



Thermomorphic solvent selection for homogeneous catalyst recovery based on COSMO-RS



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ARTICLE INFO

Article history:

Received 18 March 2015

Received in revised form 25 June 2015

Accepted 2 July 2015

Available online 23 July 2015

Keywords:

Solvent screening

Solvent design

COSMO-RS

Homogeneous catalysis

Thermomorphic solvent systems

ABSTRACT

One method that has shown much promise due to its simplicity and effectiveness in homogeneous catalyst recovery is the use of thermomorphic solvent systems (TMS). In this contribution, a novel method for TMS solvent selection based on quantum chemical predictions of catalyst solubility and phase equilibrium is presented. This allows for solvent effects on the catalyst to be incorporated directly into the solvent screening process. A framework for TMS design is developed and implemented using the hydroformylation of 1-dodecene and the rhodium-Biphosphos catalyst as an example reaction system. In this way, several promising TMS systems were identified. Experiments were then performed to validate the model based on catalyst partitioning and phase equilibrium. This was followed by conducting a series of reactions to investigate feasibility of the new TMS systems in the actual hydroformylation. In the end it was shown that although some problems arise from inconsistencies in phase equilibrium predictions, the method does provide a functioning *a priori* basis for TMS development.

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1. Introduction

Although homogeneous catalysis can deliver many benefits to a process such as high activity, good selectivity, robust catalyst systems, etc., separation and recycling of the catalyst can be quite cumbersome [1]. Additionally, the loss of expensive transition metals often used in homogeneous catalyst complexes may lead to economically infeasible processes if not recovered satisfactorily. One important yet simple method for recovering homogeneous catalysts from a post-reaction mixture is temperature controlled liquid phase separation through the use of thermomorphic solvent systems (TMS) [2]. Composed of solvents with varying degrees of polarity, these tuneable mixtures form a homogeneous phase at

reaction temperature and separate into two phases when cooled, ideally recovering the catalyst in one phase and the product in the other. TMS systems are investigated in several homogeneously catalyzed reactions including hydroaminomethylation [3], hydroformylation [4,5], and cooligomerization [6,7] where low levels of catalyst loss were realized. More specifically, the hydroformylation of 1-dodecene in a TMS composed of *n*-decane and dimethylformamide (DMF) has been the topic of much research in recent years in the areas of reaction kinetics [8] and reactor and process optimizations [9–11]. Thus the importance and practicality of TMS usage for catalyst recovery is well established.

Choosing which solvents to include in the TMS is an important task. Solvent selection methods developed have been so far successfully based on the liquid phase separation behavior of two or three solvents and their respective polarities as measured using Hansen parameters [4,5]. A framework for selecting a mediator solvent in the hydroaminomethylation of 1-octene was recently presented that more rigorously dealt with the pros and cons of using solvent descriptors and predictive thermodynamic models in selecting suitable solvent candidates [12]. Although such methods for solvent selection often lead to good candidate solvents, predictions of phase behavior or solubility are not always accurate enough to be considered completely reliable. This is something the authors experience with some of the predicted solubilities compared to those found experimentally. Thus the authors advise, as is often

Abbreviations: COSMO, Conductor-like Screening Model; COSMO-RS, Conductor-like Screening Model for Real Solvents; *D*, distribution of component between product and catalyst phases (% mass); DMF, N,N-dimethylformamide; EHS, environment, health, and safety; HRSC, high relative solubility of the catalyst; LLE, liquid–liquid equilibrium; LRSC, low relative solubility of the catalyst; P, phosphorous; Rh, rhodium; TMS, thermomorphic solvent system; *Y*, yield of tridecanal.

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the case in solvent selection, that experimental validation is still very much necessary. Although some issues are found in predictive methods for phase equilibrium, still no aspect of catalyst solubility is discussed at this point.

These methods for solvent selection rely on the fact that the usually polar catalyst will be recovered in the polar phase while the less polar product is recovered in the non-polar phase. In principle the design of the TMS system should ideally include some aspects of the thermodynamic behavior of the catalyst into the initial stage of solvent selection. This would ensure, at least at some fundamental level, that the TMS will function as intended. It is proposed that by predicting the thermodynamic properties of the catalyst ligand, a TMS effective at minimizing catalyst loss can be designed from the ground up. Since thermodynamic and experimental data regarding the solvent effects on the catalyst are limited or non-existent, the *ab initio* COSMO-RS model [13], is used as the basis for thermodynamic predictions. Solvents are to be chosen as TMS components based on catalyst complex solubilities, as represented by the catalyst ligand, and phase equilibrium characteristics. A framework is developed to systematically screen solvents and to generate a list of candidate TMS systems. These potential solvent mixtures are then investigated experimentally in order to validate the model's ability to accurately predict functioning TMS systems. In this way, several identified TMS systems are evaluated in an example reaction to ensure process feasibility.

2. Background and motivation

2.1. Thermomorphic solvent systems

The model reaction considered in this contribution is the hydroformylation of 1-dodecene, a reaction that has garnered much attention in recent years. It is desirable to convert the terminal alkene, 1-dodecene, with synthesis gas (CO , H_2) to the terminal aldehyde tridecanal. However, the reaction is not that simple and many side products are also produced. In order to achieve high selectivity and conversion, many different catalyst formulations are investigated by [14] who finds that a catalyst based on rhodium (Rh) and 6,6'-[(3,3'-di-tert-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)bis(oxy)]bis(dibenzo[d,f][1,3,2]dioxaphosphine), or Biphephos, ligands, shown in Fig. 3, delivers the best performance with respect to conversion, selectivity, and reaction rate. The downside to using this catalyst is the high cost of both Rh and Biphephos. Even low levels of leaching can lead to inordinately high process costs [15].

The primary method to recover the Rh-Biphephos catalyst complex is by using the previously mentioned thermomorphic solvent system (TMS). These special mixtures are composed of solvents with varying degrees of polarity allowing for simple temperature induced phase switching. In Fig. 1, the basic principle of the TMS is outlined. At a certain reaction temperature, T_1 , the mixture of solvents should form a homogeneous phase that allows the reaction to proceed unhindered by mass transfer limiting effects. Once the reaction is complete, the resulting mixture should form two phases upon cooling to the desired separation temperature, T_2 . Ideally the catalyst is recovered in the polar phase while the product and unconverted reactant are recovered in the non-polar phase.

Several TMS compositions are investigated for the hydroformylation of 1-dodecene [5]. One of the better performing systems uses a TMS composed of the polar solvent dimethylformamide and non-polar solvent *n*-decane. These solvents are able to provide good recovery through single-stage phase splitting of the Rh-Biphephos catalyst while still separating out modest amounts of the tridecanal product. Reaction conditions and solvent compositions used with this TMS are investigated in more detail and result in process conditions leading to lower levels of catalyst leaching in [16].

A continuous mini-plant is also designed [17] and operated [18] using this DMF and *n*-decane TMS in equal weight percentages. Since this TMS system is well analyzed and still the target of current, ongoing research, it will serve as a good benchmark for other TMS systems.

A TMS of this nature, consisting of only a pair of polar and non-polar solvents, was labeled as a Type III TMS according to [5]. In the present contribution, a method is proposed to identify an optimal Type III TMS system, exemplified on the hydroformylation of 1-dodecene. The goal is to find two solvents that produce the appropriate TMS characteristics: a polar, catalyst solvent in which the ligand Biphephos has a high affinity and a non-polar, product solvent in which catalyst solubility is low and product solubility is high. Proper miscibility at the operating point (homogeneous) and post-reaction mixture (heterogeneous) are also required.

2.2. Thermodynamic model: COSMO-RS

The primary method of solvent screening will be to estimate the solubility of the Biphephos ligand in various candidate solvents. Many methods exist for predicting thermodynamic properties of molecule for which experimental data is lacking, UNIFAC for example [19], but due to the complexity and size of Biphephos, many of these methods are unsuitable for the proposed purpose. For this reason, thermodynamic properties of the catalyst ligand in solution are predicted using the COSMO-RS method [13] as implemented in the commercial software package COSMOtherm [20]. All calculations are made using the BP_TZVP_C30.1401 parameterization.

The Conductor-like Screening Model for Real Solvents (COSMO-RS) is a method for predicting thermodynamic properties based on interacting molecular surfaces of pure component liquids or liquid mixtures. Each desired molecule is modeled in a perfect conductor in order to define the screening charge of the molecule. This is done using the efficient continuum solvation model COSMO [21]. In the "Real Solvent" extension, the three dimensional surface information is condensed into a histogram, the σ -profile, detailing the amount of surface segment type within a certain polarity interval. COSMO-RS then combines the σ -profile data with a statistical thermodynamics approach where the chemical potentials of pair-wise interactions of surface segments are calculated using important molecular interactions such as electrostatic misfit and hydrogen bonding energies. Therefore, only the energetically optimized molecular structure of each molecule is necessary to make predictions of phase behavior or solubility.

The alluring feature of using COSMO-RS for solvent screening is the absence of required experimental data. Many papers in the literature, such as those by Tung et al. [22], Hahnenkamp et al. [23], and Pozarska et al. [24] detail the use of COSMO-RS theory in predicting solubilities of pharmaceuticals as part of a *a priori* solvent screening. Bouillot et al. [25] compare several thermodynamic models including COSMO-RS on their ability to predict pharmaceutical solubilities. Another important article written relative to this topic is by Wichmann and Klamt [26], who give a detailed description of the COSMO-RS method as used in solvent screening. The conclusion in these articles is that COSMO-RS can qualitatively predict the solubility of large and complex molecules in various solvents. Therefore, the application of this method appears to be suitable for the task of qualitatively predicting catalyst ligand solubility in various solvents uniquely applied to TMS design.

3. Framework

The procedure used to screen for component solvents in the Type III TMS is outlined in Fig. 2. The framework consists of two major components: the computational solvent screening of TMS

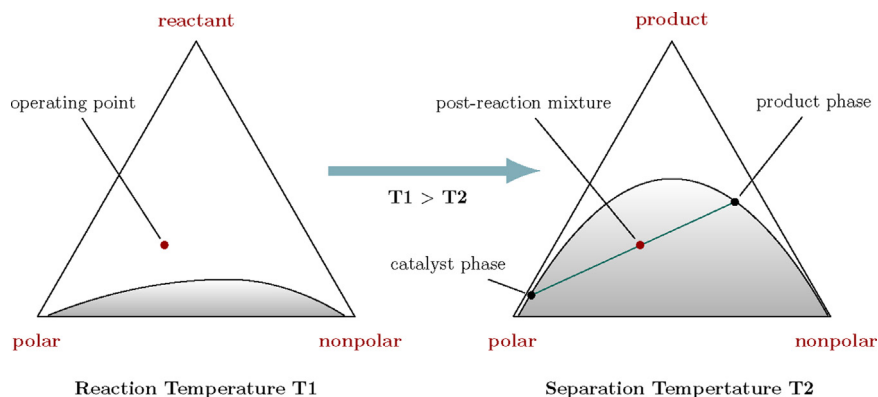


Fig. 1. TMS functionality.

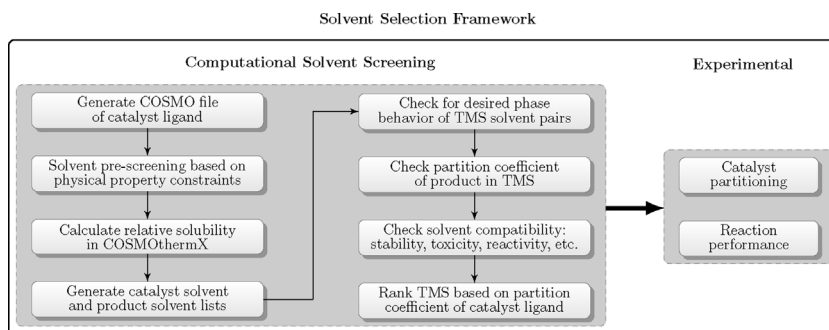


Fig. 2. Procedure for TMS design.

systems and the empirical investigation of candidate solvent mixtures. In the solvent screening section several steps are presented in order to come to feasible TMS compositions. The first step is to generate the COSMO file of the catalyst ligand. The next step is concerned with simple pre-screening of molecules included in a database to reduce the search space. Remaining steps are primarily concerned with the solvent behaviors related to predicted solubility of Biphephos in each solvent, product recovery, miscibility, and feasibility of use. After the solvent screening procedure is concluded, promising solvents are then experimentally validated in part two of the framework. Here predictions made about partition coefficients based on catalyst ligand solubilities are investigated as well as performing the hydroformylation of 1-dodecene in each chosen mixture. Each step is explained in more detail in the following sections.

3.1. Generate COSMO file of catalyst ligand

The first task is to create the COSMO file of the catalyst ligand used in the process. In this case the catalyst is the Biphephos ligand used as part of the catalyst complex for the hydroformylation of 1-dodecene. In this screening work only the catalyst ligand is considered due to its usually higher concentration in the solution and the fact that catalyst leaching has shown similarities in Rh and phosphorous leaching [14]. The molecular model is developed using [27], at the RI-DFT level of theory [28] using the def-TZVP basis set [29]. The resulting Biphephos structure with surface charge is presented in Fig. 3. This COSMO file contains all required information needed for predicting the thermodynamic properties of Biphephos for solvent screening using COSMOtherm.

At a glance, it is possible to obtain much information about a molecule just by observing its σ -profile, seen in Fig. 4 for Biphephos. Here one can see an expected and large non-polar region located

between -0.01 and 0.01 e/Å, which are usually the accepted boundaries for the hydrogen bonding region (see [30]), outside of which strong hydrogen bonds can be formed. Non-polar molecules usually do not depict such a wide profile as Biphephos. This is due to the negative p-orbitals and positive carbons of the phenyl groups giving two distinct peaks instead of one, typical for aromatic containing compounds. The small shoulder extending from 0.01 to about 0.015 e/Å corresponds to the negative charge of the oxygen and phosphorous atoms suggesting that the catalyst may prefer to be in solution with solvents showing some type of hydrogen bond donor characteristic. From this it is expected that Biphephos will show a higher affinity for polar solvents and those having broad profiles between the hydrogen bonding borders to non-polar ones.

3.2. Pre-screening of candidate solvents

Initially, a list of candidate solvents from the COSMObase (ver. 1301, COSMOlogic GmbH) extension has to be generated. To reduce the number of unsuitable molecules from the initial search space, about 7700 in total, certain molecular properties, such as molecular weight, melting temperature, boiling temperature, screening charge, and component atoms, can be used as constraints to pre-screen solvent candidates. To intentionally maintain a large search space, only boiling temperature and molecular weight are used as initial constraints. The boiling temperature of each solvent is limited to temperatures between zero and 260 °C. The upper bound is chosen to be 20 °C less than the boiling point of tridecanal in order to avoid possible azeotrope formation in a subsequent distillation unit operation. The molecular weight of each solvent chosen should also not exceed 200 g/mol, as solvents are usually preferably small owing to better solvent functionality. Using these two constraints, the solvent search space is reduced to a list containing 2813 molecules.

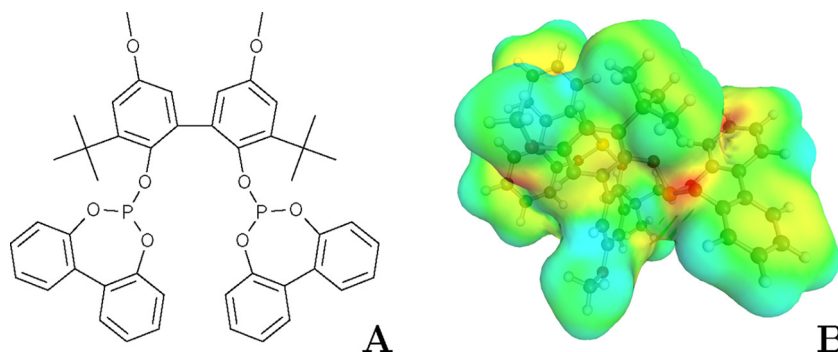


Fig. 3. Chemical structure formula of Biphephos (A) and its surface charge in a perfect conductor (B) as calculated using TURBOMOLE.

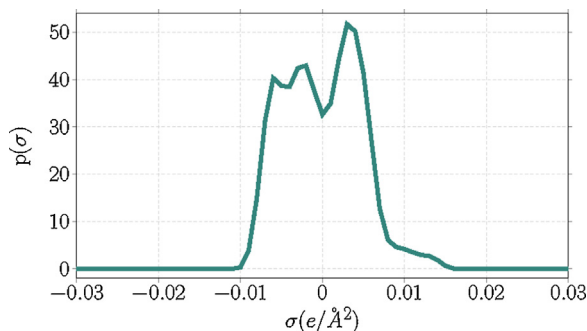


Fig. 4. Sigma profile of the Biphephos ligand.

3.3. Solvent screening: catalyst solubility

The next step, and perhaps the most important step, is to predict the relative solubility of Biphephos in each of the candidate solvents. Relative solubility is predicted using only the chemical potential, μ_i^{solvent} , of the solute at infinite dilution in the pure solvent. This chemical potential is calculated by COSMO-RS (Eq. (1)) based on statistical thermodynamics using sigma profiles of the involved components (a good reference for how COSMO-RS calculates potentials is found in [30]). Relative solubilities are calculated in a single batch, which is necessary to allow for direct comparison of different solvents. Once all calculations are complete, the solvents are ranked according to their relative solubilities starting with a maximum value of 0 (referring to maximum solubility) and decreasing therefrom. All relative solubility calculations were made using a temperature of 25 °C.

$$\ln(x_i) = \mu_i^{\text{solvent}} / RT \quad (1)$$

3.4. Solvent screening: generation of two lists

From this list of ordered solubilities, two new lists are created: one with solvents having high relative solubility of the catalyst ligand (HRSC) and the other with solvents having low relative solubility of the catalyst ligand (LRSC). For each TMS system, two solvents will be used in order to create the desired Type III system. One solvent from the HRSC list will be chosen as the catalyst solvent and one solvent from the LRSC list will be used to recover the product. For example, those solvents predicted as having the highest solubility are presented alongside those having the lowest predicted solubility in Table 1. As seen in this list, hydrofluoric acid is predicted as having the highest solubility for Biphephos while water is predicted to have the lowest solubility, being about 18 orders of magnitude less than that of hydrofluoric acid. Interestingly enough, the current HRSC solvent, DMF, used in miniplant

Table 1

List of top 5 high (HRSC) and low (LRSC) relative solubility catalyst solvents.

HRSC	$\log_{10}(x_i)$	LRSC	$\log_{10}(x_i)$
Hydrofluoric acid	0.0000	H ₂ O	-18.4128
Selenic acid	-1.0582	Formamide	-12.7388
Chlorosulfonic acid	-1.2406	Hydroxyacetoneitrile	-12.2432
ClO ₂	-2.6015	Butanedinitrile	-12.1521
1,1,1-Trifluoro-2-bromoethane	-3.0996	Dicyanomethane	-11.6746

experiments, is found to be the solvent with the 24th highest solubility of the catalyst ligand.

It should be quite obvious that not all candidate solvents shown in Table 1 are convenient for a multitude of reasons. All of the HRSC solvents listed here are highly reactive acids, strong oxidizers, or CFCs. Those solvents in the LRSC list are also quite unreasonable, with the exception of water, due to their reactivity or toxicity. As it turns out, water is a poor solvent for other reasons, especially due to its also very low solubility of the tridecanal product, something handled later. Obviously it is undesirable to manually screen each one of the almost 3000 solvents based on reactivity, toxicity, or by some other property at this stage. There are various methods of deciding the environmental, health, and safety aspects of solvents, such as the method developed by Koller et al. [31]. However due to the limited availability of information for many of the solvents in this list and the small size of the EHS tool database [32], it was not suitable for this task. Therefore selection and exclusion of solvents is based on heuristics, relying more on expertise and process knowledge. This screening step, as seen in Fig. 2, comes near the end of the process when a much smaller number of candidate solvents remain, greatly reducing the workload of this manual task. It is for this reason that a sizable number of candidate solvents needs to be selected for both the HRSC and LRSC lists. For the HRSC list an arbitrary number of solvents, 100, is chosen. These 100 solvents are those solvents having the highest relative solubility for the catalyst ligand. Due to the availability of some experimental data comparing the chain length of linear alkanes paired with DMF as TMS systems and the amount of catalyst leaching encountered, it was desirable to include several of these alkanes into the screening process [14]. Therefore, octane is chosen as the cut-off point for the LRSC list instead of an arbitrary number as with the HRSC solvents. These solvents, 403 in total, are those solvents having the lowest solubility for the catalyst and are added to the LRSC list.

3.5. Miscibility gap formation

The basis of a functioning TMS is that after the reaction, two phases are formed separating the polar, catalyst containing phase from the less polar, product containing one. This means that for each TMS system, some estimation of miscibility gap formation must be made. Using COSMO-RS once again, liquid-liquid

equilibrium calculations are made for each possible pair of solvents from the HRSC and LRSC lists, 40,300 in total. The separation temperature for each calculation was set to -25°C . This temperature is selected for two reasons: the lower bound for planned experimental validation is about this temperature and that predictive methods for thermodynamic equilibrium are not always accurate. Unreliable phase equilibrium predictions may lead to potentially interesting TMS systems being eliminated during screening due to faulty miscibility predictions made at ambient conditions. Therefore, to avoid these issues and bring predictions more in line with our experimental limits, the lower temperature is used. Solvent mixtures that are found to be feasible at lower temperatures can be investigated at higher separation temperatures at a later time as part of the final process design. In other words, a larger screening net is formed to ensure that TMS systems are not excluded due to poor LLE predictions. The screening criteria are based on simple miscibility gap formation for the same reason. Using this simple constraint, only 5225 potential TMS compositions remain.

3.6. Product distribution

The secondary function of TMS usage is the separation of the product from the mixture in the less polar phase. Therefore it is also of interest to check whether or not the TMS systems can remove the tridecanal product from the post-reaction mixture. Remember although water is a great LRSC solvent in that its solubility of the catalyst is low, this is a feature also extended to the slightly polar tridecanal. Using water would lead to practically all of the product being recycled back into the reactor making a functioning process unfeasible. In order to avoid such TMS systems from being included in the list, some measure of product removal ability must be included in the screening process. This is done in a similar way as with Biphephos, but because the screening process now involves binary solvent systems, partition coefficients as predicted by Eq. (2) were used to predict tridecanal distribution. For tridecanal partition coefficients, the volume quotient of the solvents as estimated using the liquid density/volume QSPR method from COSMOtherm is included.

The cut-off value is arbitrarily chosen based roughly on doubling the predicted partition coefficient of tridecanal between DMF and decane, which is found to be 0.118. This ensures that the TMS should have similar tridecanal separation as the current TMS while excluding those mixtures with much poorer tridecanal separation. Therefore, the partition coefficient of each TMS is restricted to being less than 0.25 (lower is better), leaving 928 potential solvent pairs.

$$\log_{10}(P_j^{(2,1)}) = \log_{10}(\exp((\mu_j^{(1)} - \mu_j^{(2)})/RT) \cdot V_1/V_2) \quad (2)$$

Here, $\mu_j^{(i)}$ is the chemical potential of species j at infinite dilution in species i , where j stands for the reaction product tridecanal, 1 for the HRSC solvent, 2 for the LRSC solvent, and V for the estimated solvent volume.

3.7. Suitable solvent solutions

The top 30 TMS systems up until now are shown in Table 2. TMS systems are ranked according to Biphephos recovery as measured using the partition coefficients as explained in Section (3.8). The majority of HRSC solvents in this list are small halogen containing alkanes, primarily bromine and iodine. They are usually paired with large alcohols or other multi-functional group containing compounds as the LRSC solvent. Some of these solvents are infeasible based on melting temperature, for example resorcinol melts at 111°C while others seem quite suitable such as cyclohexanemethanol with a fusion point of -43°C . The interesting thing about these LRSC solvents is that they have polar characteristics

unlike the non-polar solvents expected for product recovery. However, there are several problems with these TMS compositions in addition to phase characteristics. For example, the top two performing HRSC solvents iodomethane and bromomethane are both well known pesticides and, additionally, bromomethane is known to damage the ozone layer and was phased out completely in 2005 according to the Montreal Protocol and the Clean Air Act [33]. Thus it is recommended here to eliminate individual solvents for these and the various reasons mentioned below.

Solvents are individually screened here based on several aspects:

1. Species containing halogens
2. Highly reactive species that are considered too unstable
3. Solvents with carbon-carbon double or triple bonds likely to react in the hydroformylation
4. Extremely toxic species not eliminated according to the above criteria

Since there are far fewer unique HRSC solvents left in the binary solvent mixtures, 33 as compared to 158 LRSC solvents, this screening step starts with HRSC solvent elimination. In all, 13 solvents are removed for containing halogens, seven for having a carbon-carbon double or triple bond, and five for either being highly reactive, toxic, or both. This process is then repeated for the LRSC solvents remaining in the reduced number of potential TMS systems with the short list of HRSC solvents. In all, eight solvents remain in this HRSC list: acetaldehyde, DMF, acetone, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, methylacetate, N,N-diethylformamide, and N-formylpiperidine (see Table 4). Some of these chemicals are still toxic, such as DMF, and require care in handling and exposure, but are commonly used as solvents in industry and can be used in the laboratory without exceptional safety measures. Considering only those systems using one of these eight HRSC solvents, 324 TMS pairs remain. This elimination of various HRSC solvents also reduces the list of LRSC solvents to 65 possibilities in the remaining systems. Of these, 62 are branched, linear, or cyclic alkanes. The three remaining solvents not belonging to this group are dodecanol, tridecanol, and hexahydroindene. Only hexahydroindene is removed here due to its inclusion of a carbon-carbon double bond. With the removal of this solvent, five TMS pairs are eliminated and 319 TMS pairs remain.

For some LRSC solvents, 21 in total, the melting temperature is unknown; however, these solvents are all C_9 or C_{10} alkanes which generally have melting temperatures much lower than investigated here and are thus retained. Several remaining LRSC solvents have melting temperatures higher than -25°C . These include tridecanol, dodecanol, tetradecane, tridecane, dodecane, bicyclohexyl, 2,2,5,5-tetramethylhexane, and cyclodecane. The Liquid-Liquid Equilibrium (LLE) of each TMS system consisting of one of these solvents is calculated again in the same manner as outlined in Section 3.5, but the minimum temperature used before is substituted with the melting temperature of the LRSC instead. Only 25 TMS pairs consist of one of these solvents. In eight of these systems no miscibility gap is predicted, leaving 311 solvent pairs in our final list of potential TMS systems. It is evident from these results that boiling point limits are not enough in the pre-screening step and it may be desirable to initially add a melting temperature constraint.

It is also interesting to check the phase behavior at a reaction temperature of 100°C , considering this is an often used reaction temperature for the present reaction system [34]. Here, five TMS systems are predicted to form heterogeneous mixtures: DMF with dodecane, tridecane, and tetradecane, and acetaldehyde with tridecane and tetradecane. At a slightly higher maximum of 120°C , all TMS systems were homogeneous. Due to these systems all having upper critical solution temperatures below 120°C , they were

Table 2
Unfiltered list of top 30 TMS mixtures.

Rank	HRSC	LRSC	$\log_{10}(P_{\text{tridecanal}})$	$\log_{10}(P_{\text{Biphephos}})$
1	Iodomethane	Propanal,2-(hydroxyimino)-,oxime	0.1460	3.6040
2	Bromomethane	Propanal,2-(hydroxyimino)-,oxime	-0.0749	3.4292
3	Iodoethane	Propanal,2-(hydroxyimino)-,oxime	0.2419	3.3888
4	Bromoethane	Propanal,2-(hydroxyimino)-,oxime	0.1770	3.3865
5	1-Bromo-1,2-difluoroethylene	Choralhydrate	-0.0339	3.2778
6	Ethylisocyanate	Propanal,2-(hydroxyimino)-,oxime	0.1255	3.2460
7	Iodoethene	Propanal,2-(hydroxyimino)-,oxime	0.0737	3.2343
8	Iodomethane	Resorcinol	0.1454	3.2080
9	Bromomethane	Resorcinol	-0.0754	3.0331
10	Iodoethane	Resorcinol	0.2413	2.9928
11	1-Bromo-1,2-difluoroethylene	4-Methyl-1,3-benzenediol	0.1482	2.9927
12	Bromoethane	Resorcinol	0.1765	2.9905
13	Iodomethane	Methylhydroquinone	0.0589	2.9670
14	1-Bromo-1,2-difluoroethylene	Difluoroacetic acid	-0.2472	2.9523
15	Bromomethane	2,2,2-Trifluoroethanol	-0.0589	2.9509
16	Bromomethane	Pentafluoro-1-propanol	-0.1543	2.9265
17	3-Bromo-3,3-difluoro-1-propene	Pentafluoro-1-propanol	0.2062	2.9130
18	Bromoethane	2,2,2-Trifluoroethanol	0.1930	2.9082
19	Ethyleneoxide	Hexahydroindene	0.2220	2.8928
20	Bromoethane	Pentafluoro-1-propanol	0.0976	2.8838
21	Iodomethane	Orcinol	-0.0620	2.8765
22	Iodoethene	Resorcinol	0.0731	2.8383
23	Acetaldehyde	Tetradecane	0.2308	2.8324
24	Sulfurylchlorideisocyanate	Orcinol	0.2445	2.8260
25	Iodomethane	Cyclohexanemethanol	0.1229	2.8076
26	Acetaldehyde	Tridecane	0.2060	2.8038
27	Acetaldehyde	1-Tridecanol	0.1235	2.7985
28	Bromomethane	Methylhydroquinone	-0.1620	2.7922
29	Acetaldehyde	Dodecanol	0.1046	2.7905
30	2-Butyne	Methylhydroquinone	0.2250	2.7898

considered acceptable for further evaluation. These temperatures are still well within the feasible reaction temperature range.

3.8. Analysis

The final 311 TMS systems are now ranked according to the partition coefficients of Biphephos between the HRSC and LRSC solvents respectively. In this case partition coefficients are calculated using Eq. (3), with j representing Biphephos. The volume quotient of the solvents is not considered here to ensure consistency with the relative solubility calculations made in the second screening step. When the solvent volume is not considered in Eq. (2), the equation reduces to Eq. (3) which is simply the ratio of the relative solubilities calculated from Eq. (1).

$$\log_{10}(P_j^{(2,1)}) = \log_{10}(\exp((\mu_j^{(1)} - \mu_j^{(2)})/RT)) = \log_{10}(x_j^{(1)}/x_j^{(2)}) \quad (3)$$

Using the partitioning of Biphephos between the two phases should provide a good measure of which systems are best suited for use as a TMS respective to catalyst recovery. Since product partitioning is constrained within a certain performance criteria, each of the remaining solvent systems should feasibly function as a Type III TMS for the hydroformylation of 1-dodecene. The results are presented in the next section.

4. Screening results

The top 30 TMS (from the 311 total) systems based on catalyst partition coefficients are presented in Table 3. TMS systems composed of catalyst solvents acetaldehyde or DMF paired with product solvents consisting of large alkanes seem to provide good catalyst recovery with functioning product separation. With increasing alkane size, catalyst recovery capacity increases due to the increasing size of the non-polar segments of the product solvents, reducing the amount of catalyst soluble in the non-polar phase. For the same reason, tridecanal partition coefficients also increase, showing

reduced solubility of the product in the product phase. This is due to the carbonyl group of the aldehyde providing some polar characteristics and possibilities for hydrogen bonding to the otherwise dominant apolar hydrocarbon backbone. Thus, a trade-off between catalyst recovery and the efficiency of product separation exists when developing a TMS for this reaction.

Since all LRSC solvents are large alkanes, a general comparison of HRSC performance can be made when fixing the LRSC to a single solvent. Due to its extensive use in ongoing research with respect to this reaction, the availability of some experimental data, and it being the benchmark product solvent, *n*-decane is chosen for this task. Results for TMS systems using each one of the remaining HRSC solvents paired with *n*-decane are given in Table 4. Acetaldehyde, as expected, is predicted as forming the most promising TMS, due to its increased solubility of the catalyst ligand over DMF and other HRSC solvents. An explanation, based on COSMO-RS analysis, is that a slight increase in excess entropy is observed when using acetaldehyde instead of DMF in a mixture of the solvent and Biphephos. Both solvents are, however, predicted to form approximately ideal solutions with Biphephos. Also noticeable is the difference in tridecanal solubility that arises from solvents having similar catalyst solubilities. DMF and acetone, for example, have similar heats of mixing with tridecanal, but acetone forms a mixture with lower excess entropy than when using DMF leading to a slightly more favorable solution, reducing the ability of the TMS to separate the product. It can also be seen that TMS systems of acetone/decane and *N*-Methyl-2-pyrrolidone/decane would have been screened out of the possible TMS systems due to their relatively large tridecanal partition coefficients (>0.25).

As mentioned previously, it is desirable to compare TMS performance with DMF and several linear alkanes. In this case *n*-octane to *n*-tetradecane are used and this is the reason for choosing a larger set of LRSC solvents. Each of these systems is evaluated and listed in Table 5. As expected, the solubility of the catalyst and that of tridecanal in the product phase worsen as the length of the alkane chain increases. This is most likely due to the predicted increase

Table 3
List of top 30 TMS mixtures.

Rank	HRSC	LRSC	$\log_{10}(P_{\text{tridecanal}})$	$\log_{10}(P_{\text{Biphephos}})$
1	Acetaldehyde	Tetradecane	0.2308	2.8324
2	Acetaldehyde	Tridecane	0.2060	2.8038
3	Acetaldehyde	Dodecane	0.1750	2.7655
4	Acetaldehyde	Bicyclohexyl	0.0663	2.7507
5	Dimethylformamide	Tetradecane	0.2427	2.7245
6	Acetaldehyde	<i>n</i> -Undecane	0.1445	2.7231
7	Acetaldehyde	<i>n</i> -Hexylcyclopentane	0.0953	2.7151
8	Acetaldehyde	2-Methyldecane	0.1423	2.7099
9	Acetaldehyde	Pentylcyclohexane	0.0896	2.6978
10	Dimethylformamide	Tridecane	0.2180	2.6959
11	Acetaldehyde	4-Methyldecane	0.1415	2.6850
12	Acetaldehyde	Pentylcyclopentane	0.0522	2.6754
13	Acetaldehyde	<i>n</i> -Decane	0.1061	2.6713
14	Acetaldehyde	2-Methyl-nonane	0.1047	2.6643
15	Dimethylformamide	Dodecane	0.1870	2.6577
16	Acetaldehyde	1-Isopropyl-4-methylcyclohexane	0.0360	2.6495
17	Acetaldehyde	<i>trans</i> -Decalin	-0.0164	2.6443
18	Dimethylformamide	Bicyclohexyl	0.0783	2.6428
19	Acetone	Bicyclohexyl	0.2485	2.6421
20	Acetaldehyde	2,3-Dimethyloctane	0.0989	2.6407
21	Acetaldehyde	Butylcyclohexane	0.0437	2.6380
22	N,N-Dimethylacetamide	Bicyclohexyl	0.1786	2.6365
23	Acetaldehyde	2,7-Dimethyloctane	0.0997	2.6339
24	Acetaldehyde	2,2-Dimethyloctane	0.0866	2.6334
25	Acetaldehyde	3-Methyl-nonane	0.1041	2.6306
26	Acetaldehyde	4-Methyl-nonane	0.1043	2.6277
27	Acetaldehyde	1-Methyl-3-propylcyclohexane	0.0412	2.6247
28	Acetaldehyde	5-Methyl-nonane	0.1036	2.6218
29	Acetaldehyde	1-Methyl-2-propylcyclohexane	0.0391	2.6218
30	Acetaldehyde	2,2,4,6,6-Pentamethylheptane	0.1305	2.6202

Table 4
List of high relative solubility solvents and decane TMS candidates.

HRSC	LRSC	$\log_{10}(P_{\text{tridecanal}})$	$\log_{10}(P_{\text{Biphephos}})$
Acetaldehyde	<i>n</i> -Decane	0.1061	2.6713
Dimethylformamide	<i>n</i> -Decane	0.1180	2.5635
Acetone	<i>n</i> -Decane	0.2882	2.5627
N,N-Dimethylacetamide	<i>n</i> -Decane	0.2184	2.5572
N-Methyl-2-pyrrolidone	<i>n</i> -Decane	0.3017	2.5193
Methyl acetate	<i>n</i> -Decane	0.1777	2.2222
N,N-diethylformamide	<i>n</i> -Decane	0.1880	2.2166
N-Formylpiperidine	<i>n</i> -Decane	0.2487	2.1614

Table 5
Comparison of TMS composed of DMF and linear alkanes.

HRSC	LRSC	$\log_{10}(P_{\text{tridecanal}})$	$\log_{10}(P_{\text{Biphephos}})$
Dimethylformamide	<i>n</i> -Octane	0.0267	2.4158
Dimethylformamide	<i>n</i> -Nonane	0.0759	2.4982
Dimethylformamide	<i>n</i> -Decane	0.1180	2.5635
Dimethylformamide	<i>n</i> -Undecane	0.1565	2.6152
Dimethylformamide	<i>n</i> -Dodecane	0.1870	2.6577
Dimethylformamide	<i>n</i> -Tridecane	0.2180	2.6959
Dimethylformamide	<i>n</i> -Tetradecane	0.2427	2.7245

in the heat of mixing caused by the increasing non-polarity of the system. The change in excess entropy is small from mixture to mixture, as the molecular order is not drastically influenced by more of the same non-polar interactions. These results are in qualitative agreement with the experiments conducted by Brunsch [14], where similar trends are observed. This more clearly shows the trade-off between catalyst recovery and product separation performance characteristics of the TMS.

5. Experimental validation

The experimental validation of this computationally based solvent selection procedure can be considered a requirement due to the inaccuracies inherent in any predictive model or method. In this

section, results from solvent screening are empirically investigated. This is a two-step process that begins with Biphephos ligand being added to binary solvent mixtures where the amount of Biphephos in the product phase is measured. The second step is then to take each of the TMS systems and perform the hydroformylation of 1-dodecene in them. This allows for evaluation of the influence of the reactants and products on the phase behavior as well as the effect of solvent selection on reaction performance.

Since the screening results reveal that large alkanes should be used as LRSC solvents, it is preferable to again fix the LRSC solvent to *n*-decane, as is done previously in the screening result comparisons. The reasoning behind this is that the LRSC solvents are all large alkanes and that the trend accompanied by using different sized alkanes is already confirmed experimentally [14]. This makes the selection of the LRSC much less important than the HRSC, where the different structures and functional groups have a stronger effect on physical properties such as boiling temperature and phase characteristics. In this regard, the systems investigated experimentally are chosen from those mixtures listed in Table 4. Of these potential TMS mixtures, six are eventually evaluated. Acetaldehyde is not empirically considered due to its low boiling temperature of 20 °C, making experimental validation and analysis difficult. Also, no experimental analysis of N-formylpiperidine is conducted as it only appeared in one TMS system. This stems from its much higher solubility in alkanes than DMF, for which it is often used as a replacement solvent.

5.1. Experimental methods

All phase partitioning and hydroformylation experiments are carried out under an argon atmosphere using standard Schlenk techniques. Chemicals are commercially available and used without further purification.

Each phase partitioning experiment is conducted using a binary mixture of each TMS system with a 1:1 ratio of polar (15 g) and the non-polar (15 g) solvent *n*-decane being added to a double-walled

100 mL separating funnel. An amount of Biphephos proportional to the amount used in the reactions is added (116.9 mg, 0.149 mmol) and thoroughly mixed before being cooled to a temperature of -20°C . After 20 min, the phases are separated. Samples for Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) measurements are prepared using 0.230 g of the non-polar phase weighted into a Teflon cup. To this, 2.5 mL of nitric acid (65%) and 4 mL of sulfuric acid (96%) are added and digestion conducted in a Micro mPrep A microwave (MWS GmbH, Switzerland). Subsequently 2 mL of distilled water and 1 mL of hydrogen peroxide solution (30–32%, optima grade, Fisher Chemical) are added. Finally, ICP the samples are analyzed with an IRIS Intrepid optical emission spectrometer (Thermo Fisher Scientific GmbH) and the phosphorous content determined.

The hydroformylation experiments follow a similar process with the addition of the reaction step. In a typical reaction setup, the catalyst precursor $\text{Rh}(\text{CO})_2\text{acac}$ (3.8 mg, 0.0149 mmol) and the ligand Biphephos (58.4 mg, 0.0745 mmol) are weighed in a 40 mL steel autoclave. The autoclave is evaporated and flushed with argon three times. The polar solvent (6.25 g), *n*-decane (6.25 g), and 1-dodecene (2.5 g, 14.9 mmol) are then transferred into the autoclave also under an argon atmosphere. Afterwards, the reactor is pressurized to 20 bar using a mixture of CO/H_2 (1:1) and heated to 100°C . The stirrer is adjusted to 600 rpm. After 90 min the reaction is stopped by cooling the reactor with ice. After de-pressurization through removal of the remaining synthesis gas, the reaction mixture is cooled down to -20°C in a double-walled 100 mL separating funnel. The temperature is controlled by a cooling circulation thermostat (HAAKE K40, Thermo Electron Corporation HAAKE DC50, internal temperature regulation) using ethylene glycol/water (1:1) as cooling medium. The mixture is allowed to settle at this temperature for 20 min before both phases are separated and analyzed using gas chromatography and ICP-OES. For quantitative analysis of the reaction mixture an Agilent Technologies 6890N Network gas chromatograph equipped with an HP-5 column (30 m \times 0.320 mm \times 0.25 mm film thickness, Agilent J&W GC Columns) and an FI-Detector is used. Leaching values of Rh and phosphorus in the product phase are measured using an IRIS Intrepid ICP-OES spectrometer (Thermo Fisher Scientific GmbH). The identification of the products is carried out by NMR spectroscopy (Bruker model DPX 500) and using a GC-MS (Agilent Technologies 5977A MSD, 70 eV). The same procedure for preparing analysis samples is used here as is used in the phase separation experiments.

5.2. Phase partitioning

In each of the six TMS systems examined, two phases are observed at the separation temperature of -20°C except for the TMS comprised of methyl acetate and *n*-decane. This is unfortunate as methyl acetate is predicted as having a miscibility gap with decane in a binary mixture. This result is similar to the ternary LLE experiments and model comparisons conducted by [35], where the ternary LLE of the system methyl acetate, methanol, and *n*-decane is investigated at temperatures from 5°C to 35°C . They show that several of the predictive group contribution models used to estimate the phase behavior predict miscibility gap formation for the binary system methyl acetate and *n*-decane when in fact all experiments show the opposite. This seems to be the case with COSMO-RS as well and may be caused by an over representation of the polar character of the sp^2 oxygen of the otherwise weakly polar methyl acetate. In fact the σ -profile of methyl acetate is quite similar to the more polar acetone, owing to its own similar carbonyl group.

Therefore, the careful approach to miscibility gap formation chosen in the solvent screening step is insufficient in only identifying those systems with proper TMS characteristics. Another aspect

Table 6

Phase partitioning with Biphephos: D_{HRSC} , D_{dec} , and D_{P} are the distributions of the HRSC solvent, *n*-decane, and phosphorous (Biphephos) by mass between the product and catalyst phases, respectively.

HRSC	LRSC	D_{HRSC}	D_{dec}	D_{P}
Dimethylformamide	<i>n</i> -Decane	2/98	94/6	1/99
Acetone	<i>n</i> -Decane	10/90	75/25	3/97
N,N-Dimethylacetamide	<i>n</i> -Decane	5/95	91/9	1/99
N-Methyl-2-pyrrolidone	<i>n</i> -Decane	1/99	93/7	1/99
Methyl acetate	<i>n</i> -Decane	/	/	/
N,N-diethylformamide	<i>n</i> -Decane	4/96	82/18	1/99

is that with the increased predicted polarity of methyl acetate, the relative solubility of Biphephos is most likely exaggerated. It may be possible that by using other mixtures of methyl acetate and *n*-decane instead of the 1:1 mass ratio used here would lead to phase separation. This is, however, not investigated in this work and would not eliminate the possible exaggeration in the catalyst solubility prediction.

The amount of Biphephos recovered in each phase is determined from the amount of phosphorous in each phase, seen in Table 6 as the distribution of phosphorous, D_{P} . For example, in the mixture of DMF and *n*-decane, 99% of Biphephos is found in the catalyst phase and 1% is lost in the product phase. All solvents forming two phases had approximately one percent leaching levels outside of acetone which had approximately three percent leaching. Results indicate that COSMO-RS can, in this case, provide good predictions of Biphephos partitioning for those systems actually forming biphasic systems based on the very low leaching of the catalyst in each HRSC solvent. It must be noted, however, that many of the results for catalyst leaching are near the lower limit of detectability of the ICP-OES resolution which make it difficult to exactly define the performance of each solvent system. This makes a qualitative analysis and comparison with the results produced in COSMO-RS somewhat problematic. However, the predicted partition coefficients were very similar and most likely within the expected error.

5.3. Hydroformylation in each TMS

The final aspect of solvent screening for the hydroformylation of 1-dodecene is to see whether or not the screened TMS systems can facilitate the reaction and provide the desired phase separation with adequate catalyst recovery. For each of the systems that showed some type of phase separation, a reaction based on the procedure outlined in [34] is developed. It is also important to notice that tridecanal is a miscibility enhancer and that the degree of separation between the two phases is expected to worsen with its accumulation in the system. Also, solvent effects on the reaction in regard to conversion and selectivity need to be evaluated, something the screening method does not take into account. This may be related to several aspects such as the solubility of the synthesis gas components carbon monoxide and hydrogen in each TMS, which has strong effects on the active state of the catalyst [11]. This in turn influences the reaction performance and shows that it can be directly influenced by the solvent composition. Also worth mentioning is that the reaction performance also depends on the coordination effects of each solvent with the catalyst complex, something not considered in this screening process.

Results from the reaction experiments are shown in Table 7. Most noticeable among the results is that almost all TMS systems lead to similar levels of conversion of 1-dodecene and selectivity for the linear tridecanal. The variation in the *n*/*iso* ratio is insignificant and shows that the selectivity of the Biphephos ligand is not significantly affected by the choice of polar solvent. The only exception in reaction performance comes from the yield of tridecanal

Table 7

Hydroformylation results for each selected TMS system: n/iso is the ratio of linear to branched aldehyde product, Y_{tri} is the tridecanal yield, and D_{tri} , D_{dod} , D_{HRSC} , D_{dec} , D_p , and D_{Rh} are the distributions of tridecanal, dodecene, the HRSC solvent, decane, phosphorous (Biphephos), and Rh by mass between the product and catalyst phases, respectively. All values are given in percents.

	n/iso	Y_{tri}	D_{tri}	D_{dod}	D_{HRSC}	D_{dec}	D_p	D_{Rh}
Dimethylformamide	99/1	80	74/26	94/6	4/96	95/5	1/99	1/99
Acetone	99/1	81	/	/	/	/	/	/
N,N-Dimethylacetamide	98/2	77	68/32	89/11	11/89	90/10	1/99	1/99
N-Methyl-2-pyrrolidone	98/2	79	70/30	91/9	12/88	92/8	1/99	1/99
Methyl acetate	98/2	80	/	/	/	/	/	/
N,N-Diethylformamide	97/3	62	43/57	53/47	28/72	58/42	3/97	5/95

0.1 mol% $Rh(CO)_2acac$, 0.5 mol% Biphephos, 14.9 mmol 1-dodecene, 6.25 g polar solvent, 6.25 g *n*-decane, $T = 100^\circ C$, $pCO/H_2 = 20$ bar, $t = 90$ min, 600 rpm, yield (Y), ratio of linear and branched hydroformylation products (n/iso) and distribution of the solvents, products and substrate are determined by GC-FID, distribution of Biphephos and Rh is determined by ICP-OES.

when using diethylformamide as the HRSC solvent. Here, a substantially lower yield is observed which may be caused by a substantial change in synthesis gas solubility or inhibiting coordination effect when using this solvent.

The miscibility gap formed in each post-reaction mixture is also not as large as in the simple phase separation experiments as seen by the higher distribution of polar solvent between both phases. This is again expected due to the miscibility enhancing effect of the tridecanal product. In the systems using DMF, N,N-dimethylacetamide, and N-methyl-2-pyrrolidone as the HRSC solvent, the distribution of *n*-decane between the two phases remains almost the same while the distribution of the polar solvent worsens as seen by the increase in polar solvent found in the apolar, product phase. In the case of N,N-diethylformamide, the distribution of *n*-decane is much larger than in the phase separation experiment whereas the distribution of N,N-diethylformamide, albeit fairly large, changes to a lesser degree. In the case of using acetone as the HRSC, even at a separation temperature of $-30^\circ C$, biphasic separation does not occur. The behavior of the unconverted reactant 1-dodecene is unremarkable. The slight polar character of the carbon-carbon double bond in 1-dodecene does not affect its phase behavior strongly as seen in its very similar distribution to *n*-decane. Upon comparison of the predicted tridecanal partition coefficients, no general comparison between the distribution of tridecanal seen here and in the binary mixture predictions can be made. N,N-Dimethylacetamide is predicted as having a higher distribution of tridecanal than N,N-diethylformamide but performs much better, in fact, almost as well as N-methyl-2-pyrrolidone which had the highest tridecanal partition coefficient of all HRSC solvents in Table 2. In fact, the TMS with diethylformamide has more tridecanal found in the catalyst phase than in the product phase indicating a much larger partition coefficient than that predicted by COSMO-RS. This could be based on that fact that these partition coefficients do not show much variation and may well be within the average error in predictions for partition coefficients made using COSMO-RS. This suggests that no significant differences in tridecanal affinity can be made therefrom. However, it may be that concentration effects of tridecanal are significant and cannot be effectively predicted using the partition coefficient which assumes a dilute mixture. To compensate, the partition coefficient constraint should be increased to a higher value than used in this screening example. This would allow more, potentially effective candidate solvents to be considered later in the screening process.

Probably the most interesting aspect of the reaction results are found in the catalyst leaching levels. Very similar levels of catalyst ligand leaching as seen in the phase separation experiments are observed here after the separation of phases in the decanter. This is not only true for the catalyst ligand but for Rh as well. Interestingly enough, even for the poor phase separation of the TMS using N,N-diethylformamide and *n*-decane, seemingly low levels

of catalyst leaching are observed, being only about five times that of the system DMF and *n*-decane. Catalyst loss is very similar for the systems containing DMF, N,N-dimethylacetamide, and N-methyl-2-pyrrolidone, each achieving a loss of catalyst of one percent. It can be concluded that the amount of leaching is only roughly comparable to the quality of the distribution of the HRSC solvent between the two phases, showing that LLE behavior does not necessarily correlate to catalyst leaching. Also noticeable is that the leaching levels of Rh and Biphephos are quite similar. Thus the assumption that Rh and Biphephos leaching would be analogous and that predictions of catalyst leaching only require the ligand structure seem to be valid.

In the end, four functioning TMS systems identified using the solvent selection framework presented here are successfully implemented in the hydroformylation of 1-dodecene. It is found the importance of the solvent mixture depends significantly on the polar solvent chosen. Limitations in the screening methods are also evaluated and should be considered when using the method for other homogeneously catalyzed reactions. It is also worth mentioning that the quantum chemical COSMO-RS method employed for thermodynamic predictions is being continuously updated and enhanced. Therefore, screening predictions will continue to improve with time as the theory and methods become more reliable and robust.

6. Conclusion

A novel method for TMS solvent selection based on quantum chemical COSMO calculations based on reaction specific catalyst recovery is presented. For the hydroformylation of 1-dodecene, it is shown that by selectively screening for solvents based primarily on the Biphephos catalyst ligand solubility and secondarily on product recovery through partition coefficients, functioning TMS systems can be identified. The benefit of using such a model is the absence of experimental data required to make solvent selection decisions at an initial stage of process development.

In addition to the screening framework developed, experimental validation of the catalyst ligand's partitioning between the two solvents is evaluated. This important step in the process allows for the validation of the TMS systems identified in the computational screening framework. Here, it is seen that using thermodynamic models to predict phase equilibrium is still not free of pitfalls. For instance, the inclusion of methyl acetate as a feasible solvent in a TMS with *n*-decane is erroneous; in reality they are completely soluble in one another. Also, predicted partition coefficients between the solvents are found to be inaccurate in predicting which solvent systems would be most affected by tridecanal. These problems illustrate the reason for generating a sizable group of potential TMS systems for experimental validation.

Another aspect that is not covered in the thermodynamically based screening procedure is the reactivity of the solvent species

and generally how the reaction proceeds in each solvent mixture. It is shown that for the hydroformylation of 1-dodecene that the solvents selected here have a minimal effect on the reaction performance. This would mean that the solvents found here have very similar coordinating effects and/or gas solubilities. Only one exception is found in the case of N,N-diethylformamide where a lower yield of tridecanal occurs. In four of the five TMS systems investigated that formed biphasic binary systems, it is very feasible to conduct the hydroformylation of 1-dodecene. In this case, predicted catalyst leaching levels were qualitatively consistent with the predicted catalyst leaching levels found in the partitioning predictions. In the one case using acetone, the reaction proceeded quite well but cannot be used due to the absence of phase separation afterwards.

One bright spot in the use of this method is that DMF was found to be a qualitatively good solvent for catalyst recovery. In this regard, the method is successful in identifying solvents already used in this process. On the downside, expectations were high that a new, feasible solvent would be found with higher catalyst solubility than DMF. Perhaps by using a larger search space, for example a larger batch of HRSC solvents, other interesting candidate solvents can be found that lead to better reaction and recovery performance. Considering the margin of error using this method, future screening examples should also relax some constraints and increase the number of acceptable solvents. However, any increase in the number of solvents chosen during the computational screening section may lead to a larger batch of possible TMS systems, increasing the experimental time and cost. Since thermodynamic models are not yet to the point of accuracy required to really reduce the solvent search space, this may be currently the best course of action for future endeavors in this topic area.

Acknowledgments

This work was conducted in part in cooperation with the Collaborative Research Centre “Integrated Chemical Processes in Liquid Multiphase Systems”. The financial support from the German Research Foundation (DFG) under the grant SFB/TRR 63 is gratefully acknowledged. The authors would also like to thank Umico AG & Co. KG for donating the Rh precursor, Rh(CO)₂acac.

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