Solid-Liquid Biphasic Hydroformylation of Olefins Catalyzed by Rhodium Carbonyl Complexes

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Abstract: Some polymer-anchored alkenes have been hydroformylated by carrying out the reaction in a high-pressure reactor equipped with a suitably designed vial. The solid substrates are converted to the corresponding *oxo*-aldehydes in high yields. In all cases the regioselectivity was strongly shifted towards the linear aldehyde when the rhodium carbonyl complex was modified with xantphos (3:1 or 4:1 P/Rh molar ratio). Treatment with 5% of trifluoroacetic acid in dichloromethane at room temperature removed quantitatively the *oxo*-product from the polymer support, which can be purified and reused.

Keywords: aldehydes; alkenes; hydroformylation; rhodium; solid-liquid biphasic catalysis; solid-phase synthesis

Introduction

Hydroformylation of olefins is one of the most industrially important reactions involving synthesis gas for the production of aldehydes and derivatives (*ca.* 7 millions ton/year): the feature which characterizes this process today relies on the fact that rhodium carbonyl complexes, generally modified with ligands such as phosphines and phosphites, are employed as catalysts to an increasing extent because they provide high reaction rates and selectivities for the formation of the desired aldehyde.[1]

Rhodium derivatives, however, are very expensive compounds: the price of this metal is currently 32.15 $/g.[2] Moreover, since the rhodium world production does not exceed 2 – 3 t/year, a number of successful methods for recycling these catalysts have been devised.

The *oxo*-process, however, is still afflicted by several practical drawbacks, mainly the technical difficulty of separating the aldehydes produced from the solvent and from the soluble catalytically active complexes. To overcome these problems, various ingenious methods have been developed, some of which have reached industrial maturity:

- immobilization of the catalytically active metals or metal derivatives on an inorganic support or matrix;[3]
- coordination of the catalytic species to a polymeric matrix containing functional groups able to interact with the transition metals;[4–7]
- application of rhodium carbonyl complexes with water-soluble ligands (mostly sodium salts of sulphonated mono- or diphosphines) able to keep the catalyst in water, so offering the outstanding possibility of carrying out the process in an aqueous biphasic system;[8,9]
- application of rhodium carbonyl complexes with suitably fluorinated ligands, which promote their solubility in perfluorinated solvents where the reaction occurs, while the *oxo*-products migrate in an immiscible organic phase (flourous biphasic catalysis, FBC);[10,11]
- employment of carbon dioxide in supercritical phase as the reaction medium and its release as a gas at the end of the process;[12–14]
- use of ionic liquids as biphasic hydroformylation media.[15–17]

Another possibility for a smooth separation of the products from the homogeneous catalyst is provided by hydroformylation of a polymer-anchored alkene, carrying out the reaction in a solid-liquid biphasic system. Only one example of this kind of catalytic process is reported in the literature: the alkene 2-methyl-12-hydroxy-1-dodecene was attached to a polystyrene-grafted Synphase™ crown through a linker formed by

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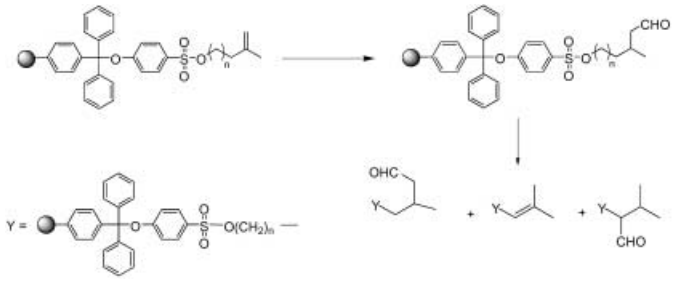
the trityl ether of *p*-hydroxybenzenesulphonic acid (Scheme 1).[18]

The hydroformylation of this anchored olefin was reported to proceed smoothly in the presence of $Rh(CO)_2(acac)$ in toluene at 40–60 °C and 40–75 atm ($CO/H_2 = 1$); using a 30 mM catalytic solution of the rhodium complex, 83% substrate conversion and 98% regioselectivity towards the useful linear *oxo*-product were claimed. This aldehyde, still linked to the polymeric support, was transformed into muscone by an intramolecular macrocyclization step. Alternatively, it can be removed from the polymer by treatment with 10% trifluoroacetic acid in dichloromethane.[18]

Our research group is involved in the preparation of biologically active compounds by using the rhodium-catalyzed hydroformylation as a key-step of the selected synthetic schemes.[19–22] In these last years we have applied the aqueous two-phase *oxo*-reaction to olefinic substrates containing functional groups using rhodium carbonyl complexes modified with easily accessible water-soluble ligands such as trisulphonated triphenylphosphine trisodium salt (TPPTS) or disulphonated xantphos disodium salt, we have obtained outstanding results producing aldehyde intermediates with high yields.[23–24] Particularly interesting is the use of hydrophilic proteins, such as seroalbumins, as rhodium ligands: these biopolymers form rather stable complexes with rhodium carbonyl precursors, which display a very high catalytic activity and exhibit peculiar selectivity properties.[25–26]



Scheme 1. First example of polymer-anchored alkene hydroformylation in a biphasic solid-liquid system.

In this context we have undertaken a study on the hydroformylation in solid liquid biphasic systems with the aim:

i) to set up this catalytic process suitably to get high yield and reproducible results;
ii) to indicate merits and limits of this reaction in view of its application to the synthesis of biologically active compounds.

Results and Discussion

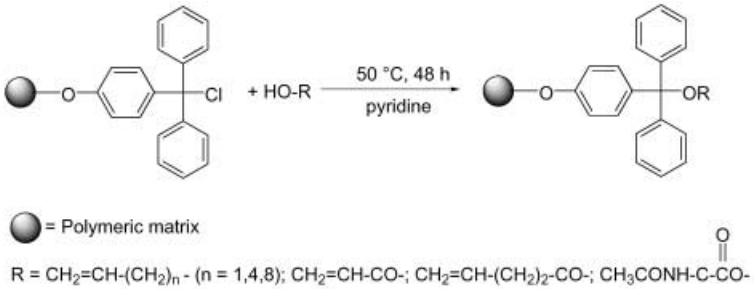
In the preparation of the substrates for hydroformylation we have used a polymeric matrix formed by a styrene-divinylbenzene copolymer (99:1) containing trityl chloride moieties as linkers. Before use the copolymer was treated with thionyl chloride in dichloromethane in the presence of pyridine to regenerate all the active sites; then it was allowed to swell by heating at 50 °C for one hour in the same solvent.[27]

Various alkenes containing suitable functions like hydroxy and carbonyl groups were linked to the polymeric matrix according to the following scheme (Scheme 2).

In Figure 1 are depicted all the substrates used by us for the biphasic solid-liquid hydroformylation:

Experimentally, the loading of the polymeric support was carried out by reaction of the unsaturated alcohol or acid with the trityl site in pyridine or diisopropylamine/pyridine in the temperature range 25–50 °C for 48 h. The yields, determined after cleavage of the linked hydroxy- or carboxyalkene with a 5% solution of trifluoroacetic acid in dichloromethane, in all cases were excellent (>99%). As *p*-hydroxystyrene is not commercially available, the loading of the polymeric matrix, in this case, was carried out by linking the *p*-hydroxybenzaldehyde to the trityl moiety of the polymer and then the aldehyde group was transformed into a vinyl group by a Wittig reaction on the solid phase (Scheme 3).[28]

When this reaction was carried out in the presence of the triphenylmethylenephosphorane obtained by dehydrobromination of the corresponding phosphonium bromide with sodium amide or butyllitium in THF, it



Scheme 2. Linking of various functionalized alkenes to a polymeric matrix.

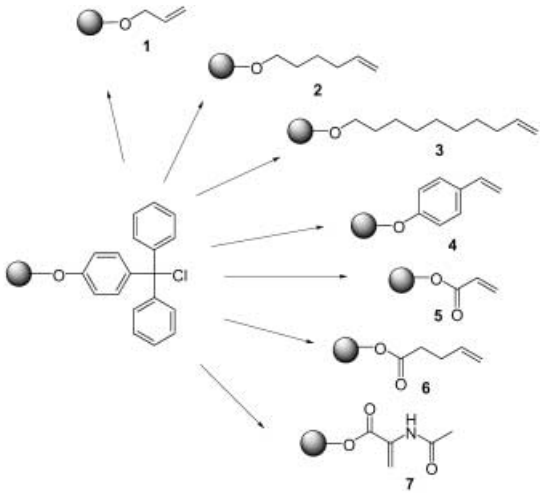
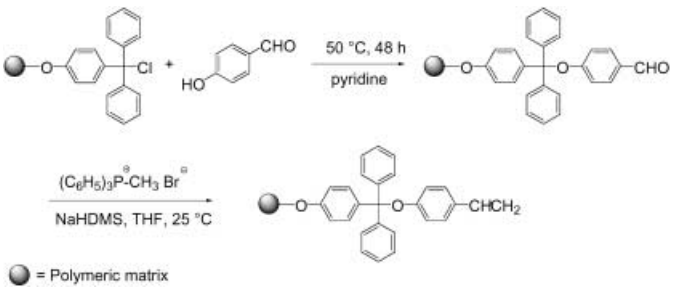


Figure 1. Substrates for biphasic solid-liquid hydroformylation using the trityl-derivatized polymeric support.



Scheme 3. Preparation of substrate **4** by Wittig reaction on solid phase.

gave unsatisfactory results; only by using sodium bis(trimethylsilyl)amide (NaHDMS) in THF, did we reach yields up to 95%.[28]

Some hydroformylation experiments were carried out on the polymer-anchored 5-hexen-1-ol (**2**) following the practical advice of Tokahashi, Ebata and Dai.[18] Unfortunately, we were not able to reproduce the good results described in the literature: also when keeping an efficient contact between the solid and the liquid phase by a vigorous stirring, the substrate conversions were very low ($\leq$20%). Moreover, the polymeric substrate showed, at the end of the reaction, to be extensively decomposed due to the friction effect. Thus, we modified the glass vial in a suitable way (as shown in Fig. 2) in order to avoid this practical drawback.

The new glass device consists of a "traditional" vial modified to be able to hold a glass basket having a porous septum as the bottom; the polymer-anchored substrate is positioned in the basket, which is partially immersed in the catalytic solution, whereas the magnetic stirring bar is on the bottom of the vial. This method allows us to have an efficient stirring without any mechanical stress of the substrate.

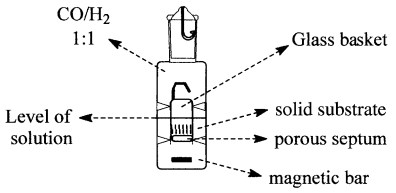
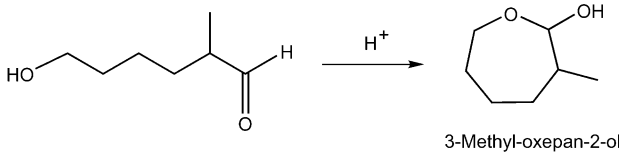
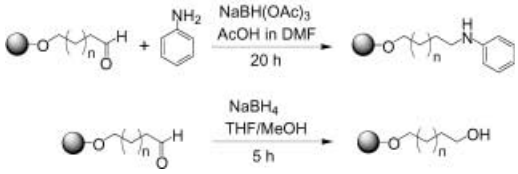


Figure 2. Special glass vial to be introduced into the high-pressure reactor for solid-liquid biphasic hydroformylation experiments.



Scheme 4. Intramolecular cyclization of 6-hydroxy-2-methylhexanal.



Scheme 5. Reductive amination and reduction of oxo-aldehydes.

The *oxo*-reactions on the substrates **1**–**3** were carried out using $Rh(CO)_2(acac)$ as the catalytic precursor at substrate-to-catalyst molar ratio of 25–50; carrying out the experiments in toluene at 40–100 °C and 20–60 atm ($CO/H_2 = 1$) very high conversions were obtained in reasonable reaction times. Reaction conditions and results are listed in Table 1.

The chemoselectivity of the hydroformylation in all runs was higher than 90% and in most cases nearly quantitative; sporadically up to 10% olefinic double bond hydrogenation was noticed if the process was carried out at 100 °C.

The cleavage of the *oxo*-hydroxyaldehydes from the polymer was rather difficult as these compounds are sensitive to acidic conditions: for instance, 6-hydroxy-2-methylhexanal during the treatment with trifluoroacetic acid (TFA) cyclized giving 3-methyloxepan-2-ol (Scheme 4).

To overcome this problem the *oxo*-aldehydes obtained were directly converted on the polymeric support into the corresponding alcohols by reduction with $NaBH_4$ in CH_3OH/THF (1:1) or into *N*-phenylamines by reductive amination in the presence of aniline using $NaBH(OAc)_3$ as reduction agent in DMF (see Experimental Section) (Scheme 5)

All these transformations were accomplished in quantitative yields and after the cleavage with TFA

the product mixtures were subjected to ^{1}H NMR and GC-MS analysis.

For all the investigated substrates the regioselectivities of the *oxo*-process were rather low and the more branched *oxo*-aldehyde was generally the most abundant isomer.

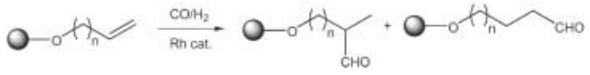
The regioselectivity was shifted towards the linear *oxo*-product only by using xantphos,[1,29] a large bite angle diphosphine ligand promoting the formation of straight chain aldehydes in the rhodium-catalyzed hydroformylation, as an external ligand (xantphos/Rh = 3:1) at low temperature and pressure (40 °C and 20 atm). [24] In the case of substrates **2** and **3** more than 80% of the corresponding linear hydroxy-aldehyde was produced.

Table 2 reports the most representative results obtained in the solid-liquid biphasic hydroformylation of *p*-hydroxystyrene (**4**): while the values of the chemoselectivity reproduce the excellent figures found in the *oxo*-reaction on substrates **1** – **3**, those of regioselectivity are quite unexpected.

The prevailing aldehyde was always the linear one, contrary to the results obtained in the homogeneous rhodium-catalyzed hydroformylation of styrene and derivatives:[1] for instance, the only experiment reported in the literature on an *oxo*-reaction of *p*-hydroxystyrene in the presence of $HRh(CO)(PPh_3)_3$ at 65 °C and 60 atm ($CO/H_2 = 1$) afforded 99.6% regioselectivity towards the formation of 2-(*p*-hydroxyphenyl)propanal.[30] When the catalytic process on substrate **4** was effected in the presence of the $HRh(CO)(PPh_3)_3$/xantphos (1:4) system at 40 °C and 20 atm, the linear aldehyde is the only reaction product. The unexpected regioselectivity obtained in this reaction is not easy to explain, however, it could be possible that steric hindering due to the polymeric matrix inhibits the insertion of the carbon monoxide in the alpha position. It is noteworthy that 3-(*p*-hydroxyphenyl)propanal represents a valuable precursor for the synthesis of several biologically interesting alkaloids, such as for instance, those belonging to the class of sceletium.[31,32]

In Table 3 the results obtained in the solid-liquid hydroformylation of three unsaturated acids linked to the polymeric matrix (**5**, **6** and **7**) are collected. It is noteworthy that the chemoselectivity of the *oxo*-process is strongly dependent on the reaction temperature: when the reaction was carried out on substrate **5** at 100 °C, no aldehyde formation was observed, instead a

Table 1. Hydroformylation of polymer anchored unsaturated alcohols catalyzed by rhodium complexes.



Substrate	Catalytic precursor	T [°C]	Pressure [atm]	Substrate/ catalyst	Reaction time [h]	Conversion [%]	Chemoselectivity [%][a]	Linear [%][a]	Branched [%]
1 (n = 1)	$Rh(CO)_2(acac)$	100	50	25	12	> 99	90	45	55
1 (n = 1)	$Rh(CO)_2(acac)$	60	50	25	24	98	99	30	70
1 (n = 1)	$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	48	95	99	65	35
2 (n = 4)	$Rh(CO)_2(acac)$	100	50	50	48	99	99	50	50
2 (n = 4)	$Rh(CO)_2(acac)$	100	50	25	12	> 99	90	45	55
2 (n = 4)	$Rh(CO)_2(acac)$	80	60	25	24	> 99	95	50	50
2 (n = 4)	$Rh(CO)_2(acac)$	60	50	25	24	98	99	52	48
2 (n = 4)	$Rh(CO)_2(acac)$/xantphos	40	20	25	48	> 99	99	64	36
2 (n = 4)	$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	48	99	99	85	15
3 (n = 8)	$Rh(CO)_2(acac)$	100	60	25	12	> 99	> 99	30	70
3 (n = 8)	$Rh(CO)_2(acac)$	60	50	25	24	85	99	23	77
3 (n = 8)	$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	96	> 99	99	82	18

Reaction conditions: substrate = 500 mg (loading 1.47 mmol/g; substrate 0.7 mmol) solvent = toluene, 20 mL; $CO/H_2 = 1:1$; xantphos/Rh = 3:1.
[a] The only secondary product observed was the hydrogenated derivative of the substrate.

Table 2. Hydroformylation on solid phase of *p*-hydroxystyrene (**4**) catalyzed by rhodium complexes.

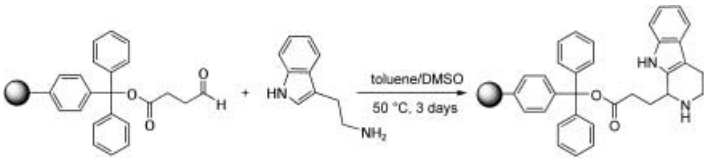
Catalytic precursor	T [°C]	Pressure [atm]	Substrate/ catalyst	Reaction time [h]	Conversion [%]	Aldehyde yield [%]	Linear [%]	Branched [%]
$Rh(CO)_2(acac)$	100	60	25	24	> 99	> 99	72	28
$Rh(CO)_2(acac)$	60	50	25	24	78	99	76	24
$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	96	> 99	> 99	> 99	< 1

Reaction conditions: substrate = 500 mg (loading 1.47 mmol/g; substrate 0.7 mmol); solvent = toluene, 20 mL; $CO/H_2 = 1:1$; xantphos/Rh = 4:1.

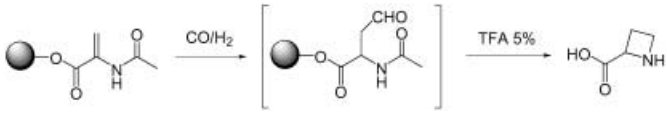
Table 3. Hydroformylation on solid phase of substrates **5 – 7**, catalyzed by rhodium complexes.

Substrate	Catalytic precursor	T [°C]	Pressure [atm]	Substrate/ catalyst	Reaction time [h]	Conversion [%]	Aldehyde yield [%]	Linear [%]	Branched [%]
5	$Rh(CO)_2(acac)$	100	60	25	20	> 99[a]	–	–	–
5	$Rh(CO)_2(acac)$	60	60	25	24	> 99	99	43	57
5	$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	100	> 99	> 99	> 99	< 1
6	$Rh(CO)_2(acac)$	100	50	25	12	> 99	85[b]	41	59
6	$Rh(CO)_2(acac)$	60	50	25	24	92	92	61	39
6	$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	48	> 99	> 99	> 99	< 1
7	$Rh(CO)_2(acac)$	100	60	25	22	> 99[a]	–	–	–
7	$HRh(CO)(PPh_3)_3$/xantphos	40	20	25	48	> 99	> 99	> 99[c]	–

Reaction conditions: substrate = 500 mg (loading 1.47 mmol/g; substrate 0.7 mmol); solvent = toluene, 20 mL; $CO/H_2 = 1:1$; Xantphos/Rh = 4:1.
[a] Complex mixture of unidentified products.
[b] 14% of pentanoic acid was detected.
[c] Recovered as 2-azetidinecarboxylic acid.



Scheme 6. Preparation of 3-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)propionic acid.



Scheme 7. Formation of 2-azetidinecarboxylic acid.

complex mixture of unidentified products was obtained, very likely due to an extensive cleavage of the acrylic acid from the polymer support. Carrying out the reaction at 60 °C and 60 atm we noticed practically complete chemoselectivity, the two aldehydes being present in the reaction mixture in mainly a 1:1 molar ratio. Analogously to the results obtained with substrates **1 – 4**, the catalytic system $HRh(CO)(PPh_3)_3$/xantphos (1:4) showed again an outstanding efficiency in promoting the formation of the desired linear aldehydes in the hydroformylation of substrates **5 – 7**.

In particular, the linear *oxo*-product deriving from the substrate **5** can be useful in the preparation of valuable building blocks to be employed in combinatorial chemistry, for instance, to prepare peptide isosteres which incorporate an electrophile, namely an aldehyde, which can be coupled with a variety of nucleophiles.[33] In this context we used the anchored 4-oxobutyric acid, obtained by hydroformylation of the substrate **5**, to prepare the 3-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)-propionic acid in an easier way, compared with the reported literature method.[34]

Furthermore, in the case of hydroformylation of substrate **7**, the unmodified carbonyl complex $Rh(CO)_2(acac)$ did not ensure the desired high chemoselectivity, even at 60 °C, but produced a complex mixture of unidentified compounds; lowering the reaction temperature to 40 °C and using an excess of xantphos were beneficial for the formation of the linear aldehyde in nearly quantitative yields. However, we were not able to separate this aldehyde from the polymeric support: after cleavage with TFA in dichloromethane only 2-azetidinecarboxylic acid was isolated from the reaction mixture (Scheme 7).

The formation of this product is very likely due to an intramolecular reductive amination of the aldehyde function with the amino group available after removal of the acetyl group by hydrogen under *oxo*-conditions.

Experimental Section

General Methods and Chemicals

IR spectra were measured with an FT-IR spectrometer Perkin Elmer model 1720 as KBr disks or Nujol dispersions as appropriate. Gas chromatography was performed with a Perkin Elmer model 8500, mass spectra were recorded by GC-MS model Helwett Packard GCD using the appropriate columns and conditions. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra of $CDCl_3$ solutions were recorded using a Varian VXR 300 s spectrometer.

Trityl chloride resin (loading 1.47 mmol/g) was purchased from Calbiochem-Nova Biochem. Allyl alcohol, hex-5-en-1-ol, dec-9-en-1-ol, *p*-hydroxybenzaldehyde, acrylic acid, 5-pentenic acid, acetylamidoacrylic acid, methyltriphenylphosphonium bromide, bis(trimethylsilyl)amide, tryptamine, $Rh(CO)_2acac$, and $HRh(CO)(PPh_3)_3$ were purchased from Sigma-Aldrich and used without further purification. Xantphos was prepared as reported in the literature [29].

All non-catalytic reactions in solid phase were carried out by using the apparatus depicted in Figure 3.

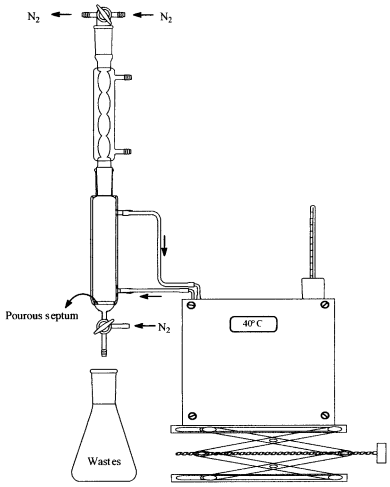


Figure 3. Apparatus to carry out solid phase reactions.

Preparation of Substrates 1–3 and 5–7

Commercial trityl chloride resin (1.5 g) was activated using thionyl chloride (2.4 mL, 32.3 mmol) and pyridine (3.15 mL) in dichloromethane (15 mL). The reaction mixture was heated at reflux for 3 hours, without stirring, and then transferred in the glass reactor shown in Figure 3. The resin was filtered and washed twice with dichloromethane and then allowed to swell in dichloromethane (20 mL) for one hour. Dichloromethane was filtered off and pyridine (20 mL) was added and the mixture stirred by nitrogen bubbling for 10 minutes.

After pyridine removal, the substrate of choice (44.0 mmol) in pyridine (15 mL) was added to the resin and allowed to react at 50 °C for 48 hours. The reaction was monitored as follows: a sample of the polymer was collected and washed with methanol and treated with a 5% solution of trifluoroacetic acid in dichloromethane for 30 minutes under a gentle stirring. The solution was neutralized by adding 0.5 g of K_2CO_3 and then filtered. The solution was concentrated to small volume (100 μL) and analyzed by TLC (glass plate) by using a mixture of ethyl acetate/petroleum ether (2/8) as the eluent. The spots were detected by spraying with a $KMnO_4$ solution and heating at 180 °C, using pure starting products as reference.

At the end of the reaction the functionalized polymer was filtered and washed with dichloromethane (20 mL): the reaction yields were, in all cases, quantitative.

Preparation of Substrate 4 by a Modified Wittig Reaction[35]

Sodium bis(trimethylsilyl)amide (251 mg, 1.37 mmol) was added to a mixture of methyltriphenylphosponium bromide (545 mg, 1.37 mmol) in anhydrous THF (15 mL) and vigorously stirred under an inert atmosphere for 30 minutes. The deep yellow mixture obtained was treated with a sample of *p*-hydroxybenzaldehyde anchored to the trityl chloride resin (200 mg; see procedure above described). After 20 hours the polymer was filtered and washed twice with THF, twice with dimethyl sulfoxide, twice with diethyl ether and then dried under vacuum. The reaction yield was quantitative.

Hydroformylation Procedure

In a glass vessel containing a solution of the rhodium catalyst (see Tables) in toluene (20 mL) were introduced, under a nitrogen purge, 200 mg (*ca*. 0.3 mmol of unsaturated starting product) of the polymeric substrate (**1–7**) put in the glass basket previously described (see Figure 2). The vessel was transferred into a 150-mL stainless steel reactor which was pressurized with syngas to the desired pressure (see Tables) and heated at 40–100 °C. The reaction was monitored at selected times by cooling to room temperature, releasing the gases and picking-up a sample of the polymer and performing on it the *p*-anisaldehyde test.[36]

The reaction products deriving from substrates **2–7** were cleaved from the polymeric matrix by using a 5% solution of trifluoroacetic acid in dichloromethane for 30 minutes under gentle stirring. The solution was neutralized by adding 0.5 g of K_2CO_3 and then filtered. After the solvent evaporation, the products were characterized by GC-MS and ^{1}H NMR.

Oxo-Products Deriving from 2

7-Hydroxyheptanal: GC-MS (70 eV): *m/e* = 130 $[M]^+$, 113, 101, 83, 56; ^{1}H NMR ($CDCl_3$): δ = 9.60 (t, *J* = 1.5 Hz, 1H), 3.60–3.50 (m, 2H), 2.35–2.25 (m, 2H), 1.80–1.32 (m, 8H).

6-Hydroxy-2-methylhexanal (identified as *3-mehyloxepan-2-ol*): GC-MS (70 eV): *m/e* = 130 $[M]^+$; 113; 97, 84, 56; ^{1}H NMR ($CDCl_3$): δ = 4.35 (t, *J* = 7.2 Hz, 1H), 3.40–3.30 (m, 2H), 1.75–1.25 (m, 7H), 0.9 (d, *J* = 6.6 Hz, 3H); anal. calcd. For $C_7H_{14}O_2$: H 10.84, C 64.58; found: H 10.91, C 64.77.

Oxo-Products Deriving from 3

11-Hydroxyundecanal: GC-MS (70 eV): *m/e* = 169 $[M-OH]^+$, 157, 143, 111, 98, 82, 69, 55; ^{1}H NMR ($CDCl_3$): δ = 9.75 (t, *J* = 1.6 Hz, 1H), 3.62–3.57 (m, 2H), 2.42–2.38 (m, 2H), 1.82–1.43 (m, 16H).

10-Hydroxy-2-methyldecanal: GC-MS (70 eV): *m/e* = 169 $[M-OH]^+$, 157, 129, 124, 111, 98, 82, 69,58; 41; ^{1}H NMR ($CDCl_3$): δ = 9.60 (d, *J* = 1.5 Hz, 1H), 3.62–3.57 (m, 2H), 2.02–1.91 (m, 1H), 1.82–1.43 (m, 14H), 0.98 (d, *J* = 6.2 Hz, 3H).

Oxo-Products Deriving from 4

*3-(*p*-Hydroxyphenyl)propanal:* GC-MS (70 eV): *m/e* = 150 $[M]^+$, 121, 107, 94, 77; ^{1}H NMR ($CDCl_3$): δ = 9.85 (t, *J* = 1.5 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 2.95–2.80 (m, 2H), 2.61–2.55 (m, 2H).

*2-(*p*-Hydroxyphenyl)propanal:* GC-MS (70 eV): *m/e* = 150 $[M]^+$, 121, 103, 92, 77; ^{1}H NMR ($CDCl_3$): δ = 9.73 (d, *J* = 1.8 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 3.53–3.51 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 3H).

Oxo-Products Deriving from 5

4-Oxobutanoic acid: ^{1}H NMR ($CDCl_3$): δ = 9.5 (t, *J* = 1.5 Hz, 1H), 3.7–3.6 (m, 2H), 2.8–2.7 (m, 2H).

2-Methyl-3-oxopropanoic acid: ^{1}H NMR ($CDCl_3$): δ = 9.4 (d, *J* = 1.5 Hz, 1H), 3.2 – 3.0 (m, 1H), 1.4 – 1.3 (m, 2H).

Oxo-Products Deriving from 6

6-Oxohexanoic acid: ^{1}H NMR ($CDCl_3$): δ = 9.78 (t, *J* = 1.4 Hz, 1H), 6,75 (s, 1H), 2.45 – 2.40 (m, 2H), 2.39 – 2.29 (m, 2H), 1.78 – 1.70 (m, 2H), 1.41 – 1.17 (m, 2H).

5-Oxo-4-methylpentanoic acid: ^{1}H NMR ($CDCl_3$): δ = 9.49 (d, *J* = 1.6 Hz, 1H), 6.68 (s, 1H), 3.41 – 3.33 (m, 1H), 2.45 – 2.40 (m, 2H), 1.78 – 1.70 (m, 2H), 1.05 (d, *J* = 7.4 Hz, 3H).

Oxo-Product Deriving from 7

2-Acetylamino-4-oxobutanoic acid (identified as *2-azetidine-carboxylic acid*): ^{1}H NMR (DMSO-d_6): δ = 5.01 (s, 2H), 4.22 – 4.18 (m, 1H), 3.45 – 3.38 (m, 2H), 1.145 – 1,25 (m, 2H); ^{13}C NMR (DMSO-d_6): δ = 172.3, 52.5, 40.7, 17.3; anal. calcd. for $C_4H_7NO_2$: H 6.98, C 47.52, N 13.85; found: H 7.00, C 47.73, N 13.98.

Reductive Amination of the Oxo-Products on a Solid Phase

The *oxo*-products deriving from **1**, due to their instability, were not isolated following the above described procedure. Their characterization was performed by transforming them into the corresponding *N*-phenylamine derivatives.

The reductive amination was carried out on the *oxo*-products deriving from substrates **1** and **3**. The hydroformylated polymer (200 mg, *ca.* 0.3 mmol of aldehydes) was allowed to swell with a 1% AcOH solution in DMF for 1 h and then an excess of $NaBH(OAc)_3$ (4 equivs., 254 mg) and aniline (4 equivs., 0.1 mL) was added. The reaction mixture was stirred by nitrogen bubbling at room temperature for 20 hours. The IR spectrum performed on a sample of this polymer did not show the presence of the carbonyl group anymore. The polymer was filtered, washed with dichloromethane and dried under vacuum.

The cleavage of the products was carried out as previously described. The yields were in all cases quantitative.

Amines Deriving from 1

N-*Phenylaminobutan-1-ol:* GC-MS (70 eV): *m/e* = 165 $[M]^+$, 149, 135, 121, 107, 55; ^{1}H NMR ($CDCl_3$): δ = 7.42 – 7.39 (m, 2H, arom), 7.20 – 7.09 (m, 3H, arom), 4.75 (s, 2H), 3.78 – 3.60 (m, 2H), 3.22 – 3.16 (m, 2H), 1.82 – 1.61 (m, 4H).

2-Methyl-N-*phenylaminopropan-1-ol:* GC-MS (70 eV): *m/e* = 165 $[M]^+$, 135, 112, 93, 55; ^{1}H NMR ($CDCl_3$): δ = 7.81 – 7.75 (m, 2H), 7.60 – 7.55 (m, 1H), 6.81 – 6.66 (m, 2H), 3.78 – 3.60 (m, 2H), 3.22 – 3.16 (m, 2H), 2.05 – 1.95 (m, 1H), 0.95 (d, *J* = 6.2 Hz, 3H).

Amines Deriving from 3

11-Phenylaminoundecan-1-ol: GC-MS (70 eV): *m/e* = 246 $[M - OH]^+$, 218, 171, 157, 93; ^{1}H NMR ($CDCl_3$): δ = 7.1 – 6.9 (m, 5H), 4.0 (s, 2H), 3.3 (m, 2H), 3.05 (m, 2H), 1.8 – 1.1 (m, 18H).

10-Phenylaminoundecan-1-ol: GC-MS (70 eV): *m/e* = 248 $[M - CH_3]^+$, 246, 171, 157, 129; ^{1}H NMR ($CDCl_3$): δ = 7.1 – 6.9 (m, 5H), 3.3 (m, 2H), 3.05 (m, 2H), 1.8 – 1.1 (m, 15H), 1.02 (d, *J* = 6.4 Hz, 3H).

Reductive Amination of the *Oxo*-Product Deriving from the Hydroformylated 5 on a Solid Phase[34]

The hydroformylated polymer (200 mg, *ca.* 0.3 mmol of aldehydes) was allowed to swell with a mixture of toluene/dimethyl sulfoxide (1:1) for 1 h and then an excess of tryptamine (20 equivs., 962 mg) and 0.2 mL of 10 N HCl were added. The reaction mixture was stirred by nitrogen bubbling at 50 °C for 72 h. The IR spectrum performed on a sample of this polymer did not show the presence of the carbonyl group anymore. The polymer was filtered, washed 3 times with dimethyl sulfoxide (20 mL), 3 times with dichloromethane (20 mL) and dried under vacuum.

The cleavage of the product was carried out as previously described. The yield was quantitative.

*3-(2,3,4,9-Tetrahydro-1*H*-β-carbolin-1-yl)-propionic acid:* ^{1}H-NMR ($CDCl_3$): δ = 10.83 (s, 1H), 9.0 (s, 1H), 8.05 (s, 1H), 7.61 – 7.04 (m, 4H), 3.82 – 3.68 (m, 1H), 3.35 – 3.02 (m, 4H), 2.65 – 1.80 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ = 170.4, 138.6, 135.0, 125.2, 121.8, 119.8, 117.2, 112.5, 110.2, 46.4, 41.4, 37.6, 34.2, 28.9; anal. calcd. for $C_{14}H_{16}N_2O_2$: H 6.60, C 68.83, N 11.47; found: H 6.62, C 68.99, N 11.52.

Reduction of the *Oxo*-Products Deriving from Substrate 2

The hydroformylated polymer (200 mg, *ca.* 0.3 mmol of aldehydes) was allowed to swell with a mixture of tetrahydrofuran/methanol (1:1) for 1 h and then an excess of $NaBH_4$ (10 equivs., 83 mg) was added. The reaction mixture was stirred by nitrogen bubbling at room temperature for 5 h. The IR spectrum performed on a sample of this polymer did not show the presence of the carbonyl group anymore. The polymer was filtered, washed 3 times with dichloromethane (20 mL) and dried under vacuum.

The cleavage of the products was carried out as previously described. The yield was quantitative.

1,7-Heptandiol: GC-MS (70 eV): *m/e* = 98 $[M - 2(OH)]^+$, 81, 68, 56, 41; ^{1}H NMR ($CDCl_3$): δ = 3.75 – 3.52 (m, 4H), 1.45 – 1.08 (m, 10H).

2-Methyl-1,6-hexandiol: GC-MS (70 eV): *m/e* = 102 $[M - CH_2OH]^+$, 98, 72, 58; ^{1}H NMR ($CDCl_3$): δ = 3.75 – 3.52 (m, 2H), 3.40 – 3.30 (m, 2H), 1.90 – 1.81 (m, 1H), 1.60 – 1.06 (m, 6H), 0.9 (d, *J* = 6,8 Hz, 3H).

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