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Rhodium catalyzed hydroformylation of nerolidol

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Abstract. The rhodium-catalyzed hydroformylation of nerolidol, a bio-renewable substrate with a strong therapeutic potential available from various essential oils, was studied in toluene and ethanol solutions in the presence of PPh_3 or P(O-*o*-^{t}BuPh)$_3$ ligands. In toluene, the reaction gave with high chemo and stereoselectivity a cyclic hemiacetal, which formally arise from the intramolecular cyclization of the primarily formed hydroxyl-aldehyde. In ethanol, the hydroformylation gave a corresponding cyclic acetal in excellent yields even without additional acid co-catalysts. In the absence of phosphorous ligands, nerolidol was resistant to hydroformylation probably due to the binding with rhodium through both the double bond and the hydroxyl group to form stable chelates. The P(O-*o*-^{t}BuPh)$_3$ ligand exerted a remarkable effect on the substrate reactivity accelerating the reaction by five to ten times as compared to the system with PPh_3. All isolated products have a pleasant sweet floral and woody scent and can be useful as components of synthetic fragrances.

Keywords: Acetalization; Biorenewables; Hydroformylation; Terpenes; Rhodium.

Introduction

Terpenes constitute a class of natural products available from essential oils of many plants and fruits. These substances represent an important renewable feedstock for flavor and fragrance and pharmaceutical industries.[1–3] For example, nerolidol (also known as peruviol or melaleucol), a sesquiterpenic allylic alcohol with a delicate sweet floral and woody odor, has demonstrated a strong therapeutic potential due to its biological activity including antiulcer, antimalarial, and antileishmanial properties.[4–7] This compound is available from essential oils of various plants and flowers, which may contain up to 50–90% of nerolidol. Nerolidol itself is widely used as a fragrance and food-flavor ingredient[7–9] and as a starting material for the synthesis of other terpenic chemicals like α-bisabolol.[10,11] Nevertheless, the use of this natural alcohol can be significantly extended by its oxyfunctionalization, with the hydroformylation reaction being one of the most important synthetic tools for this purpose.

Rhodium or cobalt catalyzed hydroformylation is an industrially important route to a variety of oxygen-containing compounds.[12] The aldehydes, which are the main products of this process performed in aprotic solvents, can be further converted to other valuable compounds such as alcohols, acetals, carboxylic acids and their esters. The applications of the hydroformylation reaction to the synthesis of fragrance compounds from alkenes, including natural terpenes, have been recently reviewed.[13] Although the hydroformylation of more abundant terpenes, such as limonene and β-pinene, has been extensively studied,[14–20] we could find in the literature only one report on the hydroformylation of nerolidol.[21] The hydroformylation of allylic alcohols has attract a considerable attention due to the possibility of the direct synthesis of substituted tetrahydrofurans and γ-butyrolactones, which can be used as subunits for biologically important compounds.[14,15,22–25] These reactions usually give five-membered hemiacetals due to the spontaneous intramolecular cyclization of primarily formed hydroxyl-aldehydes. Hemiacetals can be further converted in other useful products such as acetals, lactones or substituted dihydrofurans. The products resulting from the hydroformylation of neralidol have been reported as promising fragrance compounds which provide the perfume with the sweet smell of a natural flower.[21]

Aiming at the further valorization of natural ingredients of essential oils, we have recently directed our efforts to integrate the hydroformylation with other reactions, in particular, with acetalization, to obtain ethyl acetals directly from alkenes.[26–29] In the present communication we report the rhodium-catalyzed hydroformylation of nerolidol and tandem hydroformylation/acetalization of this substrate under mild non-acidic conditions. All isolated products have a pleasant sweet floral and woody scent and can be useful as components of synthetic fragrances.

Results and Discussion

The reactions of nerolidol (**1**) under the hydroformylation conditions have been studied in toluene and ethanol solutions using $[Rh(COD)(OMe)]_2$ as a catalyst precursor in the presence of PPh_3 or tris(*o*-^{t}butylphenyl)phosphite, $P(O\text{-}o\text{-}^tBuPh)_3$, as P-donor auxiliary ligands.

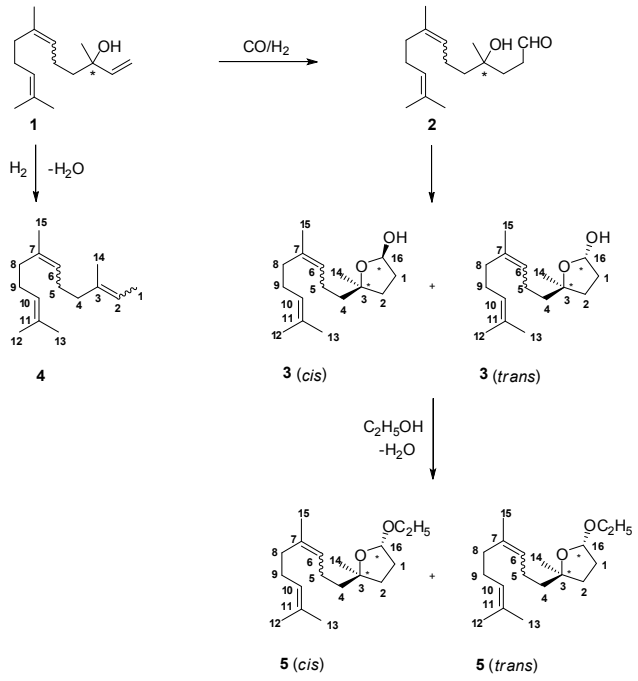
There are two natural isomers of nerolidol which differ in the geometry about the central double bond: *cis* (*Z*-nerolidol) and *trans* (*E*-nerolidol) (Scheme 1). The starting substrate used in the present work was a mixture of *Z* and *E* isomers in a ratio of ca. 40/60. Under the hydroformylation conditions in toluene, the reaction gave one major product **3** derived from the direct carbonylation of the terminal double bond of the substrate. The internal double bonds were not involved in the interaction with rhodium even in the system with the bulky $P(O\text{-}o\text{-}^tBuPh)_3$ ligand. In ethanol solutions, this primarily formed product **3** was gradually converted in the corresponding ethyl acetal **5** due to *in situ* acetalization. It is remarkable that the formation of the acetal with both phosphorous ligands occurred without using any additional acid co-catalyst.

The reaction stereoselectivity was only slightly dependent on the reaction variables and the nature of the auxiliary phosphorous ligand. In all products, we have maintained a carbon numbering conventionally used for the starting sesquiterpene molecule. The total selectivity for the hydroformylation products in most of the runs was nearly or above 90%, with GC yields for the individual products under the optimized conditions being ca. 90% in toluene and almost quantitative in ethanol solutions. Only one minor product was responsible for almost all the rest of the mass balance (see below), with very small amounts of unidentified products being detected by GC.

Hydroformylation of nerolidol in toluene solutions

In the absence of any phosphorous ligand (unmodified system), the hydroformylation of nerolidol occurred slowly giving compound **3** as a main product with 85% selectivity (Table 1, run 1, Scheme 1). The product formally resulted from the intramolecular cyclization of the primarily formed hydroxy aldehyde **2**. Compound **3** was detected as four isomers with very similar mass and NMR spectra (see Experimental). The analysis of the NMR spectra revealed that all four compounds have a structure of hemiacetal **3** rather than hydroxy aldehyde **2**, with no detectable amounts of the aldehyde itself being observed in the reaction solutions.

Hemiacetal **3** obtained from nerolidol under the hydroformylation conditions was isolated from the reaction solutions for the characterization by NMR as several mixtures of four isomers in different proportions. Each isomer of the starting substrate, *Z*-nerolidol and *E*-nerolidol, gave two isomers of the hemiacetal with different geometry at the tetrahydrofuran ring: *cis* isomer with the hydroxy and C_{11}-alkenyl groups attached to the same side of the ring and the corresponding *trans* isomer. Thus, four GC peaks assigned to hemiacetal **3** are *Z-trans*, *E-trans*, *Z-cis* and *E-cis* isomers of this compound, as shown in Scheme 1 (listed accordingly to the increase in their GC retention times). It should be mentioned that hemiacetal **3** was formed predominantly (in several runs almost exclusively) with the *cis* configuration, i.e., *Z-cis* and *E-cis* isomers.



Scheme 1. Hydroformylation/acetalization of nerolidol (**1**).

Table 1. Hydroformylation of nerolidol (**1**) catalyzed by Rh/PPh_3 [a)]

Run	P/Rh	*t* (h)	*C* (%)	TOF (h^{-1})	Selectivity (%)	
					3 (*cis*/*trans*)	**4**
1	0	4	27	28	85 (87/13)	11
		24	100		84 (91/9)	6
2	5	4	35	36	86 (96/4)	6
		24	100		90 (97/3)	5
3	10	4	54	56	85 (94/6)	8
		24	100		90 (97/3)	7
4	20	2	56	112	96 (84/16)	4
		4	100		93 (85/15)	5
5	50	4	73	90	88 (90/10)	6
		24	100		90 (87/13)	6

[a)] Conditions: nerolidol (0.20 M), $[Rh(COD)(OMe)]_2$ (0.25 mM), 50°C, 20 atm (CO/H_2 = 1/1), toluene. Conversion (*C*) and selectivity are based on the substrate reacted. TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (up to 20–40%).

Only one minor product, compound **4**, was detected in the reaction solutions in considerable amounts. Hemiacetal **3** and product **4** were responsible for 96–99% of the mass balance in most of the runs. As mentioned above, only very small amounts of unidentified products were detected by GC. Minor product **4** appeared on chromatograms as four very close peaks with virtually identical mass spectra. The analysis of the NMR spectra of these four compounds (isolated as a mixture) allowed attributing them a structure shown in Scheme 1 (*EE*, *EE*, *ZE* and *EZ* isomers). Product **4** formally resulted from the dehydration of the nerolidol molecule followed by the hydrogenation of the resulting conjugated diene moiety. Each isomer of the starting substrate gave two isomers of product **4** in nearly equal amounts with either *Z* or *E* configuration about the new formed olefinic bond. It is worthwhile noting that no products of the hydrogenation of non-conjugated double bonds in the substrate or product molecules were detected in the reaction solutions even at prolonged reaction times.

The hydroformylation of nerolidol with the Rh/PPh_3 system at 50 °C and 20 atm resulted in nearly 90 yield of hemiacetal **3** (ca. 90% *cis*, Table 1, runs 2–5). Kinetic curves for the runs with various P/Rh ratios (runs 1–5 in Table 1) are presented in Figure 1. A considerable acceleration can be seen when the P/Rh ratio increases from 0 to 20, whereas further addition of the ligand slightly decreases the reaction rate. The kinetic curves are nearly straight lines up to 80–90% conversions, except at P/Rh = 50. Thus, the substrate competes successfully with the ligand for the coordination sites on rhodium and most of the rhodium centers contain strongly coordinated nerolidol or moieties derived from nerolidol up to high substrate conversions even at high ligand concentrations. At P/Rh = 5 and 10, the *cis* isomer of **3** was formed almost exclusively (97%), with its relative amounts being only slightly decreased with the increase in the ligand concentration (runs 4 and 5, Table 1).

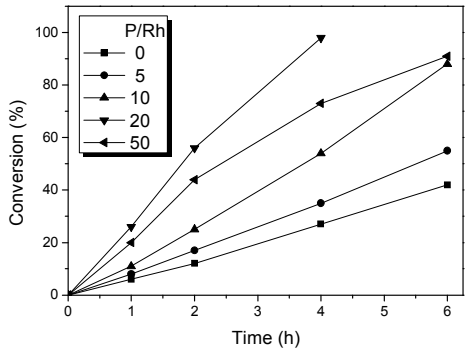


Figure 1. Hydroformylation of nerolidol catalyzed by Rh/PPh_3: effect of the P/Rh ratio. Conditions: nerolidol (0.20 M), $[Rh(COD)(OMe)]_2$ (0.25 mM), 50°C, 20 atm (CO/H_2 = 1/1), toluene.

In most modified rhodium systems, the hydroformylation rate decreases with the increase in the P-ligand concentration due to the competition between the ligand and the substrate for rhodium centers. The unusual accelerating effect of PPh_3 on the reactivity of nerolidol observed in the present work can be explained by the chelation of the substrate on rhodium through the coordination of both the double bond and the hydroxyl group. The increase in the P-ligand concentration favors the cleavage of the inactive chelates allowing the proper positioning of the C-C double bond for the hydride migration. A similar ligand effect was observed at the related hydroformylation of linalool in our earlier work.[25]

We also studied the effects of the CO and hydrogen partial pressure on the hydroformylation of nerolidol (Table 2). Under common hydroformylation conditions (10–30 atm, 70–120 °C), the reaction is generally zero order in hydrogen and negatively affected by the CO concentration.[12] Under the conditions we used, the increase in the pressure of CO indeed decreased the reaction rate (Table 2, run 1 vs. run 5; run 4 vs. run 2). On the other hand, the increase in the total pressure of the equimolar gas mixture from 20 to 40 atm accelerated the reaction (Table 2, runs 1 and 2). This should reflect a strong kinetic effect of the hydrogen concentration on the hydroformylation of nerolidol, opposite to that of CO. The accelerating effect of hydrogen suggests that the oxidative addition of hydrogen to the rhodium acyl intermediate seems to be a rate-determining step at the nerolidol hydroformylation.

Table 2. Rhodium catalyzed hydroformylation of nerolidol (**1**): effect of pressure[a)]

Run	P (H_2) (atm)	P (CO) (atm)	*t* (h)	TOF (h^{-1})	Selectivity for **3** (%) (*cis*/*trans*) [b)]
1	10	10	24	56	90 (97/3)
2	20	20	6	74	91 (97/3)
3	20	10	5	100	90 (98/2)
4	40	10	3	160	88 (97/3)
5[c)]	10	20	6	35	90 (96/4)

[a)] Conditions: nerolidol (0.20 M), $[Rh(COD)(OMe)]_2$ (0.25 mM), PPh_3 (5.0 mM), 50°C, toluene. Selectivity is based on the substrate reacted; the reaction time and selectivity are given for nearly complete conversions. TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (up to 20–40%).[b)] Selectivity for product **4** was 7–8% in all the runs.[c)] 55% of conversion for 6 hours.

The use of the P(O-*o*-^{t}BuPh)$_3$ ligand instead of PPh_3 remarkably accelerated the hydroformylation of nerolidol (Table 3, run 1 vs. Table 1, run 3). The initial turnover frequency in the run with P(O-*o*-^{t}BuPh)$_3$ was almost ten times higher than that in the reaction performed with PPh_3 under the same conditions. In a further study with P(O-*o*-^{t}BuPh)$_3$ we have decreased the temperature to slow down the

reaction and to be able to follow more precisely the reaction progress.

The hydroformylation of nerolidol with the Rh/P(O-*o*-^{t}BuPh)$_3$ system at 40 ^{o}C and 20 atm resulted in 85–90% yield of hemiacetal **3** formed predominantly as the *cis* isomer. The acceleration effect of the P(O-*o*-^{t}BuPh)$_3$ ligand was much more pronounced than that of PPh_3. In the unmodified system at 40 ^{o}C, only a 12% conversion was observed for 6 h, while with small amounts of P(O-*o*-^{t}BuPh)$_3$ the reaction was completed in 3 h (Table 3, run 4, initial TOF = 12 h^{-1} vs. run 3, initial TOF = 160 h^{-1}). A slight acceleration occurred when the P/Rh ratio was increased from 5 to 10 and then to 20, whereas the further addition of P(O-*o*-^{t}BuPh)$_3$ began to decelerate the reaction. A great advantage of using P(O-*o*-^{t}BuPh)$_3$ seems to consist in a high efficiency of this ligand to prevent the substrate chelation on rhodium and/or to break up rhodium-nerolidol chelates.

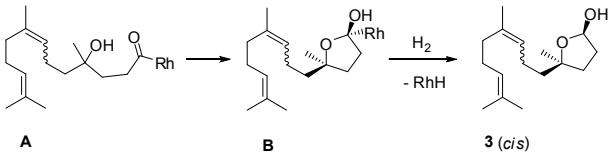
Table 3. Hydroformylation of nerolidol (**1**) catalyzed by Rh/P(O-*o*-^{t}BuPh)$_3$[a)]

Run	P/Rh	*t*	TOF	Selectivity (%)	
		(h)	(h^{-1})	**3** (*cis*/*trans*)	**4**
1[b)]	10	1	460	86 (98/2)	12
2	10	2	228	90 (70/30)	9
3	5	3	160	88 (77/23)	11
4[c)]	0	6	12	98 (93/7)	1
5	20	2	240	85 (93/7)	14
6	50	3	190	85 (93/7)	14

[a)] Conditions: nerolidol (0.20 M), [Rh(COD)(OMe)]$_2$ (0.25 mM), 40^{o}C, 20 atm (CO/H_2 = 1/1), toluene. Selectivity is based on the substrate reacted; the reaction time and selectivity are given for nearly complete conversions. TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (up to 20–40%).[b)] 50^{o}C. Average TOF is given as the reactions were too fast. [c)] 12 % conversion for 6 h.

Bulky phosphite ligands usually show much better performance in hydroformylation compared to phosphine ligands due to the combination of steric and electronic effects.[30,31] The accelerating effect of P(O-*o*-^{t}BuPh)$_3$ vs. PPh_3 is a result of the electronic properties of the phosphite and its large cone angle, which prevents the formation of bis(phosphorous ligand) rhodium species. At the same P/Rh ratio, a larger part of rhodium exists in the Rh/P(O-*o*-^{t}BuPh)$_3$ system as mono(phosphorous ligand) species, which are more active in hydroformylation. The initial reaction rate of the hydroformylation of nerolidol depended only slightly on the phosphite concentration implying that the P/Rh ratio of 10 was enough to keep most of rhodium coordinated to one phosphite and even at P/Rh = 50 bis(ligand) species were not formed in significant amounts (Table 3).

The stereochemistry of hemiacetal **3** formed predominantly as the *cis*-isomer argues for the mechanism proposed in our previous work for the related hydroformylation of linalool.[25] A spontaneous cyclization of aldehyde **2** with no participation of rhodium should give preferably the thermodynamically more stable *trans* isomer of **3** (Scheme 1). We suppose that the interaction between the hydroxyl and carbonyl groups leading to the intramolecular cyclization could also occur in the rhodium acyl intermediate **A** before its hydrogenolysis to give aldehyde **2** (Scheme 2). The cyclization of the rhodium acyl intermediate should give preferably a less hindered cyclic rhodium intermediate **B**, in which a bulky rhodium/P-ligand fragment and C_{11}-alkenyl groups are at the opposite sides of the tetrahydrofuran ring. The hydrogenolysis of this *trans* cyclic rhodium intermediate will give hemiacetal **3**(cis) with the alkenyl and hydroxyl groups in a *cis* position.



Scheme 2. Proposed mechanism for the formation of hemiacetal **3**.

Hydroformylation of nerolidol in ethanol solutions

The hydroformylation of nerolidol was performed also in the solutions of ethanol, a renewable, low cost and environmentally friendly solvent. The solvent promoted a significant effect on the product nature. The reactions with both ligands gave almost quantitatively cyclic acetal **5**, which formally resulted from the etherification of hemiacetal **3** with ethanol (Scheme 1, Table 4).

Table 4. Rhodium catalyzed hydroformylation of nerolidol (**1**) in ethanol[a)]

Run	Ligand	P/Rh	*t*	*C*	TOF	*S* (%)	
			(h)	(%)	(h^{-1})	**3**	**5**
1	PPh_3	5	6	46	32		99
			24	100			99
2	PPh_3	10	6	82	55	5	93
			24	100			97
3	PPh_3	20	6	80	72	4	50
			24	99		5	93
4[b)]	P(O-*o*-^{t}BuPh)$_3$	10	1	96	400	1	71
			4	100		6	90
5[b)]	P(O-*o*-^{t}BuPh)$_3$	20	1	96	400	2	72
			2	100		5	97

[a)] Conditions: nerolidol (0.20 M), [Rh(COD)(OMe)]$_2$ (0.25 mM), 50 ^{o}C, ethanol. Conversion (*C*) and selectivity (*S*) are based on the substrate reacted. TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (up to 20–40%). [b)] Average TOF is given as the reactions were too fast.

The acetal appeared on chromatograms as four very close peaks with very similar mass spectra. The peaks were attributed to four isomers of the acetal, i.e., *Z-trans*, *E-trans*, *Z-cis* and *E-cis*, formed from two isomers of the starting substrate, as shown in Scheme 1. The interaction of the hemiacetal with ethanol to give the acetal occurred at a lower rate than the hydroformylation of nerolidol as the hemiacetal was detected in the reaction solutions in most of the runs at early reaction times.

In ethanol solutions, the hemiacetal **3** was also formed almost exclusively with the *cis* configuration at the tetrahydrofuran ring. On the other hand, the acetal **5** was detected as a mixture of the *cis* and *trans* isomers in nearly equal amounts, with this ratio being virtually independent on the reaction conditions and ligand nature. Thus, it seems that the etherification of hemiacetal **3** in ethanol solutions occurs with opening the tetrahydrofuran ring. The use of Rh/P(O-*o*-^{t}BuPh)$_3$ instead of PPh_3 in ethanol solutions also remarkably accelerated the hydroformylation of nerolidol, with the reactions being at least 5 times faster under the same conditions. It is important to note that the efficient etherification of hemiacetal **3** occurs in ethanol solutions under the hydroformylation conditions in the absence of any additional acid co-catalyst.

Thus, the data obtained support the suggestion that the high stereoselectivity for hemiacetal **3** (ca. 90% *cis*) arises from the intramolecular attack of the hydroxyl group to the rhodium acyl fragment as shown in Scheme 2. Aldehyde **2** has been never observed in the reaction mixtures. This high stereoselectivity is lost in ethanol where the main product is the acetal (*cis/trans* ≈ 1:1) because the formation of the acetal involves the opening of the furan ring in the hemiacetal molecule, which occurs without the participation of the metal.

Conclusion

The study of the rhodium-catalyzed hydroformylation of nerolidol in toluene and ethanol solutions revealed a remarkable effect of the solvent and the nature of the auxiliary phosphorous ligand. The reaction occurs up to ten times faster in the Rh/P(O-*o*-^{t}BuPh)$_3$ system as compared to the system with PPh_3 and gives a cyclic hemiacetal in toluene solutions and corresponding cyclic acetal in ethanol. The substrate has shown a quite low reactivity towards hydroformylation in the absence of P ligands, probably, due to the binding through both the double-bond and the hydroxyl group to form stable chelates with rhodium. Several fragrance compounds (with a potential to show a biological activity like the substrate itself) can be obtained in high yields through a simple one-pot procedure starting from the sesquiterpene easily available from natural bio-renewable resources. It is important to note that the reaction can be performed in environmentally friendly solvent ethanol, in the absence of additional acid co-catalysts and, due to the high reactivity of the substrate induced by phosphorous ligands, under mild reaction conditions.

Experimental Section

All chemicals were purchased from commercial sources and used as received, unless otherwise indicated. A mixture of *Z* and *E* isomers of nerolidol [3,7,11-trimethyl-1,6,10-dodecatrien-3-ol] acquired from Aldrich was used as the substrate (*Z*/*E* ≈ 40/60). [Rh(COD)(OMe)]$_2$ (COD = 1,5-cyclooctadiene) was prepared by a published method.[32] Tris(*O*-^{t}butylphenyl)phosphite, P(O-*o*-^{t}BuPh)$_3$, was prepared as described in[33] and purified by column chromatography (silica gel 60) using mixture of hexane and $CHCl_3$ as eluents. Toluene was purified under reflux with sodium wire–benzophenone for 8 h and then distilled under argon. Ethanol was purified under reflux with magnesium turnings and iodine crystals for 6 h and then distilled under argon.

Catalytic experiments were carried out in homemade stainless steal reactors with magnetic stirring. Reactions were followed by gas chromatography (GC) by sampling the liquid phases through a valved dip tube. The products were analyzed by gas chromatography (GC- Shimadzu QP2010, Rtx®-5MS capillary column, FID detector). Conversion and selectivity were determined by GC. The GC mass balance was based on the substrate charged using dodecane as an internal standard. Initial turnover frequencies (TOFs) were measured at low conversions (up to 20–40%) taking aliquots for GC analysis at short reaction times.

In a typical run, toluene or ethanol (20.0 mL) containing [Rh(COD)(OMe)]$_2$ (5.0 μmol), phosphorus ligand (0–0.5 mmol), nerolidol (4 mmol), and dodecane (2 mmol, internal standard) was transferred under argon into a stainless steel autoclave, which was pressurized to 20–50 atm (CO/H_2 = 1/4 to 2/1), placed in an oil bath (40–50 °C), and magnetically stirred. After the reaction was carried out and cooled to room temperature, the excess CO and H_2 were slowly vented.

The products were separated by column chromatography (silica gel 60) using mixtures of hexane and CH_2Cl_2 as eluents and identified by GC-MS, ^{1}H, and ^{13}C-NMR (DEPT, COSY, HMQC, HMBC and NOESY experiments). The assignment of ^{1}H and ^{13}C-NMR signals was made using bidimensional techniques. NMR spectra were recorded in $CDCl_3$ using a Bruker 400 MHz spectrometer, with TMS as an internal standard. Mass spectra were obtained on a Shimadzu QP2010-PLUS instrument operating at 70 eV.

Compound **3**: MS (70 eV, EI): *m/z* (%): 234 (1) [M^+- H_2O], 219 (3) [M^+- H_2O - CH_3], 121 (29), 109 (29), 107 (30), 105 (24), 95 (42), 93 (40), 83 (37), 81 (52), 69 (100), 67 (28), 55 (25) (*Z-trans* isomer); 234 (1) [M^+- H_2O], 219 (3) [M^+- H_2O - CH_3], 121 (27), 109 (29), 107 (28), 105 (24), 95 (40), 93 (33), 83 (34), 81 (48), 69 (100), 67 (24), 55 (21) (*E-trans* isomer); 234 (1) [M^+- H_2O], 219 (1) [M^+- H_2O - CH_3], 121 (34), 109 (29), 107 (27), 105 (19), 95 (25), 93 (37), 83 (26), 81 (38), 69 (100), 67 (22), 55 (19) (*Z-cis* isomer); 234 (1) [M^+- H_2O], 219 (1) [M^+- H_2O - CH_3], 123 (22), 121 (44), 109 (29), 107 (30), 105 (24), 95 (27), 93 (39), 83 (25), 81 (40), 69 (100), 67 (22), 55 (20) (*E-cis* isomer). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ=1.28 (3H, s, $C^{14}H_3$, *E* isomer), 1.36 (3H, s, $C^{14}H_3$, *Z* isomer), 1.40–1.50 (4H, m, C^4H_2), 1.61 (6H, s, $C^{12}H_3$), 1.64 (3H, s, $C^{15}H_3$, *E* isomer), 1.69 (9H, s, $C^{13}H_3$ and $C^{15}H_3$, *Z* isomer), 1.75–1.85 (4H, m, C^2H_2), 1.85–2.10 (16H, m, C^1H_2, C^5H_2, C^8H_2 and C^9H_2), 5.15 (4H, br.t, C^6H and $C^{10}H$), 5.41 (1H, br.s, $C^{11}H$, *E* isomer); 5.49 ppm (1H, br.s, $C^{11}H$, *Z* isomer);

^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS), δ= 15.95 (C^{15}, *E* isomer), 17.63 and 17.68 (C^{12}), 23.03 and 23.14 (C^5), 23.38 (C^{15}, *Z* isomer), 25.69 and 25.72 (C^{13}), 26.60 and 26.73 (C^9), 28.18 and 28.22 (C^{14}), 31.92 (C^8, *Z* isomer), 33.18 and 33.46 (C^1), 34.32 and 34.54 (C^2), 39.69 (C^8, *E* isomer), 41.87 and 42.18 (C^4), 84.19 and 84.23 (C^3), 98.52 (C^{16}, *Z* isomer), 100.37 (C^{16}, *E* isomer), 124.38 and 124.55 (C^6 and C^{10}), 131.30 and 131.53 (C^{11}), 134.96 and 135.08 ppm (C^7) (mixture of *Z-trans* and *E-trans* isomers). The NMR spectra of *Z-cis* and *E-cis* isomers (isolated in a mixture with *trans* isomers) were very similar to the spectra of the *trans* isomers.

Compound **4** (mixture of *EE*, *EE*, *ZE* and *EZ* isomers): MS (70 eV, EI): *m/z* (%): 176 (1.5) [M^+ - $2CH_3$], 161 (5) [M^+ - $3CH_3$], 151 (24), 136 (30), 125 (12), 121 (10), 109 (17), 107 (25), 93 (22), 81 (11), 69 (100), 67 (21). MS spectra were virtually identical for all four isomers. ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS), δ=1.56 (12H, d, ^3J=6.8 Hz, C^1H_3), 1.60 (24H, s, $C^{12}H_3$, $C^{15(E)}H_3$, $C^{14(E)}H_3$), 1.68 (24H, s, $C^{13}H_3$, $C^{15(Z)}H_3$, $C^{14(Z)}H_3$), 1.90–2.10 (32H, m, C^4H_2, C^5H_2, C^8H_2, C^9H_2,), 5.05–5.15 (8H, m, C^6H and $C^{10}H$), 5.28 ppm (4H, q, ^3J=7.0 Hz, C^2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS), δ=12.91 and 13.00 (C^1), 15.33, 15.60 and 15.64 ($C^{14(E)}$ and $C^{15(E)}$), 17.27 and 17.33 (C^{12}), 23.06 and 23.09 ($C^{14(Z)}$ and $C^{15(Z)}$), 25.34 and 25.38 (C^{13}), 25.85, 25.94, 26.25, 26.32, 26.36, 26.40 and 26.44 (C^9 and C^5), 31.23, 31.56, 31.62 and 31.67 ($C^{4(Z)}$ and $C^{8(Z)}$), 39.40 and 39.70 ($C^{4(E)}$ and $C^{8(E)}$), 117.94 and 118.69 (C^2), 123.89, 123.99, 124.04 and 124.09 (C^6), 124.77 and 124.80 (C^{10}), 130.94 and 131.15 (C^{11}), 134.58 and 134.75 (C^7), 135.45 and 135.65 ppm (C^3).

Compound **5** (mixture of four isomers): MS (70 eV, EI): *m/z* (%): 280 (0.3) [M^+], 265 (0.5) [M^+- CH_3], 234 (1) [M^+- C_2H_5OH], 216 (2.5) [M^+- C_2H_5OH - CH_3], 147 (17), 129 (48), 123 (23), 121 (40), 109 (28), 107 (28), 105 (19), 101 (22), 95 (35), 93 (38), 85 (20), 83 (38), 81 (56), 69 (100), 67 (23), 55 (24); MS spectra of the isomers were very similar. ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ=1.18 (3H, t, ^3J=7.2 Hz, CH_2CH_3), 1.28 (3H, s, $C^{14}H_3$) 1.40–1.50 (2H, m, C^4H_2), 1.99 (3H, s, $C^{12}H_3$), 1.61 (3H, s, $C^{15}H_3$, *E* isomers), 1.67 (6H, s, $C^{13}H_3$ and $C^{15}H_3$, *Z* isomers), 1.80–2.10 (10H, m, C^1H_2, C^2H_2, C^5H_2, C^8H_2 and C^9H_2), 3.35–3.45 (1H, m, $CHHCH_3$), 3.70–3.80 (1H, m, $CHHCH_3$), 5.05–5.15 ppm (3H, m, C^6H, $C^{10}H$ and $C^{16}H$); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS), δ=15.16 and 15.24 (CH_2CH_3), 15.85 and 15.90 (C^{15}, *E* isomers), 17.61 (C^{12}), 23.06, 23.17, 23.34 and 23.52 (C^5), 23.33 (C^{15}, *Z* isomers), 25.63 (C^{13}), 26.63 and 26.73 (C^9), 28.25 and 30.09 (C^{14}), 31.92 (C^8, *Z* isomers), 32.73 and 33.33 (C^1), 34.50 and 34.88 (C^2), 39.70 (C^8, *E* isomers), 41.96, 42.26, 42.82 and 43.10 (C^4), 62.00 and 62.12 (CH_2CH_3), 84.09, 84.15 and 84.44 (C^3), 103.61 and 103.87 (C^{16}), 124.64 (C^6 and C^{10}), 131.08 and 131.29 (C^{11}), 134.66 and 134.84 ppm (C^7).

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Rhodium catalyzed hydroformylation of nerolidol

Catal. Sci. Technol. **Year**, *Volume*, Page – Page

Marina C. de Freitas, Kelley C. B. de Oliveira, Amanda de Camargo Faria, Eduardo N. dos Santos and Elena V. Gusevskaya*