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Coupling Rhodium-Catalyzed Hydroformylation of 10-Undecenitrile with Organic Solvent Nanofiltration: Toluene Solution *vs* Solvent-Free Processes

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Abstract: Intensification of the rhodium-catalyzed hydroformylation process to produce 12-oxo-dodecanenitrile from biosourced 10-undecenitrile was performed by coupling the reaction with Organic Solvent Nanofiltration (OSN) for the recycling of expensive Rh-catalyst and ligands. Four phosphorus-based ligands were compared with respect to their catalytic performance and rejection in OSN. Biphephos proved to show the best compromise and up to 3 reaction-OSN cycles were performed in toluene. A good recycling of the catalytic system was evidenced thanks to OSN (up to 88% rejection). Looking for a greener process, a similar approach was achieved in bulk (*i.e.* solvent-free medium) proving the catalyst recycling feasibility but also that the OSN optimum is not the same as that in toluene. Finally, integration of OSN in the overall production process is discussed aiming at the proposal of a hybrid separation process involving combination of OSN and distillation for an energy intensive separation step.

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Introduction

Catalysis is recommended in the 12 principles of green chemistry and is nowadays widely used in industry for the production of fine chemicals. The use of homogeneous organometallic catalysts is particularly efficient for reactions such as metathesis,[1-2] hydrogenation[3-4] and hydroformylation[5-6]. However, its main drawback lies in the difficult separation of the dissolved metal-containing species from the reaction product[7] but also the separation of the ligand, often used in excess and sometimes more expensive than the metal itself.

At industrial scale, as a general trend, the separation processes are responsible of *ca.* 70% of the operating cost and 45% of the energy consumption. This is mainly due to the current separation processes based on phase changes either energy demanding and/or using lots of solvents such as crystallization followed by classical filtrations. Moreover, they often lead to deactivation of the expensive catalyst, preventing from its reuse. Distillation allows sophisticated separations with an efficient product extraction as single pure component and solvent recycling, but may also induce catalyst degradation due to the high temperatures involved.

Contrary to distillation, liquid-liquid extraction proved to be able to maintain the catalyst activity. Kämper *et al*. reported the first recycling of a ruthenium catalyst for hydroformylation in a continuously operated mini-plant.[8] Hydroformylation of 1-octene was operated on a timescale of 90 h in DMF (with decreasing efficiency) with an imidazole-substituted phosphine ligand and Ru_3CO_{12} as the catalyst precursor. Extraction of the target aldehyde was achieved using apolar iso-octane, whereas the catalytic system remained in polar DMF. Obviously, minimization of solvent consumption would be preferred when looking for a greener approach.

Among alternative separation technologies are membrane processes, now well identified as key technologies for sustainable production and compatible with process intensification. Membrane separation can be one order of magnitude more energy efficient than heat-induced separations that use distillation.[9] The emerging Organic Solvent Nanofiltration (OSN) is an eco-friendly and energy efficient process that allows separation at molecular level and room temperature, without solvent addition nor phase or environment change. Many laboratory-scale studies have already established the potential of OSN for homogeneous catalyst recycling.[10-17] Upon tuning the type of membrane,[18-22] catalyst,[23,24] solvent [25-29] and operating conditions (mainly transmembrane pressure, TMP [27, 30,31] and sometimes temperature [28, 31,32]), almost full catalyst rejections were obtained. Nevertheless, it must be underlined that these studies usually focused on the catalyst rejection by the membrane and paid no or very little attention to the target product extraction, which is however an absolute requirement for an industrial production process.

There is not a unique answer about how coupling reaction and OSN. The choice depends on the reaction operating conditions (high temperatures are usually not compatible with resistance of polymer membranes) and the membrane selectivity towards the catalytic system and the products/by-products. Moreover, the choice may also depend on the presence or the absence of solvent that can affect both reaction and filtration performances.

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In presence of solvent, OSN of homogeneous organometallic catalysts using unreactive membranes has been coupled with reaction in two different ways:

- In the first one, OSN is considered as a post-treatment step and the final reaction mixture is transferred from the batch reactor into an OSN set-up to perform the separation. The recovered catalytic system returns back to the reaction tank for another reaction and so on until a significant catalyst deactivation. For instance, Kajetanowick *et al.* used OSN to recycle a metathesis catalyst in toluene or dichloromethane solutions.[33] The first and second catalyst uses allowed achieving high conversions but the activity significantly dropped during the third reaction.
- The second one, in line with process intensification, consists in a membrane reactor where the reaction medium is in contact with the membrane (semi-continuous or continuous mode), so that the reaction and OSN are performed with the same set-up. For instance, the use of a membrane reactor with a Starmem 122 membrane (Polyimide, PI, MET-Evonik) for a ring-closing metathesis process at room temperature in toluene highlighted that the continuous process allowed using less solvent than the discontinuous one but with a slightly lower conversion.[34] Such design required membrane materials of high stability in solvent at the reaction temperature and thus would be of limited applications.

Following the first approach, Dreimann *et al.* reported on a batch process for the hydroformylation of 1-dodecene conducted at 90 °C in toluene using a Rh-catalyst complex combined with different ligands.[35-36] Triphenylphosphine (TPP, 262 $g.mol^{-1}$) was selected as the most promising one with respect to the constant performances obtained during the synthesis from one run to another. Up to 97% of the Rh catalyst and 66 % of the free ligand were retained by OSN at 20 bar using a commercial PDMS Membrane (oNF2, GMT Membrantechnik GmbH, Germany). One originality was to perform OSN within the syngas atmosphere (CO/H_2) to prevent the catalyst deactivation, contrary to current reported experiences generally achieved under nitrogen. Two consecutive reactions were successfully achieved with OSN performed up to a Volume Reduction Ratio = 2 (VRR, for definition, see Eq. 4, Experimental section). However, because of TPP low rejection, its reload was necessary in the synthesis reactor to maintain high performances. The process was then adapted in a continuous manner and operated in a mini-plant for 40 h, keeping the same conversion and selectivity during the first 20 h.

Few studies have focused on the recycling of homogeneous metal catalysts by OSN in solvent-free media (later referred to as *bulk* media) while some studies have dealt with the influence of the solvent on the membrane performances.[25-29] Van der Gryp *et al.* studied a metathesis process coupling reaction and OSN performed in bulk. Using a Starmem 228 membrane (PI, MET-Evonik), 99% of Ru catalyst rejection was achieved with a post-reaction mixture made of residual 1-octene (substrate), 7-tetradecene (product) and 1-tetradecene (by-product).[37] The Ru catalyst was recycled 4 times, exhibiting the same performance for the first 3 reactions and then its activity dropped. Priske *et al.* integrated hydroformylation of 1-octene and 1-dodecene with OSN for the recycling of a sterically hindered Rh catalyst.[38] At 60 °C and with a dead-end OSN set-up, 99% of catalyst rejection was achieved using Starmem 122 and Starmem 240

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(PI, MET-Evonik) membranes. Nevertheless, none of these two studies clearly compared a solvent-free process with a solution one.

Hydroformylation is one of the most important application of homogeneous catalysis at industrial scale, with an annual production of 12 million tons of oxo-products.[35] However, to date, industrial Rh-catalyzed hydroformylation processes are often limited to olefin substrates smaller than C5 carbon chains. This motivates some studies about the conversion of linear long-chain olefins.[36-39] This case study deals with the improvement of a hydroformylation process for the conversion of biosourced 10-undecenitrile into 12-oxo-dodecanenitrile as a route toward polyamide-12 (Figure 1). This work aims at providing some insights about coupling a hydroformylation reaction and OSN in a bulk medium in comparison with a toluene solution process. This homogeneous reaction has been previously studied and optimized,[40-43] but here four phosphorus-based ligands (Figure 2) are also compared in terms of OSN performance. It is a challenging case study because of (*i*) the long-chain olefin used moreover being end-side functionalized and (*ii*) the complex reaction medium since several products and by-products are formed and need to be considered for OSN. Figure 3 explains what can be expected for OSN of a real mixture in toluene with respect to a single stage separation. One has to keep in mind that, generally, this is more an efficient enrichment step than a very fine purification process such as chromatography. An increase in performances can be envisioned by complexifying the OSN scheme with a membrane cascade (see Discussion).[44-51] Moreover, the membrane ability to separate the target product(s) from the unreacted substrate(s) and other by-products have to be evaluated. Once the ligand has been selected, coupling reaction and OSN for the recycling of the catalytic system has been performed and compared in toluene and in bulk. Some insights are finally discussed about the improvement of the whole production process thanks to the integration of OSN.

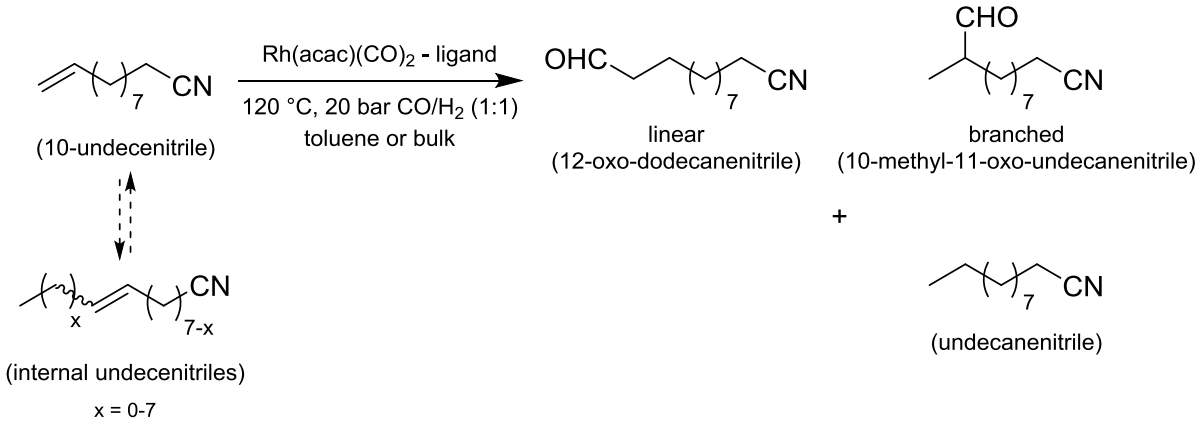


Figure 1. Diversity of products generated in the Rh-catalyzed hydroformylation reaction of 10-undecenitrile. The substrate contains few internal isomers, the amount of which increases during the reaction.[40-43]

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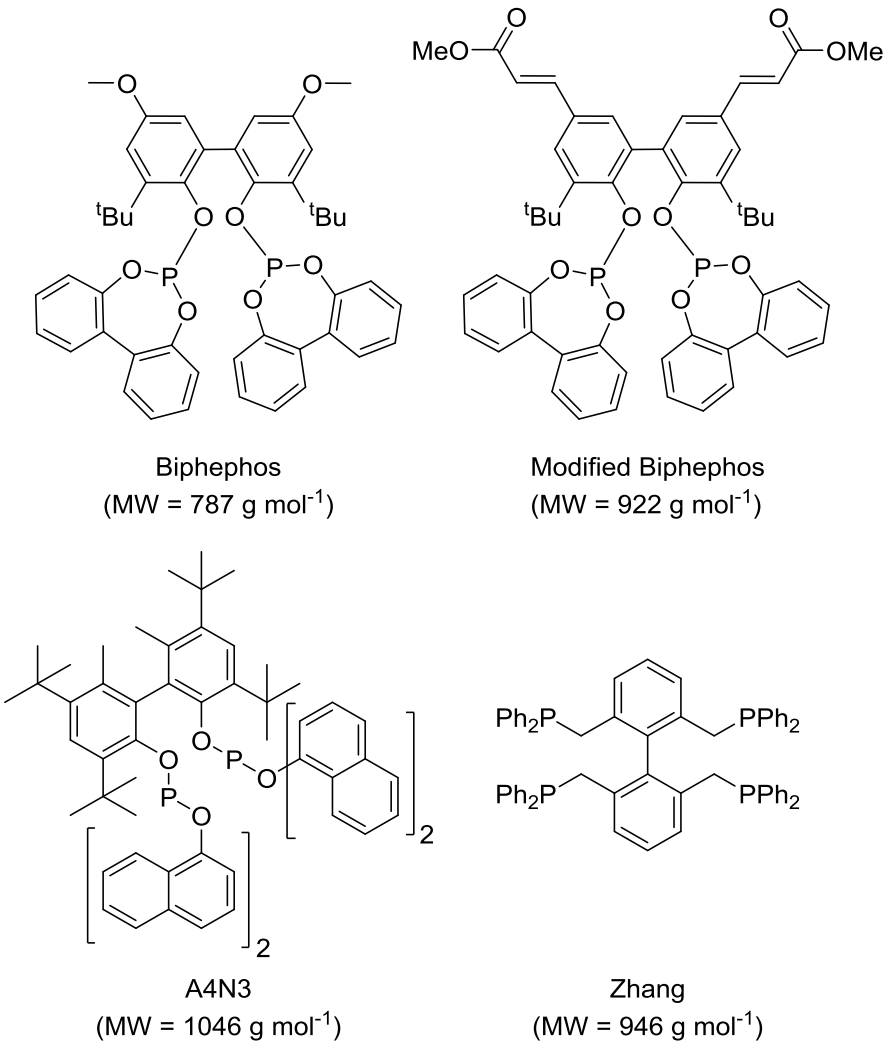


Figure 2. The four ligands investigated in the Rh-catalyzed hydroformylation of 10-undecenitrile coupled with OSN (see Experimental section).

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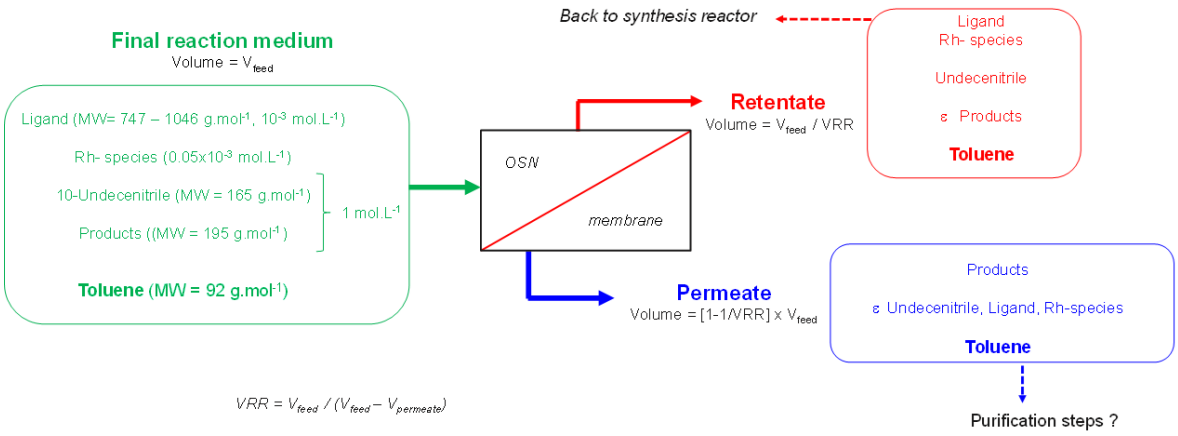


Figure 3. Expected ideal separation of a final reaction mixture in toluene by a single OSN step, also highlighting that the toluene volume in the different fractions (retentate, permeate) depends on operating conditions (VRR).

Results

It is well-known that membrane filtration performances are not intrinsic of a given membrane toward a given solute. Besides the media composition that can be of importance, rejection also depends on the operating conditions. The most extreme case study reported that the rejection of a given solute can vary from 0% to 100% using the same membrane.[52] That is why, OSN has to be optimized for each reaction medium. However, such optimization requires quite high volumes that, in the present case, were not available for all reaction mixtures. To overcome this drawback, OSN was first optimized for the Biphephos system in toluene. Then, the optimized conditions (although not the optimum for all systems) were applied to select the best ligand according to the compromise between both reaction and OSN performances. Finally, these conditions were also applied to study the catalytic system recycling either in toluene or in bulk media. Note that throughout this study, the membrane used was the Sulzer's PERVAP 4060, an organophilic membrane originally designed for pervaporation and devoted to the removal of VOCs and aroma from aqueous solutions. This membrane has already been applied to fundamental OSN studies,[53] but the present study reports its first use with sophisticated media.

1. Optimization of OSN with the Biphephos system in toluene

The rejections by the PERVAP 4060 membrane of different organic solutes of molecular weight close to that of the target aldehyde were evidenced to be based on the solution-diffusion mechanism coupled with polarization concentration depending on the operation conditions.[54-55] The cross-flow velocity cannot be tuned for the used OSN set-up, so TMP was the only parameter to vary. Experiments at transmembrane pressures in the 5-40 bar range were realized using, first, solutions of selected single solutes and, second, post-reaction mixtures in toluene

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to take into account the possible influence of all solutes on each other. OSN was limited to VRR = 2 (see experimental section) with respect to the hold-up volume of the OSN set-up when using 150 mL initial feed volume.

1.1. Rejection of the catalytic system

Figure 4a depicts that the Biphephos rejection at 1 mM (same concentration as in the reaction mixture) ranged from 73% to 95% when increasing TMP. On the contrary, rejection of the $Rh(acac)(CO)_2$ precursor at 0.05 mM (same concentration as in the reaction mixture) was quite low, both at 10 bar and 30 bar. However, note that this catalyst precursor will not be present in a reaction mixture due to the large excess of ligand and its concentration can be considered as null in all OSN achieved on real reaction mixtures.

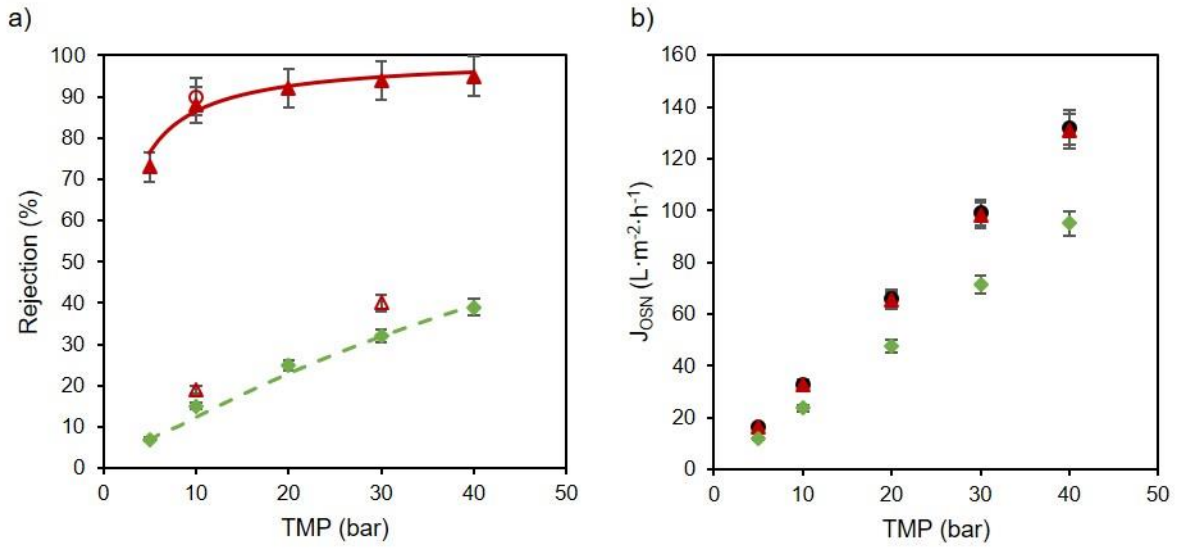


Figure 4. (a) Rejections up to VRR = 2 of different solutes in single solution in toluene by the PERVAP 4060 membrane - ▲ : Biphephos (1 mM) ; Δ : $Rh(acac)(CO)_2$ (0.05 mM), ; ○ : P-coordinated Rh species (obtained by mixing $Rh(acac)(CO)_2$ and Biphephos both at 0.05 mM in mixture) ; ♦: 10-undecenitrile (1 M), and rejection of Biphephos (1 mM, full line) and 10-undecenitrile (1 M, dashed line) according to the solution diffusion model - **(b)** Permeate flux *vs* transmembrane pressure for different solutes in single solution in toluene by the PERVAP 4060 membrane - ● : pure toluene ; ▲ : Biphephos (1 mM) ; ♦ : 10-undecenitrile (1 M).

When mixed with an equimolar amount of Biphephos (set at 0.05 mM) in toluene, $Rh(acac)(CO)_2$ instantaneously evolved in a new species further called *P*-coordinated Rh species that could be slightly different from the active catalyst because of the absence of syngas. The registered UV spectrum was different from the addition of the 2 spectra of the single components (see Figure S1 in the Supplementary materials) and, in particular, a local maximum absorbance appeared at λ = 322 nm. The *P*-coordinated Rh species remained of unknown exact composition and could be assumed to be a good stable model for the catalyst formed *in situ* before addition of syngas. Thanks to UV analysis, this compound was evidenced to be stable several days and the absorption band at λ = 322 nm was further used to UV-quantify the catalytic system at low ligand concentration. OSN of the *P*-coordinated Rh species was

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achieved at 10 bar, evidencing a high rejection increase when compared to the $Rh(acac)(CO)_2$ precursor (Figure 4a).

However, in presence of 1 mM Biphephos (and more generally 1 mM ligand), the *P*-coordinated Rh species UV bands overlapped that of the ligand, preventing the determination of the catalyst's concentration by UV. As the free Biphephos and the *P*-coordinated Rh corresponding species at 0.05 mM were evidenced to have similar rejections at 10 bar (88% and 90%, respectively), it was further assumed that the free ligand rejection could model in an acceptable way the minimum rejection of the catalyst (further noted "estimated catalyst rejection").

1.2. OSN of 10-undecenitrile

Figure 4a shows that the 10-undecenitrile rejection at 1 M increased from 7% to 39% when TMP increased from 5 to 40 bar. Aiming at evidencing the rejection variation during concentration process at 10 bar (VRR increase), OSN was also achieved at higher initial concentrations. Figure 5 evidences both the rejection and the permeate flux decrease with the initial concentration increase. As explained above, rejection may be due to a solution-diffusion mechanism that is ruled by the affinity of the solute with the membrane and the diffusion in the membrane swelled by the solvent. Both the affinity and the swelling of the membrane can change with a variation of concentration of 10-undecenitrile, hence inducing a variation of its rejection. In Figure 4, the solution-diffusion coupled with film theory (to describe concentration polarization) was fitted to the experimental data [54] for Biphephos and 10-undecenitrile in single solution in toluene. The model is in good agreement with the experimental data with a solute permeability coefficient of 0.012 $mol \cdot m^{-2} \cdot s^{-1}$ for Biphephos and 0.195 $mol \cdot m^{-2} \cdot s^{-1}$ for 10-undecenitrile. A lower permeability coefficient for Biphephos than for 10-undecenitrile is consistent with its higher rejection.

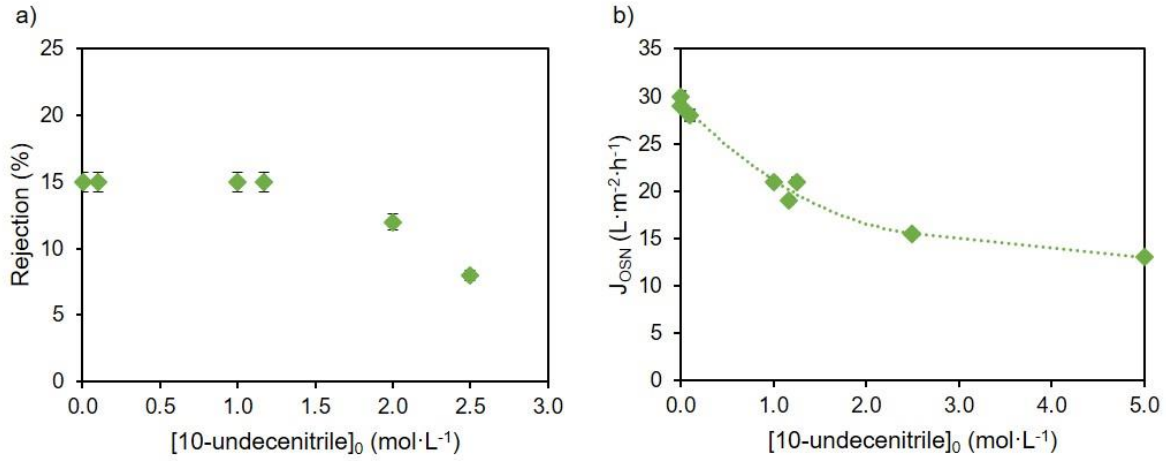


Figure 5. OSN of 10-undecenitrile by Pervap 4060 in single toluene solution at 10 bar from 1 mM to 2.5 M. (a) Rejection up to VRR = 2; (b) Permeate flux in toluene, except 5 M corresponding to bulk (pure liquid) 10-undecenitrile.

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1.3. OSN of post-reaction mixture

The rejections of all solutes are depicted in Figure 6. All rejections increased upon raising TMP from 10 to 40 bar. The increase was more pronounced for 12-oxo-dodecanenitrile (from 30% to 52% rejection) and undecenitriles (from 15% to 31% rejection) than for Biphephos whose rejection slightly increased from 88% to 95%. The flux increased linearly with TMP (data not shown). The J_{OSN}/J_0 ratio was *ca*. 0.70 and the initial flux was fully recovered after rinsing with toluene ($J_R/J_0 \approx 1.00$).

Ideally the pressure applied during the synthesis and OSN should be the same. However, this can be done only if the selectivity is sufficient. The global selectivity (S_{global}, for definition, see Eq. 6, Experimental section) between ligand/catalyst rejection and 12-oxo-dodecanenitrile transmission is depicted in Figure 6. The best compromise between high catalytic system rejection and high product and by-products transmission was obtained at 10 bar. Many advantages would arise from working at low TMP:

(i) Pressure drops along industrial membrane modules are lower at low TMP;[56]
(ii) The membranes as well as the other process equipment (valves, piping…) are less degraded at low pressure;
(iii) The cost of industrial pumps to impose the pressure is lower for 10 bar pumps than for 40 bar pumps, either on capital costs (CAPEX) and operating costs (OPEX) points of view;
(iv) Energy consumption increases with TMP.[57]

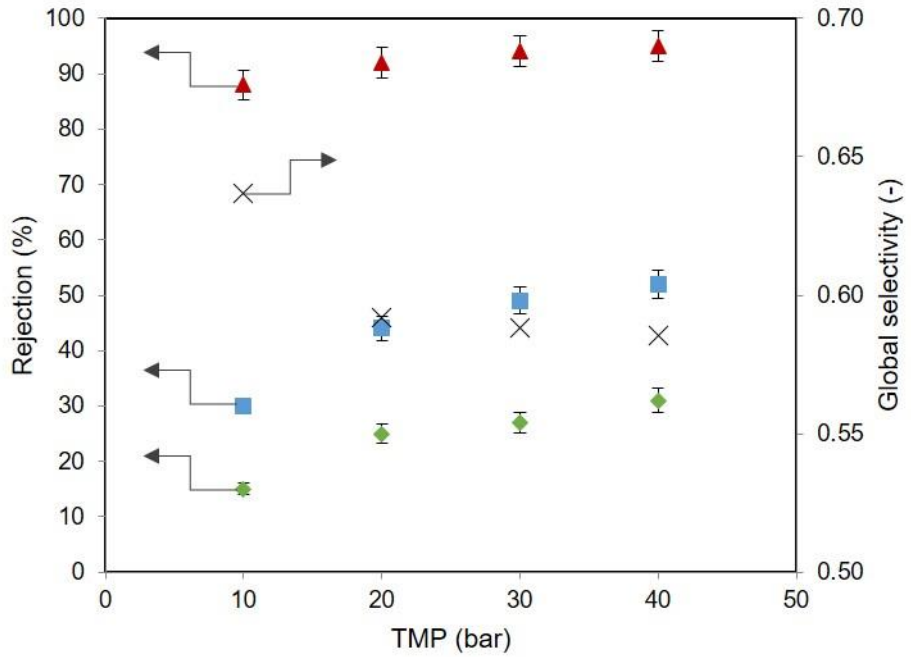


Figure 6. Rejection of all solutes and global selectivity during OSN up to VRR = 2 of post-reaction mixtures in toluene with the Rh(acac)$(CO)_2$-Biphephos system (▲: Biphephos (and estimated rejection of catalyst); ■: 12-oxo-dodecanenitrile; ♦: undecenitriles; ×: global selectivity S_{global}).

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2. Ligand screening

2.1. Hydroformylation performances in toluene

The four selected ligands were first evaluated in the hydroformylation of 10-undecenitrile using limited amounts (1.0 mol·L^{-1} in 15 mL of toluene) and then transposed to larger amounts (1.0 mol·L^{-1} in 150 mL of toluene). Comparable results were obtained with both conditions. The reaction performances are summarized in Table 1.

All catalytic systems allowed to reach near complete or high conversion of 10-undecenitrile (for conversions of 90%, a complete conversion would have been obtained by increasing the reaction time, as demonstrated in previous experiments).[40] 12-Oxo-dodecanenitrile was always the main product with a very high regioselectivity (*l/b* = 97.8/2.2 to 99.0/1.0).[58] The side products observed were the hydrogenated by-product (1-6%) and a significant amount of internal undecenitriles (*ca*. 30% with 3 out of the 4 ligands, including 6% present in the starting material). The best chemoselectivity (92% HF) [59] was obtained with Zhang's tetraphosphine ligand. We assume that the supposed better coordination of rhodium with this tetradentate ligand limits the amount of uncoordinated rhodium and/or formation of Rh "black" (colloids, nanoparticles), increasing hydroformylation *vs* other processes. The chemoselectivity (67-71%) remained good with the three sterically hindered biphosphite ligands.

Table 1. Performances of the hydroformylation reaction with different ligands in toluene[a]

Ligand	Biphephos	A4N3	Zhang	Modified Biphephos
Time (h) (unoptimized)	1.5	3	22	4
Conversion (%)	100	90	90	99
10-Undecenitrile (%)	0	10	8	1
Internal undecenitriles (%)	29	32	12	29
Undecanenitrile (%)	6	1	2	4
12-Oxo-dodecanenitrile (%)	65	56	78	66
l/b ratio (-)	99.0:1.0	97.8:2.2	98.4:1.6	99.0:1.0
%HF	69	67	92	71
Productivity	+		-	
Isomerization	+			
Chemoselectivity			+	

[a] T = 120 °C, Pressure = 20 bar CO/H_2 (1:1), $[10\text{-Undecenitrile}]_0/[Ligand]/[Rh(acac)(CO)_2]$ = 20,000:20:1, $[10\text{-Undecenitrile}]_0$ = 1.0 mol·L^{-1}, V = 150 mL for all ligands except for Zhang (100 mL)

2.2. OSN performances at 10 bar according to ligands

The post-reaction mixtures were then filtered by OSN up to VRR = 2 in order to measure the ligand rejection allowing to estimate that of the catalyst and to determine the influence of the ligand on the rejection of all other solutes. For the sake of comparison, all filtrations were performed at a TMP of 10 bar that may not be the optimum TMP for all ligands. The results are summarized in Table 2.

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The comparison of fluxes is expressed with the J_{OSN}/J_0 ratio, the initial toluene flux being the same for all experiments (J_0 = 35 $L \cdot m^{-2} \cdot h^{-1}$). For all filtrations, the permeate flux decreased to some extent depending on the ligand, but remained stable up to VRR = 2. According to our knowledge, besides TMP and the cross-flow velocity, the flux was mainly governed by the affinity between (*i*) the membrane and the solvent and (*ii*) the overall solute concentration (≈ 1 M), each compound being able to have a different impact.[45] The same flux decrease was observed with mixtures containing Biphephos and A4N3 ligands (J_{OSN}/J_0 = 0.70). The flux decrease was more pronounced with Zhang's ligand (J_{OSN}/J_0 = 0.56); this can be due to the ligand itself or more likely to the substrate/aldehyde balance that was different in the reaction mixtures (the aldehyde ratio was 78% for Zhang *vs*. 65% and 56% for Biphephos and A4N3, respectively). A lower flux decrease was observed with the mixture containing the modified Biphephos ligand (J_{OSN}/J_0 = 0.83) with respect to the lower overall concentration (initial concentration of substrate = 0.3 $mol \cdot L^{-1}$). For all experiments, the initial toluene flux was recovered after a careful toluene rinsing ($J_R/J_0 \approx 1$), which means that the flux decrease was only due to concentration polarization and/or osmotic pressure difference and there was no irreversible fouling.

Table 2. OSN results with post-reaction mixtures in toluene involving various ligands[a]

Ligand	Biphephos	A4N3	Zhang	Modified Biphephos[b]
J_{OSN}/J_0 (-)	0.71	0.70	0.56	0.83
J_R/J_0 (-)	0.98	0.96	1.05	1.01
10-Undecenitrile rejection (%)	15	14	20	15
Internal undecenitriles rejection (%)	15	14	15	14
12-oxo-dodecanenitrile rejection (%)	30	37	29	28
Ligand rejection (%)	88	89	93	88
S_{global} (-)	0.64	0.60	0.69	0.65

[a] T = 27±4 °C, cross-flow OSN at TMP = 10 bar with Sulzer PERVAP 4060 membrane up to VRR = 2
[b] $[10\text{-Undecenitrile}]_0$ = 0.3 $mol \cdot L^{-1}$

All ligand rejections were very similar (88-93%). The rejections of 10-undecenitrile and internal undecenitriles [60] were the same whatever the ligand used (*ca*. 15%). This means that these by-products (almost 30% of the final components, Table 1) were highly extracted. Similar 12-oxo-dodecanenitrile rejections were observed for experiments with Zhang's and both pristine and modified Biphephos ligands (28-30%) but was somehow higher with A4N3 (37%). To expect an efficient separation, a high catalyst rejection has to be combined to a high 12-oxo-dodecanenitrile extraction and a high permeate flux. Zhang's ligand allowed reaching the highest global selectivity (0.69) thanks to its high catalyst rejection, in spite of the lowest flux. The global selectivity for both pristine and modified Biphephos ligands was slightly lower (0.64-0.65) but with significant higher fluxes. A4N3 gave the lowest selectivity (0.60).

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2.3. Selection of the ligand

Based on the reaction and OSN performances, the ligand selection had to be a compromise in order to optimize the whole process. Several quantitative criteria were taken into account: (*i*) the efficiency of the reaction (activity, chemo- and regioselectivities), (*ii*) the J_{OSN}/J_0 ratio dealing with process productivity, (*iii*) the global selectivity dealing with the quality of the separation, and (*iv*) the access to the ligand (commercially available Biphephos and A4N3 ligands are currently easier to obtain than the two other lab-made ligands).

On the reaction point of view, although Zhang's ligand gave the best chemoselectivity, this catalytic system had a main drawback with respect to the productivity criterion: the activity was modest and the duration of the reaction to reach full conversion was very long (22 h against 2-4h for the others); in fact, during the experiments performed at small scale, the reaction rate of Biphephos system (TOF = 28,500 h^{-1}) was *ca*. 6 times higher than that of Zhang's system (TOF = 4,400 h^{-1});[**61**] in addition, both Biphephos-based ligands led to a regioselectivity (*l/b* = 99.0:1.0) higher than A4N3 and Zhang's ligands. This parameter is of importance since only the linear aldehyde is targeted. The modified Biphephos ligand and the pristine Biphephos gave very similar results (same regio- and chemoselectivity, productivity and similar reaction rate).

On the OSN point of view, the rejection values evidenced that separation of the catalytic system from all other organic solutes can be envisaged, regardless of the selected ligand. However, the separation efficiency clearly depends on the ligand, especially dealing with two main criteria: (*i*) the target product extraction and (*ii*) the permeate flux.

To conclude, the commercially available Biphephos ligand appeared as the best choice for improvement of the studied hydroformylation process since it affords the best compromise between availability, efficiency, selectivity, reaction rate, and OSN performances.

3. Reaction-OSN Coupling

Note that with respect to the membrane materials stability, OSN cannot be performed at the reaction temperature and the reaction mixture has to be cooled before the filtration process (see the Experimental section, Figure 15). It must be underlined that the recycling of all the unreacted substrate to the synthesis reactor is not possible since part of it goes to the permeate fraction due to its low OSN rejection. This means that the maximum conversion should be obtained before filtration. Moreover, the respective rejections of the target aldehyde and by-products are too close to expect their separation and all of them will be extracted in the permeate. In addition, it must be kept in mind that even a fully transmitted compound (Ret = 0) at initial C_0 concentration in the initial V_0 volume of feed entering the OSN set-up will be present in the final retentate at a final concentration $C_{final} = C_0$. This means that a certain amount ($n_{final,Ret=0} = C_0 \times V_0 / VRR$) will be recycled back to the reactor. For a solute only partly transmitted in the permeate (Ret > 0), the amount to send back to the reactor will be greater than $n_{final,Ret=0}$. However, the accumulation of the target aldehyde and by-products in the synthesis reactor during reaction-OSN cycles can be limited by increasing the VRR during OSN. Nevertheless, selection of the final VRR value cannot be done without considering its

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impact on the whole system (see below). Moreover, from an experimental point of view, the maximum reachable VRR depends on the OSN set-up capacity (300 mL) and the hold up volume (50 mL).

3.1. VRR selection for OSN in toluene

As mentioned above, the VRR increase would have also an impact on the flux during OSN and the ligand and catalyst leakage in the permeate. Once again, a compromise has to be found and an in-depth study of OSN of the selected mixtures at different VRR is required for optimization purposes.

When considering the permeate flux, the classical trend is that reported on Figure 5b. Changing 10-undecenitrile for mixtures of the reaction products and by-products would have a little impact on flux, as evidenced from experience.[54] To overcome the lack of sufficient amount of all components, preventing from an experimental determination, we have intensively studied the Biphephos/Aldehyde separation on a theoretical point of view.[44-46,53] Assuming constant rejection of 88% for Biphephos and 30% for the aldehyde, or taking into account rejection variations with the concentration, resulted in similar results in the 1-10 VRR range. Figure 7 depicts the overall simulated recoveries of Biphephos in the retentate and the aldehyde in the permeate *vs*. VRR. None of these VRR will allow to simultaneously recycle more than 99% of the catalytic system and simultaneously extract large amounts of the products.

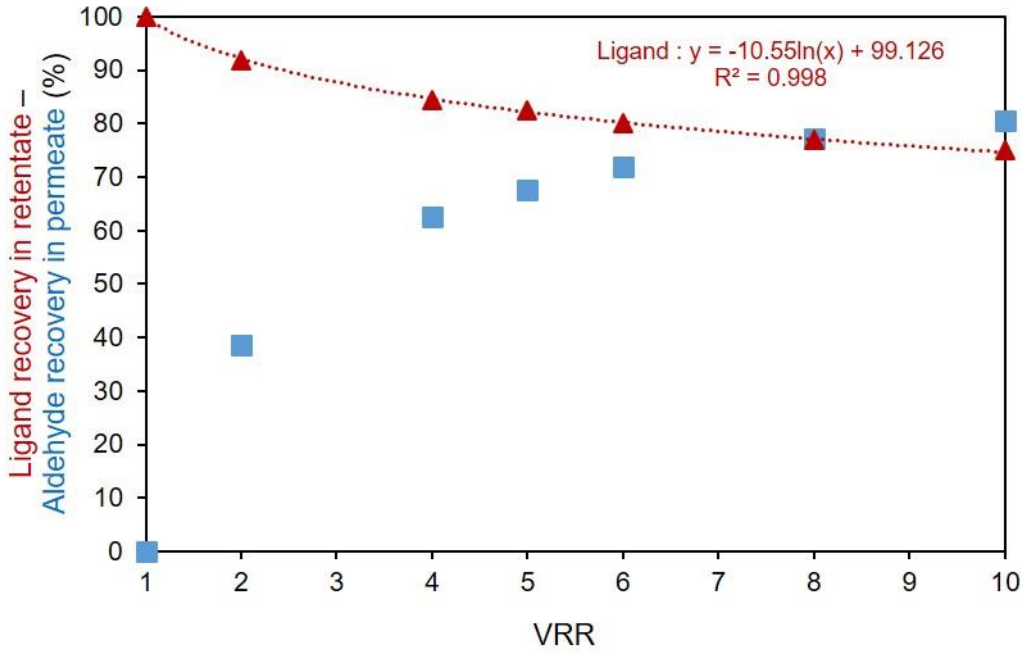


Figure 7: Overall recoveries of the Biphephos ligand in the retentate and the target Aldehyde in the permeate at different VRR based on OSN performances with the Biphephos system in toluene and Pervap 4060 membrane at 10 bar adapted from simulation.[44-46]

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Nevertheless, other OSN configurations called membrane cascades are possible at industrial scale (see Discussion). Our simulations predicted that a cascade with 4 stages and recycling between stages might allow to recover 98.9% of the initial Biphephos in the retentate and 82.2% of the target aldehyde in the permeate using VRR = 5 at each stage.[44] Unfortunately, according to the best of our knowledge, no cascade equipment is available up to now at laboratory scale to probe this simulation.

Dreimann *et al.* proved the recyclability of the Rh-catalyst at VRR = 2 in a mixture close to that studied here but using TPP ligand that was selected because of its intrinsic stability.[35-36] Yet, the TPP had to be significantly reloaded because of its poor rejection, losing the main reason of its initial choice. In addition, less than 50% of the produced products could be extracted (similar OSN configuration as here).

In the present study, assuming that recyclability would be possible at VRR = 2 and aiming at evidencing the limit of the Biphephos system, we followed a complementary strategy based on a compromise between ligand/catalyst recycling and product extraction. With respect to our OSN set-up, the maximum reachable VRR was 5, allowing to extract *ca.* 68% of the overall produced aldehyde (Figure 7). In these conditions, the Biphephos recovery in the retentate will be 82.4 % at each cycle and a limited number of reaction-OSN cycles would be anticipated since the loss will be close to $(1 - 0.824^n) \times 100$ (%) after n cycles (that is, about 18% of the catalytic system will be lost after 1 cycle, 32% and 44% after 2 and 3 cycles, respectively).
On the other hand, the target aldehyde extraction in the permeate would be 67.6% of the total content present at OSN start for each cycle. A strategy of using diafiltration was not studied because it would increase the amount of catalyst lost in the permeate for further reaction simultaneously with an increase in solvent consumption.

3.2. Reaction-OSN coupling in toluene

Three reaction-OSN cycles were performed. The first reaction results (cycle 1 in Table 3) were close to the results previously obtained (see Table 1), evidencing a successful scaling-up (from 150 mL to 250 mL) despite a lower syngas pressure (15 bar instead of 20 bar). For the first cycle, the reaction reached 91% conversion and 68% of 12-oxo-dodecanenitrile was produced. During the second and third reactions (cycles 2 and 3), a very high conversion (> 95%) was maintained but the selectivity towards the aldehyde dropped from 68% to 21% (which corresponded to a %HF drop from 79% to 22%). The *l/b* ratio also decreased for each cycle (from 99.3:0.7 for cycle 1 to 92.7:7.3 for cycle 3). In parallel, the amount of undecanenitrile (hydrogenated product) increased from 3% to 15%. It is noteworthy that previous *batch* experiments performed with a lower catalyst loadings ($[Substrate]_0/[catalyst]$ up to 50,000) did not lead to such selectivity drop.[42]

The catalytic performance decay was expected as explained above although the $[Substrate]_0/[catalyst]$ remained lower than 50,000 for all cycles. On the other hand, the excess of Biphephos gradually decreased while accumulation of the isomerizing active species occurred from one reaction to another, both of them being a possible explanation for the overall performance decay.

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Table 3. Performances of the hydroformylation reaction during the 3 reaction-OSN cycles in toluene[a]

Cycle	1	2	3
Reaction time (h)	4	4.5	5
Conversion (%)	91	95	99
10-undecenitrile (%)	8	4	1
Internal undecenitriles (%)	21	38	63
Undecanenitrile (%)	3	3	15
12-oxo-dodecanenitrile (%)	68	55	21
l/b ratio (-)	99.3:0.7	96.4:3.6	92.7:7.3
%HF	79	61	22

[a] T = 120 °C, Pressure = 15 bar CO/H_2 (1:1), $([10\text{-undecenitrile}]_0/[\text{Biphephos}]/[Rh(acac)(CO)_2])_{\text{cycle 1}}$ = 20,000:20:1, $[10\text{-undecenitrile}]_0$ = 1.0 mol·L^{-1}, V = 250 mL

Considering OSN results, for each cycle, the flux remained constant at *ca*. 26 L·m^{-2}·h^{-1} at TMP = 10 bar which was slightly better than the flux estimated from 10-undecenitrile OSN (Figure 5b). After rinsing, the initial toluene flux was fully recovered, as expected. The rejections were the same as those reported in Table 2, except the Biphephos one that increased during the last OSN (96% rejection for cycle 3 as compared to 88% for the first two cycles). This increase could be explained by a significant decrease in the ligand concentration during the final OSN.

Figure 8 shows the overall amount of each solute extracted in the permeate. The quantity of extracted Biphephos increased after each cycle and the experimental values were the same as the estimated ones for the first two cycles. For the third cycle, it was slightly overestimated because the rejection was underestimated (see section 3.1).

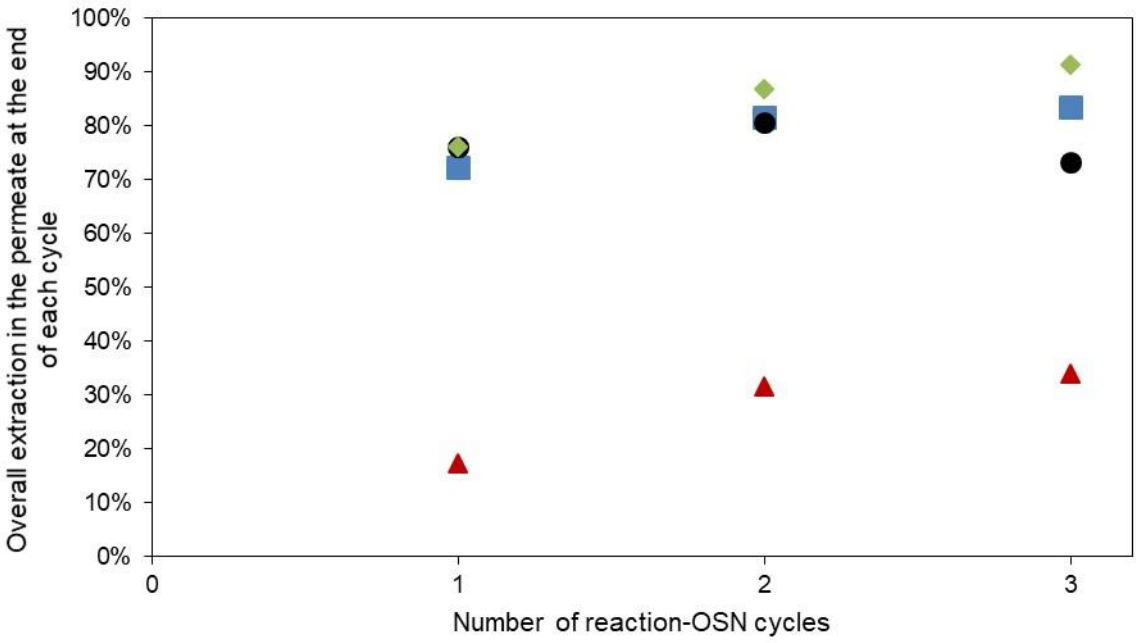


Figure 8. Overall extraction in the permeate at the end of each reaction-OSN cycle in toluene (▲: Biphephos (and estimated catalyst); ■: 12-oxo-dodecanenitrile; ♦: 10-undecenitrile; ●: internal undecenitriles.

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On the productivity point of view, the TON values increased from 18,230 to 37,230 then 57,030 from the first to the third cycle, highlighting the efficiency of reaction-OSN coupling, modulated by the isomerization. The target aldehyde overall productivity ($TON_{linear\ aldehyde}$) was 29,500 mol(linear aldehyde)·mol(Rh)$^{-1}$, knowing that 14,300 mol(linear aldehyde)·mol(Rh)$^{-1}$ were produced during cycle 1, 11,170 mol(linear aldehyde)·mol(Rh)$^{-1}$ during cycle 2 and 4,030 mol(linear aldehyde)·mol(Rh)$^{-1}$ during cycle 3, respectively (Table 5). The productivity was roughly similar during the first two cycles. These results suggest that, using OSN up to VRR = 5 in the tested configuration (continuous permeate extraction), a maximum catalyst loss that has to be evaluated more accurately in the range 18-32% could be acceptable. For higher loss OSN must be combined with a strategy of ligand + catalyst supply from one cycle to another in order to keep a high 12-oxo-dodecanenitrile production.

3.3. Reaction-OSN coupling in bulk

A second set of experiments was performed in bulk to tend to more industrially relevant conditions (solvent-free), moreover using a smaller reactor for the same produced amount (energy saving). In a batch process, being the main components, the liquid reagent/product (10-undecenitrile and 12-oxo-dodecanenitrile) would alternatively play the role of solvent at reaction start and end, respectively. Pure liquid 10-undecenitrile contains 5 mol per L (density = 0.834) whereas pure 12-oxo-dodecanenitrile reaches 4.6 mol per L (density = 0.902). Accordingly, the concentrations of Rh(acac)$(CO)_2$ and Biphephos had to be multiplied by 5 when compared to the conditions in toluene in order to respect the [Ligand]/[Rh(acac)$(CO)_2$] ratio of 20 and the [Substrate]$_0$/[Rh(acac)$(CO)_2$] ratio of 20,000.

During the OSN step, the target aldehyde being the mobile phase in bulk, its rejection will be null. As explained above, the extracted amount of the aldehyde directly depends on the VRR. So, the latter value must be high considering the higher productivity loss when compared to the same reaction volume in toluene. The rejection of the solutes (by-products, ligand, catalyst) at the same concentration would be different in bulk than in toluene with respect to affinity differences in either membrane/"solvent" or "solvent"/solutes. It could be expected that the increase of the solute concentration would decrease its rejection (see Figure 5a). A systematic study of the TMP could be achieved in order to optimize the bulk process (see section 1) and to accurately determine the best VRR. However, this systematic study was not achieved due to the lack of substrate. Only two reaction-OSN cycles were performed due to the large amount of substrate required to operate in bulk.

As first attempt, the OSN experiments were performed at 10 bar up to VRR = 5 as it was previously done in toluene. In such conditions, the experimental rejection of Biphephos in bulk was only 70% meaning that, at VRR = 5, 38% of the initial Biphephos (and catalyst) was lost in the permeate fraction reaching 52% loss after 2 cycles. These two values were greater than the maximum acceptable loss in toluene (see section 3.2).

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The rejections of 10-undecenitrile and internal undecenitriles were negative (–2% and –6%, respectively). Several authors also found negative rejections in OSN.[62,63] This means that these two compounds have a better affinity toward the membrane swelled by the aldehyde than the aldehyde itself. It is a positive aspect favoring less accumulation of by-products in the retentate to send back to the reactor.

The permeate flux decreased during the 2 cycles from an average value of 19.8 $L \cdot m^{-2} \cdot h^{-1}$ for cycle 1 to an average value of 11.3 $L \cdot m^{-2} \cdot h^{-1}$ for cycle 2, both being comparable to the flux value of pure 10-undecenitrile of close viscosity (Figure 5b). The reaction performances are summarized in Table 4.

Table 4. Performances of the hydroformylation reaction in bulk during the 2 reaction-OSN cycles[a]

	Cycle 1	Cycle 2
Reaction time (h)	6	6.25
Conversion (%)	100	95
10-undecenitrile (%)	0	5
Internal undecenitriles (%)	40	67
Undecanenitrile (%)	4	2
12-oxo-dodecanenitrile (%)	56	26
l/b ratio (-)	99.1:0.9	97.4:2.6
%HF	69	29

[a] T = 120 °C, Pressure = 15 bar CO/H_2 (1:1), $([10\text{-undecenitrile}]_0/[\text{Biphephos}]/[Rh(acac)(CO)_2])_{\text{cycle 1}}$ = 20,000:20:1, V = 250 mL

The first reaction allowed achieving complete 10-undecenitrile conversion with 56% of 12-oxo-dodecanenitrile produced, 40% of internal undecenitriles and 4% of hydrogenated by-product (69% HF). The reaction performances decreased during cycle 2: the conversion was 95% and the formation of 12-oxo-dodecanenitrile dropped down to 26% (29% HF) with *l/b* = 97.4:2.6; conversely, the formation of internal undecenitriles increased up to 67%. As discussed above, the chemoselectivity drop could be due to the lower amount of ligand/catalyst in cycle 2. It is worth noting that the regioselectivity of cycle 2 in bulk is slightly higher than that of cycle 2 in toluene having produced much lower amounts of products with respect to the engaged mol of substrate.

On the productivity point of view, at the end of cycle 2, 85% of the produced 12-oxo-dodecanenitrile was extracted in the permeate with 69% of the unconverted 10-undecenitrile, and 79% of internal undecenitriles. The overall productivity was 39,000 with an overall chemoselectivity of 50% and overall regioselectivity *l/b* of 98.3:1.7. This represents a productivity in linear aldehyde of 19,100 mol(linear aldehyde)·$mol(Rh)^{-1}$ (*ca*. 13,700 mol(linear aldehyde)·$mol(Rh)^{-1}$ produced during cycle 1 and 5,400 mol(linear aldehyde)·$mol(Rh)^{-1}$ during cycle 2, Table 5).

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3.4. Comparison of reaction-OSN coupling in toluene and in bulk

Table 5 compares bulk and toluene hydroformylation processes. During the first cycle in bulk and the first two cycles in toluene, the TON values per cycle were close.

Table 5. Comparison between bulk and toluene hydroformylation processes for the synthesis of 12-oxo-dodecanenitrile with 2 reaction-OSN cycles (VRR = 5).

	Bulk process		Toluene process		
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 3
Volume of toluene added per cycle (mL)	0	0	200	150	150
10-undecenitrile added per cycle (mol)	1.25	1.25	0.25	0.25	0.25
$Rh(acac)(CO)_2$ added per cycle(mmol)	0.625	0	0.0125	0	0
Biphephos added per cycle(mmol)	1.25	0	0.25	0	0
TON per cycle (mol(linear aldehyde)·mol(Rh)$^{-1}$)	13,700	5,400	14,300	11,170	4,030
Overall TON (mol(linear aldehyde)·mol(Rh)$^{-1}$)	13,700	19,100	14,300	25,470	29,500
J_{OSN} (L·m^{-2}·h^{-1})	19.8	11.3	26.1	25.9	25.9
12-oxo-dodecanenitrile extraction (%)	79	85	72	81	83

During OSN, the permeate flux was higher in toluene than in bulk. However, the efficiency needs to be considered according to the volume to treat. For instance, to reach VRR = 5 in 1 h with 1 L of initial bulk solution, 0.05 m² of membrane would be necessary assuming 15.6 L·m^{-2}·h^{-1} permeate flux as the average experimental value between cycles 1 and 2. For the same amount of substrate, the initial volume to treat in the toluene process would be 5 L and 0.15 m² of membrane would be necessary to reach VRR = 5 in 1 h (J_{OSN}=26 L·m^{-2}·h^{-1}). This calculation shows that bulk OSN may be more economically feasible in terms of membrane investment. The membrane lifetime should also be studied to consolidate this analysis.

At TMP = 10 bar, the difference between ligand/catalyst and 12-oxo-dodecanenitrile rejections was higher in bulk (70% and 0% rejection, respectively, leading to 70 points difference) than in toluene (88% and 30% rejection, respectively, leading to 58 points difference). This means that, for a given VRR, a larger amount of 12-oxo-dodecanenitrile would be extracted in the permeate with the bulk process; this is in line with the results in the last entry in Table 5. However, this good extraction was counter-balanced by more catalyst loss. Nevertheless, it can be guessed that the ligand/catalyst rejection could be increased at higher TMP in bulk (if the rejection trend is similar to that in toluene, see Figure 4) with always a null rejection of the target aldehyde, the modulation of the permeate flux value having to be determined. In conclusion, a subtle compromise could be found between ligand/catalyst recycling for reaction efficiency and product extraction. Yet, optimal OSN conditions for the toluene and bulk processes will be different. Regardless of the selected process either in toluene or bulk, the final permeate remained a mixture of the target aldehyde and the by-products and further purification is required.

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Discussion

The discussion deals with the possible integration of OSN in the overall production scheme of 12-oxo-dodecanenitrile from 10-undecenitrile. To better appreciate the interest of membrane filtration, a reference production scheme using distillation is first presented, then a hybrid process combining OSN and distillation is studied. The discussion is mainly conducted in the case of the toluene process because of the more accurate experimental results available for the filtration step. For the sake of simplification, only one reaction-OSN cycle is detailed for exemplification. Some trends related to the bulk process are also commented.

1. Reference process: synthesis in toluene & distillation

The flowsheet of the reference process was inspired from already patented industrial processes in which the separations are only based on distillation.[64] Roughly, the synthesis would be conducted in a reactor, often operating in a batch mode (discontinuous). The final reaction mixture would be separated thanks to a distillation train of 4 columns (Figure 9). The first column would be devoted to toluene separation from all other compounds. The second one would allow the separation of all products from the catalytic system that can be degraded due to the high temperatures involved in the distillation. If the catalyst is not active anymore, a reloading can be considered. However, during this second distillation, about 10% of the aldehyde would be lost while the Rh species and the ligand remaining in the heated residue would be at least partly destroyed preventing from their recycling. The last two columns would allow to separate the pure target aldehyde from all other by-products remaining in the mixture (note that the last distillation is only necessary if "heavy" by-products are generated in the previous columns).

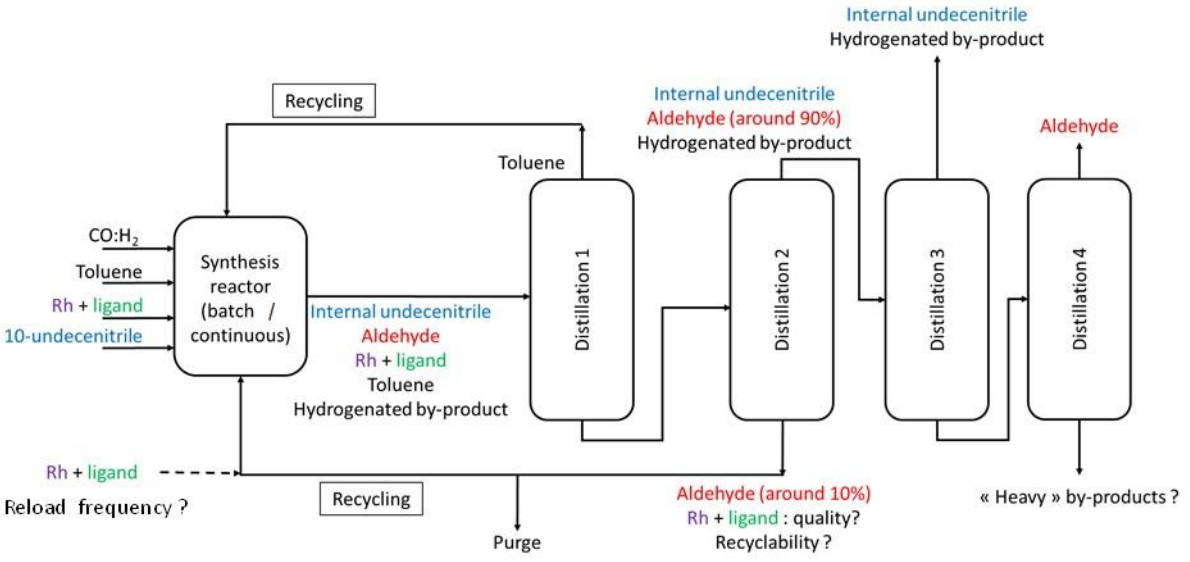


Figure 9. Flowsheet of the hydroformylation reference process using distillation for all separations.

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Classically, such synthesis achieved at industrial scale would be made at 1 M initial substrate concentration in toluene. For 1 L total volume entering the first distillation column, 200 mL would be due to the organic compounds (target product + by-products) whereas 800 mL would be toluene. Assuming close boiling points for all these organics, the relative operating costs (OPEX) will be roughly estimated from the volume to treat. Thus, the OPEX of distillation would be mainly due to the distillation of toluene.

For a same amount of organic compounds produced in bulk, the reactor size could be divided by 5 accompanied by the energy saving required to heat a smaller volume. Moreover, the first column could be avoided and only 200 mL of target product + by-products would be distilled, decreasing both the OPEX due to distillation and the CAPEX quite significantly. However, the issue of reload of ligand and Rh precursor would not be solved as both could be partly destroyed during distillation as explained above.

Considering the possibility of catalyst recycling thanks to liquid-liquid extraction and knowing that often the extraction volume is roughly similar to the process volume, two cases can be envisioned:

1. if the reaction is achieved in toluene, the first distillation (Figure 9) would remain but toluene would be replaced by the extraction solvent and, besides the recycling of precious Rh, the gain would only be in the difference in boiling points between the extraction solvent and toluene.
2. if the reaction is achieved in bulk, the extraction volume would be significantly reduced but its distillation would remain necessary, preventing from the cancellation of the first distillation column.

2. Integration of OSN into a hybrid process

Based on our experimental results, Figure 10 depicts the flow sheet of an alternative hybrid process in toluene. A separation step by OSN would immediately follow the reactor allowing a near complete Rh and ligand recycling toward the reactor, depending on the OSN arrangement (see below). Simultaneously, a toluene fraction, the volume of which depends on the VRR, would be sent back to the reactor without any distillation. Only the permeate would be sent to distillation, limiting the OPEX of the first distillation column compared with the first column of Figure 9.

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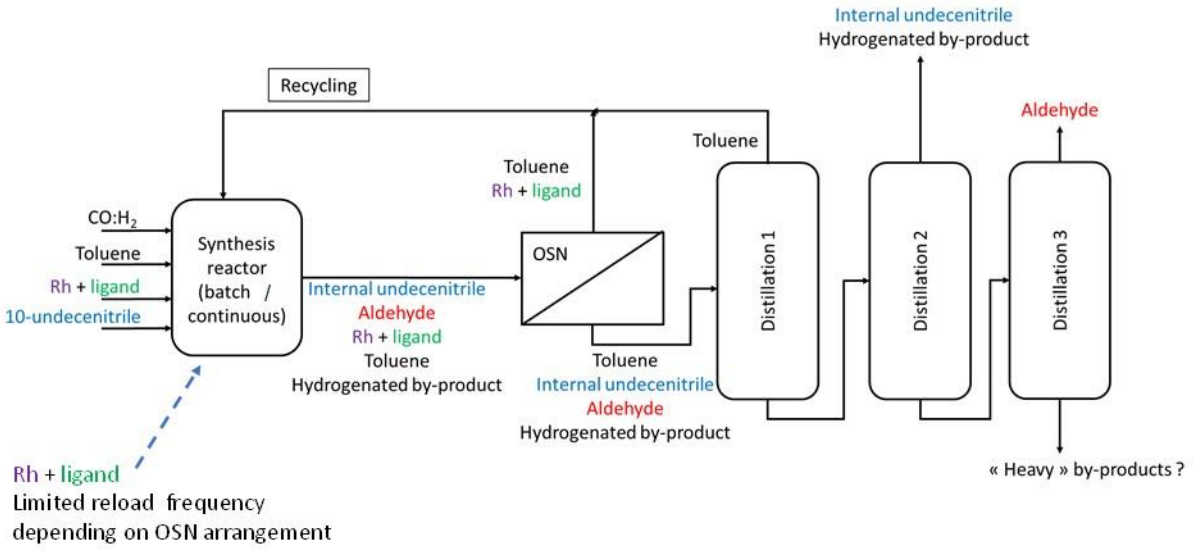


Figure 10. Flowsheet of the hydroformylation hybrid process in toluene using OSN and distillation for separations.

As already mentioned, there is not a single way to perform OSN. In the following, among all simulations performed,[44-45, 53] we have selected two different cases in order to highlight two consequences based on different strategies: single OSN *vs* membrane cascade.

First, if OSN is achieved as a single step process at TMP = 10 bar with a continuous extraction of the permeate up to VRR = 5 (Figure 11), then 82% of the catalytic system could be recycled after one reaction-OSN cycle and only 80% of the feed volume (permeate) would enter the first distillation column, knowing that toluene would be 82% of this permeate volume. We estimated that the OSN OPEX would be 0.5 kWh·m^{-3}.[45] In that case, the distillation would be achieved on 66% of the initial feed volume and the energy saving during distillation would be high. In addition, the reduced OPEX due to the Rh and ligand reload must be taken into account, both extent and frequency being decreased compared with a process without any recycling. The economic evaluation must also take into account that only 72% of the produced target aldehyde would be recovered (Table 5).

Second, if the OSN is achieved through a 4-stage cascade as shown in Figure 12, such configuration would allow to recycle 98.9% of Biphephos (and 99.3% of catalyst) and to extract 82.2% of the produced aldehyde in a single operation. We estimated that the OSN OPEX would be 1.7 kWh·m^{-3}, that is 16 times less than a process only based on distillation.[44, 53] In that case, the distillation would be achieved on 94% of the initial feed volume and the energy saving during distillation would be quite limited. So the decision is based on the energy cost versus the ligand cost knowing that the most selective ligands are also the most expensive ones.

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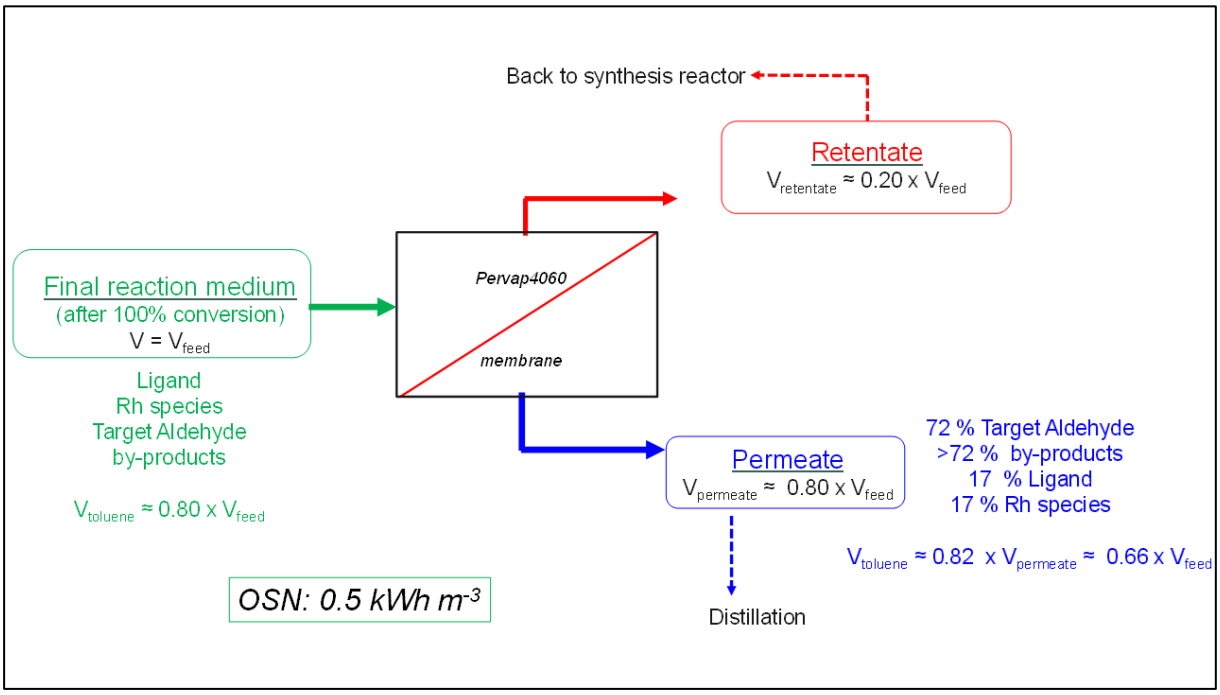


Figure 11. OSN operated at TMP = 10 bar with the Pervap 4060 membrane with VRR = 5, calculated from theoretical simulations.[44-45, 53]

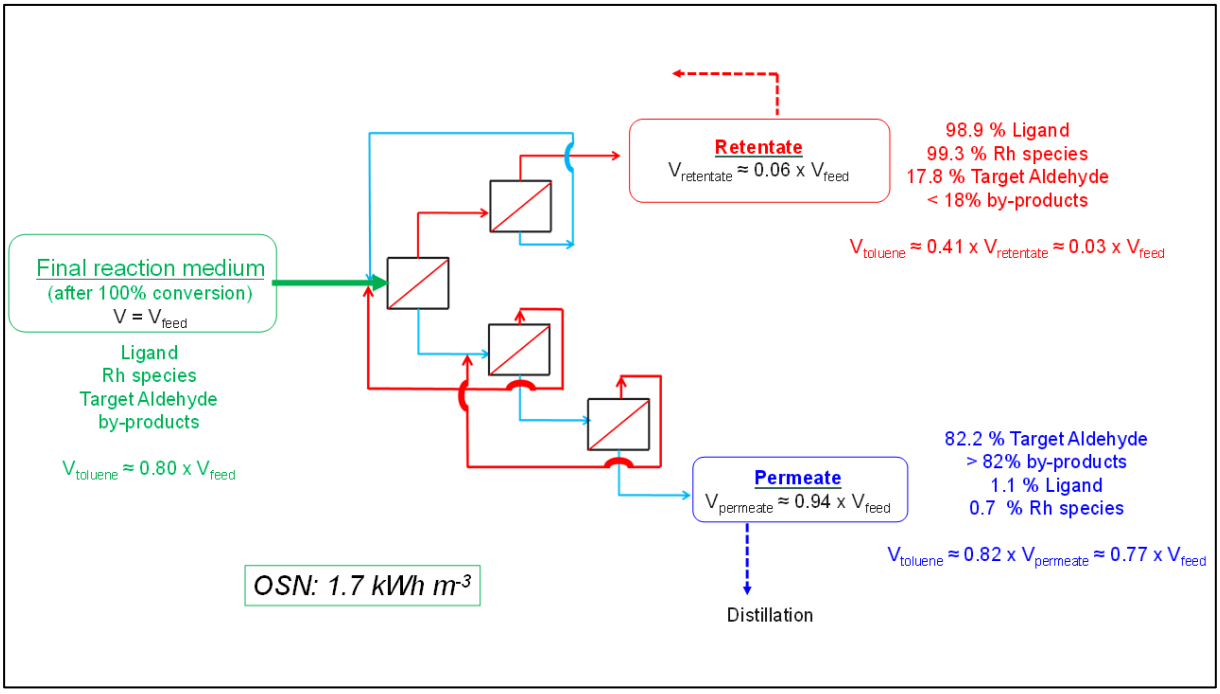


Figure 12. 4-stage OSN cascade running at TMP = 10 bar with the Pervap 4060 membrane with VRR = 5 at each stage, calculated from theoretical simulations of cascades.[44-45, 53]

The hybrid process scheme of Figure 10 combined with OSN achieved as shown in Figure 11 could be adapted to the bulk process allowing to cancel the first distillation column. However, in that case, the VRR might be as high as possible, probably much higher than VRR = 5 to

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avoid an important loss of the target product. With the membrane selected for the present study, a TMP of 10 bar was not sufficient and the effect of a TMP raise up to 40 bar might be checked. If the rejection of the catalytic system remains too low, then the hybrid process combining Figure 10 and OSN achieved according to Figure 12 (probably at 40 bar) should be studied in detail. It would be the more intensive process. Regardless of the technical feasibility, the final decision would be based on the economic balance with respect to the number of possible recyclings of the catalytic system.

Conclusion

Through the case study of the Rh-catalyzed hydroformylation of 10-undecenitrile into 12-oxo-dodecanenitrile, the comparison of four ligands in toluene allowed to optimize both the reaction and the OSN steps. Pristine Biphephos proved to be the best compromise in terms of reaction performances and high OSN selectivity, whose best selectivity between high ligand/catalyst rejection (88%) and high product transmission (*ca.* 68%) was achieved at a transmembrane pressure of 10 bar. With these process conditions, reaction-OSN coupling was first performed in toluene up to 3 cycles. An efficient substrate conversion was reached whatever the cycle (91-99%) but the selectivity towards hydroformylation dropped (79% to 22%), at the extent of isomerization and hydrogenation side-reactions during cycles 2 and 3. This was mainly attributed to the high loss of the catalytic system, since only 44% of the initial load was still present after 3 cycles, and also to the sensitivity of the Rh-active species. Thus, VRR = 5 may be too ambitious with respect to the overall catalytic system rejection but appears as an interesting choice with respect to the product extraction.

Transposition to a bulk process with concentrations five times higher than those of the toluene process was studied. The first cycle allowed to reach the same TON value as that obtained with the first two cycles in toluene.

Finally, a hybrid separation process coupling OSN and distillation was discussed aiming at highlighting that the best strategy could be different in toluene and in bulk. The comparison between bulk and toluene processes is actually subtle because, for a given 12-oxo-dodecanenitrile productivity, a compromise has to be found between operation parameters. All the advantages and drawbacks of toluene and bulk processes need to be balanced in a technical and economic analysis to choose the best process.

Experimental section

1. Reaction medium

The substrate of the reaction was composed of a mixture of 10-undecenitrile (94%, MW = 165 $g \cdot mol^{-1}$) and various internal undecenitriles (6%, mainly 9-undecenitrile, MW = 165 $g \cdot mol^{-1}$). The reaction was performed either in toluene, which previously proved to be the most efficient solvent for hydroformylation of 10-undecenitrile at an initial substrate concentration = 1.0 $mol \cdot L^{-1}$.[42-43] or in bulk (solvent-free) conditions, in presence of a catalytic system composed

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of $Rh(acac)(CO)_2$ as metal precursor and an excess of ligand (20 equiv. to ensure complete coordination of all rhodium with the ligand [40-43]). The active catalyst was formed *in situ* under syngas pressure; hence the term "catalyst" refers to the active species. The desired valuable product is the linear aldehyde (12-oxo-dodecanenitrile; MW = 195 $g \cdot mol^{-1}$). The side-product from hydroformylation is the branched aldehyde (10-methyl-11-oxo-undecanenitrile; MW = 195 $g \cdot mol^{-1}$). The linear-to-branched aldehyde ratio (*l*/*b*) represents the regioselectivity of the reaction and is the key parameter to optimize since linear and branched aldehydes cannot be separated in further stages. However, it has to be noticed that no other internal aldehydes were detected during all the process. Two other by-products were also formed during the course of the reaction: a mixture of internal undecenitriles (essentially 8-undecenitrile and 9-undecenitrile; also referred to as internal isomers; MW = 165 $g \cdot mol^{-1}$) arising from isomerization of undecenitrile and undecanenitrile (MW=167 $g \cdot mol^{-1}$) that arises from undecenitrile hydrogenation.[41-43]

2. Chemicals

Toluene of analytical grade (>99.3% purity) and $Rh(acac)(CO)_2$ (98% purity) were purchased from Sigma Aldrich. Toluene was purified over alumina columns using a MBraun system. 10-Undecenitrile was kindly supplied by Arkema Co. (Colombes, France). Biphephos and A4N3 were purchased from Strem Chemicals and MCAT (99% purity), respectively. The Zhang-type ligand was synthesized according to Zhang *et al.*'s procedure.[65] All ligands were stored in a glove box under inert atmosphere.

A modified ethyl cinnamate-substituted Biphephos ligand with an increased isosteric volume that would facilitate its rejection by the membrane was synthesized. The synthetic pathway - involving a cross-metathesis with ethyl acrylate - is shown in Figure 13, indicating the yield of each step. The first 4 steps of the synthesis were achieved according to the procedure reported by Jana and Tunge.[66] The cross-metathesis step was applied on the Boc-protected intermediate with 100% selectively. Formation of the target ligand was achieved by reaction of (1,1′-biphenyl-2,2′-dioxy)chlorophosphine[67] with the diphenol compound obtained after Boc-deprotection with a 9% (non-optimized) overall yield.

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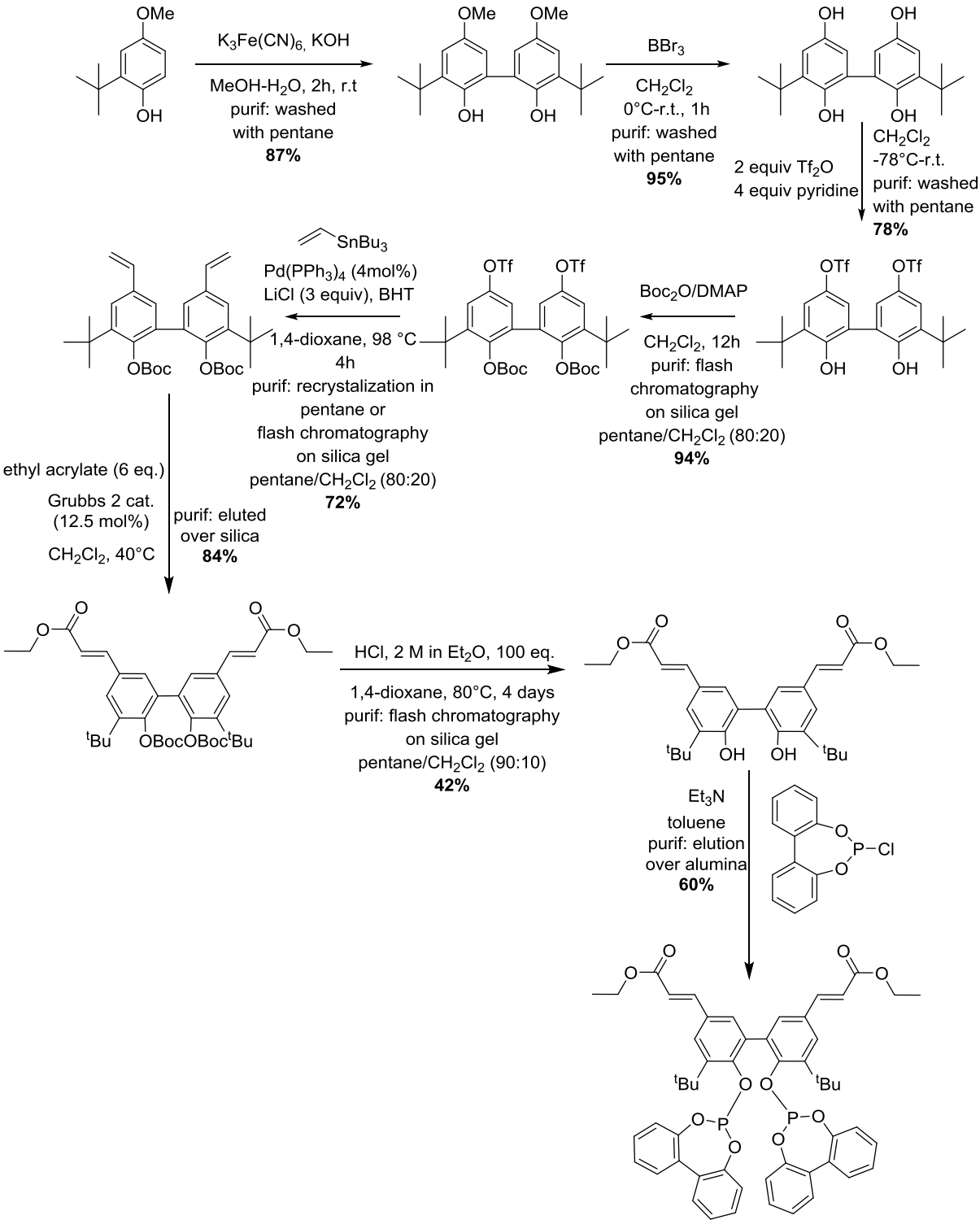


Figure 13. Synthesis of the modified, ethyl cinnamate-substituted Biphephos ligand.

3. Analyses

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer to monitor the progress of the reaction. The NMR characteristics for 10-undecenitrile, its internal isomers, the hydroformylation products and the hydrogenation product have been reported previously.[40-42]

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Gas chromatography (GC) was used to measure the concentrations of the substrate and the products in the reaction mixture. A GC-2014 SHIMADZU apparatus equipped with a PDMS-PDPS (95%–5%) semi-capillary column (Supelco, Equity-5, 30 m × 0.53 mm × 1.5 µm film thickness) was used (injection at 250 °C, analysis at constant oven temperature of 210 °C and detection by FID at 300 °C). The carrier gas was nitrogen at 18 kPa. Using these conditions, 10-undecenitrile and undecanenitrile were not separated, but the amount of the latter product was negligible (< 5%) under the operating conditions.[40] Hence, the overall concentration of 10-undecenitrile and its internal isomers were further globally considered. When needed punctually the oven temperature was decreased to separate all components.[44,53] Quantifications were obtained using an internal calibration mode with toluene as a standard. Accuracy on concentrations was ± 2%.

UV analyses were achieved with a JASCO-V360 spectrophotometer and concentrations determined thanks to the Beer-Lambert law with an accuracy of ± 5% over the respected calibration ranges. Quantifications of free Biphephos and of all other ligands were achieved at a wavelength of λ= 317 nm (we have checked the negligible overlapping with Rh species at 0.05 mM at the studied concentrations of the ligands, **supplementary materials 1**). Similarly, the $Rh(acac)(CO)_2$ concentration was measured at λ= 334 nm for OSN experiments achieved with the pre-catalyst in single solution at 0.05 mM in toluene.

4. Hydroformylation reaction

All hydroformylation reactions were performed in a stainless-steel autoclave equipped with a magnetic stirrer bar, according to detailed reported procedures.[40-43] During the experiments carried out for ligand screening, the reaction conditions were settled at a pressure of 20 bar CO/H_2 (1:1) and a temperature of 120 °C. The [Ligand]/[$Rh(acac)(CO)_2$] ratio was 20 and the $[Substrate]_0/[Rh(acac)(CO)_2]$ ratio was 20,000. The initial concentration of the starting material was 1.0 $mol \cdot L^{-1}$ except with the (less available) modified Biphephos ligand for which the initial concentration was set at 0.3 $mol \cdot L^{-1}$.

For experiments with recycling of the catalyst (reaction-OSN coupling), the volume of solution was raised to 250 mL. In that case, the reactor allowed only 15 bar pressure (CO/H_2 1:1). The OSN retentate (containing the catalyst in all of its forms either pre-catalyst or deactivated species) was kept under argon and directly used in the following reaction. A desired amount of fresh substrate was added to reach the target $[Substrate]_0$/[Catalyst] ratio. No reload of the ligand was done. All the other reaction conditions remained unchanged, either performed in bulk or in toluene.

After the appropriate reaction time, the reactor was cooled down to room temperature. The solution was then analyzed by ^1H NMR spectroscopy (after removal of toluene if needed). The conversion of 10-undecenitrile was calculated considering the initial quantity of internal undecenitriles in the substrate according to equation (1).

$$\text{Conversion (10-undecenitrile)} = \frac{[\text{12-oxo-dodecanenitrile}]+[\text{by-products}]-[\text{internal undecenitriles}]_0}{[\text{10-undecenitrile}]_0} \quad (1)$$

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Where [12-oxo-dodecanenitrile] is the 12-oxo-dodecanenitrile concentration at the end of the reaction, [by-products] is the sum of the concentrations of branched aldehyde, internal undecenitriles and undecanenitrile at the end of the reaction, $[\text{internal undecenitriles}]_0$ is the initial internal undecenitriles concentration and $[\text{10-undecenitrile}]_0$ is the initial 10-undecenitrile concentration.

The turnover number (TON) values were calculated from the conversion of the substrate (10-undecenitrile) at final reaction time according to (2):

$$\text{TON} = \text{Conversion (10-undecenitrile)} \times \frac{[\text{Substrate}]}{[\text{catalyst}]} \quad (2)$$

5. Organic Solvent Nanofiltration

5.1. OSN cross-flow filtering conditions

OSN was performed with a 17 cm² filtering area flat polymer membrane inserted in a cross-flow filtration set-up (MET-Cell, Evonik) using a recirculation pump delivering a flowrate of 1.24 $L \cdot min^{-1}$. The transmembrane pressure (TMP) was obtained by nitrogen pressure applied on the feed tank and the temperature was almost constant during all experiments (27 ± 4 °C). Before use, all membrane coupons were conditioned in toluene at TMP = 40 bar until a constant permeate flux was reached. The membranes were stored in toluene when unused.

The permeate flux J_p ($L \cdot m^{-2} \cdot h^{-1}$) was regularly measured during the filtration, by sampling of a given volume of permeate and its weighing and then calculated according to the following equation:

$$J_p = \frac{V_{permeate}}{A \times t} \quad (3)$$

Where $V_{permeate}$ is the permeate volume (L), A the membrane geometric area (m²) and *t* the duration of the sample measurement (h). The accuracy on flux was better than ± 3 %.

For all experiments, the initial flux in pure toluene (J_0) was first measured, then the flux during OSN of the hydroformylation post-reaction medium (J_{OSN}) was measured over time. Finally, after rinsing with toluene, the recovered flux (J_R) was measured to evidence if any fouling remained on the membrane.

OSN cross-flow filtration was achieved with continuous extraction of the permeate and recirculation of the retentate into the feed tank. Accordingly, the Volume Reduction Ratio (VRR) increased continuously:

$$VRR = \frac{V_{feed,initial}}{V_{feed,initial} - V_{permeate}} \quad (4)$$

Where $V_{permeate}$ and $V_{feed,initial}$ are the extracted permeate volume and the initial volume of the feed, respectively.

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OSN experiments were performed up to VRR = 2 for ligand screening and up to VRR = 5 for catalyst recycling experiments (reaction-OSN coupling, see below).

5.2 Membrane selection

Membrane selection was achieved after a first screening of 4 commercial OSN membranes: Starmem 122 (Polyimide, MET-Evonik, NL) and siloxane-based membranes provided by Solsep BV, NL: Solsep NF030306, Solsep NF030306F & NF010206. The Solsep NF030306F was rejected because of a poor flux toluene. The 3 other membranes were used for filtration of 10-undecenitrile (1 M) and Biphephos (1 mM) in mixture. The permeate fluxes were quite low and the rejections were not satisfying with respect to our objective (Table 6).
A fifth commercial membrane made of PDMS was finally tested. The PERVAP 4060 membrane provided by SULZER is a membrane initially designed for pervaporation (gas separation) and not for OSN. This membrane was used in OSN by Ben Soltane *et al.* looking for a commercial PDMS materials for sake of fundamental explanations.[53] Its performances proved to be much better than those of the OSN membranes tested (Table 6). Moreover, its permeance in pure toluene ($L_{p,27°C}$ = 3.3 $L \cdot m^{-2} \cdot h^{-1} \cdot bar^{-1}$) was 4-5 times that of the 3 previous membranes (0.15, 0.50 and 0.66 $L \cdot m^{-2} \cdot h^{-1} \cdot bar^{-1}$ for Solsep NF010206, Solsep NF030306 and Starmem 122, respectively). It was also greater than the permeance reported by Dreimann *et al.* for the PDMS GMT-oNF2 ($L_{p,25°C}$= 2 $L \cdot h^{-1} \cdot m^{-2} \cdot bar^{-1}$ [**35-36**]). Finally, we also checked the good stability of the PERVAP 4060 membrane in toluene over 18 months at room temperature (Figure 14).

Table 6. Rejection (%) of Biphephos (1 mM) and 10-undecenitrile (1 M) at VRR = 2.

TMP (bar)	Sulzer PERVAP 4060		Solsep NF030306		Solsep NF010206		Starmem 122	
	undecenitrile	Biphephos	undecenitrile	Biphephos	undecenitrile	Biphephos	undecenitrile	Biphephos
10	15	88	10	44	47	53	17	67
30	32	94	10	48	-	-	39	80

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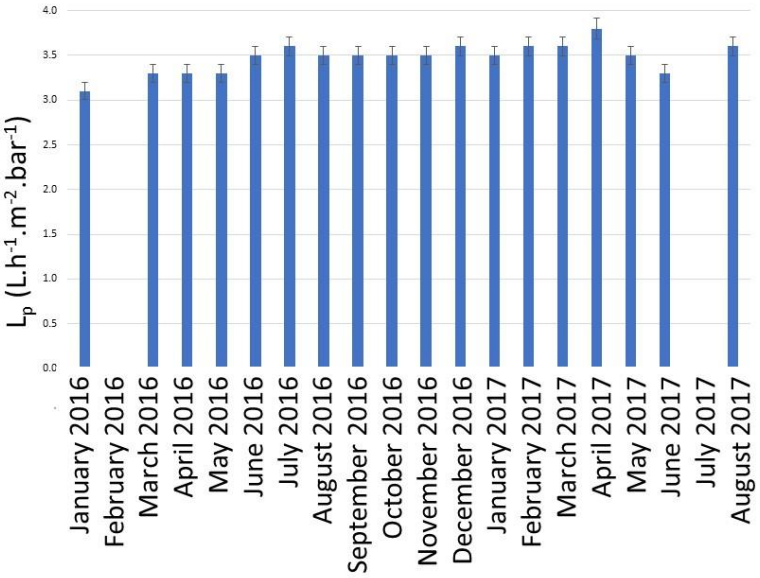


Figure 14. Permeance at 27± 4 °C of a PERVAP 4060 membrane in pure toluene over 18 months. OSN experiments of the hydroformylation media were performed in the course of these measurements. (measurements were not achieved in February 2016 and July 2017).

5.3 Rejection and selectivity

As a general trend, besides cross-flow velocity and TMP, the solute concentration has also an impact on rejection. The rejection of any solute i (Ret(i), equation 5) was measured at the end of the filtration (final VRR) using last permeate and final retentate concentrations measured by GC or UV, as explained above.

$$\mathrm{Ret(i)} = 1 - \frac{C_{P,i}}{C_{R,i}} \quad (5)$$

where $C_{P,i}$ is the permeate concentration (mol·L^{-1}) and $C_{R,i}$ is the retentate concentration (mol·L^{-1}) at final VRR.

As a general rule, the error bars on figures take into account the standard deviation calculated from the experimental results obtained with two membranes tested in series, acting as a replicate experiment and the accuracy of the analysis with respect to the used technique.

In order to compare the separation efficiency with the different ligands and operating conditions, the global selectivity, S_{global}, between catalyst rejection and 12-oxo-dodecanenitrile transmission was used (equation 6). It was defined as the selectivity targeting the catalyst recovery (first term) times the selectivity targeting the extraction of the product (second term).

$$S_{global} = \frac{\mathrm{Ret(catalyst)}}{\mathrm{Ret(catalyst)+Ret(12\text{-}oxo\text{-}dodecanenitrile)}} \times \frac{1-\mathrm{Ret(12\text{-}oxo\text{-}dodecanenitrile)}}{(1-\mathrm{Ret(catalyst)})+(1-\mathrm{Ret(12\text{-}oxo\text{-}dodecanenitrile)})} \quad (6)$$

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where Ret(catalyst) is the catalyst rejection and Ret(12-oxo-dodecanenitrile) is the rejection of 12-oxo-dodecanenitrile.

6. Coupling reaction and OSN: recycling of the catalyst

For the reaction-OSN coupling, reactions were performed as follows: The reaction media was cooled down to room temperature. It was thereafter transferred into the OSN set-up. OSN was carried out as described above until the desired VRR was reached. In order to keep the catalyst integrity, all the process was performed under inert atmosphere. At the end of the OSN process, the remaining retentate was transferred under argon back to the reaction tank. A proper amount of substrate (and toluene if diluted mixture) was added in order to reach the same substrate concentration (*i.e.,* 1.0 mol·L^{-1} for the diluted mixture). No fresh metal precursor nor ligand was added for the new reaction. The coupling experimental procedure is summarized in Figure 15. The word "cycle" now refers to a reaction followed by an OSN separation step.

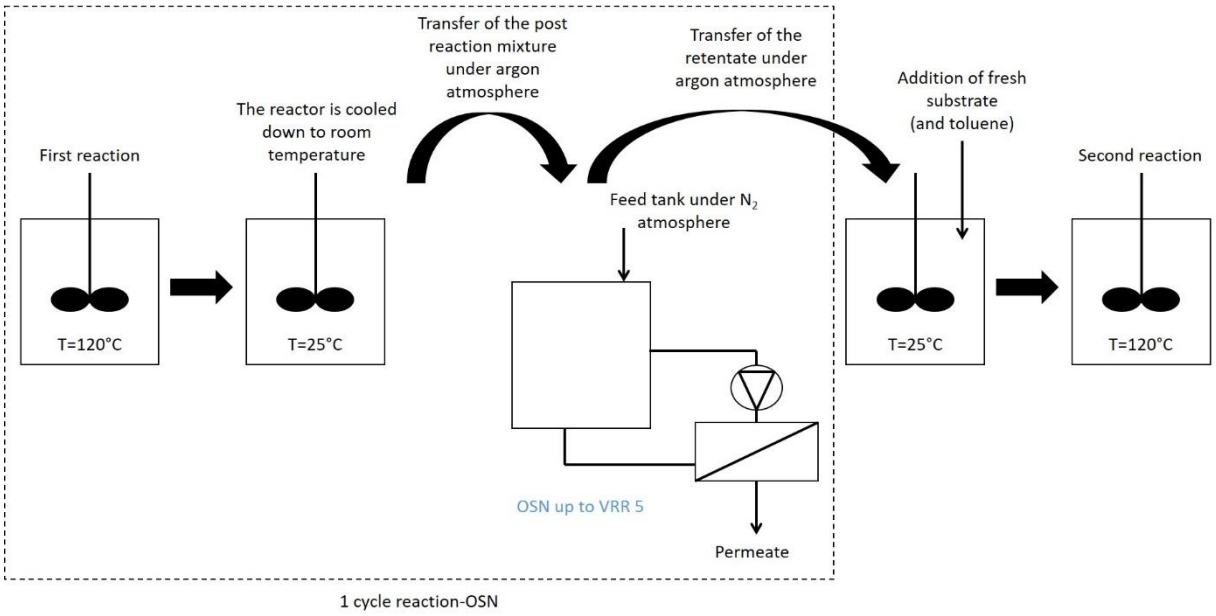


Figure 15. Schematic representation of the reaction-OSN coupling.

In order to quantify the process performances, the overall extraction of each solute in the permeate was calculated at the end of each cycle. It is defined as the number of moles of a solute recovered in the permeate divided by the number of moles of the same solute synthesized (for the products) or involved in the reactions (for the substrate and the catalyst).

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