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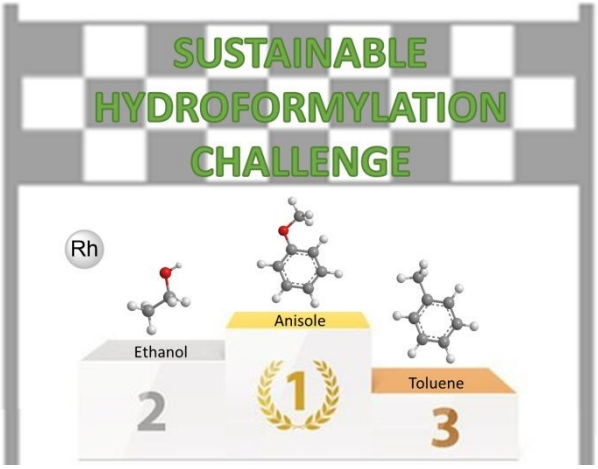

Anisole, a solvent with an impressive sustainability rank, is an excellent alternative for hydroformylation, an industrially important homogeneously catalyzed reaction.

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ARTICLE

Anisole: a further step to sustainable hydroformylation

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Hydroformylation, also known as "oxo" process, is a major industrial process that employs rhodium or cobalt catalysts in solution; therefore the solvent of the process is a critical issue for its sustainability. Although several innovative solutions have been proposed recently, traditional fossil-derived solvents dominate the scenario for this reaction. In this paper, we studied a series of solvents considered more sustainable in recent ranks in hydroformylation of a series of olefins. Anisole, a solvent with an impressive sustainability rank and very scarcely exploited in hydroformylation, proved to be an excellent alternative for this reaction.

Introduction

Hydroformylation (the "oxo process") represents a powerful and atom-economical access to aldehydes and alcohols. The reaction consists in the metal catalyzed addition of a carbon monoxide and hydrogen mixture ("syngas") to olefins. This transformation is one of the most important homogeneously catalyzed reactions appliedin the chemical industry, responsible for the global annual manufacture of more than 10 million tons of products.[1,2]Hydroformylation is widely used for the production of both bulk and fine chemicals and is especially important for the flavor&fragrance industry due to the remarkable olfactory properties of aldehydes.[3] The majority of academic and industrial hydroformylation processes involve rhodium as the most active and selective catalyst.

Within the green chemistry concept, an ideal option would be performing the reaction under solvent-free conditions; however, most applications require solvents. Besides the obvious function of dissolving reactants, catalysts and products, the use of solvents provides important advantages for many chemical processes, related to, e.g., the selectivity and exothermicity control, viscosity and mass transfer problems, safety and handling issues.[4,5] As solvents usually represent a significant part of the whole material involved in a chemical process, their replacement for "greener" alternatives is an effective way to improve the process sustainability and to reduce its environmental footprint.[4,5]

In the specific case of hydroformylation, if one of the reactants is liquid, it is possible in principle to run the reaction without solvents in neat reactants,[6] but this may be detrimental to the activity of the system.[7] In the majority of the cases, a solvent is required for industrial processes, e.g., in the rhodium-catalyzed hydroformylation of propene, the largest application of hydroformylation. In the Low Pressure Oxo Process (LPO),[8] a high boiling point solvent is used to keep the catalyst dissolved during the distillation of the products, but this leads to the thermal stress of the catalyst. A major breakthrough for propene hydroformylation was developed by Ruhrchemie/Rhône Poulenc, in which the rhodium catalyst was kept in a water solution by the employment of a water soluble phosphorous ligand.[2] The catalyst is recovered by decantation of the water phase *before the distillation step*. This strategy inspired the development of other biphasic systems, such as fluorous phase,[9] and ionic liquids systems.[10] Alternative solvents, such as supercritical carbon dioxide,[11] and thermomorphic solvents systems[12-15] have also been the subject of intense research in recent years.

Solvents derived from biomass like gamma-valerolactone,[16] methyl-THF,[17] *p*-cymene[18] or organic carbonates, such as propylene carbonate,[19] diethyl carbonate (DEC)[17,18] and dimethyl carbonate (DMC),[18] now produced through green routes, have been recently used in hydroformylation. Nevertheless, the sustainability rank of these solvents is not completely set, and there are still some concerns about their sustainable use; thus, alternative solutions are necessary. To the best of our knowledge, though, monophasic systems containing conventional solvents, such as toluene and THF, with low sustainability ranks still dominate the scenario of hydroformylation in both academia and industry.

In the present work, our efforts have been focused on the use of anisole as a solvent for hydroformylation. This low-cost, non-toxic and biodegradable compound occupies a prestigious position in recent solvent selection guides[20,21] and is highly recommended, with an impressive overall ranking comparable to those of ethanol and water. Although nowadays the production of anisole relies on petrochemicals, it can also be obtained from renewable sources such as lignin and guaiacol.[22]

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In spite of that, the use of anisole in hydroformylation has been overlooked and thus we decided to exploit in details its performance in this reaction.

Results and discussion

To set our comparison for greener solvents in hydroformylation, we chose 1-octene as a model substrate, once it is easy to manipulate and to get pure at relatively low prices. 1-octene is used as a model substrate in many studies involving hydroformylation. The catalytic system was based on $[Rh(COD)(OMe)]_2$, a convenient Rh(I) pre-catalyst largely employed in hydroformylation studies, as well as PPh_3, which is the most common promoter for Rh(I) catalysts.

Nowadays, toluene is the most employed solvent in hydroformylation due to its high efficiency and relatively low price and toxicity. Nevertheless, recent rankings classify toluene as a problematic solvent.[20,21] In the present work, toluene was chosen just as a benchmark to compare with the solvents considered greener or more sustainable in modern solvent selection guides.

In Table 1, the results for the hydroformylation of 1-octene under standard hydroformylation conditions in toluene solutions are presented (run 1). As expected, the linear aldehyde (**1b**) was predominately formed (75% selectivity), along with the branched aldehyde (**1c**) (25% selectivity) (Scheme 1). Under these mild conditions, the products of the double-bond isomerization were not observed and the turnover frequency (TOF) reached expected values of about 10^3 h^{-1}. The reaction in *p*-cymene, an aromatic solvent with a higher sustainability rank than toluene,[18,21,23] was ca. 25% faster than in toluene (Table 1, run 2). We also tested organic carbonates as solvents for hydroformylation, based on our previous experience.[17,18]Under the standard conditions, diethylcarbonate (DEC) presented a poor performance in terms of activity (TOF = 480 h^{-1}, Table 1, run 3). Conversely, the reaction in dimethylcarbonate (DMC) was even faster than in toluene (Table 1, run 4). The position of organic carbonates in recent ranks is not consensual, since some parameters are still lacking for the evaluation of these solvents. For instance, propylene carbonate is one of the greenest alternatives in the GSK rank,[21] but is classified as problematic in CHEM21 rank,[20] mostly due to the environmental score. DMC is recommended in both ranks, but it has the drawback of being water sensitive.

Ethanol is among the cheapest and less toxic alcohols and it has been used in hydroformylation as a solvent for quite a long time.[24] Thus, ethanol was chosen in this work as a reaction media for hydroformylation as a representative of the class of alcohols. The catalytic activity in ethanol was similar to that in DMC (Table 1, runs 4 and 5); however, even under these mild conditions, aldehydes were partially converted into the corresponding diethylacetals. Under harsher temperature conditions (100 °C, Table 1, run 6), which are usually required for more demanding substrates, the acetals were responsible for 13% of the products at the complete substrate conversion. Although the acetalization of aldehydes may be even desired[25-27] and can be easily reverted in basic media, if undesired; it may be considered as a drawback for this solvent, once it will require a further step of deprotection. For the sake of comparison, the results of the more detailed study on the hydroformylation in ethanol solutions for various olefins were included in ESI (Table S1).

Finally, we tested anisole as a solvent for the hydroformylation of 1-octene (Table 1, run 7; Fig. 1). To our surprise, the activity was considerably higher than in toluene (TOF of 960 h^{-1}*vs*. 820 h^{-1} in toluene, run 1). It is important that anisole figures as one of the greenest solvent alternatives in the GSK rank,[21] and is also highly recommended in the CHEM21 rank.[20]

The regioselectivity of the hydroformylation of 1-octene remained essentially the same for all the solvents employed in the present work (linearity of 71-75%). It is well established that in the hydroformylation of α-olefins regioselectivity is strongly dependent on the nature and number of ligands coordinated to rhodium.[1a] As the coordination ability of the solvents varies considerably in the series without changing the regioselectivity of hydroformylation, it seems reasonable to suggest that, under the conditions employed, the coordination of the solvent to the metal center should not play an important role in the process.

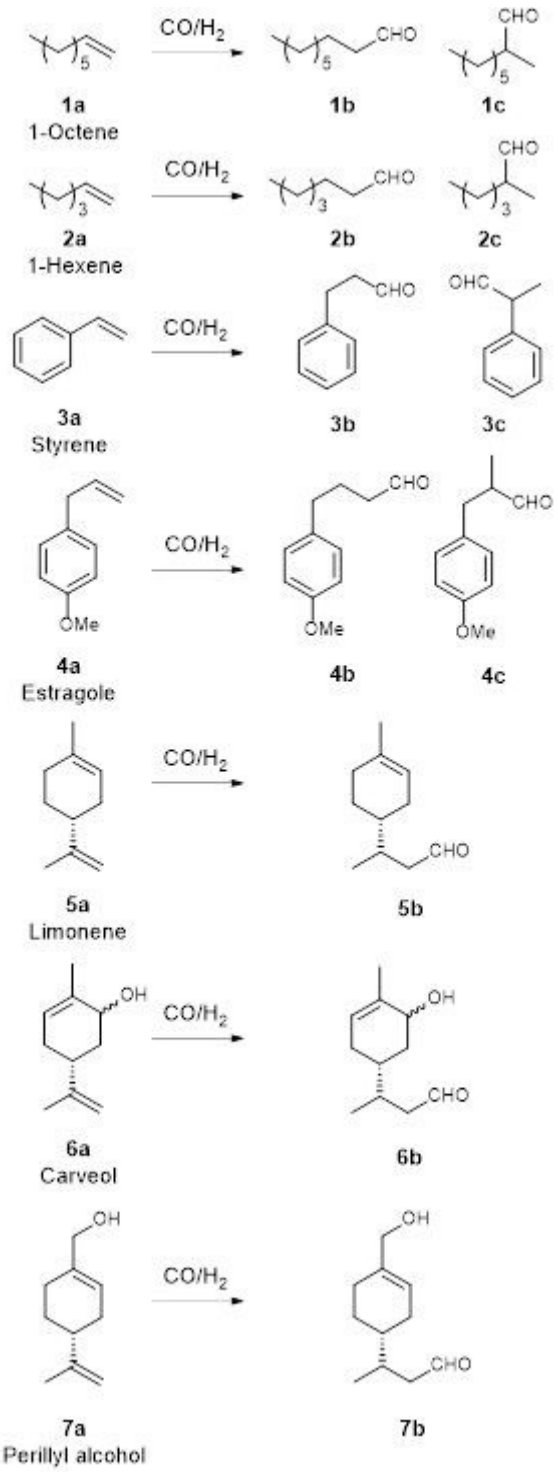
Table 1 Hydroformylation of 1-octene (1a) in various solvents[a]

Run	Solvent	Time (h)	*C* (%)	TOF[b] (h^{-1})	Selectivity for aldehydes (%)	
					Linear **1b**	Branched **1c**
1	Toluene	2.0	100	820	75	25
2	*p*-Cymene	1.5	100	1040	73	27
3	DEC	4.0	100	480	75	25
4	DMC	1.5	100	880	73	27
5[c]	Ethanol	2.0	100	880	71	26
6[d]	Ethanol	1.0	100	2200	65	22
7	Anisole	1.5	99	960	75	25

[a] Conditions: 1-octene – 0.40 M (8 mmol), $[Rh(COD)(OMe)]_2$ – 0.25 mM (5 μmol), ligand – PPh_3 (P/Rh = 10), gas phase – 40 atm (CO/H_2 = 1/1), 80 °C, solvent – 20 mL. Conversion (*C*) and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene). DMC: dimethyl carbonate, DEC: diethyl carbonate. . [b]TOF – turnover frequency (mol of 1-octene converted per mol of Rh per hour) calculated based on the slope of the nearly linear section of the kinetic curve. Kinetic curves in all the runs presented were nearly straight lines after the induction period up to ca. 90% conversions. [c] 3% of the aldehydes were converted to the corresponding diethylacetals. [d] 100 °C; 13% of the aldehydes were converted to the corresponding diethylacetals.

The changes in the hydroformylation rate did not neatly correlate with the intrinsic properties of the solvents, such as dielectric constant or dipole moment. In principle, the solvent can affect a catalytic reaction in many different ways, as recently reviewed in the excellent "perspective" article by Dyson and Jessop.[28] An acceleration effect can be related to the direct participation of the solvent in coordination-dissociation of ligands and reactants, the stabilization of transition states in relation to ground states, the change in the solubility of reactive gases, as well as the change in the rate of the mass transfer of reactive gases into the liquid phase in

different reaction media. We suppose that in the case of hydroformylation, the difference in the solubility of hydrogen and carbon monoxide is especially important for the solvent effect. However, regardless of the explanation, anisole showed to be the most promising solvent because of the rate enhancement and, more importantly, because of its better position in sustainability ranks.



Scheme 1 Hydroformylation of substrates **1a–7a**.

The examples of the utilization of anisole as a solvent in hydroformylation are very scarce,[29-31] although more recently it has been used to make-up the apolar phase in a water/organic phase system[32] and as a solvent in the hydroaminomethylation reaction,[33] which is related to hydroformylation. Considering the new concerns in modern chemistry and the fact that anisole is among the best solvents in terms of sustainability, we have decided to exploit further its potential in hydroformylation for other substrates and other catalytic systems, employing toluene as the benchmark solvent. The results are presented in Tables 2 and 3.

1-Hexene (**2a**), along with 1-octene, is commonly applied as a model reactant for the investigation of new catalytic systems in hydroformylation of terminal monosubstituted double bonds. The hydroformylation of 1-hexene was significantly faster (ca. 20%) in anisole than in toluene solutions (Table 2, runs 1 and 2). The results followed the same tendency observed for 1-octene (Table 1, runs 1 and 7). The regioselectivity was also of value expected for such kind of reactants and catalytic system (linearity of ca. 70%).

The reaction with styrene (**3a**), which is frequently used as a model substrate in the hydroformylation of vinylarenes, occurred at a nearly the same rate and with the same chemo- and regioselectivity in both solvents (Table 2, runs 3 and 4). As expected for the rhodium catalytic systems promoted by monophosphines, the branched aldehyde (**3c**) was predominantly formed (ca. 90%, Scheme 1).

Estragole (**4a**) is a naturally occurring propenylbenzene available from biorenewable essential oils of various plants. Aldehydes derived from propenylbenzenes show biological and phytosanitary activities and are also used in flavor and pharmaceutical industries. We have found that in the hydroformylation of estragole, toluene can be substituted by anisole without any loss in catalytic activity or in selectivity (Table 2, runs 5 and 6). The linear aldehyde **4b**was formed as a major product in both solvents, with the linear/branched ratio being of ca. 70/30 in both reactions (Scheme 1).

The kinetic curves in the runs with all these substrates **1a–4a** showed ca. 15 min induction periods and were nearly straight lines up to at least 90% conversion. The induction period is required for the formation of active catalytic species from the rhodium precursor (Fig. 1; Fig. S1, ESI). It means that in both solvents the rate was virtually independent on the substrate concentration and most of the metal centers contained the substrate or fragments derived from the substrate during the whole the reaction course, even at high conversions.

The substrate scope was extended to the compounds containing 1,1-disubstituted C-C double bonds, as well as hydroxyolefins. We have chosen a group of biomass-based olefins as model substrates: monoterpenic compounds limonene (**5a**), carveol (**6a**), and perillyl alcohol (**7a**). Terpenes are easily available from essential oils and traditionally have many direct applications in fragrance and pharmaceutical industries. The introduction of an aldehyde group in their structure through hydroformylation provides an access to

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Table 2 Hydroformylation of terminal olefins **2a–7a** in toluene or anisole solutions[a]

Run	Substrate	Solvent	Time (h)	*C* (%)	TOF[b] (h^{-1})	Selectivity for aldehydes (%)	
						linear	branched
1	1-Hexene (**2a**)	toluene	1.5	98	860	73(**2b**)	27(**2c**)
2	1-Hexene (**2a**)	anisole	1.0	98	1200	73(**2b**)	27(**2c**)
3	Styrene (**3a**)	toluene	1.5	99	960	10(**3b**)	90(**3c**)
4	Styrene (**3a**)	anisole	1.5	98	900	9 (**3b**)	91 (**3c**)
5	Estragole(**4a**)	toluene	1.5	99	740	70(**4b**)	30(**4c**)
6	Estragole(**4a**)	anisole	1.5	100	740	69(**4b**)	31(**4c**)
7	Limonene (**5a**)	toluene	24	82	69	100(**5b**)	
8	Limonene (**5a**)	anisole	24	85	76	100(**5b**)	
9	Carveol (**6a**)	toluene	24	78	100	100(**6b**)	
10	Carveol (**6a**)	anisole	24	97	190	100(**6b**)	
11	Perillyl alcohol (**7a**)	toluene	24	86	106	100(**7b**)	
12	Perillyl alcohol (**7a**)	anisole	24	97	200	100(**7b**)	

[a]Conditions: substrate – 0.40 M (8 mmol), $[Rh(COD)(OMe)]_2$ –0.25 mM (5 µmol), ligand – PPh_3 (P/Rh = 10), gas phase – 40 atm (CO/H_2 = 1/1), 80 ºC, solvent – 20 mL. Conversion (*C*) and selectivity were calculated based on the substrate reacted using an internal standard (*p*-xylene). [b] TOF – turnover frequency (mol of the substrate converted per mol of Rh per hour) were calculated based on the slope of the nearly linear section of the kinetic curve for substrates **2a** – **4a** and at low conversions (≤ ca. 30-40%) for substrates **5a** – **7a** .

(poly)functionalized compounds with useful olfactory properties.[3]

As expected, the reactions with disubstituted terminal olefins **5a–7a** (Scheme 1, Table 2, runs 7-12) were nearly 10 times slower than those with monosubstituted terminal olefins **2a–4a** (Table 2, runs 1-6). The hydroformylation of limonene (**5a**) in the anisole-based systems occurred slightly faster than in toluene (Table 2, runs 7 and 8). As the conditions were relatively mild, only the terminal double bond was involved in the reaction, while the endocyclic bond remained intact.

The isomeric alcohols carveol (**6a**) and perillyl alcohol (**7a**) have the same carbon structure as limonene (**5a**), but with a hydroxyl group in allylic positions with respect to the endocyclic double bond. Whereas the hydroformylation of limonene, one of the most abundant terpenes, was extensively studied during the last two decades,[3] the works dealing with functionalized terpenic substrates are much scarcer. We could find only one publication describing the hydroformylation of perillyl alcohol[34] and no reports at all on the hydroformylation of carveol. Aldehyde **6b** (a mixture of two diasteroisomers) derived from carveol is described for the first time in this paper and details for its characterization are presented in Supplementary Information (ESI).

The replacement of toluene by anisole produced a remarkable beneficial effect on the hydroformylation of both hydroxyolefins **6a** and **7a**: the initial reaction rates (TOF) increased nearly two times (Table 2, runs 9–12; Fig. 1 for carveol). The corresponding aldehydes **6b** and **7b** resulted from the hydroformylation of the terminal double bonds were practically the only reaction products. The excellent regioselectivity was expected for 1,1-disubstituted double bonds and the endocyclic double bonds in both substrates remained intact, due to the relatively mild reaction conditions employed. An important difference in the reaction pattern

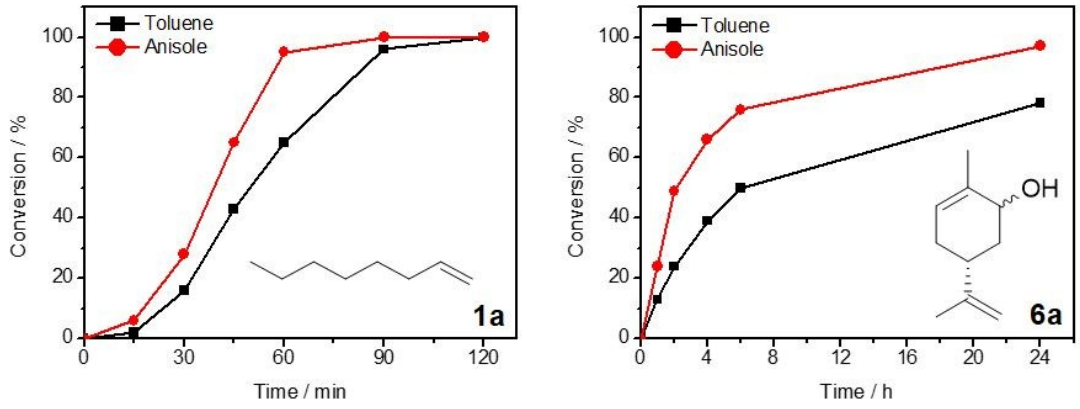


Figure 1 Hydroformylation of 1-octene (**1a**) and carveol (**6a**) in toluene and anisole solutions. Conditions: substrate - 0.40 M (8 mmol), $[Rh(COD)(OMe)]_2$ - 0.25 mM (5 µmol), ligand - PPh_3 (P/Rh = 10), gas phase – 40 atm (CO/H_2 = 1/1), 80 ºC, solvent – 20 mL.

with **6a** and **7a** as compared to **1a–4a** caught our attention: whereas the kinetic curves in the runs with substrates **1a–4a** were approximately straight lines up to nearly complete conversions, the reactions with **6a** and **7a** began to slow down significantly after 30–50% conversion and (Fig. S2, ESI). This behavior could be explained taking in to account that 1,1-disubstituted olefinic bonds are more difficult to coordinate to the metal center and the substrate concentration influences more markedly the rate in the range observed.

To explain the marked accelerative effect of anisole in the hydroformylation of hydroxyolefins **6a** and **7a**, the interaction of these substrates with anisole should be considered. In our previous studies,[17,35-37] we have suggested that some hydroxyolefins (i.e., linalool, nerolidol and nopol) can coordinate on rhodium through both their functionalities (OH and C=C) to form chelate complexes, and are less active in hydroformylation for this reason. We demonstrated that changes in reaction conditions, e.g., by increasing the ancillary ligand concentration, favored the break of chelates and accelerated the reactions. In this context, the promoting effect of anisole on the reactivity of alcohols **6a** and **7a**can be attributed to the formation of the hydrogen bond between the methoxy group of the solvent and the hydroxyl group of the substrate. Due to this interaction, the coordination of the hydroxyl group to the rhodium center in the intermediates of the catalytic cycle is disfavored. In other words, the solvent helps to prevent the substrate chelation to rhodium, accelerating in this way the whole hydroformylation process. The hydroformylation of the terminal double bond in carvyl acetate, a substrate similar to carveol **6a** but with a protected OH moiety, occurred at similar rates in toluene and anisole, supporting this hypothesis (see Table S2 in ESI).

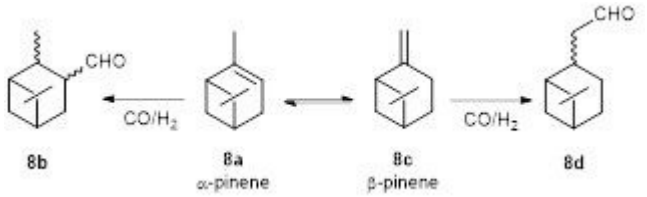
In order to further exploit the performance of anisole in hydroformylation, we selected challenging terpenes with encumbered endocyclic trisubstituted double bonds: α-pinene (**8a**), myrtenol (**9a**) and nopol (**10a**) (Table 3; Fig. S3, ESI). A systematic study of the hydroformylation of myrtenol and nopol has been recently reported by us[17] and the hydroformylation of α-pinene was also described elsewhere.[38] The hydroformylation of this kind of substrates requires special promoters to occur. We chose for this work the bulky phosphite (2,4-di-^{t}buPhO)$_3$P, a ligand of proven efficiency in the hydroformylation of internal olefins and available commercially in large scale at relatively low prices. The beneficial effect of bulky phosphites as auxiliary ligands has been largely exploited in hydroformylation and is associated with the favourable combination of their steric and electronic properties, i.e., large cone angles as well as strong electron-withdrawing properties.[39,40]

The rate of the hydroformylation of α-pinene (**8a**) was ca. 30% greater in anisole than in toluene solutions, with the selectivity remaining essentially unchanged (Table 3, runs 1 and 2). The major aldehyde **8b**was derived from the direct hydroformylation of α-pinene; whereas minor aldehyde **8d** was the result of the hydroformylation of β-pinene (**8c**), which was formed due to the double bond isomerization in the α-pinene molecule (Scheme 2). As the hydroformylation of β-pinene, the compound containing a terminal olefinic bond, occurred faster than that of α-pinene, the contribution of isomeric aldehyde **8d** was significant at the end of the reactions (ca. 30%).

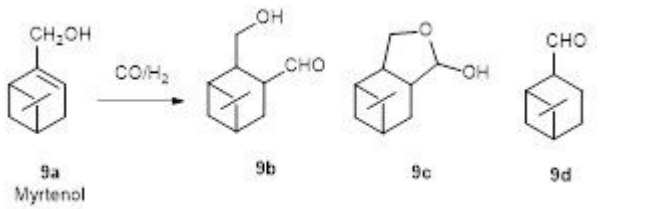
Myrtenol (**9a**) and nopol (**10a**) gave three main products each under the hydroformylation conditions: i) aldehydes **9b** and **10b** resulted from the carbonylation at the less substituted olefinic carbon atoms; ii) hemiacetals **9c** and **10c** resulted from the spontaneous intramolecular cyclization of aldehydes **9b** and **10b**, respectively; and iii) saturated aldehydes **9d** and **8d**resulted from the rhodium catalyzed isomerization of the substrates (Schemes 3 and 4).

Anisole appeared to be an excellent alternative for toluene in the hydroformylation of myrtenol (Table 3, runs 3 and 4). The substrate conversion in anisole was slightly slower; however, the combined selectivity for the hydroformylation products (**9b** and **9c**) was much higher than in toluene: 75% *vs*. 59% at nearly complete substrate conversions. About 40% of the substrate was converted into isomeric aldehyde **9d** in toluene solutions, whereas in anisole only 23%. Considering the difference in the reaction selectivity (i.e. subtracting the isomerized substrate from the total amount of the reacted substrate) showed that the initial rate of the myrtenol hydroformylation in anisole was ca. 20% higher than in toluene.

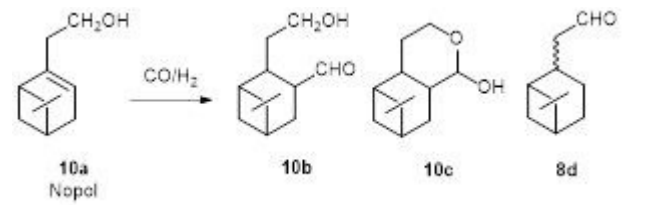
The much lower reactivity of nopol **10a** as compared to myrtenol **9a** was attributed in our previous work[17] to the formation of less reactive five membered chelate complexes through the simultaneous coordination of both C=C and OH functionalities of the substrate on rhodium. The equivalent chelation of myrtenol would give less stable complexes containing four membered rings. Probably, for this reason, the hydroformylation of nopol in anisole solutions occurred much faster (ca. 50%) than in toluene (Table 3, runs 5 and 6). As in



Scheme 2 Hydroformylation of α-pinene (**8a**).



Scheme 3 Hydroformylation of myrtenol (**9a**).



Scheme 4 Hydroformylation of nopol (**10a**).

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Table 3 Hydroformylation of internal olefins α-pinene (**8a**), myrtenol (**9a**) and nopol (**10a**) in toluene and anisole solutions[a]

Run	Substrate	Solvent	Time (h)	*C* (%)	TOF[b] (h^{-1})	Selectivity (%)		
						Hydroformylation		Isomerization
						aldehyde	hemiacetal	
1[c]	α-Pinene (**8a**)	toluene	48	66	15	68 (**8b**)		32 (**8d**)
2[c]	α-Pinene (**8a**)	anisole	48	86	20	67 (**8b**)		33 (**8d**)
3	Myrtenol (**9a**)	toluene	48	90	12	54 (**9b**)	5 (**9c**)	40 (**9d**)
4	Myrtenol (**9a**)	anisole	96	94	10	70 (**9b**)	5 (**9c**)	23 (**9d**)
5[d]	Nopol (**10a**)	toluene	96	65	4	75 (**10b**)	3 (**10c**)	20 (**8d**)
6[d]	Nopol (**10a**)	anisole	96	80	6	63 (**10b**)	14 (**10c**)	17 (**8d**)

[a] Conditions: substrate – 0.20 M (4 mmol), $[Rh(COD)(OMe)]_2$ – 0.25 mM (5 μmol), ligand – (2,4-di-^{t}buPhO)$_3$P (P/Rh = 10), gas phase – 40 atm (CO/H_2 = 1/1), 100 ºC, solvent – 20 mL. Conversion (*C*) 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] substrate – 0.40 M (8 mmol), gas phase – 80 atm (CO/H_2 = 1/1), aldehyde **8d** resulted from the hydroformylation of β-pinene was considered as the isomerization product. [d] P/Rh = 30, 120 °C.

the case of carveol **6a** and perillyl alcohol **7a**, the beneficial effect can be related to the protection of the hydroxyl group in the nopol molecule from the coordination on rhodium due to the hydrogen bond formation with the solvent (anisole).

Thus, anisole proved to be an appropriate solvent for the rhodium catalyzed hydroformylation of challenging substrates α-pinene (**8a**), myrtenol (**9a**) and nopol (**10a**), in which the use of bulky phosphites promoters as well as harsher reaction conditions was required.

Conclusions

In spite of the recent developments of biphasic solvent systems for hydroformylation, the monophasic solvent systems remain relevant, markedly in the context of fine chemicals production. As the solvent plays a central role in sustainability, it is important to develop processes employing solvents with good sustainability ranks. In this work we compare the performance of toluene, used in most of the current hydroformylation studies, with solvents with better sustainability ranking, namely, *p*-cymene, dimethylcarbonate, diethylcarbonate, ethanol and anisole. Anisole, a surprisingly underexploited solvent in hydroformylation in spite of its high sustainability rank in recent classifications, was the focus of our work. We studied a broad range of substrates including α-olefins, monoterpenes containing disubstituted and trisubstituted C-C double bonds, as well as hydroxyfunctionalyzed monoterpenes. Furthermore, we employed two major catalytic systems used in hydroformylation: monophosphine promoted and bulky monophosphite promoted rhodium catalysts. In the large majority of the cases tested, the systems employing anisole as a solvent surpassed the activity of those employing toluene (the benchmark solvent) and kept the same selectivity under otherwise the same reaction conditions. Thus, we conclude that anisole is a highly recommended solvent for hydroformylation, in terms of both the catalyst performance and sustainability.

Experimental

All chemicals were received from commercial sources and used without special treatment, unless otherwise indicated. 1-hexene (≥99%), 1-octene (98%), (R)-(+)-limonene (97%), (S)-(–)-perillyl alcohol (≥95%), L-carveol (mixture of *cis* and *trans* isomers in comparable amounts, ≥95%), (1R)-(–)-myrtenol (≥95%), (1R)-(–)-nopol (98%), styrene (>99%), estragole (≥98%), (1S)-(-)-α-pinene (98%) triphenylphosphine (PPh_3) and tris(2,4-di-tert-butylphenyl)phosphite, (2,4-di-^{t}buPhO)$_3$P, were purchased from Sigma-Aldrich. $[Rh(COD)(OMe)]_2$ (COD = 1,5-cyclooctadiene), used as the catalyst precursor was synthesized by a previously reported method.[41] Toluene was refluxed for 8 h in the presence of sodium lumps and benzophenone and then distilled under argon. (anhydrous, 99.7%), toluene (anhydrous, 99.8%), dimethyl carbonate (DMC) (anhydrous, ≥99%), and *p*-cymene (99%) were purchased from Sigma-Aldrich. . Anisole, purchased in a Sure/Seal™ bottle, was opened and stored in the glove box and used without special treatment. DMC and DEC were distilled under argon and stored over 4Å molecular sieves. *p*-cymene was distilled in a Kugelrohr distillation apparatus, collected under argon and stored in the glove box. α-Pinene was treated with Magnesol® and Celite® (ca. 1 wt%) for 1 h at 80 °C, then distilled under argon and stored in the glove box.

Catalytic reactions were run in a 100 mL homemade stainless steel pressure reactor with magnetic stirring. The reaction solutions were periodically sampled from the reactor through a valved dip tube without depressurization. The samples were analyzed by gas chromatography (GC) (GC-Shimadzu GC2010 instrument, Rtx®-Wax or Rtx®-5MS capillary columns, 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 (4–8 mmol), $[Rh(COD)(OMe)]_2$ (5.0 μmol), phosphorus ligand (0.1–0.3

mmol) and *p*-xylene (4 mmol, GC internal standard) in a specified solvent was transferred into the autoclave under argon; then the autoclave was pressurized to 40 atm (CO/H_2 = 1/1) and heated to the indicated temperature. Finally, the reaction solution was stirred with a magnetic stirrer for the reported time.

Reaction products were analyzed/identified by gas chromatography/mass spectrometry (GC-MS) on a Shimadzu QP2010-PLUS equipment operating at 70 eV. Product **6b** was separated (as a mixture of four stereoisomers) by column chromatography (silica gel 60, hexane/ethyl acetate mixtures) and identified by NMR spectroscopy (DEPT, COSY, HMQC and HMBC experiments) on a Bruker 400 MHz spectrometer ($CDCl_3$, TMS). Spectroscopic data for product **6b** are presented in ESI

Conflicts of interest

There are no conflicts to declare.

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