Applied Catalysis A, General 591 (2020) 117406

Contents lists available at ScienceDirect

Applied Catalysis A, General

journal homepage: www.elsevier.com/locate/apcata

Hydroformylation of recalcitrating biorenewable compounds containing trisubstituted double bonds

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ARTICLE INFO

Keywords:
Biorenewables
α-Ionone
Hydroformylation
Limonene
Terpineol
Rhodium

ABSTRACT

Hydroformylation is a useful tool in industrial organic syntheses and it is easily applied to substrates containing terminal C—C double bonds. Applying this reaction to substrates containing other functionalities or trisubstituted C—C double bonds is not straightforward. Herein, the hydroformylation of several biorenewable alkenes with these features, namely: α-terpineol, terpinen-4-ol, limonene (double hydroformylation), and α-ionone, is presented. Only by the judicious choice of the catalytic system and reaction conditions, was it possible to obtain good yields and selectivity for these substrates.

1. Introduction

Transition-metal-catalyzed hydroformylation is one of the most powerful tools for the formation of carbon-carbon bonds in industrial organic synthesis. The reaction offers an access to aldehydes starting from olefins through the addition of carbon monoxide and hydrogen ("syngas") and represents one of the largest industrial applications of homogeneous catalysis [1–6]. A high potential of hydroformylation for the production of flavor&fragrance compounds is widely recognized; however, commercial applications of this reaction in fine chemical industry are still limited [5,7,8]. The use of biorenewable olefins as substrates in hydroformylation is especially valuable within the green chemistry concept as it allows decreasing the dependence of chemical industry on fossil resources [9–12]. The solvent nature is another important issue for liquid phase chemical processes [13–15]. Most of the hydroformylation reactions in both academia and industry are currently performed in the presence of solvents, usually rather toxic aromatic compounds such as benzene and toluene. The replacement of these solvents for eco-friendly alternatives would also contribute in the sustainability of hydroformylation processes.

Terpenes are natural compounds easily available from essential oils of plants and flowers. Due to remarkable olfactory properties and biological activity, terpenes are traditionally used as ingredients in fragrance, cosmetic and pharmaceutical compositions [16–18]. Moreover, terpenes can be transformed into other commercially valuable products through a variety of chemical reactions [8,9,19–21]. Hydroformylation is a particulary atractive method for upgrading of terpenes as an aldehyde functionality usually confers a pleasant scent on the whole molecule. The hydroformylation of simple terpenes containing terminal olefinic bonds, such as limonene, β-pinene and camphene, is well documented in the literature [8,22–30]. On the other hand, examples of using functionalized terpenes, especially those with sterically hindered C—C double bonds, as substrates in hydroformylation are much more scarce [8,31–35].

α-Terpineol is the most important monoterpenic alcohol and one of the top 30 commonly used fragrance ingredients. This alcohol has a pleasant lilac smell and occurs in various essential oils, such as conifer, lavander, cajuput and petitgrain oils. For technical applications α-terpineol is produced from α-pinene or limonene by acid catalyzed isomerization/hydration or through the partial dehydration of terpin hydrate obtained from turpentine oil [17,36,37]. The commercial mixtures of synthetic α-terpineol usually contain considarable amounts of γ-terpineol, which is much less common in nature than α-terpineol. Another isomer, terpinen-4-ol, is also a by-product in the production of α-terpineol from terpin hydrate. Terpinen-4-ol presents a spicy, woody-earthy, nutmeg-like and lilac smell and occurs in significant amounts in many essential oils, such as pine and eucalyptus oils [17]. The hydroformylation of terpineols could provide an access to polifunctionalized compounds with interesting olfactory characteristics; however, it is a challenging task as the C—C double bonds in their molecules are endocyclic and sterically hindered. We could find only one work on the hydroformylation of α-terpineol, which described the formation of a complex mixture of aldehydes under drastic reaction conditions (160 °C, 70 bar) in toluene solutions [38]. The aldehyde mixture

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https://doi.org/10.1016/j.apcata.2019.117406
Received 21 October 2019; Received in revised form 27 December 2019; Accepted 29 December 2019
Available online 31 December 2019
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Table 1
Hydroformylation of α-terpineol (**1**) in toluene solutions: ligand effect[a].

Run	Ligand	TOF[b]	Time	Conversion	Selectivity for aldehydes		
	(P/Rh)	(h^{-1})	(h)	(%)	Total	**1a**	**1b**
1	PPh_3 (5)	2	6	4	100	49	51
			24	8	100	55	45
2	none	22	6	26	62	45	17
			24	66	77	58	19
3	(2,4-di-^{t}Bu$C_6H_3O)_3P$ (2)	40	6	50	87	57	30
			24	92	97	62	35
4	(2,4-di-^{t}Bu$C_6H_3O)_3P$ (5)	36	6	44	100	66	34
			24	91	100	66	34
5	(2,4-di-^{t}Bu$C_6H_3O)_3P$ (10)	34	6	47	100	65	35
			24	91	100	65	32
6	(2,4-di-^{t}Bu$C_6H_3O)_3P$ (20)	30	6	43	100	65	35
			24	90	100	68	32
7	(2,4-di-^{t}Bu$C_6H_3O)_3P$ (30)	26	6	36	100	65	35
			24	84	100	68	32

[a] Conditions: [α-terpineol] – 0,20 M (4 mmol), $[Rh(COD)(OMe)]_2$ – 0,25 mM (5 μmol), 120 °C, gas phase – 40 atm (CO/H_2 = 1/1), toluene – 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene); the rest of the mass balance was due to the formation of isomers of α-terpineol.
[b] TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (≤ ca. 30–40 %).

presented a pleasant woody and nutty aroma. As concerns terpinen-4-ol, we could not find any reports on the hydroformylation of this substrate starting the present project.

α − Ionone is a natural product found in various essential oils, such as rose oil, and is also produced synthetically in a large industrial scale. α − Ionone is also a terpenoid compound belonging to the specific class of norisoprenoids. Ionones are highly required as comercial fragrance ingradients and also known to present important pharmacological properties [17,39]. The catalytic functionalization of the molecule of α-ionone, which contains two olefinic bonds and a ketone moiety, could offer the access to new compounds with pharmaceutical and fragrance potential [40]. No studies on the hydroformylation of α-ionone were previously reported in the literature as far as we know.

Herein, we present a first systematic study on the hydroformylation of α-terpineol and terpinen-4-ol. Catalytic systems and conditions were found to allow the synthesis of corresponding hydroxyaldehydes in good yields. The expertise obtained in these studies has been extended to related compounds, *α*-ionone and limonene, which have a similar trisubstituted endocyclic C—C double bond in their structures. We also demonstrated that the reactions can be performed in environmentally more benign solvents, as compared to conventionally used toluene, such as anisole, *p*-cymene, and diethylcarbonate.

2. Experimental

All chemical products were from commercial sources and used without special treatment, unless otherwise indicated. (*R*)-(+)-limonene (97 %), α-terpineol ((≥95 %), (−)-terpinen-4-ol (≥95 %), α-ionone (90 %), triphenylphosphine (PPh_3) and tris(2,4-di-tert-butylphenyl)phosphite, (2,4-di-^{t}Bu$C_6H_3O)_3P$, were received from Sigma-Aldrich. The catalyst precursor, $[Rh(COD)(OMe)]_2$ (COD = 1,5-cyclooctadiene), was synthesized by a previously reported method [41]. Toluene (anhydrous, 99.8 %), diethyl carbonate (DEC) (anhydrous, ≥99 %), anisole (anhydrous, 99.7 %) and *p*-cymene (99 %) were purchased from Sigma-Aldrich. Toluene was passed through a silica column and stored in an argon-filled glove box. Anisole, purchased in a Sure/Seal™ bottle, was opened, stored in the glove box and used without special treatment. DEC was distilled under argon and stored over 4 Å molecular sieves. *p*-Cymene was distilled in a Kugelrohr distillation apparatus, collected under argon and stored in the glove box.

Catalytic reactions were run in a 100 mL homemade stainless steel autoclave with magnetic stirring. Aliquots were periodically taken from the reaction solutions using a valved dip tube without depressurization of the reactor. The samples were analyzed by gas chromatography (GC) using a GC- Shimadzu GC2010 chromatograph equipped with a Rtx®-5MS capillary column and FID detector. Conversion and selectivity were calculated based on the reacted substrate using *p*-xylene as an internal standard. Initial turnover frequencies (TOFs) were calculated at low conversions, usually less than 40 %. In a typical run, a solution (20.0 mL) of the substrate (4 mmol), $[Rh(COD)(OMe)]_2$ (5.0 μmol), phosphorus ligand (0–0.30 mmol) and *p*-xylene (2 mmol, GC internal standard) in a specified solvent was placed into the reactor under argon; the reactor was pressurized with "syngas" to 40–80 at m (CO/H_2 = 1/2 to 2/1) and heated to the specified temperature. Then, the reaction mixture was stirred with a magnetic stirrer for the specified time.

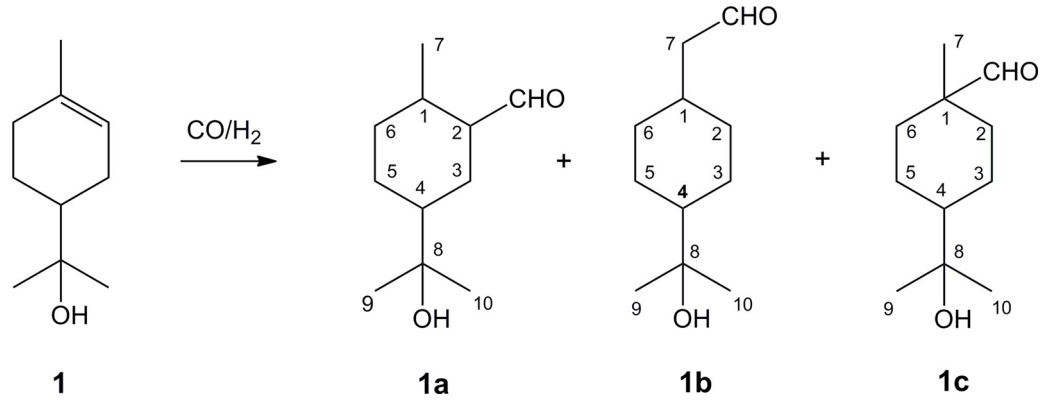
After the reaction, the solutions were analyzed by gas chromatography/mass spectrometry (GC–MS) on a Shimadzu QP2010-PLUS equipment operating at 70 eV. Main reaction products were isolated from the reaction solutions by column chromatography (silica gel 60, hexane/ethyl acetate mixtures) and identified by NMR spectroscopy (DEPT, COSY, HMQC, HMBC and NOESY experiments) on a Bruker 400 MHz spectrometer ($CDCl_3$, TMS) (see Supplementary Material).

3. Results and discussion

3.1. Hydroformylation of α-terpineol

As the endocyclic olefinic bond in the molecule of α-terpineol (**1**) is sterically hindered, the hydroformylation was expected to be a challenging task for this substrate. The attempts to run the reaction in the presence of triphenylphosphine were unsuccessful. Only 8 % of α-terpineol was consumed for 24 h at 120 °C and 40 atm of syngas (Table 1, run 1). However, in a non-promoted system, i.e, in the absence of auxiliary phosphorous ligands, α-terpineol showed much higher reactivity. Under the same conditions as in run 1 for 24 h, nearly a 70 % substrate conversion was achieved with the formation of hydroformylated products in 77 % combined selectivity (Table 1, run 2). The rest of the mass balance was due to the appearance of several isomers of α-terpineol, such as other *para*-menthenic alcohols and isoborneol (identified based on their characteristic mass-spectra and GC retention times).

The hydroformylation products were isolated from the reaction solutions by column chromatography and characterized by MS and NMR spectroscopy. The major product (ca. 60 % selectivity) was identified as endocyclic aldehyde **1a** derived from the carbonylation of the less substituted olefinic carbon in the α-terpineol molecule. The second main product formed in smaller amounts (ca. 20 % selectivity) was terminal aldehyde **1b** with the formyl group at exocyclic carbon



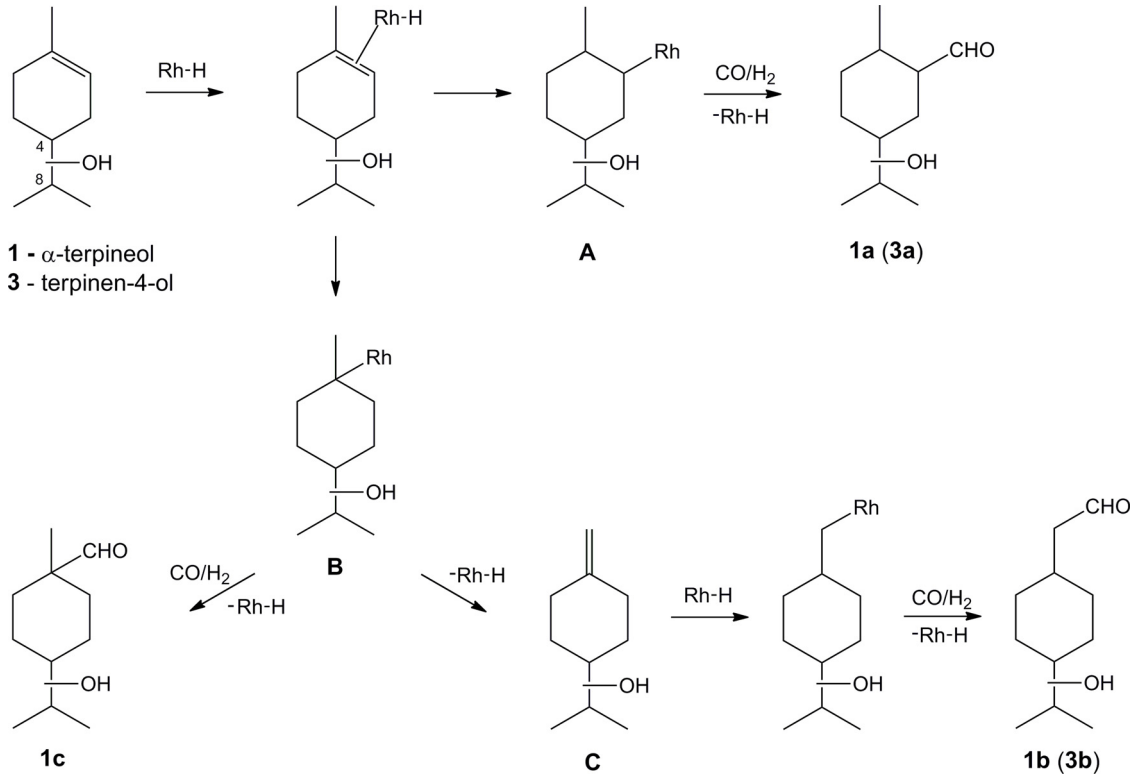
Scheme 1. Hydroformylation of α-terpineol (**1**).

C7. Quaternary aldehyde **1c** with the formyl group at carbon C1 was detected only in trace amounts. The determined structures of products **1a**, **1b** and **1c** are presented in Schemes 1 and 2.

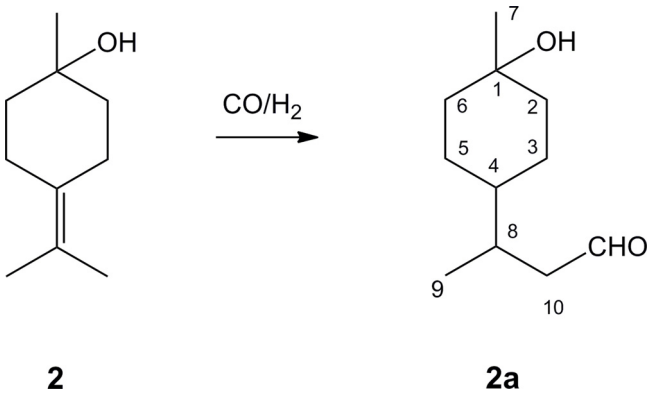
The appearance of terminal aldehyde **1b** in significant amounts among the products suggests two alternative reactions pathways. The first alternative (not shown in Scheme 2) would consist in the formation of rhodium η^3-allylic intermediates involving C1, C2 and C7 carbons, followed by their carbonylation. However, this pathway looks unlikely because i) the carbonylation of η^3-allylic complexes would give terminal aldehyde **1b** in greater amounts as compared to endocyclic aldehyde **1a** for steric reasons; ii) rhodium η^3-allylic complexes are known to be very resistant to the insertion of carbon monoxide [28,29,42]; iii) quaternary aldehyde **1c** could not be formed at the carbonylation of η^3-allylic complexes. The alternative which involves the formation of rhodium η^1-alkyl intermediates shown in Scheme 2 seems more reasonable for the hydroformylation of α-terpineol.

The major aldehyde **1a** arises from intermediate **A** with rhodium attached to the less substituted carbon of the olefinic bond; whereas intermediate **B** with rhodium at the quaternary carbon originates aldehydes **1b** and **1c**. The Markovnikov type addition of Rh-H to the olefinic bond gives intermediate **B**, but the attack of the tertiary alkyl ligand by the carbonyl, the next step for the hydroformylation cycle, is disfavored by steric reasons and the β-elimination to yield intermediate **C** is the preferred path. For this reason, quaternary aldehyde **1c** is expected to be formed only in small amounts. On the other hand, terminal aldehyde **1b**, which is also derived from intermediate **B**, is formed in significant amounts (20–30 % selectivity based on the reacted α-terpineol). Aldehyde **1b** is the product of the hydroformylation of terminal olefin **C**, the isomer of the original α-terpineol (Scheme 2). Due to the much higher reactivity of the terminal double bond in hydroformylation, terpineol **C** was not observed in the reaction solutions, it was readily converted into aldehyde **1b**.

The NMR analysis showed the presence of ca. 5 % of γ-terpineol (**2**) in the commercial α-terpineol used as the substrate. It was observed that under the hydroformylation conditions, γ-terpineol reacted faster than α-terpineol yielding hydroformylation product **2a** (Scheme 3), in



Scheme 2. Mechanistic scheme for the hydroformylation of α-terpineol (**1**) and terpinen-4-ol (**3**).



Scheme 3. Hydroformylation of γ-terpineol (**2**).

amounts corresponding to the γ-terpineol content in the original substrate mixture. Aldehyde **2a** was isolated from the reaction solutions as an individual compound and fully characterized by MS and NMR spectroscopy.

The addition of (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P as an auxiliary ligand allowed to nearly double the hydroformylation rate as compared to the non-promoted system and also to increase the combined selectivity for main aldehydes **1a** and **1b** up to 97 % (Table 1 run 3 vs. run 2). The advantageous effect of bulky phosphites in hydroformylation of sterically hindered olefins can be explained by their steric and electronic properties [1,43,44]. The large cone angles prevent the coordination of more than one phosphite ligand on the same rhodium atom to give bis-ligand species, which are expected to be catalytically less active due to the lack of space for the olefin coordination. In addition, the weaker electron-donating and stronger electron-withdrawing ability of bulky phosphite ligands, as compared to triphenylphosphine, benefit the dissociation of carbon monoxide and coordination of the olefin on the metal centre. Low concentrations of (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P (P/Rh = 2 and 5) induced a beneficial effect on the reaction rate; however, with larger ligand amounts (P/Rh = 10, 20 and 30) the reaction became slower, probably, due to the difficulty for the bulky substrate to compete with the also bulky ligand for the coordination sites on rhodium (Table 1, runs 3–7).

In the system promoted by (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P with P/Rh ≥ 5, aldehydes **1a** and **1b** were virtually exclusive reaction products, with no substrate isomerization occurring in an appreciable extent (Table 1, runs 4–7).

We also studied the effects of the total pressure of syngas (Table 2) both for (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P promoted (runs 1 and 2) and non-promoted (runs 3 and 4) systems. Under doubled pressure of the equimolar carbon monoxide/hydrogen mixture, the reaction occurred at much higher rates, under both conditions: with and without the auxiliary ligand. Considering that our first attempts to apply the non-promoted rhodium system, the selectivity for the hydroformylation products was significantly lower than in the Rh/phosphite system: 77% at 66% conversion (Table 1, run 2), working with higher pressure (80 atm) showed to be an excellent alternative for non-promoted systems. Moreover, the isomers of α-terpineol seem to be consumed to yield exclusively aldehydes **1a** and **1b** at longer reaction times under higher pressures (Table 2, run 4).

In a further work we directed our efforts to substitute toluene, a fossil-based and rather toxic solvent conventionally used in hydroformylation, by the solvents considered greener in modern solvent selection guides [45,46]. As the solvent usually responds for the major part of the environmental impact caused by the industrial chemical process, the replacement of solvent for more benign alternative would significantly contribute for the process sustainability. The hydroformylation of α-terpineol in different solvents was compared with that in toluene for the systems with (Table 4) and without (Table 3) the auxiliary (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P ligand. *p*-Cymene, considered as a renewable and low-toxic compound, showed nearly the same performance as a reaction medium for the hydroformylation of α-terpinol as compared to that of toluene, in terms of both catalytic activity and selectivity. *p*-Cymene, a natural compound occurring in various essential oils, is currently produced from petrochemical materials; however, it can be also obtained in a large scale from limonene, one of the most abundant in nature terpenic compound.

Diethylcarbonate (DEC) and anisole are highly recommended green solvents by solvent selection guides with even better score than *p*-cymene [45,46]. Being low-toxic and biodegradable, DEC and anisole occupy in these guides prestigious positions with impressive overall rankings comparable to those of ethanol and water [45,46]. Both DEC and anisole showed an excellent performance as the solvents to perform the hydroformylation of α-terpineol. Aldehydes **1a** and **1b** were obtained with 95–97 % combined selectivity.

As it can be noticed in Tables 3 and 4, *p*-cymene and DEC are better alternatives than toluene for this reaction as they give similar outputs as toluene and are environmentally preferable. Anisole, a low-cost, non-toxic and biodegradable compound, deserves a special attention as the greenest option with the highest sustainability rank within the solvent series tested. Although the manufacture of anisole is currently based on petrochemicals, it can be also produced from renewable materials such as lignin and guaiacol. In anisole solutions, the reaction in the

Table 2
Hydroformylation of *α*-terpineol (**1**): effect of pressure[a].

Run	$P(H_2)$	$P(CO)$	TOF[b]	Time	Conversion	Selectivity for aldehydes		
			(h^{-1})	(h)	(%)	Total	**1a**	**1b**
1	20	20	36	6	44	100	66	34
				24	91	100	66	34
2	40	40	56	6	60	90	65	25
				24	95	96	68	28
3[c]	20	20	22	6	26	62	45	17
				24	66	77	58	19
4[c]	40	40	54	6	56	89	60	29
				24	94	100	70	30

[a] Conditions: [*α*-terpineol] – 0,20 M (4 mmol), [Rh(COD)(OMe)]$_2$ – 0,25 mM (5 μmol), ligand – (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P (P/Rh = 5), 120 °C, toluene – 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene); the rest of the mass balance was due to the formation of isomers of *α*-terpineol.

[b] TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (≤ ca. 30–40 %).

[c] In the absence of (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P.

Table 3
Hydroformylation of *α*-terpineol (**1**) with non-promoted Rh system in various solvents[a].

Run	Solvent	TOF[b]	Time	Conversion	Selectivity for aldehydes		
		(h^{-1})	(h)	(%)	Total	**1a**	**1b**
1	Toluene	54	6	56	89	60	29
			24	94	100	70	30
2	*p*-Cymene	46	6	55	89	60	29
			24	94	97	65	32
3	DEC	52	6	60	91	63	28
			24	95	96	64	32
4	Anisole	50	6	58	88	61	27
			24	95	95	65	30

[a] Conditions: [*α*-terpineol] – 0,20 M (4 mmol), [Rh(COD)(OMe)]$_2$ – 0,25 mM (5 μmol), 120 °C, gas phase – 80 atm (CO/H_2 = 1/1), solvent – 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene); the rest of the mass balance was due to the formation of isomers of *α*-terpineol. DEC: diethylcarbonate.

[b] TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (≤ ca. 30–40 %).

Table 4
Hydroformylation of α-terpineol (**1**) with Rh/(2,4-di-^{t}BuC$_6$H$_3$O)$_3$P system in various solvents[a].

Run	Solvent	TOF[b]	Time	Conversion	Selectivity for aldehydes		
		(h^{-1})	(h)	(%)	Total	**1a**	**1b**
1	Toluene	56	6	60	90	65	25
			24	95	96	68	28
2	*p*-Cymene	48	6	62	100	69	31
			24	97	100	70	30
3	DEC	50	6	63	99	68	31
			24	97	100	67	29
4	Anisole	66	6	73	97	68	29
			24	97	98	65	33

[a] Conditions: [α-terpineol] – 0,20 M (4 mmol), [Rh(COD)(OMe)]$_2$ – 0,25 mM (5 μmol), ligand – (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P (P/Rh = 5), gas phase – 80 atm (CO/H$_2$ = 1/1), 120 °C, solvent – 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene); the rest of the mass balance was due to the formation of isomers of α-terpineol. DEC: diethylcarbonate.

[b] TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (≤ ca. 30–40 %).

phosphite promoted system occurred even faster than in toluene (Table 4, run 4 vs. run 1), reinforcing the recommendation of this solvent for hydroformylation, as disclosed in our recent work [15].

3.2. Hydroformylation of terpinen-4-ol

To the best of our knowledge, this is the first time that the hydroformylation of terpine-4-ol is described. Representative results are presented in Table 5. The products were isolated from the reaction solutions and identified by MS and NMR spectroscopy. All isolated compounds and their mixture have a pleasant smell. Two main products were endocyclic aldehyde **3a** derived from the carbonylation of the less substituted olefinic carbon and terminal aldehyde **3b** with the formyl group at exocyclic carbon C7 (Scheme 4). In the molecule of terpinen-4-ol, the hydroxyl group is closer to the C—C double bond as compared to α-terpineol. For this reason, aldehyde **3a** undergoes a partial (20–30 %) intramolecular cyclization to give the bicyclic compound **3c**. Such cyclization does not take place in the aldehydes **1a-c**. All three hydroformylation products were obtained with virtually 100 % combined selectivity. The regioselectivity of hydroformylation was similar for both substrates: endocyclic/terminal carbonylated products ≈ 70/30. The reaction scheme for terpinen-4-ol under hydroformylation conditions is analogous to that for α-terpineol presented in Scheme 2, added the cyclization step. The formation of terminal aldehyde **3b** was suggested to occur due to the migration of the original double bond to the terminal position to give isomeric terpineol **C** followed by its fast hydroformylation. The hydroformylation of terpinen-4-ol was successfully performed both in non-promoted and (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P promoted systems at similar rates and with similar product distribution (Table 5, runs 1 and 2). The increase in the concentrations of phosphite decelerated the reaction due to the more severe competition for the coordination sites on rhodium between the bulky ligand and the also bulky substrate. It should be mentioned that although non-promoted systems have an advantage to be less costly; the presence of phosphorous ligands usually allows stabilizing better rhodium species in solutions and makes easier the catalyst recovery.

Table 5
Hydroformylation of terpinen-4-ol (**3**)[a].

Run	P/Rh	TOF[b]	Time	Conversion	Selectivity (%)		
		(h^{-1})	(h)	(%)	**3a**	**3b**	**3c**
1	0	31	6	41	66	21	13
			24	87	64	24	12
2	5	35	6	48	62	21	17
			24	90	60	24	16
3	20	16	6	25	61	22	17
			24	71	62	24	14
4[c]	5	42	6	55	61	21	18
			24	95	62	24	14

[a] Conditions: [terpinen-4-ol] – 0,20 M (4 mmol), [Rh(COD)(OMe)]$_2$ – 0,25 mM (5 μmol), ligand – (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P, 120 °C, gas phase – 80 atm (CO/H$_2$ = 1/1), toluene – 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene).

[b] TOF – initial turnover frequency (mol of the substrate converted per mol of Rh per hour) measured at low conversions (≤ ca. 30–40 %).

[c] Solvent – anisole.

It is noteworthy that the hydroformylation of terpinen-4-ol occurred slower than that of α-terpineol. Two hypothesis may explain this fact: i) stronger deactivation of the double bond toward the interaction with rhodium (I) species by the electron-withdrawing hydroxyl group in a homoallylic position; ii) the coordination of **3** on rhodium through both C═C and OH moieties to give a chelate complex, which is less prone to react via the hydroformylation mechanism. In addition, the hydroformylation of terpinen-4-ol can be also performed in eco-friendly anisole even at a higher rate as compared to toluene (Table 5, run 4 vs. run 2).

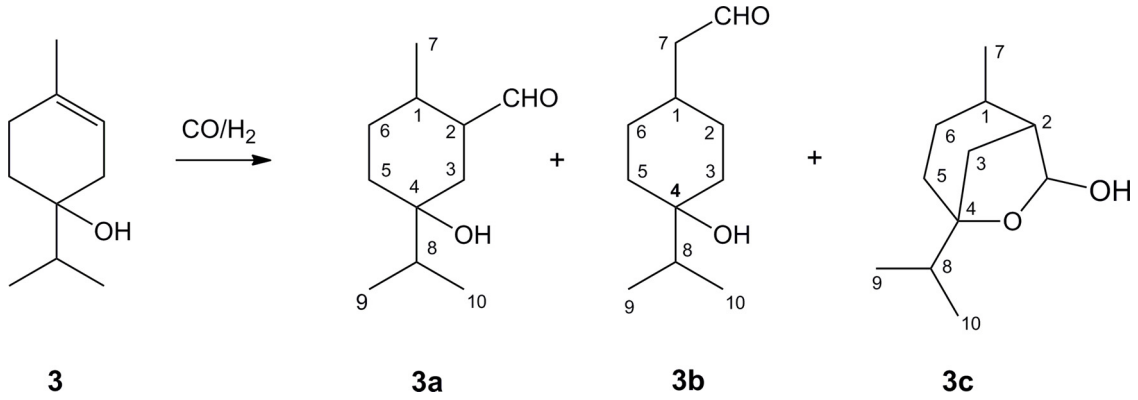
3.3. Hydroformylation of endocyclic double bonds in related substrates

3.3.1. Double hydroformylation of limonene

Encouraged by the results obtained at the hydroformylation of terpineols, we directed our attention to limonene, one of the most abundant and low cost terpenic compounds available (Table 6). The molecule of limonene (**4**) has two C—C double bonds: the terminal and the endocyclic ones, the latter being similar to the double bonds in the molecules of terpineols. The relatively facile hydroformylation of limonene in the terminal position to give monoaldehyde **4a** (Scheme 5) has been reported in several previous studies [8,22,23]. However, the reports dealing with the double-hydroformylation of limonene, which involves in the reaction its trisubstituted endocyclic double bond, are really scarce [47].

The first hydroformylation of limonene, i.e. the hydroformylation of the terminal double bond to give monoaldehyde **4a**, readily occurred at 80 °C resulting in a complete limonene conversion in ca. 2 h (Table 6, run 1). However, under these conditions, aldehyde **4a** was extremely resistant toward hydroformylation, with only small amounts of dialdehydes **4b** and **4c** appearing even after 48 h of the reaction. We expected that the hydroformylation of the endocyclic double bond in aldehyde **4a** could be performed under more severe temperature conditions, similarly to the hydroformylation of terpineols. The increase in the reaction temperature to 100 and then to 120 °C allowed to accelerate the second hydroformylation step and to achieve a nearly complete conversion of the monoaldehyde in 48 h (Table 6, runs 2 and 3). The products of double-hydroformylation, dialdehydes **4b** and **4c**, were isolated from the reaction solution and identified by NMR spectroscopy (Scheme 5). The product **4b** contains two formyl groups in endocyclic and terminal positions, whereas both formyl groups in minor product **4c** are in terminal positions (**4b**/**4c** ≈ 2:1 in most of the runs).

Nevertheless, the combined selectivity for dialdehydes **4b** and **4c** did not exceed 65 %, even after the attempts to optimize the reaction conditions (Table 6, runs 3–5). The rest of the mass balance was due to the isomerization of limonene and the hydroformylation of these isomers to give corresponding aldehydes (identified based on their characteristic mass-spectra and GC retention times). A significant improvement in selectivity was achieved by running the reaction in two consecutive steps: first, transforming completely limonene into monoaldehyde **4a** at lower temperature and then increase the temperature of the mixture. With this procedure we expected suppressing isomerization because, differently from the original limonene, aldehyde **4c** does



Scheme 4. Hydroformylation of terpinen-4-ol (**3**).

Table 6
Hydroformylation of limonene (**4**)[a].

Run	P/Rh	*P*	*T*	Time	Conversion	Selectivity for aldehydes		
		(atm)	(ºC)	(h)	(%)	**4a**	**4b**	**4c**
1	10	40	80	2	94	97	0	0
				48	100	83	12	4
2	10	40	100	2	99	91	0	0
				48	100	31	44	17
3	10	40	120	2	99	87	8	4
				48	100	1	47	20
4	5	40	120	2	99	80	10	5
				24	100	6	46	20
5	5	80	120	2	98	70	11	1
				24	100	6	46	15
6[b]	10	80	70	9	96	98	0	0
			120	24	100	5	65	23
7[b]	0	80	60	4	96	96	0	0
			120	48	100	7	50	20
8[bc]	10	80	70	9	98	98	0	0
			120	24	100	3	67	24
9[bc]	0	80	60	4	95	96	0	0
			120	48	100	4	53	28

[a]Conditions: [limonene] - 0,20 M (4 mmol), $[Rh(COD)(OMe)]_2$ - 0,25 mM (5 μmol), ligand – (2,4-di-^{t}Bu$C_6H_3O)_3$P, gas phase – CO/H_2 = 1/1, toluene - 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene); the rest of the mass balance was due to the formation of isomers of limonene and their aldehydes. [b] After the indicated time, the temperature was increased to 120 °C and the reaction was continued for the indicated time. [c] Solvent – anisole.

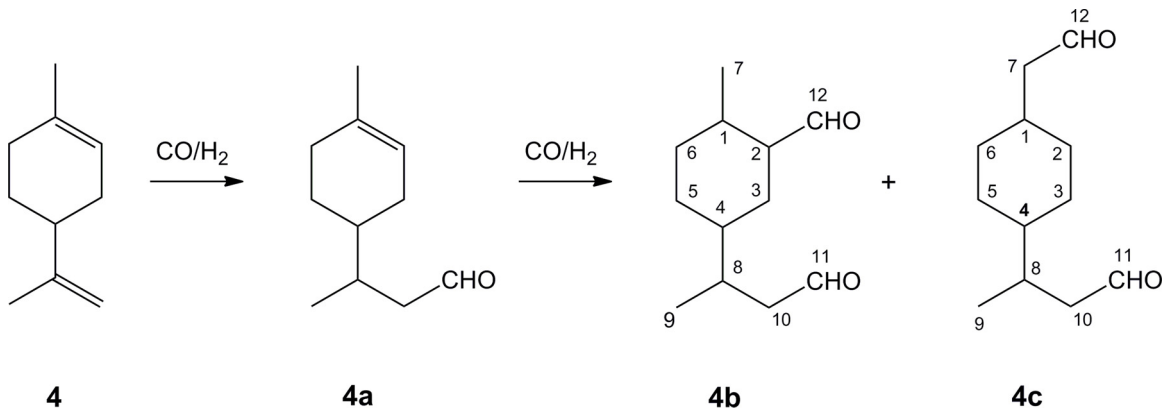
Table 7
Hydroformylation of α-ionone (**5**)[a].

Run	P/Rh	Time	Conversion	Selectivity (%)		
		(h)	(%)	**6**	**6a**	**6b**
1	0	5	100	96	4	0
		24	100	77	21	2
		170	100	20	43	32
2	5	5	98	97	3	0
		24	100	70	28	2
		170	100	13	46	30
3[b]	5	5	96	95	5	0
		24	100	68	26	2
		170	100	10	49	30

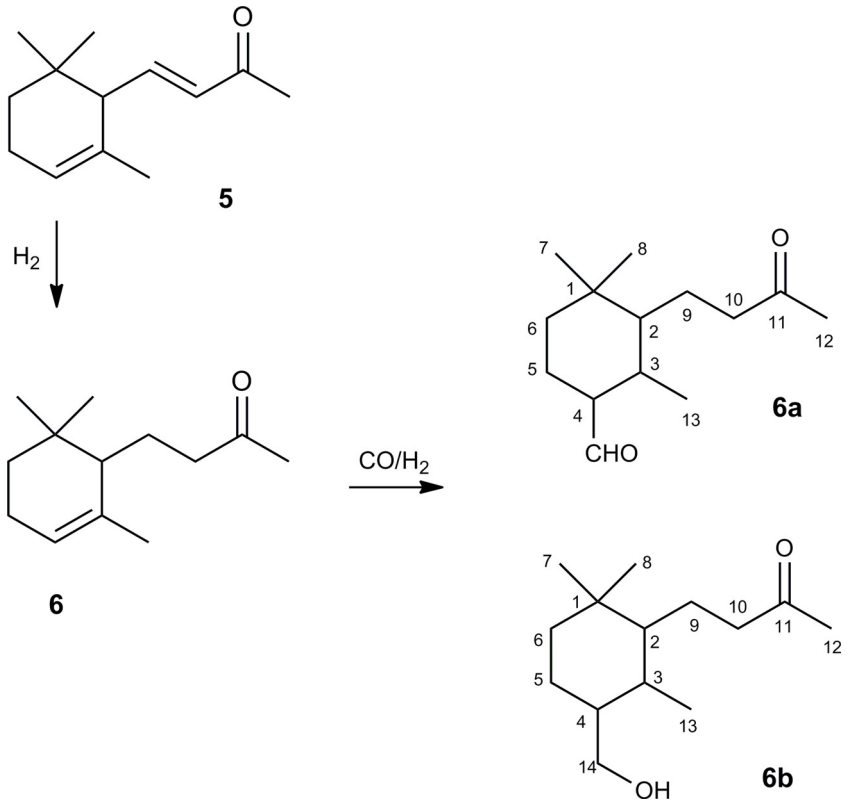
[a] Conditions: [α-ionone] – 0,20 M (4 mmol), $[Rh(COD)(OMe)]_2$ – 0,25 mM (5 μmol), ligand – (2,4-di-^{t}Bu$C_6H_3O)_3$P, 120 °C, gas phase – 80 atm (CO/H_2 = 1/1), toluene – 20 mL. Conversion and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene); the rest of the mass balance was due to the formation of the isomers of aldehyde **6a**.
[b] Solvent – anisole.

not contain a terminal double bond and is therefore more stable toward isomerization. Indeed, it was the case.

Representative data on the two-step hydroformylation of limonene in toluene and anisole solutions are presented in Table 6. The combined selectivity for dialdehydes **4b** and **4c** of ca. 90 % was obtained in both solvents in the presence of (2,4-di-^{t}Bu$C_6H_3O)_3$P ligand, which is the best result ever reported for this reaction as far as we know (Table 6, runs 6 and 8). The process can also be performed in the absence of phosphite; however, with slightly lower selectivity in the second step (Table 6, runs 7 and 9). Both dialdehydes derived from limonene and their mixture presented a pleasant smell. It is important that the dihydroformylation of limonene can be successfully performed in the solutions of environmentally benign anisole without any loss in the catalyst performance. In the non-promoted system, the reaction in anisole showed higher selectivity for dialdehydes (81 %) as compared to that in toluene (70 %) (Table 6, run 9 vs. run 7).



Scheme 5. Hydroformylation of limonene (**4**).



Scheme 6. Transformations of α-ionone (**5**) under hydroformylation conditions.

3.3.2. Hydroformylation of α-ionone

As hydroformylation is an interesting way of adding a new functionality in the molecule, herein we report for the first time the hydroformylation of α-ionone, which is also a terpenoid compound belonging to the specific class of norisoprenoids. Representative results are shown in Table 7. Under hydroformylation conditions, it was observed a relatively fast hydrogenation of the exocyclic double bond in α-ionone to give compound **6** shown in Scheme 6. This compound showed to be rather resistant to hydroformylation, even under quite harsh reaction conditions. With non-promoted system (Table 7, run 1), after 24 h only 23 % of **6** was transformed into hydroformylation products shown in Scheme 6. After 170 h the yield increase to 80 %, but a fair amount of aldehyde **6a** was reduced to corresponding alcohol **6b**. In the presence of (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P the results were only slightly better. The reaction can be also performed in the solutions of anisole, a green eco-friendly solvent (Table 7, run 3).

Thus, our studies have demonstrated that α-ionone is a particularly difficult substrate to be transformed through hydroformylation, but the combined yield of the hydroformylation products may reach ca. 80 % under harsh conditions and at long reaction times.

4. Conclusions

In this work the reactivity of several biorenewable terpenic substrates recalcitrant to undergo hydroformylation was exploited. To achieve the goal, it was necessary to employ comparatively harsh reaction conditions and rhodium systems with electron-withdrawing ligands which allow room to facilitate substrate coordination, namely CO (non-promoted system) or (2,4-di-^{t}BuC$_6$H$_3$O)$_3$P, a bulky phosphite that produces mostly rhodium species containing only one phosphite ligand. With this strategy it was possible to carry out the hydroformylation of α-terpineol, terpinen-4-ol, and α-ionone. A two-step protocol to promote the double hydroformylation of limonene was also developed with unprecedented yields and selectivity for corresponding dialdehydes. Finally, it was demonstrated that these reactions can be carried out in anisole, a highly recommended green solvent, or alternative solvents such as *p*-cymene and diethylcarbonate, all having better sustainability ranking than the now standard toluene.

CRediT authorship contribution statement

Amanda de Camargo Faria: Conceptualization, Investigation, Writing - original draft. **Mileny P. de Oliveira:** Investigation, Validation. **Amanda C. Monteiro:** Investigation, Validation. **Rayssa L.V. Mota:** Investigation, Validation. **Kelley C.B. Oliveira:** Methodology, Project administration. **Eduardo N. dos Santos:** Conceptualization, Writing - review & editing. **Elena V. Gusevskaya:** Conceptualization, Supervision, Writing - review & editing.

Acknowledgments

CNPq, CAPES, FAPEMIG, and INCT-Catálise (Brazil) are gratefully thanked for the financial support and fellowships.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.apcata.2019.117406.

References

[1] P.W.N.M. van Leeuwen, C. Claver, Rhodium Catalyzed Hydroformylation, Kluwer Academic Publishers, Dordrecht, 2000.
[2] A. Börner, R. Franke, Hydroformylation. Fundamentals, Processes, and Applications in Organic Synthesis, Wiley-VCH, Weinheim, 2016.
[3] C.W. Kohlpaintner, R.W. Fischer, B. Cornils, Appl. Catal. A Gen. 221 (2001) 219–225.
[4] H.-W. Bohnen, B. Cornils, Adv. Catal. 47 (2002) 1–64.
[5] R. Franke, D. Selent, A. Börner, Chem. Rev. 112 (2012) 5675–5732.
[6] J. Hibbel, E. Wiebus, B. Cornils, Chem. Ing. Tech. 85 (2013) 1853–1871.

[7] G.T. Whiteker, C.J. Cobley, Top. Organomet. Chem. 42 (2012) 35–46.
[8] E.V. Gusevskaya, J. Jimènez-Pinto, A. Börner, ChemCatChem 6 (2014) 382–411.
[9] A. Behr, A.J. Vorholt, K.A. Ostrowski, T. Seidensticker, Green Chem. 16 (2014) 982–1006.
[10] A. Behr, L. Johnen, Ch-J. Li (Ed.), Handbook of Green Chemistry, Volume 7: Green Synthesis, first ed., Wiley-VCH, Weinheim, 2012, pp. 69–92.
[11] T. Vanbésien, E. Monflier, F. Hapiot, Eur. J. Lipid Sci. Technol. 118 (2016) 26–35.
[12] S.A. Jagtapa, E. Monflier, A. Ponchel, B.M. Bhanage, Mol. Catal. 436 (2017) 157–163.
[13] C.J. Clarke, W.C. Tu, O. Levers, A. Bröhl, J.P. Hallett, Chem. Rev. 118 (2018) 747–800.
[14] Y.L. Gu, F. Jerome, Chem. Soc. Rev. 42 (2013) 9550–9570.
[15] F.G. Delolo, E.N. dos Santos, E.V. Gusevskaya, Green Chem. 21 (2019) 1091–1098.
[16] C. Sell, The Chemistry of Fragrances: From Perfumer to Consumer, Vol. 2, second ed., RSC Publishing, Dorset, UK, 2006, pp. 52–88.
[17] H. Surburg, J. Panten, Common Fragrance and Flavor Materials. Preparation, Properties and Uses, Wiley-VCH, Weinheim, 2006.
[18] E. Breitmaier, Terpenes. Flavors, Fragrances, Pharmaca, Pheromones, Wiley-VCH, Weinheim, 2006.
[19] K.A.D. Swift, Top. Catal. 27 (2004) 143–155.
[20] J.L.F. Monteiro, C.O. Veloso, Top. Catal. 27 (2004) 169–180.
[21] E.V. Gusevskaya, ChemCatChem 6 (2014) 1506–1515.
[22] L. Kollár, J. Bakos, B. Heil, P. Sándor, G. Szalontai, J. Organomet. Chem. 385 (1990) 147–152.
[23] L. Kollár, G. Bódi, Chirality 7 (1995) 121–127.
[24] F. Azzaroni, P. Biscarini, S. Bordoni, G. Longoni, E. Venturini, J. Organomet. Chem. 508 (1996) 59–67.
[25] K. Soulantica, S. Sirol, S. Koinis, G. Pneumatikakis, Ph. Kalck, J. Organomet. Chem. 498 (1995) C10–C13.
[26] M.C. de Freitas, C.G. Vieira, E.N. dos Santos, E.V. Gusevskaya, ChemCatChem 5 (2013) 1884–1890.
[27] C.M. Foca, E.N. dos Santos, E.V. Gusevskaya, J. Mol. Catal. A Chem. 185 (2002) 17–23.
[28] C.M. Foca, H.J.V. Barros, E.N. dos Santos, E.V. Gusevskaya, J.C. Bayon, New J. Chem. 27 (2003) 533–539.
[29] H.J.V. Barros, J.G. da Silva, C.C. Guimarães, E.N. dos Santos, E.V. Gusevskaya, Organometallics 27 (2008) 4523–4531.
[30] C.G. Vieira, J.G. da Silva, C.A.A. Penna, E.N. dos Santos, E.V. Gusevskaya, Appl. Catal. A Gen. 380 (2010) 125–132.
[31] J.G. da Silva, H.J.V. Barros, E.N. dos Santos, E.V. Gusevskaya, Appl. Catal. A Gen. 309 (2006) 169–176.
[32] M.C. de Freitas, K.C.B. de Oliveira, A. de Camargo Faria, E.N. dos Santos, E.V. Gusevskaya, Catal. Sci.Technol. 4 (2014) 1954–1957.
[33] C.G. Vieira, E.N. dos Santos, E.V. Gusevskaya, Appl. Catal. A Gen. 466 (2013) 208–215.
[34] C.G. Vieira, M.C. de Freitas, K.C.B. Oliveira, A. de Camargo Faria, E.N. dos Santos, E.V. Gusevskaya, Catal. Sci.Technol. 5 (2015) 960–966.
[35] F.G. Delolo, K.C.B. Oliveira, E.N. dos Santos, E.V. Gusevskaya, Mol. Catal. 462 (2019) 1–9.
[36] P.A. Robles-Dutenhefner, K.A. da Silva, M.R.H. Siddiqui, I.V. Kozhevnikov, E.V. Gusevskaya, J. Mol. Catal. A Chem. 175 (2001) 33–43.
[37] M. Román-Aguirre, L. De la Torre-Sáenz, W. Antúnez Flores, A. Robau-Sánchez, A. Aguilar Elguézabal, Catal. Today 107-108 (2005) 310–314.
[38] F. Fujioka, R.M. Boden, J. Schreiber, (to International Flavors & Fragrances), US 4,491,537, (1985).
[39] M. Ansari, S. Emami, Eur. J. Med. Chem. 123 (2016) 141–154.
[40] M. dos Santos Costa, A.L.P. de Meireles, E.V. Gusevskaya, Asian J. Org. Chem. 6 (2017) 1628–1634.
[41] R. Uson, L.A. Oro, J.A. Cabeza, Inorg. Synth. 23 (1985) 126–127.
[42] P.W.N.M. van Leeuwen, C.F. Roobeek, J. Mol. Catal 31 (1985) 345–353.
[43] P.W.N.M. van Leeuwen, C.F. Roobeek, J. Organomet. Chem. 258 (1983) 343–350.
[44] H. Tricas, O. Diebolt, P.W.N.M. van Leeuwen, J. Catal. 298 (2013) 198–205.
[45] C.M. Alder, J.D. Hayler, R.K. Henderson, A.M. Redman, L. Shukla, L.E. Shuster, H.F. Sneddon, Green Chem. 18 (2016) 3879–3890.
[46] D. Prat, A. Wells, J. Hayler, H. Sneddon, C.R. McElroy, S. Abou-Shehada, P.J. Dunn, Green Chem. 18 (2016) 288–296.
[47] R. Franke, D. Fridag, D. Hess, F. Klasovsky, (to Evonik Industries AG), WO 2014/135413 A1, (2014).