphine ligands.



Scheme 6.

It is known that catalytic systems based on platinum/$SnCl_2$ complexes are able to promote the formation of linear *oxo*-aldehydes even in the absence of phosphine ligands [35]. On the basis of these interesting results, we carried out some *oxo*-experiments using olefin **V** as the substrate. The data reported in Table 5 clearly show that the chemoselectivity of the reaction catalyzed by Pt(II)/$SnCl_2$ complexes is very low due to the formation of both 2-tosyloxyethylbenzene (**X**) and high boiling by-products, likely olefin dimers and oligomers (Scheme 6). The linear aldehyde selectivity was never below 50% and it reached very high values ranging from 85 to >99% when the catalytic complex Pt(Xantphos)Cl_2 was used.

Finally, 2-chromanol (**II**) can be easily obtained in almost quantitative yield by deprotecting the phenol moiety of aldehyde **VII** [36] or **IX** [37], followed by spontaneous cyclization of the formed 3-(2-hydroxyphenyl)propanal to the target compound.

4. Conclusions

2-Hydroxystyrene is a thermally unstable compound, therefore it brings about a considerable amount of undesired polymerization products during the hydroformylation under standard *oxo*-conditions. Much better chemoselectivity results were obtained using a protected hydroxystyrene, such as 2-tosyloxy- or 2-benzyloxystyrene, as the substrate for the *oxo*-reaction.

However, we were not able to obtain more than 70% of the desired linear aldehydes **VII** and **IX** using $Rh(CO)_2$acac with excess Xantphos as catalytic system at 80 °C and 10 atm pressure. This regioselectivity value seems to represent a threshold hard to be overcome in the hydroformylation of styrene using rhodium carbonyl complexes modified by large bite-angle diphosphine ligands.

After all, it seems more convenient to hydroformylate protected 2-hydroxystyrenes with unmodified rhodium carbonyl complexes at high temperature and low pressure, in order to obtain up to 79% of the linear aldehyde **IX**: in this way we can avoid the use of rather expensive diphosphine ligands.

Rather encouraging results were obtained in the hydroformylation of 2-benzyloxystyrene (**IV**) in water/toluene biphasic system catalyzed by $Rh(CO)_2$acac modified with Xantphos $(SO_3Na)_2$, the water-soluble version of Xantphos itself. In this case up to 85% of the linear aldehyde **IX** was achieved, even if the reaction proceeded sluggishly and a large excess of the ligand was required. The best result for what regioselectivity is concerned was obtained in olefin **V** hydroformylation catalyzed by the complex Pt(Xantphos)Cl_2 in toluene. In this case, only the linear aldehyde **VII** was obtained; however, the aldehyde yield was rather low owing to the unsatisfactory chemoselectivity of the catalytic process.

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